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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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[1]Evaluated in 1998 JMPR but omitted from the report

1999 Joint FAO/WHO Meeting on Pesticide Residues

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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
AR	applied radioactivity
ASAT	aspartate aminotransferase
BBA	Biologische Bundesanstalt für Land- und Forstwirtschaft
bw	body weight
BOD	biological oxygen demand
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
CCRVDF	Codex Committee on Residue of Veterinary Drugs in Food
ChE	cholinesterase
CI	chemical ionization
CNS	central nervous system
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
DT-50	time for 50% decomposition (i.e. half-life)
DT-90	time for 90% decomposition
EBDC	ethylenebis(dithiocarbamate)
EC	(1) emulsifiable concentrate (2) electron-capture [chromatographic detector]
ECD	electron-capture detector
EI	electron-impact
EMDI	estimated maximum daily intake
EPA	Environmental Protection Agency
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
FI(D)	flame-ionization (detector)
FP(D)	flame-photometric (detector)
g (not gm)	gram
µg	microgram
GAP	good agricultural practice(s)
GC-MS	gas chromatography - mass spectrometry
GC-MSD	gas chromatography with mass-selective detection
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
HR	highest residue in the edible portion of a commodity found in the trials used to estimate a maximum residue level in the commodity
HR-P	residue in a processed commodity calculated by multiplying the HR of the raw agricultural commodity by the corresponding processing factor
i.d.	internal diameter
IEDI	international estimated daily intake
IESTI	international estimate of short-term intake
i.m.	intramuscular
i.p.	intraperitoneal
IPCS	International Programme on Chemical Safety
IR	infrared
IRDC	International Research and Development Corporation (Mattawan, Michigan, USA)
i.v.	intravenous
JMPR	Joint FAO/WHO Meeting on Pesticide Residues (Joint Meeting of the FAO Panel of Experts on Pesticide Residues in Food and the Environment and the WHO Core Assessment Group
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
μm	micrometre (micron)
MFO	mixed function oxidase
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
MSD	mass-selective detection or detector
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
NOEL	no-observed-effect level
NP(D)	nitrogen-phosphorus (detector)
NTE	neuropathy target esterase
OECD	Organization for Economic Co-operation and Development
OP	organophosphorus pesticide
PHI	pre-harvest interval
ppm	parts per million. (Used only with reference to the concentration of a pesticide in a 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
RAC	raw agricultural commodity
RBC	red blood cell
r.d.	relative density. (Formerly called specific gravity)
RfD	reference dose (usually in the phrase '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)
SPE	solid-phase extraction
STMR	supervised trials median residue
t	tonne (metric ton)
T_3	tri-iodothyronine
T_4	thyroxine
TADI	Temporary Acceptable Daily Intake
tert	tertiary (in a chemical name)
TLC	thin-layer chromatography
TMDI	theoretical maximum daily intake
TMRL	Temporary Maximum Residue Limit
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
WHO	World Health Organization
WP	wettable powder
<	less than
≤	less than or equal to
>	greater than
≥	greater than or equal to
*	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 1999 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 on Pesticide Residues (JMPR) was held at FAO, Rome (Italy), from 20 to 29 September 1999. The FAO Panel of Experts had met in preparatory sessions from 15 to 19 September.

The Meeting was opened by Dr Niek A. Van der Graaff, Chief of the Plant Protection Service, FAO Plant Production and Protection Division, on behalf of the Directors General of FAO and WHO. Dr Van der Graaff emphasized the growing importance of the work of the JMPR for the establishment of international standards, as maximum residue limits (MRLs) for pesticide residues in food set by the Codex Alimentarius Commission had been incorporated into the Agreement on Sanitary and Phytosanitary Measures of the World Trade Organization (WTO). He stressed the increasing workload of the members of the JMPR with the constant increase of data, and the need that governments should give necessary recognition to their work which provides the basis of all Codex MRLs.

The Meeting was marked by the introduction of acute dietary risk assessments for compounds for which MRLs and STMRs were considered at the Meeting and for which an acute reference dose (acute RfD) had been established, in commodities for which consumption data were available. While the Meeting recognised the deficiencies of the limited data base and the differences in national approaches, improvement is expected if more countries will submit the necessary information.

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 Joints Meetings (see References, Section 7) contain information on ADIs, 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 evaluations of analytical methods.

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 Core Assessment Group was responsible for reviewing toxicological and related data and for estimating, where possible, ADIs for humans of the pesticides.

The Meeting evaluated 30 pesticides, including one new compound and 12 compounds that were completely re-evaluated, for toxicology or residues or both, within the Periodic Review Programme of the Codex Committee on Pesticide Residues (CCPR).

The Meeting allocated ADIs and Acute Reference Doses (Acute RfDs), estimated maximum residue levels which it recommended for use as MRLs by the CCPR, and estimated Supervised Trials Median Residue (STMR) levels as a basis for the estimation of dietary intakes.

The Meeting devoted particular attention to the estimation of the dietary intakes (both acute and chronic) of the pesticides reviewed in relation to their ADIs or acute RfDs. In particular, in the case of compounds undergoing a complete evaluation or re-evaluation it distinguished between those whose estimated intakes were below their ADIs and those whose intakes might exceed their ADIs by marking the MRLs recommended for the latter with footnotes. A proposal to make this distinction and its rationale are described in detail in the report of the 1997 JMPR[1] (Section 2.3) and its revision is explained in this report (Section 2.2).

Especial thanks and appreciation were extended to Mr. Tony Machin who had developed the format and edited the FAO JMPR publications for more than twenty five years and set a high standard of quality in these publications.

[1] *Pesticide residues in food - 1997. Report of the Joint Meeting of the FAO Panel of Experts on Pesticide Residues in Food and the Environment and the WHO Core Assessment Group on Pesticide Residues*. FAO Plant Production and Protection Paper 145.

2. GENERAL CONSIDERATIONS

2.1 INCREASING WORKLOAD OF JMPR PARTICIPANTS

The 1999 CCPR, after considering the 1998 JMPR Report *The capacity of the JMPR to undertake periodic reviews,* requested the JMPR Secretariat to prepare a short paper for consideration at the next Session with practical proposals to address this issue (31st Session of the CCPR, ALINORM 99/24A, para 21).

The Meeting was pleased to note that the CCPR had recognized the problems for the JMPR participants associated with the increasing workload arising, as explained in the 1998 report, from the need for transparency and the increasing quantities of data being evaluated.

The amount of work required has increased because of the high level of detail in modern data submissions. For example, it may not always be apparent that many points must be checked in evaluating residue trials that are generally not recorded in the published evaluations, including plot areas, description of application equipment, application calibration, treatment dates, sampling and harvest dates, analysis dates, freezer storage periods and comparison with the periods in freezer storage studies, procedural recoveries, sample sizes, nature of the replications (if any), analyses of field control samples and weather and irrigation, all of which may influence residue levels. Similarly, details such as data on individual animals in toxicological studies must often be reviewed. Because of the necessity for clear communication of risk assessments, the reports and evaluations are becoming more detailed and complex.

The use of national evaluation documents aids the Meeting in its toxicological evaluations of the original reports of the studies and other pertinent information that are reviewed. Although the use of national documents does not eliminate the need to evaluate the original studies, it helps to identify the studies that are available to ensure that the full database has been evaluated. On the other hand, the use of national residue evaluation documents is generally of limited assistance, because national evaluations focus mainly on national uses and national data whereas the JMPR makes a detailed examination of labels from around the world and compares trials with the relevant GAP. This is a different process from national residue evaluation and registration. National residue evaluations will provide helpful additional information for some sections, e.g. farm animal metabolism and feeding, but the Meeting did not believe that the use of national evaluations would decrease the workload.

The work currently required by a JMPR member to evaluate the data before each JMPR is equivalent to up to 3 months full time. In many cases the situation that has developed is that members are not afforded sufficient time during working hours, but devote their personal time to the bulk of the work. Some members have advised that they cannot continue devoting so much of their personal time to the work required for the JMPR.

The value of a JMPR member’s knowledge and experience to his or her own organization and national government should not be underestimated even when the time is mainly oriented towards the establishment of international food standards. A working knowledge of the JMPR/CCPR system is invaluable in aligning national and Codex standards and preparing data submissions to develop Codex MRLs.

The Meeting recommended

1. That the contribution of expertise and time of the JMPR members be formally recognized as a contribution by national governments to the Codex/FAO/WHO system.

2. That national governments agree, when members are appointed to the FAO Panel or WHO Core Assessment Group, to provide them with sufficient time and resources to complete their work to a standard expected of the JMPR.

2.2 MAXIMUM RESIDUE LIMITS FOR MONITORING (MRLM)

The 1997 JMPR (Report, Section 2.3) proposed a mechanism to distinguish MRLs for pesticides for which the estimated dietary intakes in one or more regional diets might exceed the ADI from MRLs for pesticides whose estimated intakes were below the ADIs. When recommendations of the JMPR for MRLs are considered in the Codex procedure, the recommended MRLs for those compounds whose ADIs or acute RfDs might be exceeded are not readily distinguishable from those whose ADIs or acute RfDs would not be exceeded, according to the dietary intake estimates of the JMPR. Without some differentiation, MRLs for both groups appear to have JMPR endorsement. The risk manager, i.e. the CCPR, needs to be aware of those MRLs which are for compounds for which the JMPR's evaluation of the available information indicates that the dietary intake might exceed the ADI or the acute RfD and MRLs for compounds where the information is insufficient for the JMPR to provide an estimate.

The 1997 JMPR considered only situations where the ADIs for chronic risk appeared to be exceeded. The present Meeting is incorporating estimates of acute dietary risk into the evaluation process. It is therefore also appropriate to consider a procedure to distinguish MRLs associated with a dietary intake that may exceed the acute reference dose (acute RfD).

Various means of identifying MRLs for compounds whose intake the JMPR concluded might exceed the ADI in one or more regional diets were considered by the 1997 JMPR.

1. Estimate the maximum residue levels, but do not recommend them to Codex for use as MRLs. This would not be equitable to countries that can make more refined national estimates of dietary intake or to those that have no problem because of negligible consumption of those food items that contribute to the residue. This procedure also removes the risk management function from Codex.

2. Create a term to distinguish the MRLs that are associated with an exceeded ADI from other MRLs. The term maximum residue limit for monitoring (MRLM) was proposed. An MRLM was 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."

3. Distinguish the MRLs that are associated with a possibly exceeded ADI from other MRLs by the use of footnotes on the problematic MRLs.

The 1997 JMPR decided upon the second of these options and recommended that MRLMs be used with new and periodic review compounds considered by future FAO Panels of the JMPR. It was also recommended that the information needed by the JMPR to refine its estimates of dietary intakes be clearly stated in the JMPR reports and evaluations.

The 31st Session of the Codex Committee on Pesticide Residues (1999) discussed the recommendation, with some delegations supporting the proposal, others supporting the proposal with reconsideration of the term chosen, and one delegation preferring the first option. The Committee supported the 1997 JMPR proposal and decided that the MRLMs "…would be treated as normal MRLs which would be footnoted indicating that assurance could not be provided that intake would not exceed the ADI." It was decided that such MRLs would not be advanced to Step 8. The JMPR was invited to reconsider the term "MRLM" as the word "monitoring" was considered confusing (ALINORM 99/24A, para 18-19).

The present Meeting recalled that the 1997 JMPR had discussed several possible terms, but ended with the MRLM term originally proposed. Each proposal was not preferred by one or more Panel members. It is likely that a similar situation will persist in the CCPR, as already witnessed, for the same reason.

The Meeting noted that estimates of dietary intake which exceed the ADI (“chronic intakes”) apply to the pesticide itself rather than to specific commodities, whereas estimates of dietary intake which exceed the acute RfD (“acute intakes”) apply to one or more specific commodities.

The Meeting agreed that the simplest solution would be to mark the pesticide (for potential chronic dietary intake concerns) or specific commodities (for potential acute dietary intake concerns) with a footnote with a statement such as:

“The information provided to the JMPR precludes an estimate that the dietary intake would be below the ADI (acute RfD) - JMPR Year”.

Conclusion

The Meeting decided to abandon the use of the term MRLM, and to use footnotes applying to the pesticide for those cases where the available information indicates that the ADI might be exceeded and the use of one or more footnotes applying to specific commodities where the available information indicates that the acute RfD of the pesticide might be exceeded. It was agreed to implement the practice at the present Meeting.

The Meeting further agreed to continue the practice of clearly stating in the JMPR reports the information needed by the JMPR to refine its estimates of dietary intakes for chronic exposure situations.

2.3 CONSIDERATION OF RECOMMENDATIONS ARISING FROM THE INFORMAL JMPR/JECFA HARMONIZATION MEETING (FEBRUARY 1999, ROME)

The objectives of the JMPR/JECFA Harmonization Meeting held earlier this year were to discuss issues relating to the use of chemicals as both pesticides and veterinary drugs. Differences between the JMPR and JECFA evaluation processes have led to different approaches to residue definitions, estimations of dietary intake, commodity descriptions for analysis, and recommendations for MRLs. The topics discussed included the analysis and commodity descriptions of meat/muscle, fat, milk and eggs, definitions of residues, and the estimation of dietary intake and risk assessment.

Papers on the various discussion items were presented and the main points are summarised in the *Report of the Informal JECFA/JMPR Harmonisation Meeting, 1–2 February 1999, Rome Italy*[1]. The Meeting discussed only those recommendations addressed to the JMPR. The recommendations are listed below with comments.

Tissue

3. For the determination of fat-soluble pesticide and/or veterinary drug residues in meat/muscle for enforcement or monitoring purposes, laboratories are advised to collect and analyse trimmable fat and to report the residue on a lipid basis, i.e. in meat (fat) for the JMPR and in fat for JECFA. For meat without trimmable fat, the entire commodity should be analysed as meat/muscle, but only where the MRL has been set on a meat/muscle basis.

The recommendation is in agreement with current JMPR practice in recommending MRLs for fat-soluble compounds.

4. For the determination of non-fat-soluble pesticide or veterinary drug residues in meat/muscle, laboratories are advised to analyse meat/muscle with trimmable fat removed, as far as is practical.

The Meeting agreed that the JMPR practice (past and present) in recommending MRLs for non-fat-soluble compounds in animal commodities is in accord with the recommendation. Data are reviewed for muscle, but the recommended MRL is expressed as applying to ‘meat’ for analytical purposes.

5. Where JECFA and JMPR have recommended MRLs for the same chemical with the same residue/marker residue definitions on the same commodity, the higher MRL shall prevail.

The JMPR is aware of this situation. Although the JMPR will evaluate the data received and report the estimated maximum residue level the recommended MRL will take into account the CCRVDF MRL. The reviewer (JMPR or JECFA) should be alerted to the current status of the MRLs in both the CCPR and CCRVDF systems.

Milk

7. For the determination of fat-soluble pesticide/veterinary drug residues in milk, the milk-fat portion of fresh milk should be analysed, and the results should be expressed on a whole milk basis using 4% as the nominal fat content.

[1] The document is available from the JMPR FAO Joint Secretary on request

The JMPR agrees with the recommendation, as this is its current practice in the evaluation of fat-soluble pesticide residues in milk.

Harmonization

13. The working group noted disparate residue definitions by CCPR and CCRVDF for abamectin and recommended that CCRVDF/JECFA consider expansion of its residue definition to include other isomers, such as the photodegradation isomer of B1a. CCPR/JMPR should consider its need to include the various isomers as part of the periodic review of abamectin.

The JMPR agrees that residue definitions should be harmonised where possible and will consider the recommendation at the next periodic evaluation of abamectin. The scheduling of the periodic review of the compound is a matter for discussion by the CCPR Priorities Committee.

14. "Cypermethrin" and "alpha-cypermethrin" should remain as the marker residue definitions for cypermethrin and alpha-cypermethrin respectively when used as veterinary drugs, and "cypermethrin (sum of isomers)" should remain as the residue definition for the pesticide cypermethrin. Guidance should be supplied to laboratories on the designation of the measured residue as cypermethrin or alpha-cypermethrin based on the chromatography of the test substance.

Cypermethrin is scheduled for periodic evaluation by the JMPR in September 2004 and this issue will be considered further at that time. Cypermethrin is also scheduled for evaluation by JECFA in February 2000. However, it is noted that there may be enforcement problems if products containing the unresolved mixture of isomers are still registered alongside products containing a single pair of isomers, (alpha-cypermethrin) or two isomeric pairs (zeta-cypermethrin) where different MRLs exist for the different products. In addition, animals may be exposed to more than one type of product and problems may again occur if laboratories are monitoring only a single marker residue and not the sum of the isomers.

15. Harmonization efforts should be undertaken on a case-by-case basis where marker residue definition/residue definition differences occur between JECFA and JMPR.

The JMPR agrees that residue definitions should be harmonised where relevant. The JMPR may adopt different definitions for enforcement and for the estimation of dietary intake, and this should be taken into account when harmonization is considered.

17. CCPR should amend the note explaining the "V" designation for MRLs. The present description, "the MRL accommodates veterinary uses," is confusing and should be amended to "the MRL accommodates external animal treatments."

The Meeting agreed to use the suggested amendment and include the amended terminology in future recommendations.

18. For compounds that are common to both, JMPR and JECFA should use the more specific animal commodity descriptions to enhance harmonization. For example, separate MRLs for

cattle muscle, goat muscle, horse muscle, pig muscle, and sheep muscle are preferable to meat of cattle, horses, pigs and sheep.

The JMPR agrees that when there are MRLs recommended to accommodate direct veterinary treatments (JMPR/JECFA), they should be species-specific rather than generic. This will allow JECFA to see clearly that the MRL relates to specific animal uses as opposed to exposure from consuming treated feed items.

Dietary intake estimation and risk assessment

19. Each expert panel needs a better understanding of the other's procedures for food safety assessments for estimating MRLs and dietary exposure, for example. JECFA will provide JMPR its guidance document describing the JECFA evaluation procedures when the draft version is finalized. The JMPR FAO Manual (1997) will be distributed to the JECFA members at the February 1999 meeting.

The JMPR looks forward to the publication of the JECFA manual with interest and notes that the FAO manual has been distributed to JECFA members.

20. The JECFA/JMPR Group acknowledged the very different approaches used for dietary exposure determinations. JMPR will provide JECFA with detailed reports of its assessments, dietary intake calculations and % ADI determinations for compounds of interest to JECFA. When the data are available, JECFA will provide JMPR with median and upper limit animal commodity residue values and dietary intake calculations/% ADI determinations for compounds of interest to JMPR.

There is a need to discuss further the two approaches to dietary intake calculations and investigate in detail the current approaches used by JECFA. The JMPR is aware that in future intake estimates there is a need to take into account residues in animal commodities resulting from direct veterinary treatments for those pesticides which are not used on major animal feed commodities, e.g. thiabendazole and deltamethrin. It is noted that JECFA will provide median residue levels to the JMPR FAO Panel for inclusion in dietary intake assessments in place of the STMRs.

21. JECFA and JMPR should consider the exchange of one panel member each for a portion of the expert panel meetings to facilitate the harmonization of MRLs and risk assessment for substances used as veterinary drugs and pesticides.

The JMPR is willing to support the exchange of Panel members when there is a common interest in the review of a particular compound. The Meeting was aware that the Joint Secretaries had arranged for a JMPR Panel member to attend the JECFA meeting in 2000.

22. The Joint Secretary for JMPR will attend the JECFA meeting, and the Joint Secretary for JECFA will attend the JMPR meeting, particularly when MRLs and risk assessments of substances used as veterinary drugs and as pesticides are being considered.

The JMPR notes that this exchange may be useful.

23. Joint meetings of JMPR and JECFA should be held on an ad hoc *basis to address issues of a mutual interest, for example, how to address MRL and ADI issues for classes of compounds with common modes of action, e.g. organophosphorate compounds.*

Dietary intake assessments and other matters should be discussed at *ad hoc* meetings in the interest of continued harmonisation.

24. For compounds of mutual interest, JMPR and JECFA should have each other's recommendations/reports available when conducting evaluations. The Joint Secretaries will have responsibility for obtaining and distributing the documents and information, as appropriate.

The Joint Secretaries should have the appropriate evaluation reports and it is essential that this information is given to the Joint Secretaries when the compounds are scheduled. The Meeting recommended that the information should be provided to the Panel member reviewing the compound at a very early stage and should include the full evaluation report.

2.4 PROGRESS ON ACUTE DIETARY INTAKE ESTIMATION - INTERNATIONAL ESTIMATE OF SHORT TERM DIETARY INTAKE (IESTI)

The Meeting noted the report of the *ad hoc* Expert Meeting on Acute Dietary Intake of Pesticide Residues (attached as Annex V), which was held before the 1999 Session of the CCPR. Since development of the IESTI by the Geneva Consultation in 1997, the Meeting had gained experience in using these calculations. It considered ways to refine guidance on the use of the calculations and recommended where further information should be sought to continue the refinement of this process. The reader is referred to Section 3 of this Report for information on the development of the IESTI calculations.

International diets for the IESTI have been developed by the WHO on the basis of consumption data and related information provided by the Australian, Netherlands, French, Japanese, UK and USA governments. In recommending an appropriate level of consumption, the highest 97.5th centile (eaters only) was taken from the data provided. While the Meeting recognised the deficiencies of the limited database and the differences in national approaches, it endorsed the continued use of the highest 97.5th centile consumption level in the calculation of the IESTI.

The use of the appropriate residue level in the case 1 calculation (Section 3 of this Report) was discussed. The *ad hoc* meeting had recommended the use of the highest level from supervised residue trials (RL) in place of the MRL, in accordance with the suggested consideration of the Case 1 equation described in the report of the Geneva Consultation (1997) and as discussed at the UK Conference (York 1998). The Meeting supported this recommendation and also coined new terminology to describe the 'highest residue' in the supervised trials.

Account should be taken of any changes in residues caused by processing. The Meeting questioned whether use of the MRL-P may be considered appropriate in the Case 1 situation. While it was recognised that this was a 'worst-case scenario', the MRL can be influenced by the geometric progression regularly used in its derivation. Also, rounding of values at an intermediate stage in calculating processing factors and the MRL-P is

undesirable. Using the MRL-P in the IESTI calculation may also have some influence on the maximum residue level estimated for the processed commodity, which was not considered desirable; using the RL-P removes this influence. It was also noted that the use of the MRL-P in the calculation was not sufficiently discriminatory to allow the estimate to be used as a screening technique. It was agreed that IESTIs should be calculated using the RL-P, which should be referred to in the future as the "highest residue – processed commodity" or HR-P.

The Meeting defined HR as the highest residue in the edible portion from the trials used for estimating maximum residue levels. The HR-P is the residue in a processed commodity calculated from the HR of the raw agricultural commodity and the corresponding processing factor.

In selecting the appropriate body weight, the *ad hoc* meeting recommended the use of 15 kg for children aged 6 and under and 60 kg for the general population. Since it is necessary to convert the consumption to kg/person/day to assess units consumed, the Meeting recommended that body weights provided by the appropriate national Governments should be used in the calculation. The Meeting agreed that where these were not available, default values of 15 or 60 kg should be used.

The *ad hoc* Meeting considered the use of the appropriate unit weight for the first term in the Case 1 and Case 2 calculations and agreed that the median of the data provided to WHO should be used. The Meeting recognized that this term had a strong influence on the overall calculated level and that, given the variation in a range of commodities in international trade, it would be appropriate to use the unit weight appropriate to the region where GAP had been used to recommend the MRL. It was noted that Governments had so far submitted only limited data and that there was an urgent need for further information to be provided. The Meeting agreed that in cases where no data had been supplied the calculation would not be carried out unless it could be concluded that a typical unit size was generally similar from region to region.

The Geneva Consultation agreed that the variability factor *v* should be 10 for medium sized unit items and 5 for large sized unit items in the diet. The Consultation recommended that the JMPR should refine the variability factor as more information became available. The Meeting noted that in most cases a variability factor of 10 was conservative. However, on the basis of the data available at the time, specific situations where a variability factor of 10 was appropriate could not be distinguished from those where a lower factor might be applicable.

Available data from a number of sources (including industry and registration authorities) had been published in the *Report of the International Conference on Pesticide Residue Variability and Acute Dietary Intake* [1]. In the Report, 81 sets of results from 10 crops were considered where at least 75% of the units analysed contained detectable residues. Most of the results were based on the analysis of 100 individual units. The variability factor was calculated in three ways: Rmax/mean, R 97.5th percentile/mean and R95th percentile/mean. The Meeting noted that the data from R97.5th/mean and R95th/mean were well matched and after discussion of the available information concluded that a variability factor (R97.5th/mean) of 7 for medium sized units could be used on a temporary basis until the database was further refined.

[1] PSD, 1999; http://www.maff.gov.uk/aboutmaf/agency/psd/news/finalrep.pdf

The lower variability factor (7) would not apply to granular soil treatments where the factor of 10 should be retained for medium sized units. The Meeting noted that insufficient data were available to recommend a revised < for leafy crops or further refine < for large unit items. It was understood that further research to refine < was in progress. The Meeting welcomed this and would make the best use possible of any information provided.

The *ad hoc* Meeting had noted that probabilistic modelling was a useful tool to aid decision making and risk management but, at an international level, this type of calculation was not yet practicable. The Meeting endorsed this view and noted that it would be interested to follow developments of this method at a national level.

2.5 OECD WORKING GROUP ON PESTICIDES - WORKSHOP ON DEVELOPING MINIMUM RESIDUE DATA REQUIREMENTS FOR ESTIMATING MRLs AND IMPORT TOLERANCES

The Meeting welcomed a draft copy of the recommendations from the Workshop on Minimum Data Requirements for Establishing Maximum Residue Limits (MRLs), including Import Tolerances. This was an initiative funded by the European Commission to develop guidelines on the minimum or core data requirements. The terms of reference were outlined in the proposal presented and agreed by the November 1996 OECD Pesticide Forum. The primary objective was to examine those areas which represent the greatest obstacles to the establishment of national import tolerances and the acceptance of international MRLs.

The Meeting had previously noted the need for such work in 1994[1] and welcomed this initiative. It recognised that the workshop had promoted work in this area which should ensure that more relevant data would be available for evaluation by allowing comparabilities, particularly between countries. The recommendations were generally based on a compromise between national requirements but some, particularly on extrapolation, were a formalisation of current working practices. The Meeting considered that the value of the recommendations in this area could be strengthened by the production of a scientific report justifying them.

The Meeting was aware of the differences between the working practices of the JMPR and registration authorities; such authorities need to ensure that guidelines are rigidly applied to ensure consistency between registrants. However it noted that requirements for studies of plant and farm animal metabolism and animal transfer studies had shown a high degree of uniformity and acknowledged that their application would ease the work of the JMPR in evaluating studies in these areas.

It was acknowledged that the recommendations should be useful particularly with respect to minor crops, but that difficulties might arise owing to data being insufficient for statistical evaluation. The recommendations require few decline curve trials and the Meeting stressed the value of such trials, particularly in defining tolerances around GAP and so allowing data within a wider tolerance of GAP conditions to be used.

The Meeting looked forward to receiving information on developments in this area in the future.

[1] JMPR, 1994. General considerations 2.4. Data required for estimating maximum residue levels

2.6 ISSUES AFFECTING STUDIES OF THE EFFECTS OF PROCESSING ON RESIDUES

Processing studies are among the critical supporting studies required for the evaluation of a new compound or a periodic review (FAO Manual 3.1.6.2[1]). The effects of industrial processing and/or household preparation on residues have to be studied to estimate residue levels in processed products. Requirements on this point are set out in guidelines such as EPA OPPTS 860.1520[2] and the EU Council Directive 91/414/EEC (explained in detail in a guidance document 7035/VI/95 rev.5)[3].

1. Objectives of processing studies

Processing studies have the following objectives.

To obtain information about breakdown or reaction products which require a separate risk assessment.

To determine the quantitative distribution of residues in the various processed products, allowing the estimation of processing factors for products which may be consumed.

To allow more realistic estimates to be made of the chronic or acute dietary intake of pesticide residues.

2. Need for processing studies

Studies are not normally required if

the plant or plant product is normally only eaten raw, e.g. head lettuce
only simple physical operations such as washing and cleaning are involved

no residues above the limit of determination occur

Studies are necessary if significant residues occur in plants or plant products which are processed. “Significant residues” normally means residues above 0.1 mg/kg. If the pesticide concerned has a low acute RfD or ADI consideration has to be given to conducting processing studies with analyses for residues below 0.1 mg/kg. In the case of hops this level should be 5 mg/kg (residues in beer are then <0.01 mg/kg because of the dilution factor). For residues of a fat-soluble pesticide in oilseeds, the possibility of concentration in the oil has to be taken into account.

[1] FAO manual on the submission of pesticide residue data for the estimation of maximum residue levels in food and feed, point 3.1.6.2, p. 27. FAO Rome, 1997
[2] EPA Residue Chemistry Test Guidelines OPPTS 860.1520 Processed Food/Feed. EPA 712-C-96-184, 5 August 1996
[3] Guidelines for the generating of data concerning residues as provided in Annex II part A, section 6 and Annex III, part A, section 8 of Directive 91/414/EEC concerning the placing of plant protection products on the market. Doc. 1607/VI/97 rev.1, 22/7/1997. Appendix E: Processing studies. Doc. 7035/VI/95 rev. 5, 22/7/1997

Determinations of the nature of pesticide residues in processed products are basic to processing studies. They make it possible to confirm the definition of the residue for processed products or to define extra breakdown products to be determined in further studies.

3. Guidelines for the conduct of processing studies

3.1 Effects on the nature of the residue

3.1.1 Objectives

The objective of studies of the nature of residues is to establish whether or not breakdown or reaction products of residues in the raw commodities are formed during processing which may require a separate risk assessment.

3.1.2 Test conditions

On examining the effects of processing on pesticide residues one will find that the main procedures (e.g. preparation of fruit juices, preserves, wine) will be mainly hydrolytic, because processes involving heating would generally inactivate enzymes present in the commodity. Studies of hydrolysis are therefore chosen as the model for degradation in processing. Since the substrate itself is not likely to have a major effect, the presence of the commodity during such studies is not required.

The hydrolysis conditions listed below are selected to cover most processing procedures.

Temperature, °C	Time, min	pH	Processes represented
90	20	4	Pasteurisation
100	60	5	Baking, brewing, boiling
120	20	6	Sterilization

Depending upon the potential range of uses of the pesticide, one or more of the representative hydrolysis situations should be investigated. The studies are normally conducted with a radiolabelled form of the active substance or the residue in question.

The effects of processes other than hydrolysis (e.g. oxidation, reduction, enzymic or thermal degradation) may also have to be investigated if the properties of the pesticide or its metabolites indicate that such processes may produce toxicologically significant degradation products.

The JMPR will take into account the nature of the major products in the hydrolysis study, dilution or concentration factors during processing, and the initial residue levels in the raw agricultural commodity when evaluating the results of the studies.

3.2 Effects on residue levels

3.2.1 Objectives

Processed products can be classified according to certain types of process. The studies have to take into account the importance of the processed product in human or animal diets. Degradation products of toxicological significance occurring in the hydrolysis studies have to be taken into consideration as well as residues of concern found in plant metabolism studies.

For a core set of data on an active ingredient the processing studies should be conducted on representative commodities such as citrus fruits, apples, grapes, tomatoes, potatoes, cereals and oilseeds. By using core processing procedures and selected crops it should be possible to extrapolate to other crops processed by the same procedure. Only in cases where it is not possible to derive consistent processing factors or where a very low ADI is established would it be necessary to conduct processing studies on every crop.

In some cases further trials may be necessary to cover particular circumstances. Examples are the determination of residues in oil produced from oilseeds with no significant residues where the active substance has a log P_{OW} above 4, and extended studies on active substances with a very low ADI.

3.2.2 Test conditions

Processing procedures

The procedures to be used in processing studies should always correspond as closely as possible to those that normally occur in practice. Thus products of household preparation (e.g. cooked vegetables) should be produced using the equipment and preparation techniques normally used in households, whereas industrial items such as cereal products, preserves, fruit juices or sugar should be produced by procedures representative of commercial food technology.

In some cases more than one commercial process may be routinely used (e.g. the different UK and US commercial practices in the production of potato chips; see the 1998 JMPR evaluation of maleic hydrazide). Detailed reasons have to be given for the chosen process.

Great importance should be attached to carrying out processing studies for commodities included in GEMS/Food diets[1] and for animal feedstuffs derived from crops (e. g. products of cereals, oilseeds, apples, citrus and tomatoes). This list could be extended if appropriate dietary information becomes available.

Nature of the studies

The studies should be designed so that processing factors can be derived and/or MRLs recommended for processed foods and feed important in international trade. For consistent processing factors the results of more than one study are necessary.

Processing studies should simulate commercial or household practices as closely as possible. The raw agricultural commodity (RAC) used in the studies should be a field-treated commodity containing quantifiable residues, so that processing factors for the processed

[1] GEMS/Food RegionalDiets. Regional Per Capita Consumption of Raw and Semi-processed Agricultural Commodities. WHO/FSF/FOS/98.3

products can be determined. This may require field treatment at an exaggerated application rate to obtain sufficiently high residue levels. Processing studies with spiked samples are not acceptable unless it can be demonstrated that the residue in the RAC is entirely on the surface.

Evaluation of results

All the residues (parent and relevant metabolites) determined in the RAC also have to be determined in the processed products. In addition, any degradation products found in studies of the nature of the residue which require a separate dietary risk assessment also have to be considered. The residue has to be calculated according to the definition relevant for compliance with MRLs and/or the estimations of dietary intake.

As a result of the processing studies, it will be possible to recognise reductions and concentrations and to calculate processing factors for important products.

$$\text{Processing factor} = \frac{\text{residue level [mg/kg] in processed product}}{\text{residue level [mg/kg] in RAC}}$$

Whenever more than one processing study has been conducted for a particular pesticide in the same RAC, the average processing factor for each process should be used for each processed commodity. If several studies are available and a step that is routinely used in the processing of that RAC (e.g. cleaning, washing) is omitted, it may be inappropriate to include that study in the calculation of the average processing factor.

To estimate a maximum residue level for a processed product the MRL or maximum residue level of the RAC is multiplied by the processing factor. To calculate an IEDI the STMR of the RAC is multiplied by the processing factor to give the STMR of the processed product.

If data are available for the residues in the edible portion of the commodity (e.g. in banana pulp), an STMR should be estimated directly from the residues in the edible portion found in supervised trials at the maximum registered rate of use.

2.7 SENSITIVITY OF INFANTS AND CHILDREN TO PESTICIDES

The Codex Committee on Pesticide Residues (CCPR) at its 31st Session asked the JMPR to consider possible toxicological concerns unique to infants and young children because of their physiological and developmental characteristics. In considering this issue, the Meeting recognized that children and infants may differ from adults in their susceptibility to the effects of xenobiotics. For any particular compound, the difference might be qualitative (i.e. result in different types of toxicity) and/or quantitative (i.e. different dose-response relationships for the same effect), or there may be no difference at all. As it cannot be predicted which of these possibilities pertains to a particular compound, an increased susceptibility of children and infants to toxicants cannot consistently be implied. The Meeting emphasized that possible differences between adult and developing mammals is currently addressed in the commonly performed studies of reproductive and developmental

toxicity in various animal species. In addition, useful information might be obtained by a comparison of data from cases of poisoning in infants and children with those in adults as collected, for instance, by poison control centres. The Meeting was also aware that the US Environmental Protection Agency has asked that certain active ingredients be tested for developmental neurotoxicity and neurotoxicity in adult animals. The results of these studies will be compared with one another. The Meeting agreed that it would be useful to compare the critical NOAELs identified during this exercise with those identified from conventional data packages. The Meeting concluded that it currently has no basis for changing its approach to addressing the susceptibility of developing mammals as compared with that of adult organisms in the toxicological evaluation of pesticides. The routine use of safety factors in addition to those currently used is not justified on the basis of current information.

As in all areas of biology relevant to risk assessment, the JMPR will continue to take into account new information on differences in susceptibility between adults and developing mammals that have implications for the evaluation of active ingredients.

2. 8 RELEVANCE OF PESTICIDE SPECIFICATIONS FOR JMPR EVALUATIONS

The Meeting noted the recent FAO publications on pesticide specifications as the development of FAO pesticide product specifications is an essential element in the process of establishing voluntary standards to reduce risks associated with the use of pesticides. Good Agricultural Practice (GAP) starts with the use of pesticide products of high and satisfactory quality as described/defined through specifications. Pesticides**,** evaluated by FAO and complying with those specifications can be considered satisfactory for any toxicological and residue evaluation. A clear, qualitative and quantitative description/definition of these parameters, together with compliance with those parameters will continue to ensure that the JMPR evaluations are always based on products of standardised and defined quality and will ensure that products do not present any unexpected hazards.

With the latest (fifth) edition of the FAO *Manual on the development and use of FAO specifications for plant protection products* (FAO Plant Production and Protection Paper No.149, published May 1999) a new procedure has been introduced. The WHO Pesticide Evaluation Scheme (WHOPES) follows the guidelines of the FAO Manual when developing WHO specifications for pesticides used in public health to ensure harmonization with the specifications developed by FAO for pesticides used in agriculture.

Under this new procedure the data requirements have been expanded dramatically. FAO in co-operation with WHO now evaluates, in confidence, the physico-chemical properties, the impurity, toxicological and ecotoxicological profiles of technical materials. The evaluations will ensure that specifications include all relevant impurities. These impurities, following the definition in the *FAO-Manual,* are those by-products of the manufacture or storage of a pesticide which, compared with the active ingredient, are toxicologically significant to health or the environment, are phytotoxic to treated plants, cause taint in food crops, affect the stability of the pesticide, or cause any other adverse effect. Besides the assessment of the toxicological, ecotoxicological and/or impurity profile data by WHO, FAO seeks also access to registration data from competent authorities to be able to assess whether or not:

(i) the technical material for which an FAO specification is proposed is equivalent to that registered by the authority, as assessed by a comparison between the data submitted to FAO and those submitted for registration; or
(ii) their decision that technical materials from different manufacturers are equivalent was based on data similar to those provided to FAO.

FAO specifications will apply now only to products for which the technical materials produced by each manufacturer have been evaluated by these organisations. This is a radical change because, under the previous (old) procedure, the FAO specification could be taken to apply to any nationally similar product. To take account of this change, the new procedure also defines the process for the determination of equivalence (similarity) of technical pesticides, so that an FAO specification can be extended to truly equivalent products.

The new procedure, including the definition of equivalence, was developed to enhance the product quality, to improve pesticide user and consumer protection as well as to reduce side effects on the environment. This procedure is accepted widely now by multi-national companies as well as by manufacturers of generic compounds.

This Meeting recommended that FAO and/or WHO specifications for the technical material using their respective procedures should be developed before pesticides are evaluated within the Periodic Review Programme of CCPR or for new pesticides. Companies (sponsors) should indicate in their submissions of data to JMPR whether the pesticides used in their studies are in compliance with the new specifications. An FAO and/or WHO specification for the technical material should be required before establishing ADIs, acute RfDs or, where relevant**,** recommending MRLs. However the Meeting recognised that it will take some time before this recommendation is fully implemented.

2.9 STATISTICAL EVALUATION OF RESIDUES DATA

The 1990 JMPR discussed the statistical evaluation of residues data for estimating maximum residue levels[1] and recommended that the JMPR evaluate a BBA (German Federal Biological Research Centre for Agriculture and Forestry) model as well as other procedures. Since that time FAO Panel members have sometimes used the procedures to assist them in decision making.

The main deficiency with the procedures in 1990 was that there were no clear guidelines on which trials and which residues should be included in the statistical calculations. The estimation of the maximum residue level by identifying the highest residues arising from the use of the pesticide according to GAP was, and still is, quite effective in deciding on a suitable MRL.

The introduction of the STMR for estimating chronic dietary intake and the development of procedures for determining STMRs mean that the set of residue data for inclusion is much clearer. Residue evaluations now routinely list the relevant residues in rank order to obtain the STMR and the maximum residue level. The set of relevant residue levels is now more readily available for statistical assessment.

[1] JMPR Report. 1990. *2.6 Statistical evaluation of residues data for estimating maximum residue levels.* FAO Plant Production and Protection Paper 102.

The Meeting stressed that the statistical calculations were not themselves meant to establish maximum residue levels, but were intended to assist the Meeting in coming to decisions. The Meeting takes into account other information besides the strictly numerical values from the trials, e.g. metabolism and chemical reactions of the compound, levels and fate of residues in related crops or animals, and residues occurring from uses outside the range of GAP.

The Meeting recommended the use of statistical calculations on relevant residues as a further tool to assist in the estimation of maximum residue levels. The Meeting also recommended re-examining the situation in a future year when more practical experience had been gained in the application of statistical methods to the readily available residue populations produced by the STMR procedure.

2.10 PERIODIC REVIEW OF RESIDUE DATA FOR COMPOUNDS CURRENTLY UNDER NATIONAL RE-REGISTRATION

The Meeting has noted when reviewing compounds under the CCPR Periodic Review Programme that further consideration needed to be given to the timing of these reviews and of the submission of the required data, in particular for compounds which are undergoing re-registration by national or regional authorities.

It appeared that in the framework of national or regional re-registration, the uses of several compounds were being substantially revised. For instance, reduced application rates and extended pre-harvest intervals should result in lower residues to meet more stringent safety criteria. In these cases the data submissions to the JMPR included current registered uses as well as labels awaiting approval by national Governments. Most of the field trial data submitted, however, were related to the envisaged new uses. In accordance with the Periodic Review procedure the Meeting could neither recommend new or amended MRLs nor recommend maintaining the existing MRLs. Situations also ocurred where old and revised labels existed simultaneously. The registered uses at higher rates on old labels precluded the evaluation of new data from trials at lower rates.

The Meeting was aware of the practical consequences of changing current agricultural uses, requiring a transitional period to withdraw existing registrations and introduce new labels. The situation affects the efficiency of the JMPR however as an additional review is warranted at such time as new labels come into force.

The Meeting recommended that this issue should be brought to the attention of the CCPR, so that Governments wishing to include compounds for periodic review in the priority list should be requested to give detailed information on the registration status at the time of notification and again later when the compound is actually scheduled for review by the JMPR in a specified year.

The Meeting invited the CCPR to consider an alternative approach in the case of periodic reviews of compounds for which GAP is being changed significantly to meet increased safety requirements, namely that the JMPR should recommend MRLs on the basis of trials data reflecting the amended uses provided the notifying Government gives a clear statement that old labels will be withdrawn and by what date.

3. DIETARY RISK ASSESSMENT FOR PESTICIDE RESIDUES IN FOOD

Chronic dietary risk assessment

Chronic dietary risk assessments were conducted for compounds for which MRLs were recommended and STMRs estimated by the present Joint Meeting. The dietary intakes were calculated by multiplying the residue concentrations (STMRs or recommended MRLs) by the average daily *per capita* consumption estimated for each commodity on the basis of the GEMS/Food Regional diets[1,2]. International Estimated Daily Intakes (IEDIs) were estimated only where STMRs, not MRLs, were used in the calculation. Codex MRLs whose withdrawal has been recommended by the JMPR have not been included.

Chronic dietary intakes are expressed as a percentage of the ADI for a 60 kg person. If the percentage is higher than 100 for a compound for which an IEDI was calculated, the information provided to the JMPR does not allow an estimate that the dietary intake would be below the ADI. New compounds and compounds under periodic review with percentages of the ADI above 100 are identified by a footnote in the Table below.

At the national level further refinements of the calculations of dietary intake are possible, taking into account more detailed information on food consumption, monitoring and surveillance data, total diet data and/or reliable data on the percentage of the crop treated.

A summary of the chronic dietary intake estimates by the present Meeting is given in the Table below. The percentages of the ADI are rounded to one significant figure for values up to and including 100% and to two significant figures for values above 100%. The detailed chronic dietary intake calculations are given in Annex III.

Chronic dietary intakes estimated by the 1999 JMPR

Summary of chronic intake assessments

Code	Name	ADI	Exposure range	
			% of ADI	Type of assessment [a]
173	buprofezin	0.01	2-10	DIE
96	carbofuran	0.002	7-30	IEDI
145	carbosulfan	0.01	0	IEDI
17	chlorpyrifos	0.01	6-30	TMDI
187	clethodim	0.01	3-30	DIE
22	diazinon	0.002	20-180	DIE
151	dimethipin	0.02	0-2	TMDI
87	dinocap	0.008	0-2	IEDI
106	ethephon	0.05	2-20	DIE
149	ethoprophos	0.0004	20-40	TMDI
35	ethoxyquin	0.005	NO MRLS [b]	

[1] WHO 1997a. *Guidelines for predicting dietary intake of pesticide residues.* 2nd revised edition, GEMS/Food Document WHO/FSF/FOS/97.7, World Health Organization, Geneva

[2] WHO 1997b. *Food consumption and exposure assessment of chemicals*. Report of a FAO/WHO Consultation. Geneva, Switzerland, 10-14 February 1997. World Health Organization, Geneva

Code	Name	ADI	Exposure range	
			% of ADI	Type of assessment [a]
85	fenamiphos	0.0008	3-10	IEDI
188	fenpropimorph	0.003	10-90	DIE
193	fenpyroximate	0.01	0-1	IEDI
41	folpet	0.1	0-9	IEDI
175	glufosinate-ammonium	0.02	3-10	DIE
49	malathion	0.3	0	IEDI
132	methiocarb	0.02	0	IEDI
120	permethrin	0.05	20-30	TMDI
56	2-phenylphenol	0.4	0	IEDI
150	propylenethiourea (ptu)	0.0003	not assessed	
60	phosalone	0.02	0-4	IEDI
113	propargite	0.01	30-210	TMDI
63	pyrethrins	0.05	30-60	TMDI
200	pyriproxifen	0.1	0	IEDI
196	tebufenozide	0.02	0-1	IEDI

[a] TMDI = Theoretical Maximum Daily Intake
DIE= Dietary Intake Assessment
IEDI = International Estimated Dietary Inake
[b] All MRLs recommended for withdrawal
[c] Dietary intake of PTU will be assessed during periodic review of propineb

Acute dietary risk assessment

Acute dietary risk assessments were conducted for compounds for which MRLs were recommended and STMRs estimated by the present Joint Meeting and for which an acute reference dose (acute RfD) had been established, in commodities for which consumption data were available. The procedure for the acute intake calculations was defined primarily at the Geneva Consultation[1], followed by the International Conference in York[2] and the *ad hoc* Expert Meeting held before the 1999 Session of the CCPR and refined at this Meeting, as described in Section 2.4 of this Report. Large-portion consumption data were provided by Australia, France, The Netherlands, Japan, the UK and the USA. Data on unit weights and edible portion percentages were provided by France, the UK and the USA. Body weights for adults and children aged 6 and under were provided by Australia, France, The Netherlands, the UK and the USA.

International estimate of short-term intake (IESTI)

Depending on the commodity consumption data, the IESTI for each commodity is calculated according to the equation for the relevant case as described below (Case 1, Case 2a, Case 2b and Case 3). The following definitions apply to all the equations.

[1] WHO 1997b. *Food consumption and exposure assessment of chemicals*. Report of a FAO/WHO Consultation. Geneva, Switzerland, 10-14 February 1997. World Health Organization, Geneva

[2] PSD 1998. *Pesticide Residues Variability and Acute Dietary Risk Assessment*. York, UK, 1-3 December 1998. The Pesticide Safety Directorate, York.

LP: Highest large portion reported (97.5th centile of eaters), in kg food/day

HR: Highest residue in composite sample of edible portion found in the supervised trials used for estimating the maximum residue level, in mg/kg

HR-P: Highest residue in a processed commodity, in mg/kg, calculated by multiplying the HR in the raw commodity by the processing factor

bw: Body weight in kg, provided by the country from which the LP was reported

U: Unit weight of the edible portion, in kg, provided by the country where the trials which gave the highest residue were carried out

ν: Variability factor

STMR Supervised trials median residue, in mg/kg

STMR-P: Supervised trials median residue in processed commodity, in mg/kg

Case 1

Where the residue in a composite sample (raw or processed) reflects the residue level in a meal-sized portion of the commodity (unit weight of the whole portion is below 25g).

$$\text{IESTI} = \frac{\text{LP} * (\text{HR or HR-P})}{\text{bw}}$$

Case 2

Where the meal-sized portion, such as a single fruit or vegetable piece might have a higher residue than the composite (unit weight of the whole portion is above 25g). The variability factors, ν shown below are to be applied in the equations.

Commodity characteristic	ν
Unit weight of the whole portion is >250 g	5
Unit weight of the whole portion is ≤250 g	7
Leafy vegetables with unit weight of the whole portion ≤250 g	10
Residue is derived from granular soil treatment with unit weight of the whole portion ≤250 g	10

Case 2a

Where the unit weight of the whole portion is lower than the LP

$$\text{IESTI} = \frac{\text{U} * (\text{HR or HR-P}) * \nu + (\text{LP-U}) * (\text{STMR or STMR-P})}{\text{bw}}$$

Case 2b

Where the unit weight of the whole portion is higher than the LP

$$\text{IESTI} = \frac{\text{LP} * (\text{HR or HR-P}) * \nu}{\text{bw}}$$

Case 3

For a processed commodity, where bulking or blending means that the STMR-P represents the highest likely residue.

$$\text{IESTI} = \frac{\text{LP} * \text{STMR-P}}{\text{bw}}$$

An acute risk assessment was carried out for each commodity-compound combination by assessing the IESTI as a percentage of the acute RfD of the compound. If the percentage is higher than 100, the information provided to the JMPR does not allow an estimate that the acute dietary intake of the residue in that commodity would be below the acute reference dose. Such a compound is identified in the Table below.

The 1998 and present Joint Meeting have concluded that an acute RfD is unnecessary for some compounds. The conclusion is based on a determination that the pesticide is unlikely to present an acute toxicological hazard. Therefore, as the residues are unlikely to present an acute risk to consumers, acute intakes were not estimated for bitertanol, buprofezin, clethodim, ethoxyquin, glufosinate-ammonium, 2-phenylphenol and pyriproxyfen. The present Joint Meeting recommended that the acute toxicities of the following pesticides be evaluated as soon as possible: carbofuran, carbosulfan, diazinon, ethephon, fenpropimorph, fenpyroximate, folpet, malathion, oxydemeton-methyl, phosalone and tebufenozide.

In the case of compounds for which an acute RfD might be necessary but has not yet been established IESTIs were calculated, but the acute risk assessments could not be finalized.

A summary of the IESTIs and their percentages of the acute RfDs for both the general population and for children aged 6 years and under is given below. The percentages of the acute RfD are rounded to one significant figure for values up to and including 100% and to two significant figures for values above 100%. The detailed acute dietary intake calculations are given in Annex IV.

Acute intakes estimated by the 1999 JMPR

Code	Compound	Acute RfD (mg/kg bw)	IESTI (mg/kg bw/day)		% of acute RfD	
			General population	Children	General population	Children
096	Carbofuran	Acute RfD: May be necessary but has not yet been established	0.00035 – 0.00063	0.00135 – 0.00258	-	-
145	Carbosulfan	Acute RfD: May be necessary but has not yet been established	0.00005 – 0.00009	0.00021 – 0.0004	-	-
022	Diazinon	Acute RfD: May be necessary but has not yet been established	0.004 – 0.008	0.016 – 0.028	-	-
087	Dinocap	0.008	0.008	0.0087	100	110[1]
106	Ethephon	Acute RfD: May be necessary but has not yet been established	0.005 – 0.031	0 – 0.099	-	-

Code	Compound	Acute RfD (mg/kg bw)	IESTI (mg/kg bw/day)		% of acute RfD	
			General population	Children	General population	Children
085	Fenamiphos[2]	0.0008	0.00006 – 0.0069	0.00012 – 0.023	8-860	15-2900
188	Fenpropimorph	Acute RfD: May be necessary but has not yet been established	0.0045	0.018		
193	Fenpyroximate	Acute RfD: May be necessary but has not yet been established	0 – 0.008	0 – 0.032	-	-
041	Folpet	Acute RfD: May be necessary but has not yet been established	0 – 0.15	0 – 0.49	-	-
049	Malathion	Acute RfD: May be necessary but has not yet been established	0 – 0.017	0 – 0.058	-	-
132	Methiocarb	0.02	0.005	0.008	23	38
060	Phosalone	Acute RfD: May be necessary but has not yet been established	0 – 0.034	0 – 0.118	-	-
196	Tebufenozide	Acute RfD: May be necessary but has not yet been established	0.001– 0.015	-	-	-

[1]The information provided to the JMPR precludes an estimate that the acute dietary intake would be below the acute reference dose

[2] The information provided to the JMPR precludes an estimate that the acute dietary intake of some items would be below the acute reference dose

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

4.1 BENTAZONE (172)

TOXICOLOGY

On the basis of a review of the toxicological monograph and monograph addendum on bentazone prepared in 1991 and 1998, the Joint Meeting concluded that the establishment of an acute reference dose is unnecessary because bentazone has low acute toxicity after single oral doses and the NOAELs in short-term studies were at least two orders of magnitude higher than those used for establishing the ADI. No specific acute effects were identified.

RESIDUE AND ANALYTICAL ASPECTS

The Meeting wished to clarify the statement in the report of the 1998 Joint Meeting (p. 53, last para) that "Metabolism studies in lactating goats and hens showed that the main residue component in meat, milk and eggs was the parent bentazone with small amounts of 6- or 8-hydroxybentazone and their glucuronide and sulfate conjugates."

The statement was based on the 1995 residue evaluation of the compound. Reconsideration of that evaluation indicated that the identified components of the residues in the milk and tissues of goats dosed with bentazone were bentazone and its *N*-glucuronide. "No 6-hydroxy-bentazone, 8-hydroxy-bentazone or AIBA (2-aminoisopropylbenzamide) could be found in the milk or tissues."[1] When hens were dosed with bentazone the main component of the residue in liver, muscle, fat and eggs was the parent compound. The liver contained bentazone (0.92 mg/kg) and its *N*-glucuronide conjugate (0.12 mg/kg). In the excreta 6-hydroxybentazone accounted for 15% of the radioactivity[2].

Residues of 6-hydroxybentazone and 8-hydroxybentazone and their sulfates were identified in the milk and tissues of goats dosed with the 6- and 8-hydroxy compounds, and 6-hydroxybentazone was found after dosing lactating goats with mixtures of bentazone and 6-hydroxybentazone.

It is emphasized that this clarification does not affect the conclusions of the 1998 Joint Meeting.

DIETARY RISK ASSESSMENT

Chronic intake

Chronic intakes were estimated by the 1998 Joint Meeting. Estimated Theoretical Maximum Daily Intakes for the five GEMS/Food regional diets, based on existing MRLs, were in the

[1] 1995 residue evaluation, p. 9, para 4
[2] " " " , p. 11, penultimate para

range of 0–1% of the ADI. The Meeting concluded that the intake of residues of bentazone resulting from its uses that have been considered by the JMPR is unlikely to present a public health concern.

Acute intake

The Meeting concluded that an acute RfD for bentazone is unnecessary. This conclusion was based on a determination that the pesticide is unlikely to present an acute toxicological hazard, and residues are therefore unlikely to present an acute risk to consumers.

4.2 BITERTANOL (144)

RESIDUE AND ANALYTICAL ASPECTS

Bitertanol, 1- (biphenyl - 4 - yloxy) - 3, 3 - dimethyl -1- (1 *H*-1,2,4-triazol-1-yl) butan-2-ol (2 diastereoisomers), is an effective fungicide used as a foliar spray on fruits and vegetables and as a seed treatment for cereals for certain diseases. The compound was originally evaluated for residues in 1983 when MRLs were recommended for a number of commodities. The fungicide was evaluated under the CCPR Periodic Review Programme in 1998 for toxicology and by the present Meeting for residues.

The Meeting received information on animal and plant metabolism, environmental fate, analytical methods, updated GAP, supervised trials on crops, animal feeding studies and the effects of processing on residues.

Metabolism and environmental fate

In animal metabolism studies, the compound was uniformly-labelled with ^{14}C in the phenyl ring remote from the oxygen. The absorption, distribution, metabolism and excretion of [^{14}C]bitertanol has been studied in rats, cows and hens.

Bitertanol is rapidly absorbed from the intestinal lumen, and is readily distributed within the body. The excretion of the parent compound and its biotransformation products is fast (in rats almost complete within 72 h) and occurs mainly in the faeces (about 90%) by biliary excretion, owing to the lipophilic nature of the compound.

The main metabolic reactions are hydroxylation of the phenyl ring in the *para* position and oxidation of the *tert*-butyl moiety to form bitertanol alcohol and the corresponding carboxylic acid. There is no significant difference between the metabolism in rats, cows and poultry. Unchanged bitertanol and its *para*-hydroxylated metabolite in free and conjugated form were the main residues in the edible tissues and eggs of poultry (75-92% and 81-83% of the total ^{14}C respectively), and in the edible tissues and milk of the dairy cow (23-51% and 84% of the total ^{14}C respectively).

Plant metabolism studies were carried out with biphenyl- and triazole-labelled bitertanol on apples, peanuts, cotton (foliar spray treatment) and wheat (seed treatment).

Bitertanol was metabolised slowly in the investigated crop species after foliar spray application (half-lives 141 days in peanuts, 150 days in apples). Unchanged bitertanol was

the main residue in apple fruits (83% of the biphenyl label, 96% of the triazole label), peanut shoots (86% of the total ^{14}C) and cotton plants (79% of the total ^{14}C). Oxidation of the hydroxyl group yields the keto analogue (BUE 1662) and oxidative cleavage of the biphenyl moiety yields bitertanol benzoic acid (BUE 2684). The compound is also conjugated at the free hydroxyl group to form a malonyl glucoside.

After seed treatment of wheat at a commercial application rate, the metabolites detected at harvest in the grain from the triazole label were derivatives of 1,2,4-triazole: triazolylalanine (50–66% of the total ^{14}C, 0.12–0.16 mg/kg) and triazolylacetic acid (22–34% of the total ^{14}C, 0.04–0.07 mg/kg). The parent compound was not detectable.

The degradation of bitertanol does not lead to environmentally significant levels of degradation products in soil or water.

The degradation of bitertanol in soil was comparable in all the studies. It was quickly degraded (half-life <1 to 9 days). At the end of the test period the degradation curve flattened, so the DT-90 value was 15 to 102 days depending on the soil type. The main degradation product was CO_2 (50-64% of the applied ^{14}C). Owing to the rapid degradation only small amounts of intermediate products were detected. Bitertanol benzoic acid (BUE 2684) represented less than 0.3% of the applied ^{14}C; no other degradation products were identified. The unidentified compounds in the extracts represented $\leq$4.2% of the applied ^{14}C. Unextractable residues, which were bound to the stable humin fraction, increased within the first 22 days up to 30-50% of the applied ^{14}C, then decreased while mineralisation continued.

Aged bitertanol residues exhibit only a very low mobility in soil. In BBA standard soil 2.1 which showed the highest mobility the TRR in the leachate at 22°C and after 30 days of ageing was 0.5–1% of the applied radioactivity after 48 h rainfall, indicating that the leaching potential is negligible, which would be expected from the strong adsorption to the soil matrix. Photolysis on soil surfaces plays a minor role in the environmental destruction of the compound.

Bitertanol is stable to hydrolysis in aqueous solutions but it can easily be degraded by light owing to the chromophoric biphenyl moiety. However the photolytic effect might be of little significance under environmental conditions since only little light of the relevant wavelengths (<290 nm) penetrates water.

In water/sediment systems a high proportion of the applied radioactivity was transported into the sediment, reaching a maximum of 69-91% after 25 days. This decreased to 38-44% of the applied ^{14}C at the end of the test period of 120 days. Only 2-3% of the applied ^{14}C was identified as the parent compound in the surface water after 53 days. In the sediment extracts 24-59% of the applied ^{14}C was identified as bitertanol at 53 days, decreasing to 3-4% at 120 days. The mineralization rate is high and intermediate products are found only in trace amounts.

Residues in rotational crops were determined in kale, mustard, sugar beet, and wheat planted in the soil 31, 118 and 364 days after treatment (DAT) of the target crop of peanuts with biphenyl-labelled bitertanol eight times at 0.56 kg ai/ha as a foliar spray. Total radioactive residues in harvested samples ranged from 0.1 mg/kg (118 DAT) to 0.02 mg/kg (364 DAT) in leafy vegetables (kale, mustard), from 0.38 mg/kg (118 DAT) to 0.01 mg/kg

(364 DAT) in sugar beet roots, and from 0.23 (31 DAT) to 0.01 mg/kg (364 DAT) in wheat ears.

No information was reported on the fate of the 1,2,4-triazole moiety in succeeding crops.

Methods of residue analysis

Residue analytical methods for bitertanol *per se* in plant and animal products are based on extraction with acetone/water, clean-up by liquid-liquid partition with dichloromethane, and purification of the organic phase by gel permeation chromatography. Bitertanol is determined by gas chromatography using a nitrogen-selective thermionic detector. This method has been modified in the clean-up procedures (e.g. by the use of Chem-Elut). Validation for plant and animal commodities showed recoveries of about 70-110%. The typical limits of determination in plant materials and animal products are 0.01- 0.05 mg/kg.

The analytical method provided by The Netherlands is based on a similar extraction. There is no clean-up for plant materials but animal products are cleaned up by gel permeation chromatography (GPC), HPLC or liquid-liquid partitioning (LLP). Determination is carried out by gas chromatography with an ion trap detector or nitrogen-phosphorus detector (NPD). The LOD was reported as 0.05 mg/kg for non-fatty and fatty foods and recoveries were generally between 90 and 100%.

A method was developed to quantify bitertanol and its metabolites ("total bitertanol") in bovine and poultry tissues, milk and eggs. Extraction was with various solvents (acetone, methanol, hexane), depending on the sample, and the extracts were acid-hydrolysed to release 1,2,4-triazole. The 1,2,4-triazole was derivatized to form triazolylpinacolone which was determined by gas chromatography using a thermionic nitrogen detector. Several clean-up steps were required including partitioning, ion exchange chromatography and high performance liquid chromatography. Recoveries were determined at 0.05 mg/kg and 0.1 mg/kg from all samples and additionally at 0.5 mg/kg and 2 mg/kg from bovine liver. The recoveries were between 60 and 120%.

For the enforcement determination of bitertanol in ground and drinking water a thin-layer separation with UV detection, based on automated multiple development (AMD), was developed. Recoveries were between 85 and 116%, and the LOD was 0.05 µg/l.

Information was submitted on the stability of bitertanol residues in various stored analytical samples. The Meeting concluded that the compound was stable for the duration of the studies (at least 3.5 years in apples, 2 years in cherries and peaches, 1 year in green and dry beans and 2 years in bovine tissues).

Definition of the residue

On the evidence of studies with foliar spray treatments of apples, cotton and peanuts, the residue of concern was bitertanol *per se*.

After seed treatment of wheat at a commercial application rate, the metabolites detected at harvest in the grain from the triazole label were conjugates of 1,2,4-triazole:

triazolylalanine (50–66% of the total ^{14}C) and triazolylacetic acid (22–34% of the total ^{14}C). Neither the parent nor free 1,2,4-triazole were detectable.

As 1,2,4-triazolylalanine can arise as a plant metabolite of several pesticides that contain a 1,2,4-triazole moiety, being formed by the conjugation of the latter with serine, it was evaluated by the 1989 JMPR for toxicology and residues. A biotransformation study on rats showed that 1,2,4-triazolylalanine is rapidly absorbed and excreted, mainly as the unchanged compound in the urine. The 1989 Meeting concluded that residues of 1,2,4-triazolylalanine arising from the use of triazole fungicides do not present a toxicological hazard.

The animal metabolism studies on rats, a cow and laying hens indicate that the parent compound bitertanol and the metabolite *p*-hydroxybitertanol (free and conjugated) are the main residue components in animal tissues, milk and eggs.

As bitertanol has no acidic or basic properties in aqueous solution, the partition coefficient will not be influenced by the pH. The octanol-water partition coefficients (log P_{OW} = 4.04 diastereomer A, 4.15 diastereomer B) indicate that bitertanol is fat-soluble.

The Meeting concluded that the following residue definitions are appropriate.

For compliance with MRLs. For plant and animal products: bitertanol.

For estimations of dietary intake. For plant products: bitertanol. For animal products: sum of bitertanol, *p*-hydroxybitertanol and the acid-hydrolysable conjugates of *p*-hydroxybitertanol.

Residues resulting from supervised trials

Information was reported to the Meeting on registered uses of bitertanol and on supervised residue trials on apples, cherries, plums, nectarines, peaches, bananas, tomatoes, cucumbers, barley, oats, rye, wheat, cereal fodder and forage. Most trials were carried out in Europe. It was assumed that for the conduct of residue trials the European climatic conditions and weather influences could be divided into two regions.

Northern and central Europe: Sweden, Norway, Denmark, the UK, Ireland, northern and central France, Belgium, The Netherlands, Germany, Poland.
Southern Europe and the Mediterranean: Spain, Portugal, southern France, Italy, Greece.

Pome fruits. Trials on apples were reported from France, Germany, Italy, Spain and South Africa and on pears from Germany. French and Greek GAP for the use of bitertanol on pome fruit call for a spray concentration of 0.025 kg ai/hl with a PHI of 14 days for preventive and curative treatments. The labels recommend 2 applications with an interval of 1 week for curative treatments followed by preventive sprayings every 10-14 days. The labels also require an increase in concentration of the pesticide if the spray volume is reduced.

Twelve German trials on apples were carried out according to French and Greek GAP (8-12 x 0.025 kg ai/hl, PHI 14 days). These trials, which can also be used to represent the residue situation in Northern France, gave residues in rank order of 0.08, 0.09, 0.13, 0.13, 0.23, 0.25, 0.55, 0.62, 0.7, 0.86, 1.0 and 1.8 mg/kg.

In the 7 Southern European apple trials (1 in Spain according to Spanish GAP; 2 in Spain, 3 in Italy and 1 in France according to French GAP) the residues after 5 applications were 0.08, 0.09, 0.18, 0.23, 0.24, 0.34 and 0.36 mg/kg.

Current GAP for South Africa includes 1 or 2 treatments at 0.008 kg ai/hl with a PHI of 14 days, but the 9 apple trials reported were at higher rates (6-7 x 0.013–0.025 kg ai/hl). The residues were from 0.25 to 0.71 mg/kg.

In summary, the bitertanol residues in apples from trials according to French, Spanish and Italian GAP in rank order (median underlined) were 0.08, 0.08, 0.09, 0.09, 0.13, 0.13, 0.18, 0.23, 0.23, 0.24, 0.25, 0.34, 0.36, 0.55, 0.62, 0.7, 0.86, 1.0 and 1.8 mg/kg.

Twelve German trials on pears were carried out according to the German registered application rate (0.0125 kg ai/hl), but the number of treatments was 12 instead of the 5 specified on the label. The residues at the GAP PHI of 14 days in rank order were 0.22, 0.23, 0.25, 0.33, 0.63, 0.65, 0.91, 0.92, 0.92, 0.93, 0.97 and 1.1 mg/kg. The Meeting noted that higher residues could occur in pears than in apples from the same application rate.

The Meeting agreed to recommend maintaining the CXL of 2 mg/kg for pome fruits. An STMR of 0.24 mg/kg was estimated for pome fruits on the basis of the residues found in apples.

Stone fruits

The residues from trials carried out before 1996 were mainly reported for fruit without stones, but from trials in 1996 as fruit including stones. The Meeting was informed that the stone represents about 10% of the whole fruit weight and agreed to combine the data on fruit with and without stones.

Cherries. Residue trials were conducted in Germany and France. The trials in Germany were evaluated against German GAP (3 x 0.038 kg ai/hl, PHI 21 days), and the trials in southern France against Greek GAP (0.025-0.038 kg ai/hl, PHI 10 days). The samples from the southern French trials were analysed including the stones, but the residues from Germany were reported for fruit without stones, although the residue in the whole fruit was calculated in 2 trials, where the fruit pulp represented 82–92% (mean 87.6%) of the whole fruit weight.

Of the 14 German trials on sour cherries, 6 trials with 3–4 treatments after flowering with 0.038 kg ai/hl (+ 34%) and a PHI of 21 days complied with GAP. The remaining 8 trials were with 5 treatments after flowering or no sample was taken at the recommended PHI. The results showed residues in fruits without stones of 0.19, 0.36, 0.52, 0.68, 0.83 and 0.85 mg/kg.

In 6 French trials sweet cherries were treated twice at 0.03 kg ai/hl. Four of the trials were carried out in southern France and evaluated against Greek GAP. The residues in fruit with stones were 0.08, 0.15, 0.17 and 0.37 mg/kg. The 2 other trials in northern France could not be evaluated against Greek GAP and did not comply with German GAP.

The bitertanol residues in all the evaluated German and French trials in rank order (median underlined) in fruit **without**/with stone were 0.08, 0.15, 0.17, **0.19**/0.17, **0.36**/0.32,

0.37, **0.52**, **0.68**, **0.83** and **0.85** mg/kg. The Meeting estimated an STMR of 0.365 mg/kg and a maximum residue level for bitertanol in cherries of 1 mg/kg to replace the CXL (2 mg/kg).

Plums. Residue trials were carried out in Germany (12), southern France (4) and Portugal (1).

In the German trials, the residues were reported for fruit without stones, but with calculation of the residue in the whole fruit in 4 trials. In the samples at the GAP PHI, the fruit pulp represented 93–95% (mean 94%) of the whole fruit weight. The results of the French trials were also reported for fruit without stones but with calculation of fruit including stone in one trial.

The German trials were evaluated against French GAP (0.02–0.03 kg ai/hl, PHI 14 days, number of preventive, curative and eradicative treatments not specified). Based on a water rate of 1000 and 1500 l/ha, the spray concentration was 0.025 and 0.38 kg ai/hl. The number of treatments after flowering was 3 in 6 trials, 4 in 1 trial and 5 in 5 trials. The residues in rank order in fruit **without**/with stone were **0.04**, **0.15**, **0.16**, **0.19**, **0.21**, **0.33**, **0.58**/0.55, **0.59**, **0.89**/0.85, **0.94**, **1.4**/1.3 and **1.8**/1.7 mg/kg.

Portuguese GAP (2 x 0.02 kg ai/hl, PHI 7 days) was used to evaluate 4 trials in southern France. Fruits **without**/with stones showed residues of **0.09**, **0.34**, **0.36** and **0.49**/0.45 mg/kg.

All results evaluated gave residues in rank order of **0.04**, **0.09**, **0.15**, **0.16**, **0.19**, **0.21**, **0.33**, **0.34**, **0.36**, **0.49**/0.45, **0.58**/0.55, 0.59, **0.89**/0.85, **0.94**, **1.4**/1.3 and **1.8**/1.7 mg/kg.

On the basis of the German and French residue data the Meeting estimated an STMR of 0.35 mg/kg and agreed to recommend maintaining the CXL of 2 mg/kg.

Peaches and nectarines. GAP is the same for nectarines and peaches in southern Europe and South Africa.

Residue trials on nectarines were carried out in Italy (3), southern France (2) and South Africa (3). The Italian and southern French trials with 1-2 x 0.018-0.019 kg ai/hl, PHI 7 days, complied with Portuguese GAP (1-2 x 0.017-0.02 kg ai/hl, PHI 7 days). The residues in fruits without stones were 0.12, 0.13, 0.20, 0.23 and 0.25 mg/kg.

Two of the 3 South African trials on nectarines could not be evaluated because the application rate was twice the rate prescribed by GAP or samples were not taken at the PHI of 35 days. In the third trial conducted according to GAP, the residue in the fruit without stone was 0.1 mg/kg at day 35, but 0.17 mg/kg at day 49.

On peaches, 6 trials were conducted in Spain, 1 in Portugal and 6 in South Africa. The Portuguese and Spanish trials with 3 x 0.03-0.038 kg ai/hl were according to Spanish GAP (1-3 x 0.025-0.038 kg ai/hl, PHI 15 days) and most of them also complied with Greek GAP (0.025-0.038 kg ai/hl, PHI 10 days). The residues in fruit **without**/with stones were **0.05**, **0.10**, **0.26**/0.24, **0.27**/0.26, **0.43**/0.41, **0.54**/0.49, and **0.74**/0.71 mg/kg.

Four of the 6 South African trials on peaches could not be evaluated because the application rate was twice the rate prescribed by GAP or samples were not taken at the PHI

of 35 days. In both the 2 trials according to GAP, the residues were 0.12 mg/kg at day 35 in fruit without stones.

Because GAP for nectarines and peaches is the same, a maximum residue level and STMR were estimated from the combined data. All the residues in nectarines and peaches **without**/with stone in rank order were **0.05**, **0.10**, **0.12**, **0.12**, **0.12**, **0.13**, **0.17**, **0.20**, **0.23**, **0.25**, **0.26**/0.24, **0.27**/0.26, **0.43**/0.41, **0.54**/0.49 and **0.74**/0.71 mg/kg.

The Meeting estimated a maximum residue level of 1 mg/kg (the same as the CXL) and an STMR of 0.17 mg/kg for peaches and nectarines.

Apricots. As no residue data were provided, the Meeting agreed to propose the withdrawal of the CXL of 1 mg/kg.

Bananas. Bitertanol is registered in Belize, Costa Rica, the Dominican Republic, Guatemala, Nicaragua and Panama with application at 0.15 kg ai/ha and 0.5-1.4 kg ai/hl. Further uses are in Honduras (0.15 kg ai/ha, 0.02-0.2 kg ai/hl), Cameroon (0.15 kg ai/ha, 1.5-3 kg ai/hl), Philippines (0.15-0.2 kg ai/ha, 0.5-0.65 kg ai/hl) and Taiwan (0.12 kg ai/ha, 0.4 kg ai/hl). The PHI is either 0 days or not specified. Residue trials were carried out in Costa Rica, Honduras, the Philippines, Taiwan and Cameroon.

Five trials in Costa Rica at 10–16 x 0.12-0.24 kg ai/ha, 0.2-0.25 kg ai/hl could not be evaluated because the interval between the final application and harvest was 4 and 8 days whereas GAP permits a 0-day PHI. The residues in 2 further trials with treatments of 9 x 0.44 kg ai/hl, PHI 3 days (88% of the lowest recommended concentration rate) in the whole fruit/pulp were 0.24/0.11 mg/kg unbagged and 0.03/0.02 mg/kg bagged.

Five trials in Honduras with 12 x 0.69–1.3 kg ai/hl were evaluated as they complied with the GAP of the other Central American countries. On day 0, the residues in the whole fruit/pulp were 0.1/0.04, 0.32/0.13 and 0.06/0.03 mg/kg in unbagged bananas, and 0.02/0.02, 0.03/<0.01 and 0.03/0.02 mg/kg in bagged. Four further trials in Honduras (12 x 0.06 kg ai/hl, PHI 0 days) were according to Honduras GAP (0.02-0.2 kg ai/hl). The residues in the whole fruit/pulp in unbagged bananas were 0.06/0.03 and 0.36/0.17 mg/kg and in bagged bananas 0.06/0.01 and 0.04/0.02 mg/kg.

Four trials were carried out in the Philippines: 2 were at exaggerated rates (10 x 1.25 kg ai/hl) and the others (26 x 0.69–0.87 kg ai/hl) approximated GAP. As the residues were determined in bagged bananas, they were <0.05 mg/kg in fruit, pulp and peel.

The 2 trials in Taiwan (12 x 0.094 kg ai/hl) could not be evaluated because they did not comply with GAP.

The 2 trials in Cameroon could not be evaluated because the intervals between the final applications and harvest were 6 and 12 days whereas Cameroon GAP does not specify a PHI, implying that 0 days is permitted.

In summary, the residues in unbagged whole bananas in trials in accordance with GAP were Costa Rica 0.24 mg/kg, Honduras 0.06, 0.06, 0.1, 0.32 and 0.36 mg/kg. The respective values for bagged bananas were Costa Rica 0.03 mg/kg, Honduras 0.02, 0.03,

0.03, 0.04, 0.06 mg/kg, and the Philippines <0.05 mg/kg (2). An STMR was estimated from the residues in the pulp of unbagged bananas: 0.03, 0.03, 0.04, 0.11, 0.13 and 0.17 mg/kg.

The Meeting estimated a maximum residue level of 0.5 mg/kg, the same as the current CXL, and an STMR of 0.075 mg/kg.

Tomatoes. Ten trials were carried out in The Netherlands according to GAP with 3 x 0.03 kg ai/hl in a greenhouse. At the GAP PHI of 3 days the residues in normal sized tomatoes ranged from 0.39 to 0.98 mg/kg. In cherry tomatoes, the residues were twice as high: 2.1 and 2.4 mg/kg. All the residues in normal and cherry tomatoes in rank order were 0.39, 0.41, 0.48, 0.54, 0.56, 0.96, 0.96, 0.98, 2.1 and 2.4 mg/kg.

The Meeting estimated a maximum residue level of 3 mg/kg and an STMR of 0.76 mg/kg for tomatoes.

Cucumbers. Greenhouse trials were carried out in southern France (2) and The Netherlands (8).

The French trials (3 x 0.02 kg ai/hl, PHI 17 days) were not according to GAP.

The residues in the 8 trials carried out in The Netherlands according to GAP (3 x 0.03 kg ai/hl) in rank order were 0.1, 0.11, 0.16, 0.17, 0.19, 0.21, 0.22 and 0.22 mg/kg.

The Meeting estimated a maximum residue level of 0.5 mg/kg (the same as the existing CXL) and an STMR of 0.18 mg/kg for cucumbers.

Common beans, bean forage, peanuts, peanut forage. As no data on GAP or residue trials were provided, the Meeting agreed to recommend the withdrawal of the CXLs of 0.5 mg/kg for common bean, 10 mg/kg for bean forage, 0.1* mg/kg for peanut and 20 mg/kg for peanut forage (green).

Seed treatments

Barley. The highest application rates are in Sweden (0.07 kg ai/100 kg seed) and The Netherlands (0.056 kg ai/100 kg seed). Eight supervised trials were conducted in Germany, 6 with 0.07-0.075 kg ai/100 kg seed according to Swedish GAP and 2 with 0.057 kg ai/100 kg seed according to GAP in The Netherlands. The residues were below the LOD of 0.05 mg/kg in grain harvested 100 to 144 days after treatment in all the samples.

Oats. The highest application rates are in Sweden (the same as barley) and Austria (0.038-0.075 kg ai/100 kg seed). In Germany, The Netherlands and the UK the rate is 0.056 kg ai/100 kg seed. Seven supervised trials were conducted in Germany, 3 at 0.075 kg ai/100 kg seed according to Swedish GAP and 4 at 0.055-0.057 kg ai/100 kg seed according to GAP in Germany, The Netherlands and the UK. The residues were below the LOD of 0.05 mg/kg in all samples harvested 113 to 147 days after treatment.

Rye. The highest application rates are in Austria (0.038-0.075 kg ai/100 kg seed), Germany, The Netherlands, Sweden and the UK (all 0.056 kg ai/100 kg seed). In nine trials in Germany, 8 were with 0.056 kg ai/100 kg seed and 1 with 0.07 kg ai/100 kg seed. The

residues were below the LOD of 0.05 mg/kg in all grain samples harvested 289 to 322 days after treatment.

Wheat. The highest application rates are in Germany (0.075 kg ai/100 kg seed), Poland (0.07 kg ai/100 kg), Sweden (0.056-0.07 kg ai/100 kg), The Netherlands (0.056 kg ai/100 kg) and the UK (0.038-0.056 kg ai/100 kg). In Germany 11 supervised trials were carried out on spring wheat and 2 on winter wheat at 0.07-0.076 kg ai/100 kg. The residues were below the LOD of 0.05 mg/kg in all the grain samples.

Triticale. Uses are registered in Denmark, Poland and the UK and are identical with those for wheat and/or rye in those countries. The Meeting agreed to extrapolate the results from wheat and rye to triticale.

The Meeting estimated a maximum residue level of 0.05* mg/kg for bitertanol in barley, oats, rye, triticale and wheat as being a practical limit of determination, and recommended the withdrawal of the existing CXLs for oats, rye and wheat (0.1* mg/kg). As the residues were below the LOD in all samples, and this was consistent with the results of a metabolism study with [^{14}C]bitertanol where no parent compound was detected in the grain at harvest, an STMR of 0 mg/kg was estimated.

Straw and fodder of cereal grains. Supervised trials according to GAP in several European (0.056-0.075 kg ai/100 kg seed) were carried out on barley (8), oats (7), rye (9) and wheat (13). The residues in all straw and forage samples were below the LOD of 0.05 mg/kg.

The Meeting agreed to recommend the withdrawal of the current CXLs for straw and fodder (dry) of oats, rye and wheat of 0.1* mg/kg. A maximum residue level of 0.05* mg/kg was estimated for the straw and fodder (dry) of barley, oats, rye, triticale and wheat as a practical limit of determination. As no detectable residue is to be expected in cereal straw after seed treatment, an STMR of 0 was estimated.

Oat and rye forage. Cereals such as oats and rye are grown to a limited extent as forage crops. The immature crop is fed to livestock animals as succulent forage or as silage.

Seven supervised trials on oats and 9 on rye with seed treatments of 0.055-0.075kg ai/100 kg seed were reported. Green oats and rye were harvested at 63-101 and 218-254 days after application respectively. The residues were not detected in any of the green plants.

The Meeting recommended replacement of the current CXLs for oat and rye forage (green) of 0.1* mg/kg by 0.05* mg/kg (dry weight basis) as a practical limit of determination. According to the results of the metabolism study, the possibility of residues of bitertanol in cereal forage after seed treatment cannot be excluded, and an STMR of 0.05 mg/kg was estimated.

Animal feeding studies

Groups of 3 cows were dosed by capsule for 28 days with bitertanol at levels corresponding to 25, 75 and 250 ppm in the feed or 0.63, 1.88 and 6.25 mg/kg bw per day. Milk samples were collected from all cows on days 0, 7, 14, 21 and 28. At the end of the test period, the

animals were slaughtered and their tissues and milk analysed for total extractable bitertanol and metabolite residues. The results are summarized in the following table.

Dose mg/kg bw/day	Total bitertanol residues, mg/kg									
	Milk		Liver		Kidney		Muscle		Fat	
	high	mean	high	mean	high	mean	high	mean	high	mean
0.63	0.01	<0.01	0.78	0.63	0.05	0.037	0.06	0.03	0.06	0.027
1.88	0.07	0.04	1.9	1.4	0.36	0.32	0.09	0.08	0.18	0.17
6.25	0.26	0.24	3.7	2.8	1.1	0.77	0.44	0.32	1.3	0.85

In a metabolism study on a dairy cow dosed for 5 days with 0.2 mg/kg bw/day the milk contained only 0.008 mg/kg bitertanol equivalents (0.2% of the applied ^{14}C) but the residues had not reached a plateau. In the tissues the total ^{14}C residues were liver 0.82, kidney 0.11, muscle 0.01 and fat 0.03 mg/kg bitertanol equivalents.

As the residue of bitertanol in the milk reached a plateau slowly (3-4 weeks after treatment at the earliest), the STMRs of the feed items should be used to estimate the dietary burden. The highest exposure to bitertanol residues may arise from the consumption of wet apple pomace with an STMR level of 0.648 mg/kg. With the theoretical assumption that the daily maximum feed consumption of beef cattle (body weight 550 kg) would be 20 kg on a dry matter basis, including 40% of wet pomace (containing 40% dry matter), the intake may be calculated as follows.

0.648 mg/kg wet weight is equivalent to 1.62 mg/kg on a dry matter basis.
As apple pomace forms 40% of the diet it will contribute 1.62 x 0.4 = 0.648 ppm in the total feed on a dry matter basis.
On this basis beef cattle may be exposed to 0.0236 mg bitertanol/kg bw/day.

The lowest dose rate in the feeding study represents approximately 27 times the estimated dietary burden (0.63/0.0236). The Meeting noted the high ratio and concluded that an extrapolation downwards to the real intake would result in residues below the 0.05 mg/kg reported as a practical limit of determination in the official method of analysis of The Netherlands.

The Meeting estimated 0.05* mg/kg as a maximum residue level for milk, edible offal and meat (fat) and 0.05 mg/kg as an STMR for milk, edible offal and meat. As the metabolism is similar in rats and cows, these levels are estimated for cattle, goats, sheep and pigs.

A metabolism study in hens showed that approximately 98% of the dose was recovered in the excreta. Eggs contained <0.2% of the total dose.

Laying hens (10 birds/group) were fed daily rations containing bitertanol at total residue levels of 1, 3 and 100 ppm for 28 days. Additional hens were fed the 100 ppm diet for 28 days and then maintained on untreated rations for an additional 14 days (five birds) or 28 days (three birds) before slaughter to determine the rate of decline of residues in the tissues and eggs. The tissues and eggs were analysed for total extractable bitertanol and metabolite residues.

Tissues from the 3 ppm and 100 ppm treatment groups were pooled in each group and analysed. Eggs from those groups were analysed at 7, 14, 21 and 28 days. The residues found in the 100 ppm group were liver 1.03 mg/kg, gizzard 0.23 mg/kg, heart 0.10 mg/kg, muscle

0.07 mg/kg and fat 0.07 mg/kg. Liver, gizzard and muscle samples from the 3 ppm group contained quantifiable residues, the liver having the highest level (0.21 mg/kg), followed by gizzard (0.07 mg/kg) and muscle (0.01 mg/kg). The residues in the livers at the lowest feeding level (1 ppm) were below 0.01 mg/kg, and other tissues were not analysed as the residues from the higher dose rates were so low. The residues in eggs were only quantifiable in the 100 ppm feeding group; day 28 eggs from that group contained 0.11 mg/kg bitertanol. All tissue and egg residue levels in the residue decline group were below 0.01 mg/kg 28 days after the birds had been returned to untreated feed except in the liver, which contained 0.04 mg/kg).

The exposure to bitertanol residues would arise from cereal grains, with a maximum residue level of 0.05* mg/kg (STMR 0 mg/kg).

With the theoretical assumption that the daily maximum feed consumption of a chicken (bw 1.9 kg) is 0.12 kg dry matter consisting of 100% cereal grains (e.g. wheat or oats with 89% dry matter) the intake may be calculated as follows.

> A maximum residue of 0.05 mg/kg wet weight is equivalent to 0.056 mg/kg on a dry weight basis.
> As cereal grain forms 100% of the diet, the bitertanol residue in the total feed (dry matter basis) is equivalent to 0.056 ppm, and hence to an intake of 0.0035 mg/kg bw/day.

In view of the results of the metabolism and feeding studies, no residues are to be expected in edible tissues or eggs. The Meeting estimated an STMR of 0 and a maximum residue level of 0.01* mg/kg for eggs, poultry meat, and edible offal of poultry as a practical limit of determination.

Processing

Studies have been carried out to determine the effect of processing on residues of bitertanol in apples, cherries, peaches, plums and tomatoes.

Apples containing 0.08, 0.23, 0.55 and 1 mg/kg bitertanol were processed to juice and sauce, which did not contain residues above the LOD of 0.02 mg/kg.

In 2 further trials, the residues in raw apples were 0.49 and 8.2 mg/kg, in juice 0.09 and 0.84 mg/kg and in wet pomace 1.37 and 21 mg/kg. The wet pomace in the second trial (8.2 mg/kg in unprocessed apples) was processed to dry pomace, which contained a residue of 61 mg/kg (processing factor 7.4).

The Meeting agreed to calculate the STMR levels on the basis of the trials which included the determination of bitertanol in the pomace, which is a potential feeding-stuff. From the STMR of 0.24 mg/kg for apples and mean processing factors of 0.14 for juice and 2.7 for wet pomace as well as the factor of 7.4 for dry pomace, the Meeting estimated STMRs of 0.0336 mg/kg for apple juice and sauce, 0.648 for wet apple pomace and 1.78 mg/kg for dry apple pomace.

The processing data on stone fruit indicate that residues of bitertanol do not concentrate in any processed commodity which may be used as food. Three trials were carried out on cherries and 2 each on peaches and plums. The peach trials could not be

evaluated as the residues in washed and unwashed fruit were inconsistent and it was not clear which fruit was further processed.

Cherries were processed into juice, preserve and jam, and plums into sauce and jam. The procedures for jam production were nearly identical for cherries and plums. The processing factors for cherry juice were 0.028, 0.115 and 0.375 (mean 0.17), for cherry jam 0.36 and 0.54 (mean 0.45), for cherry preserve 0.5, 0.58 and 0.68 (mean 0.59), and for plum jam 0.57 and 0.64 (mean 0.605).

On the basis of the mean processing factors and the STMRs of 0.365 mg/kg for cherries and 0.34 mg/kg for plums, the Meeting estimated the following STMRs. Cherries: 0.062 mg/kg juice, 0.16 mg/kg jam, 0.22 mg/kg preserve. Plum jam 0.21 mg/kg.

One processing study on tomatoes was reported. The residues of bitertanol were lower in juice and preserves (processing factors 0.135 and 0.365), but higher in paste (processing factor 2.1). The Meeting estimated STMRs of 0.1, 0.28 and 1.6 mg/kg for tomato juice, preserve and paste respectively, based on the STMR for tomato of 0.76 mg/kg.

DIETARY RISK ASSESSMENT

Chronic intake

International Estimated Dietary Intakes (IEDIs) of bitertanol were estimated from the STMRs of 23 commodities.

International Estimated Daily Intakes for the five GEMS/Food regional diets, based on estimated STMRs, were in the range of 2% to 10% of the ADI. The Meeting concluded that the intake of residues of bitertanol resulting from its uses that have been considered by the JMPR is unlikely to present a public health concern.

Acute intake

The 1998 JMPR concluded that it was unnecessary to establish an acute RfD because bitertanol has been classified by WHO as unlikely to present an acute hazard in normal use and has not shown any specific adverse effects (teratogenicity, neurotoxicity) after single doses 100 times the lowest relevant NOAEL in long- and short-term studies that were used to establish the ADI. The Meeting therefore concluded that the short-term dietary intake of bitertanol residues is unlikely to present a risk to consumers.

4.3 BUPROFEZIN (173)

TOXICOLOGY

On the basis of a review of the toxicological monograph on buprofezin prepared in 1991, the Joint Meeting concluded that the establishment of an acute reference dose is unnecessary because buprofezin has low acute toxicity after single oral doses and the NOAELs for other potentially relevant endpoints (e.g. developmental toxicity) were about 50 times higher than those used for establishing the ADI. No specific acute effects were identified.

RESIDUE AND ANALYTICAL ASPECTS

Buprofezin was first evaluated by the 1991 JMPR, which recommended a temporary MRL for oranges pending the delivery of required information by 1995.

The 1995 JMPR concluded that the available data were inadequate for citrus fruits and recommended that the existing temporary MRL for oranges be withdrawn. The 1995 Meeting also concluded that if citrus MRLs were contemplated in a future submission a citrus processing study, including analyses for the main metabolites, would be required, and experimental evidence that the thiobiuret metabolite does not occur during citrus metabolism would be desirable.

The 1995 JMPR also listed the following items as desirable.

1. Analysis of reserve cow liver and kidney samples from the ruminant metabolism studies for the presence of dihydroxybuprofezin, hydroxymethoxy buprofezin and the thiobiuret metabolite.

2. A conventional animal processing study to determine residues of buprofezin, *p*-hydroxybuprofezin and (in milk) *p*-acetamidophenol.

The Meeting received follow-up studies on metabolism in a lactating dairy cow and in citrus fruit, information on GAP and residue trials on citrus fruits, a feeding study on dairy cows and a processing study on citrus fruits. Further information was provided by Germany, The Netherlands, Poland and the UK.

Liver, kidney and milk samples from the previously reported study of metabolism in a lactating dairy cow were re-examined to identify more of the residue. Despite extensive additional clean-up and identification work no new metabolites were identified. The large amount of unextractable and polar residue was taken as evidence of extensive incorporation. No more than about 20-30% of the residue in the liver, kidneys and milk could be identified, but only in the liver did an unknown (at 0.07 mg/kg) exceed 0.05 mg/kg in a tissue, i.e. the levels of individual unknowns were low.

Additional standard compounds were available in the follow-up study, including 1-*tert*-butyl-3-isopropyl-5-phenyl-2-thiobiuret, the ‘thiobiuret’ metabolite BF-25 and 2-*tert*-butylimino-5-(4-hydroxy-3-methoxyphenyl)-3-isopropyl-1,3,5-thiadiazinan-4-one, the ‘hydroxymethoxybuprofezin’ metabolite BF-27, both of which were identified in rats. Neither was detected in the cow tissues or milk. The remaining possibility, the ‘dihydroxybuprofezin’ metabolite, was not included in the study but it is closely related to metabolite BF-27, so desirable information point 1 (*analysis of reserve cow liver and kidney samples from the ruminant metabolism trials on the presence of the dihydroxybuprofezin, hydroxymethoxybuprofezin and the thiobiuret metabolites*) is substantially satisfied.

Metabolites in extracts from the study of metabolism in lemons were re-examined to determine the identity of the residue that produced 2-amino-2-methylpropyl 2-isopropyl-4-phenylallophanate (BF-26) on acid hydrolysis and to check primary extracts for the presence of 1-*tert*-butyl-3-isopropyl-5-phenyl-2-thiobiuret (BF-25). Various enzyme hydrolyses were tried but released little of the bound ^{14}C. The evidence strongly suggests that the main metabolite is a non-glucose hexose conjugate of 2-(2-hydroxy-1,1-dimethylethylimino)-3-

isopropyl-5-phenyl-1,3,5-thiadiazinan-4-one (BF-4). The BF-4 cannot be liberated from the conjugate without further degradation to BF-26, 3-isopropyl-5-phenyl-1,3,5-thiadazinane-2,4-dione (BF-9) and 1-isopropyl-3-phenylurea (BF-12). Unhydrolysed extracts from the lemons were examined by TLC for metabolite BF-25 (the 'thiobiuret' metabolite), but none was detected. This satisfies the request from the 1995 JMPR for *experimental evidence that the thiobiuret metabolite does not occur during citrus metabolism*.

Analytical methods for residues of buprofezin and some metabolites in oranges, orange commodities and kidney, liver, fat, muscle and milk were reported. The methods were used in the supervised trials, processing studies and animal feeding studies.

Samples were extracted and the extracts cleaned up by solvent partition and an aminopropyl solid-phase extraction cartridge, and analysed by GLC with an NPD. The exact procedure was tailored to the sample. LODs were in the range 0.01 to 0.1 mg/kg. Recoveries were usually in the 70-100% range, but individual recoveries dropped below 50% for residues in orange processing fractions.

Buprofezin, BF-9 and BF-12 added separately at 0.1 mg/kg to orange homogenate did not decrease perceptibly when stored for 6 months at approximately -18°C, but with the analytical error at levels of 0.1 mg/kg, a decrease of 20-30% would be necessary to be discernible.

The Meeting was informed that the results of a 1-year freezer storage stability study for residues in milk, fat and liver would be available in the year 2000.

The Meeting received information on registered uses of buprofezin on citrus fruits in 14 countries. It is usually applied as a foliar spray in the concentration range of 0.013-0.038 kg ai/hl, with typical intervals of 7-14 days specified before harvest, although South Africa has a 45 days PHI. Labels for uses on citrus were available from Italy, South Africa and Spain.

Supervised residue trials with buprofezin on oranges were reported from Spain and Italy, which included analyses for BF-9 and BF-12 as well as buprofezin.

In Spain buprofezin is registered for application to citrus trees with a spray concentration of 0.010-0.013 kg ai/hl and harvest 7 days later. Buprofezin residues were 0.06 and 0.07 mg/kg in oranges from 2 Spanish trials complying with GAP.

Buprofezin is registered for use on citrus trees in Italy at a spray concentration of 0.025-0.038 kg ai/hl. A ±30% tolerance on 0.038 kg ai/hl extends from 0.026 to 0.049 kg ai/hl so the trials, at 0.025 and 0.051 kg ai/hl, were at the margins of the allowable range of application rates. Trials on oranges in Italy and Spain complying with Italian GAP, including 3 trials reported in the 1995 Residue Evaluations, produced residues of 0.03, 0.03, 0.06, 0.13, 0.24, 0.26 and 0.43 mg/kg.

An orange trial in South Africa, reported in the 1995 Residue Evaluations, where buprofezin was used according to South African GAP (2 applications of 0.015 kg ai/hl, 45 days PHI) produced residues of 0.02 mg/kg.

In summary, buprofezin residues in 10 trials according to GAP in Italy, Spain and South Africa in rank order, median underlined, were 0.02, 0.03, 0.03, 0.06, 0.06, 0.07, 0.13, 0.24, 0.26 and 0.43 mg/kg. The STMR for whole oranges is 0.065 mg/kg.

The mean processing factor for orange pulp was 0.17, calculated from data in the 1991 and 1995 Residue Evaluations. The estimated STMR for buprofezin in the edible portion of oranges then becomes $0.065 \times 0.17 = 0.011$ mg/kg.

The Meeting estimated a maximum residue level of 0.5 mg/kg and an STMR of 0.011 mg/kg for buprofezin in oranges.

In a farm animal feeding study, dairy cows were dosed with buprofezin at the equivalent of 5, 15 and 50 ppm in the feed for 28 days. Buprofezin itself was detected in milk only at the highest feeding level and in only 1 of the 3 animals with the first detection occurring on day 2 and continuing only in this animal throughout the study. When day 28 milk was separated into skimmed milk and cream no residues were detected in the skimmed milk, but buprofezin residues were present in the cream from cows in the 15 and 50 ppm feeding groups. Metabolite BF-12 was not detected in milk, skimmed milk or cream. Metabolite BF-23 (acetaminophen or paracetamol) was detected in milk on days 24 and 28 both in samples from some treated groups and control samples, all at 0.01 mg/kg, suggesting contamination.

Buprofezin was detected at the LOD in the liver of one animal from the 50 ppm feeding group and at 0.07, 0.11 and 0.12 mg/kg in the perirenal fat of the 3 animals of the 50 ppm feeding group. The metabolites BF-12 and 2-*tert*-butylimino-5-(4-hydroxyphenyl)-3-isopropyl-1,3,5-thiadiazinan-4-one (*p*-hydroxy-buprofezin, BF-2) were not detected in any tissue. This provides the desirable information item 2 from the 1995 JMPR *a conventional animal transfer study in which residues of buprofezin, p-hydroxybuprofezin and (in milk) p-acetamidophenol are determined.*

The residue is defined as buprofezin, which is suitable both for compliance with MRLs and for the estimation of dietary intake. The buprofezin log P_{ow} of 4.3 (JMPR Residue Evaluations, 1991) and the presence of buprofezin in tissue fat and milk fat but not in muscle or skimmed milk in the dairy cow feeding study imply fat-solubility.

The Meeting agreed that buprofezin should be described as fat-soluble.

The Meeting received information on the fate of buprofezin and metabolites BF-9 and BF-12 during the processing of oranges to juice, oil and dry pulp. Oranges were harvested 66 days after treatment with buprofezin at an exaggerated rate (11 kg ai/ha). Fruit and juice were stored frozen for approximately 5 months before analysis, a period covered by the storage stability study on orange homogenate. Oil and dry pulp were stored for approximately 15 months before analysis without supporting evidence of stability for this period.

The calculated processing factors for buprofezin residues were oil 43, juice 0.18, dry pulp 4.1. The residues of the metabolites were below or about the LOD (0.01 mg/kg) in the fruit so it is not possible to estimate processing factors, but BF-9 tended to be concentrated in the oil, while BF-12 was concentrated in the dry pulp.

The orange processing study meets the requirement of the 1995 JMPR for a citrus processing study that includes the main residues identified in the metabolism study.

From these processing factors and the STMR for whole oranges (0.065 mg/kg) the Meeting estimated an STMR for orange juice of 0.012 mg/kg and for dry orange pulp of 0.27 mg/kg.

Dry processed orange pulp is an animal feeding material that may represent 20% of the diet for dairy and beef cattle. The estimated maximum dietary burden of buprofezin for beef and dairy cattle (on the basis of the estimated maximum residue level for oranges, 0.5 mg/kg, and the processing factor for dry pulp, 4.1) was equivalent to 0.45 ppm in the diet. The lowest feeding level in the dairy cow study was 5 ppm, which did not produce detectable levels of buprofezin in the tissues or milk, so the Meeting estimated maximum residue levels at or about the LOD for buprofezin residues in cattle milk (0.01* mg/kg), cattle meat (0.05* mg/kg), cattle kidney (0.05* mg/kg) and cattle liver (0.05* mg/kg), but could not recommend these maximum residue levels as being suitable for use as MRLs until the stabilities of the residues during freezer storage are confirmed.

The STMR for dry processed orange pulp is 0.27 mg/kg and the corresponding dietary burden for cattle, 0.059 ppm, is suitable for estimating STMRs for animal commodities.

The residues were below LOD in the muscle and kidney at the 5, 15 and 50 ppm feeding levels, and in the liver, fat and milk at the 5 and 15 ppm levels. Residues of buprofezin were detected in the fat and liver at the 50 ppm level and in milk fat at the 15 and 50 ppm levels. The Meeting noted that the dietary burden of 0.059 ppm was much less than the lowest feeding level where no residues were detected and, as an approximation for extrapolation, assumed proportionality between tissue level and dietary intake.

STMR (animal commodity) = LOD × (STMR dietary burden) ÷ (feeding level)

STMR for meat = 0.05 × 0.059 ÷ 50 = 0.00006 mg/kg (no detections at 50 ppm feeding level)

The same applies to kidney. For liver and milk there were no detections at the 15 ppm feeding level, so calculated STMRs are 0.0002 and 0.00004 mg/kg respectively. The Meeting regarded these calculated values as effectively zero and estimated STMRs of 0 mg/kg for meat, kidney, liver and milk, but the STMRs would not apply until MRLs are recommended.

FURTHER WORK OR INFORMATION

Desirable

Information is needed on the freezer storage stability of residues in animal commodities to validate the dairy cow feeding study. The Meeting was informed that the results of a 1-year freezer storage stability study for milk, fat and liver would be available in the year 2000.

DIETARY RISK ASSESSMENT

Chronic intake

A revised MRL for buprofezin in oranges has been recommended in addition to previous recommendations. STMR levels have been estimated for oranges and some processed commodities. The other values (2) used for the intake estimation are previously established CXLs.

The dietary intake of buprofezin is presented in Annex III. Estimated dietary intakes for buprofezin for the 5 GEMS/Food regional diet were in the range of 2-10% of the ADI. The Meeting concluded that intake of buprofezin resulting from its uses that have been considered by JMPR is unlikely to present a public health concern.

Acute intake

The Meeting concluded that an acute RfD for buprofezin is unnecessary. This conclusion was based on a determination that the pesticide is unlikely to present an acute toxicological hazard, and residues are therefore unlikely to present an acute risk to consumers.

4.4 CARBOFURAN (096)

RESIDUE AND ANALYTICAL ASPECTS

Carbofuran was evaluated for residues by the 1997 JMPR in the CCPR Periodic Review Programme. At the 31st (1999) Session of the CCPR it was asked (ALINORM 99/24A, para79), whether the recommendations for MRLs for sorghum and sweet corn should be asterisked (*).

The 1999 CCPR also noted (ALINORM 99/24A, para 79) that, although the 1997 JMPR had concluded that an MRL for citrus fruits should be established for carbofuran and carbosulfan, only an MRL for oranges (sweet, sour) had been recommended. It was requested that an MRL for mandarin be elaborated.

Asterisk

The recommendations by the 1997 JMPR were 0.1* mg/kg for sorghum and 0.1 mg/kg for sweet corn (corn-on-the-cob).

In all sorghum residue trials used for estimating maximum residue levels, the residue was <0.01 mg/kg (the estimated limit of detection) and so it is safe to say that no residues were present. However, since the practical limit of determination in plant commodities is 0.1 mg/kg the Meeting agreed to maintain the current recommendation of 0.1* mg/kg for sorghum.

In the residue trials on sweet corn used for estimating maximum residue levels the residues were <0.03–0.08 mg/kg (n=16, 10 residues >0.03 mg/kg). In this case residues were clearly present. Therefore, although the proposed MRL of 0.1 mg/kg is at the practical limit

of determination, it should not be asterisked. The Meeting confirmed the 1997 recommendation of an MRL of 0.1 mg/kg for sweet corn (corn-on-the-cob).

MRL for mandarin

There is no registered use of carbofuran on citrus fruit, so all carbofuran residues arise from the use of carbosulfan. There are registered uses of carbosulfan on oranges in Mexico and Brazil and on oranges and mandarins in Spain. The supervised trials used by the 1997 JMPR to estimate a maximum residue level were mainly with oranges, some with mandarins (6 of about 28 trials). The residues in mandarins were comparable to those in oranges. The Meeting agreed to maintain the current recommendation for an MRL of 0.5 mg/kg for carbofuran in sweet and sour oranges and recommended the same MRL for carbofuran in mandarins. The STMR of 0.1 mg/kg for oranges was also extended to mandarins. The residue is defined as the sum of carbofuran and 3-hydroxycarbofuran, expressed as carbofuran. A group MRL for citrus fruits cannot be recommended since registered uses are solely on oranges and mandarins.

Residues in the edible pulp. Residues of carbosulfan, carbofuran and 3-hydroxycarbofuran were determined separately in the peel, pulp and whole fruit in several trials reported in the 1997 evaluation of carbosulfan. Five of the trials showed residues in the pulp, with a mean ratio of pulp to fruit residue of 0.0726. Since the highest residue of carbofuran + 3-hydroxycarbofuran found in the whole fruit was 0.5 mg/kg and the estimated STMR was 0.1 mg/kg, the corresponding residues in the pulp were estimated as 0.0363 mg/kg and 0.00726 mg/kg.

DIETARY RISK ASSESSMENT

Chronic intake

An STMR for mandarins was added to the extensive list of STMRs estimated by the 1997 Meeting (Annex III).

International Estimated Daily Intakes for the 5 GEMS/Food regional diets, based on estimated STMRs, were in the range of 7-30% of the ADI. The Meeting concluded that the intake of residues of carbofuran resulting from its uses that have been considered by the JMPR is unlikely to present a public health concern.

Acute intake

The International Estimate of Short Term Intake (IESTI) for carbofuran was calculated as described in Section 3 of this report for commodities for which MRLs were recommended and STMRs estimated and for which consumption data (large portion consumption, unit weight) were available. The results are shown in Annex IV. The IESTI ranged from 3.5×10^{-4} to 6.3×10^{-4} mg/kg bw in the total population and from 1.35×10^{-3} to 2.58×10^{-3} mg/kg bw in children. As no acute reference dose has been established, the acute risk assessment for carbofuran was not finalized.

4. 5 CARBOSULFAN (145)

RESIDUE AND ANALYTICAL ASPECTS

Carbosulfan was evaluated for residues by the 1997 JMPR in the Periodic Review Programme. At the 31st (1999) Session of the CCPR it was noted (ALINORM 99/24A, para 79) that, although the 1997 JMPR had concluded that an MRL for citrus fruits should be established for carbofuran and carbosulfan, only an MRL for oranges (sweet, sour) had been recommended. It was requested that an MRL for mandarin be elaborated if it is considered to be more appropriate to recommend MRLs for individual commodities.

Carbofuran is a main metabolite of carbosulfan, as well as being itself a pesticide. Residues of carbosulfan are defined as carbosulfan, and residues of carbofuran are defined as the sum of carbofuran and 3-hydroxycarbofuran, expressed as carbofuran. The 1997 JMPR recommended MRLs for oranges (sweet, sour) of 0.1 mg carbosulfan/kg and 0.5 mg carbofuran/kg.

The 1997 JMPR recommended an MRL of 0.1 mg/kg and estimated an STMR of 0.01 mg/kg for carbosulfan in whole oranges (sweet, sour). A total of 53 samples gave a highest residue of 0.08 mg/kg in whole oranges. A ratio of 0.0726 was estimated for pulp : whole fruit residues from five trials which gave rise to residues in the pulp. The highest residue in the edible portion was therefore estimated as 0.08 mg/kg x 0.0726 = 0.0058 mg/kg, and the STMR in the edible portion was estimated as 0.01 mg/kg x 0.0726 = 0.00726 mg/kg.

There is no registered use of carbofuran on citrus fruit so all carbofuran residues arise from the use of carbosulfan. There are registered uses of carbosulfan on oranges in Mexico and Brazil and on oranges and mandarins in Spain. The supervised trials used by the 1997 JMPR to estimate a maximum residue level were mainly with oranges, some with mandarins (6 of about 28 trials). The residues in mandarins were comparable to those in oranges. The Meeting agreed to maintain the current recommendations for MRLs of 0.1 mg carbosulfan/kg and 0.5 mg carbofuran/kg for oranges (sweet, sour) and recommended in addition MRLs of 0.1 mg carbosulfan/kg and 0.5 mg carbofuran/kg for mandarin. A group MRL for citrus fruits cannot be recommended since registered uses of carbosulfan are solely on oranges and mandarins.

DIETARY RISK ASSESSMENT

Chronic intake

An STMR for mandarins was added to the STMR for oranges estimated by the 1997 Meeting (Annex III).

International Estimated Daily Intakes for the 5 GEMS/Food regional diets, based on estimated STMRs, were all 0% of the ADI. The Meeting concluded that the intake of residues of carbosulfan resulting from its uses that have been considered by the JMPR is unlikely to present a public health concern.

Acute intake

The International Estimate of Short Term Intake (IESTI) for carbosulfan was calculated as described in Section 3 of this report for commodities for which MRLs were recommended and STMRs estimated and for which consumption data (large portion consumption, unit weight) were available. The results are shown in Annex IV. The IESTI ranged from 5 x 10^{-5} to 9 x 10^{-5} mg/kg bw in the total population and from 2.1 x 10^{-4} to 4 x 10^{-4} mg/kg bw in children. As no acute reference dose has been established, the acute risk assessment for carbosulfan was not finalized.

4.6 CHLORMEQUAT (015)

TOXICOLOGY

Chlormequat was evaluated by the JMPR in 1970, 1972 and 1994. An ADI of 0-0.05 mg/kg bw was allocated in 1972 on the basis of a study of reproductive toxicity in rats, but in 1994 the Meeting withdrew this ADI on the grounds that the data package was inadequate. The compound was reviewed again by the 1997 Meeting, when an ADI of 0-0.05 mg/kg bw was allocated. The compound was considered by the present Meeting solely to determine an acute reference dose, as requested by the 1999 CCPR (ALINORM 99/24A) and studies in dogs, long-term studies in rats and mice, a development study in rabbits and a 2-generation study in the rat, were reviewed.

The oral LD_{50} of chlormequat was 200-1000 mg/kg bw in rodents and >800 mg/kg bw in monkeys but was much lower in cats and dogs, approximately 50 mg/kg bw.

In a one-year study in dogs given chlormequat chloride (purity 67.4%) in the diet at concentrations of 0, 150, 300, and 1000 ppm, diarrhoea was seen at 300 ppm in two males during the first and second weeks of the study, and salivation was also seen at this dose, starting at week 1 and intermittently thereafter. Consequently, the NOAEL was 150 ppm, equal to 4.7 mg/kg bw per day, on the basis of diarrhoea and salivation at the next highest dose. Because these findings were seen early in the study, they were considered relevant to setting an acute reference dose.

Three long-term studies, two in rats and one in mice, showed that chlormequat was not carcinogenic. None of the studies showed acute effects.

In a study of developmental toxicity in rabbits given chlormequat chloride at doses of 0, 1.5, 3, 6, and 12 mg/kg bw per day by gavage on days 6-18 after insemination, the body-weight gain of animals at the highest dose was decreased and the feed consumption of all treated animals was affected, possibly because of reduced palatability. The NOAEL for maternal toxicity was 6 mg/kg bw per day and that for developmental toxicity was 12 mg/kg bw per day, the highest dose tested.

In a two-generation reproductive toxicity study in rats given chlormequat in the diet, clinical signs such as tremor were seen at the highest dose (250 mg/kg bw per day). Reproductive toxicity was also seen at this dose and systemic toxicity at the intermediate

dose (69 mg/kg bw per day). The NOAEL for systemic toxicity was 23 mg/kg bw per day and the NOAEL for reproductive toxicity was 69 mg/kg bw per day.

An acute reference dose of 0.05 mg/kg bw was established on the basis of the NOAEL of 4.7 mg/kg bw per day in the one-year study in dogs, as the clinical signs that were found were considered to be acute. A 100-fold safety factor was used.

An addendum to the toxicological monograph was prepared.

TOXICOLOGICAL EVALUATION

Levels that cause no toxic effects

Mouse: 150 ppm, equal to 23 mg/kg bw per day (two-year study of toxicity and carcinogenicity)

Rat: 940 ppm, equal to 42 mg/kg bw per day (two-year study of toxicity and carcinogenicity)
900 ppm, equal to 69 mg/kg bw per day (reproductive toxicity in a two-generation study of reproductive toxicity)
300 ppm, equal to 23 mg/kg bw per day (systemic toxicity in a 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 (developmental toxicity 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 an acute reference dose

0.05 mg/kg bw

The Meeting recommended that a residue evaluation should be scheduled shortly so that an acute risk assessment can be conducted.

4.7 CHLORPYRIFOS (017)

TOXICOLOGY

Chlorpyrifos is a broad-spectrum organophosphorus pesticide. The toxicology of chlorpyrifos was first evaluated by the 1972 Joint Meeting when an ADI of 0-0.0015 mg/kg bw was established on the basis of a NOAEL of 0.014 mg/kg bw per day in a 1-month study in humans. Additional biochemical and toxicological information was considered by the 1977 JMPR, when the ADI was changed to 0-0.001 mg/kg bw. Additional reports on the toxicology of chlorpyrifos were reviewed by the 1982 Joint Meeting and the ADI was increased to 0-0.01 mg/kg bw, based on a NOAEL of 0.1 mg/kg bw per day in humans exposed to chlorpyrifos for 9 days and using a 10-fold safety factor. This ADI was supported by findings in rats and dogs. Chlorpyrifos was reviewed at the present meeting under the Codex Committee on Pesticide Residues (CCPR) Periodic Review Programme.

After oral administration to rats, radiolabelled chlorpyrifos was rapidly and extensively absorbed (up to about 90% of the dose) and eliminated, predominantly in the urine (68-93%) and faeces (6-15% of the dose), within about 72 h of administration. The urinary metabolites included the glucuronide (about 80%) and sulfate (about 5%) conjugates of chlorpyrifos, and 3,5,6-trichloro-2-pyridyl phosphate (3,5,6-TCP; about 12%). The tissue concentrations of residues of ^{14}C-chlorpyrifos were very low (generally <1 ppm) within 72 h of dosing. The longest half-life of residues in rats was 62 h in fat, and low levels were also detected in the fat of several other species and in the milk of goats.

In humans who were poisoned with chlorpyrifos formulations, diethylphosphorus metabolites were excreted in the urine by first-order kinetics, with an average elimination half-life of 6.1 $\pm$ 2.2 h in the fast phase and of 80 $\pm$ 26 h in the slow phase. In volunteers, the time to C_{max} for 3,5,6-TCP in the blood was 0.5 h after oral dosing and 22 h after dermal treatment, but the elimination half-life by both routes was 27 h, and the percentage of the administered dose recovered from the urine was 70% after oral dosing and 1.3% after dermal administration.

Chlorpyrifos is rapidly metabolized by mixed-function oxidases to the highly reactive chlorpyrifos oxon by oxidative desulfuration. The oxon can be deactivated by hydrolysis to diethylphosphate and 3,5,6-trichloropyridinol, while a minor reaction pathway is hydrolysis to monoethyl 3,5,6-trichloro-2-pyridinyl phosphorothioate.

The lowest oral LD_{50} value was 96 mg/kg bw (range, 96-475 mg/kg bw) in rats and 100 mg/kg bw (range 100-150 mg/kg bw) in mice. Female rats were generally more sensitive to the acute effects of chlorpyrifos than males. The signs of acute intoxication with chlorpyrifos were consistent with cholinesterase inhibition. The acute dermal LD_{50} of chlorpyrifos was >2000 mg/kg bw in rats and >1200 mg/kg bw in rabbits.

WHO has classified chlorpyrifos as “moderately hazardous”.

Chlorpyrifos was irritating to the eye and skin of rabbits, but it did not sensitize the skin of guinea-pigs in Magnusson-Kligman maximisation or Buehler tests.

In short-term studies, the NOAEL for inhibition of erythrocyte cholinesterase activity was 0.03 mg/kg bw per day in dogs and 0.1 mg/kg bw per day in rats. The NOAEL for inhibition of brain cholinesterase activity was 1 mg/kg bw per day in dogs and rats. The signs of toxicity were largely limited to cholinergic signs and decreased body weights and/or food consumption. The NOAEL for these effects in short-term studies was 1 mg/kg bw per day in rats, and the NOAEL for clinical signs was 3 mg/kg bw per day in dogs. In mice, ocular effects and histopathological alterations (including adrenal lipogenic pigmentation and ocular keratitis) were observed (NOAEL 50 ppm, equal to 7 mg/kg bw per day). In rats, the NOAEL for increased fatty vacuolation of the adrenal zonal fasciculata and changes in haematological and clinical chemical parameters was 5 mg/kg bw per day. When rats received chlorpyrifos dermally for 21 days, the NOAEL for inhibition of cholinesterase activity in erythrocytes and brain was 5 mg/kg bw per day.

In long-term studies, inhibition of cholinesterase activity was again the main toxicological finding in all species. In rats, the NOAEL was 0.1 mg/kg bw per day for inhibition of erythrocyte acetylcholinesterase activity and 1 mg/kg bw per day for inhibition

of brain acetylcholinesterase activity, but clinical signs were not seen at doses up to 10 mg/kg bw per day and the NOAEL for reduction in body weight was 1 mg/kg bw per day. In mice, erythrocyte and brain acetylcholinesterase activities were inhibited at 50 ppm, equal to 6.1 mg/kg bw per day, and the NOAEL was 5 ppm, equal to 0.7 mg/kg bw per day. Cholinergic signs and reductions in body weight were reported only at the highest dietary concentration of 250 ppm (equal to 32 mg/kg bw per day). Other treatment-related findings included effects on the liver in mice, with a NOAEL of 50 ppm (equal to 6.6 mg/kg bw per day), and increased adrenal weight in rats with a NOAEL of 1 mg/kg bw per day. There was no treatment-related increase in the incidence of neoplastic lesions in any of the long-term studies. The Meeting concluded that chlorpyrifos is unlikely to pose a carcinogenic risk to humans.

Chlorpyrifos was not genotoxic in an adequate range of studies *in vitro* and *in vivo*. The Meeting concluded that chlorpyrifos is not genotoxic.

In multigeneration studies of reproductive toxicity in rats, the treatment-related effects of chlorpyrifos administration were limited to inhibition of cholinesterase activity, consistent with that seen in other short- and long-term studies, and fetotoxicity characterized by reduced pup viability, body weights and survival. No significant, treatment-related clinical signs were reported. The NOAEL for inhibition of maternal acetylcholinesterase activity was 0.1 mg/kg bw per day for erythrocytes and 1 mg/kg bw per day for brain. The NOAEL for developmental toxicity was 1 mg/kg bw per day. No effects on reproductive parameters were observed at the highest dose tested, 5 mg/kg bw per day.

In studies of developmental toxicity in mice, rats and rabbits, the maternal effects included inhibition of erythrocyte and/or brain acetylcholinesterase activity and cholinergic signs (lowest NOAEL 1 mg/kg bw per day in rats and mice) and reductions in body weight and food consumption (lowest NOAEL 2.5 mg/kg bw per day in rats). The observed fetal toxicity (lowest NOAEL 2.5 mg/kg bw per day in rats) and developmental toxicity (NOAEL 1 mg/kg bw per day in rats) findings were consistent with treatment-related maternal toxicity; there was no evidence of treatment-related malformations in any of the studies. There was no effect on cognitive function (learning, memory and habituation) in pups exposed to chlorpyrifos *in utero* and for a period *post partum* at doses up to and including the highest dose of 5 mg/kg bw per day, while inhibition of cholinesterase activity, decreased brain weight, and delayed development were seen at lower doses, consistent with findings in other studies.

In studies of delayed neurotoxicity, chlorpyrifos was given to chickens as either single or repeated doses. Significant inhibition of both cholinesterase and neuropathy target esterase activity was observed and mild delayed neuropathy was seen in a number of studies; aggressive antidotal therapy was always necessary to allow at least some of the treated birds to survive. Despite the marked cholinergic toxicity of chlorpyrifos, there was no evidence that it caused delayed neurotoxicity and there was no increase in the incidence of histopathological lesions in the nerve tissues of birds treated at doses up to 10 mg/kg bw per day for up to 91 days. In a number of studies in rats given single doses of up to 100 mg/kg bw, repeated doses of up to 10 mg/kg bw per day for four weeks, or repeated doses of up to 15 mg/kg bw per day for 13 weeks, there were no treatment-related neurological lesions or effects on cognition and no inhibition of neuropathy target esterase activity, although significant inhibition of erythrocyte, brain and peripheral tissue cholinesterase activity was seen at a number of doses. In a study with single doses that included a functional

observational battery of tests, clinical signs of intoxication were observed only when brain acetylcholinesterase activity was inhibited by more than 60% or when whole-blood cholinesterase activity was inhibited by more than 80%.

When chlorpyrifos was applied as a single dose of up to 5 mg/kg bw to the skin of volunteers for 12 h, erythrocyte cholinesterase activity was not significantly inhibited. Plasma cholinesterase activity was inhibited after 20 12-h dermal exposures to 5 mg/kg bw per day over four weeks or after three daily 12-h exposures to 25 mg/kg bw per day on consecutive days, but erythrocyte cholinesterase activity was not inhibited under any treatment regimen.

A single oral dose of up to 1 mg/kg bw or repeated doses of up to 0.1 mg/kg bw per day for nine days did not significantly inhibit erythrocyte acetylcholinesterase activity in volunteers. No clinical signs were observed in these studies. Inhibition of erythrocyte acetylcholinesterase activity was observed in a single female volunteer (of a group of six males and six females) given a single oral dose of 2 mg/kg bw.

In a case of human poisoning with chlorpyrifos at an estimated dose of 300-400 mg/kg bw, significant inhibition of neuropathy target esterase in lymphocytes and plasma and erythrocyte acetylcholinesterase activity was reported, with severe cholinergic signs which required aggressive, extensive antidotal therapy and artificial ventilation. Mild distal axonopathy consistent with organophosphate-induced delayed polyneuropathy (OPIDN) was reported some weeks after the poisoning incident.

The ADI of 0-0.01 mg/kg bw established by the 1982 Meeting was based on a NOAEL of 0.1 mg/kg bw per day for inhibition of erythrocyte acetylcholinesterase activity in humans. The present Meeting affirmed this ADI on the basis of the NOAEL of 1 mg/kg bw per day for inhibition of brain acetylcholinesterase activity in studies in rats, mice and dogs using a 100-fold safety factor and on the NOAEL of 0.1 mg/kg bw per day for inhibition of erythrocyte acetylcholinesterase activity in the study of human subjects exposed for nine days using a 10-fold safety factor.

The Meeting allocated an acute reference dose of 0.1 mg/kg bw on the basis of the NOAEL of 1 mg/kg bw for inhibition of erythrocyte acetylcholinesterase activity in a study in which volunteers received a single oral dose of chlorpyrifos and with a safety factor of 10.

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

TOXICOLOGICAL EVALUATION

Levels that cause no toxic effect

Mouse: 5 ppm, equal to 0.7 mg/kg bw per day (toxicity in a 79-week study of toxicity and carcinogenicity)
1 mg/kg bw per day (maternal toxicity in a study of developmental toxicity)
10 mg/kg bw/day (fetal toxicity in a study of developmental toxicity)

Rat: 1 mg/kg bw per day (toxicity in two-year studies of toxicity and carcinogenicity)
1 mg/kg bw per day (developmental and parental toxicity in a two-generation study of reproductive toxicity)
1 mg/kg bw per day (maternal and developmental toxicity in a study of developmental toxicity)
2.5 mg/kg bw per day (fetal toxicity in a study of developmental toxicity)

Rabbit: 81 mg/kg bw per day (maternal and fetal toxicity in a study of developmental toxicity)

Dog: 1 mg/kg bw per day (toxicity in a two-year study of toxicity)

Human: 0.1 mg/kg bw per day (no inhibition of erythrocyte cholinesterase activity at highest dose tested in men dosed orally for 9 days)
1 mg/kg bw (inhibition of erythrocyte cholinesterase activity in adult volunteers after single oral dose)

Estimate of acceptable daily intake for humans

0-0.01 mg/kg bw

Estimate of acute reference dose

0.1 mg/kg bw

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

Further observations in humans

List of relevant endpoints for setting guidance values for dietary and non-dietary exposure

Absorption, distribution, excretion and metabolism in mammals	
Rate and extent of oral absorption	Up to 90% in rats within 72 h About 70% in humans in 96 h
Dermal absorption	Less than 2% in humans in 180 h Not determined in animals
Distribution	Initially widely distributed; highest residues in liver, kidneys and fat at 72 h in rats
Potential for accumulation	Elimination half-lives of <24 h and low tissue residues after 72 h in rats. No evidence of potential for accumulation
Rate and extent of excretion	>95% within 72 h in rats, mainly in urine (68-93%) and faeces (6-15%)
Metabolism in animals	Rapidly metabolized by mixed-function oxidases to chlorpyrifos oxon via oxidative desulfuration and an electrophilic phosphooxathiiran intermediate. Degradation by conversion directly to 3,5,6-trichloro-2-pyridyl phosphate and diethyl thiophosphate. The oxon is hydrolysed to diethyl phosphate and 3,5,6-

	trichloropyridinol, while a minor reaction pathway is by hydrolysis to monoethyl 3,5,6-trichloro-2-pyridinol phosphorothioate.
Toxicologically significant compounds (animals, plants and environment)	Parent compound and oxon.
Acute toxicity	
Rat LD_{50} oral	96 mg/kg bw
Rat LD_{50} dermal	>2000 mg/kg bw
Rat LC_{50} inhalation	>36 mg/m^3 (4 h, vapour, nose only exposure) 560 mg/m3 (4 h, nebulized particles <5 μm, whole-body exposure)
Skin irritation	Slightly irritating in rabbits
Eye irritation	Slightly irritating in rabbits
Skin sensitization	Not a sensitizer in guinea pigs
Short-term toxicity	
Target/critical effect	Inhibition of brain cholinesterase activity
Lowest critical oral NOAEL	1 mg/kg bw per day, dog, 2 years 1 mg/kg bw per day, rat, 13 weeks
Lowest relevant dermal NOAEL	5 mg/kg bw per day, rat; 21 days
Lowest relevant inhalation NOAEL	20.6 ppb (296 μg/m^3), rat; 13 weeks
Genotoxicity	
	Not genotoxic
Long term toxicity and carcinogenicity	
Target/critical effect	Inhibition of brain cholinesterase activity
Lowest relevant NOAEL	year, rat; 1 mg/kg bw per day 78-week mouse; 0.7 mg/kg bw per day
Carcinogenicity	Not carcinogenic in rats and mice
Reproductive toxicity	
Reproduction target/critical effect	Neonatal toxicity (reduced pup body weight and survival)
Lowest relevant reproductive NOAEL	2- generation, rat; 1 mg/kg bw per day
Developmental target/critical effect	Fetal and perinatal toxicity at maternally toxic doses (including an increase in delayed ossification, reduced crown-rump length, reduced pup weight, increase in postimplantation loss, delayed sexual maturity)
Lowest relevant developmental NOAEL	Developmental studies in rats; 1 mg/kg bw per day

Neurotoxicity/Delayed neurotoxicity	Reversible neurotoxicity consistent with cholinesterase inhibition. No evidence of delayed neurotoxicity or evidence of histopathological changes in nerves of hens (10 mg/kg bw per day) and rats (15 mg/kg bw per day) for up to 13 weeks. At high acute doses (up to 150 mg/kg bw), significant NTE inhibition and mild delayed neuropathy in hens, but at this dose, extensive and aggressive antidote treatment required for birds' survival.
Other toxicological studies	No effect on cognitive function in rat pups in a developmental study at doses up to 5 mg/kg bw per day
Medical data	No inhibition of erythrocyte acetylcholinesterase activity in volunteers after repeated oral doses of up to 0.1 mg/kg bw per day (for 9 days), single oral doses of up to 1 mg/kg bw, or single dermal doses of 5 mg/kg bw. Poisoning case presented with severe cholinergic effects, with evidence of delayed polyneuropathy and/or distal axonopathy at a dose that required antidotal treatment and artificial ventilation.

Summary	Value	Study	Safety factor
ADI	0-0.01 mg/kg bw	Rat, 2-year dietary Rat, reproduction Mouse, developmental Dog, 2-year dietary Human, 9-day oral	100 10
Acute reference dose	0.1 mg/kg bw	Human, single dose	10

DIETARY RISK ASSESSMENT

Estimated Theoretical Maximum Daily Intakes for the five GEMS/Food regional diets, based on existing MRLs, were in the range of 6-30% of the ADI. The Meeting concluded that the intake of residues of chlorpyrifos resulting from its uses that have been considered by the JMPR is unlikely to present a public health concern.

4. 8 CLETHODIM (187)

TOXICOLOGY

On the basis of a review of the toxicological monograph on clethodim prepared in 1994, the Joint Meeting concluded that the establishment of an acute reference dose is unnecessary because clethodim is of low acute toxicity following single doses and the NOAELs for other potentially relevant endpoints (e.g. developmental toxicity) were at least two orders of magnitude higher than those used for establishing the ADI. No specific acute effects were identified.

RESIDUE AND ANALYTICAL ASPECTS

Clethodim was evaluated by the JMPR in 1994 and 1997. In the first evaluation MRLs were recommended for several crops and animal feed commodities. At the 1996 CCPR (28th Session), several matters were referred to the JMPR for further consideration. These included the characterization and quantification of metabolites in plant metabolism studies and a lactating goat study, methods of analysis for clethodim and sethoxydim, and the lowest reported limit of determination in animal commodities.

In the 1997 evaluation some of the above issues were discussed, including a compound-specific method which allowed residues arising from the use of clethodim to be distinguished from those from sethoxydim. Additional studies on alfalfa, artichokes, cabbage, field peas, lupins, carrots, cauliflower, clover, celery, flax, garlic, cucumbers, leeks, lentils, lettuce, onions, peaches, peppers, spinach, summer squash (zucchini) and tomatoes were reviewed. MRLs for beans, sunflower seed and sunflower seed oil (crude and edible) were recommended for withdrawal.

At the 1999 CCPR, comments were made in relation to the MRLs recommended for cattle meat and cattle offal and the corresponding limits of determination for the two commodities. Moreover, it was noted that no justification was provided for the animal commodity MRLs on the basis of the levels of clethodim found in treated feed items. It was suggested that the JMPR should provide an estimate of the exposure of livestock through the feeding of treated commodities.

For the present evaluation, new trials on cucumbers, dry beans, peppers and sunflowers were reported, together with processing data for canola (rape seed), cotton seed, peanuts, soya beans, sugar beet, sunflowers and tomatoes. Data from previously reviewed Canadian trials on potatoes were also submitted with new data to allow a review of the MRL for potato. Data on photodegradation, adsorption and fate in water/sediment systems were also submitted for evaluation. In order to respond to some of the issues raised by the CCPR, some metabolism and feeding studies reviewed in 1994 and 1997 were re-examined.

The predominant metabolites formed by the biochemical transformation of clethodim in hens and goats are clethodim sulfoxide, clethodim sulfone and *S*-methyl-clethodim sulfoxide. In plants, the main metabolites are clethodim sulfoxide and imine sulfoxide. In the metabolism studies, a comparison between the method used to determine the total radioactivity and a non-specific enforcement method in goat liver and kidney, hen muscle and soya beans was reported. The comparison shows that total residues determined by the routine methods of enforcement are very similar to the total radioactive residues found in the tissues

and soya beans, and confirms that the residue definition for routine enforcement is appropriate. The routine method is not compound-specific however, and does not differentiate between residues originating from the use of clethodim and those arising from the use of sethoxydim.

The rates of degradation of clethodim, clethodim sulfoxide and clethodim sulfone were investigated in sterile and non-sterile soils. The calculated half-lives for the degradation of all the compounds were higher in sterile than in non-sterile soils, indicating that degradation is a function of microbial activity as well as temperature.

The adsorption and desorption of clethodim, clethodim sulfoxide and clethodim sulfone in five different soils were investigated. The results showed that all three compounds are weakly adsorbed to the soils tested, with K_d values ranging from <0.2 to 1.6.

Clethodim is degraded rapidly by photolysis in water in the presence of a photosensitiser such as acetone. Calculated half-lives were 0.94, 1.22 and 0.52 days, respectively, in solutions at pH 5, 7 and 9 which were exposed to natural sunlight for up to 30 days. Photolytic mechanisms of transformation include oxidation at the thioethyl function, elimination of the chloroallyl side chain to form clethodim imine and clethodim oxazole, and further oxidation to the oxazole sulfoxide and the sulfide and sulfoxide of dimethyl 3-[2-(ethylsulfonyl)propyl]pentanedioate (DME).

The hydrolysis of clethodim was investigated in sterile water at pH 5, 7 and 9 in the dark. HPLC analysis of the solutions at intervals up to 32 days showed that at pH 5 and 7, clethodim was an equilibrium mixture of two oxime forms, *anti* and *syn* conformations caused by H-bond formation between the oxyimino oxygen and the hydroxyl group on the hydroxy-cyclohexenone ring. Interconverison was fastest at pH 5. The resulting degradation products included an oxazole and a hydroxyvinyl compound.

In response to questions raised by the CCPR regarding a compound-specific method of analysis, new validation experiments were reported with milk, eggs and hen liver. A limit of 0.02 mg/kg was reported for clethodim, clethodim sulfoxide and *S*-methyl-clethodim sulfoxide in milk. In the goat metabolism study, the radioactivity in milk was predominantly due to clethodim sulfoxide, *S*-methyl-clethodim sulfoxide and lactose derivatives at levels of 20%, 5.5% and 30-50% respectively, so the method has been validated and recoveries determined with the appropriate metabolites. The limit of determination of total residues in milk was <0.04 mg/kg.

In tissues, the limit of determination was reported as 0.2 mg/kg with recoveries of clethodim sulfoxide at that level reported for hen tissues, beef liver and beef muscle. Results from the hen and goat metabolism studies showed that clethodim sulfoxide and *S*-methyl sulfoxide were the predominant sources of the radioactivity in tissues. The compound-specific method has therefore been validated for one of the main metabolites, with acceptable recoveries reported in hen and cattle tissues. The limit of determination for total residues by the non-specific common moiety method would be 0.04 mg/kg in tissues or thereabouts. This is comparable to the limit of determination found in the cow and hen feeding studies, where the common moiety method was employed.

In eggs, the compound-specific method was validated at 0.05 mg/kg and recoveries were determined at this level with clethodim sulfoxide. In the hen metabolism

study, clethodim sulfoxide was the main source of the radioactivity in egg white and egg yolk during the 5-day dosing period. The method is therefore capable of quantifying clethodim residues in eggs down to a limit of 0.05 mg/kg.

Specialised methods were reported for soil and water where total clethodim residues included clethodim sulfoxide, clethodim sulfone, and the oxazole sulfoxide and oxazole sulfone. These compounds were characterized in studies of degradation in soil and water.

Studies of the storage stability of clethodim residues in alfalfa (forage and hay), celery, clover, cotton seed, beans (seeds, vines and hay), onions, peanuts and their processed commodities, sugar beet (tops and roots), sunflower seeds, tomatoes and their processed commodities, chicken tissues and eggs, and bovine tissues and milk were reported. In all the studies, clethodim residues were adequately stable during the period of storage. Discernible losses (≤20%) occurred in peanut soapstock at 429 days and in tomato paste and juice after 153-162 days. Freshly fortified samples were analysed concurrently with the stored samples. The Meeting agreed that <20% decrease in stored samples did not constitute degradation.

Residue data were submitted for cucumbers, dry beans, peppers (sweet and chilli), potatoes and sunflowers. Registered use patterns were reported only for these crops; further information on GAP is reported in the 1994 and 1997 monographs.

Data on residues in potatoes were submitted in response to questions raised at the 1999 CCPR on the registered use pattern in Canada and the establishment of an import tolerance in the USA. In the 1994 evaluation, data from France, Italy and the Ukraine were reviewed and an MRL of 0.2 mg/kg was recommended. The new data from Canada show that residues above 0.2 mg/kg were found in potatoes treated in accordance with Canadian GAP (single application at 0.09 kg ai/ha and a PHI of 60 days). The residues in the tubers were <0.1-0.46 mg/kg at PHIs of 45 or 46 days and <0.1-0.34 mg/kg at PHIs of 59 or 60 days. The residues in rank order were <0.1 (15), 0.137, 0.141, 0.19, 0.232, 0.326, 0.339, 0.348 and 0.463 mg/kg. The Meeting estimated a maximum residue level of 0.5 mg/kg. An STMR could not be estimated as the previously reviewed data from France, Italy and the Ukraine were not re-submitted.

Data on cucumbers were reported from trials in the USA and a trial in Poland. The trials in the USA are indicated as being in accordance with GAP, but the use pattern is not yet registered with the USEPA. The Meeting did not estimate a maximum residue level or an STMR as the registration was only pending.

Residue data on dry beans were generated in Brazil and the USA. In the 1994 evaluation data from Brazil only were the basis of the recommended MRL of 0.1 mg/kg. In 1997 an STMR of 0.05 mg/kg was estimated. The manufacturer resubmitted data previously reviewed in 1994 and 1997. The registered use pattern in Brazil allows application of clethodim at rates of 0.084-0.11 kg ai/ha with a PHI of 40 days. The registered use pattern in the USA allows 1 or 2 applications at rates equivalent to 0.11-0.28 kg ai/ha and a PHI of 30 days. The new data from the USA include residues in the whole seeds, hay and dry vines. The residues in the dry beans in rank order were <0.1, <0.5, 0.64, 0.79, 0.81, 0.98, 1.1, 1.41 and 1.6 mg/kg. On the basis of the combined Brazilian and US data, the Meeting recommended an MRL of 2 mg/kg and estimated an STMR of 0.81 mg/kg for dry beans. The 1997 Meeting recommended the withdrawal of the draft MRL of 0.1 mg/kg.

The residues in bean hay in rank order were <0.1, 1.3, 1.4, 1.5, 1.8, 2.0, 2.3, 3.3 and 5.5 mg/kg. The Meeting recommended an MRL of 10 mg/kg for bean fodder (hay) and estimated an STMR of 1.8 mg/kg for animal feed purposes. The residues were not corrected for dry matter content (88%).

The residues in dry bean vines in rank order were <0.1, 0.23, 1.2, 1.5 (2), 1.8 (2), 2.2 and 2.8 mg/kg. The Meeting recommended an MRL of 5 mg/kg for bean forage and estimated an STMR of 1.5 mg/kg for animal feed purposes. As the residues in vines were expressed on a dry weight basis, a correction for dry matter content is not required for the calculation of the dietary burden for livestock.

Supervised residues trials on peppers were conducted in Italy and the USA. No registered use pattern or label was provided from Italy so the data could not be compared to relevant GAP. In the USA the registration of clethodim for use on peppers is pending. The proposed GAP is given as 1 or 2 applications at rates of 0.14-0.28 kg ai/ha with a PHI of 20 days. The residues in bell peppers (capsicums) and chilli peppers in trials which corresponded with the proposed GAP were 0.11-0.89 mg/kg. As the registration for peppers is pending, the Meeting did not estimate a maximum residue level or STMR.

Trials on sunflowers were carried out in Argentina, Canada, France, Italy and the USA. The Argentinian data were reviewed in 1994 and an MRL of 0.2 mg/kg was recommended. In the following review in 1997, the recommendation was withdrawn as there were too few results from trials according to GAP. The registered use pattern in Argentina allows single applications at rates of 0.16-0.24 kg ai/ha and a PHI of 100 days. GAP in Canada allows 1 or 2 applications at rates of 0.045-0.09 kg ai/ha with a PHI of 72 days and in France rates of 0.18-0.48 kg ai/ha with a PHI of 100 days. As a label from Italy was not provided, the Italian data were evaluated against French GAP. In the USA there is a pending use pattern of 0.11-0.28 kg ai/ha and a PHI of 70 days; the number of applications is not specified. As the registration is pending the US data were not used in the estimation of the STMR or maximum residue level. The residues in sunflower seed in rank order were <0.03 (3), <0.04 (5), <0.05, 0.051, <0.06 (3), 0.065, <0.07 (2), <0.08, 0.085, 0.12, 0.13 (2), 0.14, 0.15, 0.16, 0.20 and 0.33 mg/kg. The Meeting recommended an MRL of 0.5 mg/kg and estimated an STMR of 0.06 mg/kg. The draft MRL of 0.2 mg/kg was recommended for withdrawal by the 1997 JMPR.

A processing factor of 0.2 for crude sunflower seed oil was derived from a processing study on sunflowers. This processing factor may be applied to the recommended MRL to estimate a maximum residue level for crude sunflower seed oil. The STMR is calculated as 0.012 mg/kg for intake estimation. In the 1997 evaluation the draft MRLs for crude and edible sunflower seed oil were recommended for withdrawal owing to insufficient data. The Meeting recommended an MRL of 0.1* mg/kg for crude sunflower seed oil.

Feeding studies with laying hens and dairy cattle were reviewed in 1994 and 1997. The studies are repeated here for completeness. Doses in both studies were composed of a mixture of clethodim and clethodim sulfoxide (5:95), to simulate the exposure that may occur from feeding treated crops and processed commodities. At the 1999 CCPR, the JMPR was requested to justify the recommended MRLs for animal commodities by estimating the dietary exposure to livestock from feeding treated crops. Tables listing various treated feed commodity items and the residues likely to be found in them were constructed for a hen and dairy cow diet, and estimates of the composition of the diets were based on figures given in

the FAO Manual and listed in USEPA guideline OPPTS 860.1000. Estimates of the likely dietary exposure of dairy cattle and hens were 2.9 and 7 ppm in the diet respectively, or 43.4 and 1.05 mg/animal/day.

The lowest feeding levels in both studies were 10 ppm in the diet. Continuous feeding at 10 ppm in the diet of dairy cattle led to total clethodim residues of <0.15 mg/kg in muscle and fat. The residues in liver and kidney were <0.16 and <0.151 mg/kg respectively. In milk the total residues were <0.0375 mg/kg over the 28-day period of the feeding study. As the highest exposure of dairy cattle is estimated as one third of the lowest level in the feeding study, it is expected that residues above the limit of determination would not be found in milk or cattle tissues. The method of analysis for the determination of clethodim and metabolites in milk and bovine tissues is a common moiety or non-specific method, and the limits of determination in tissues and milk would be 0.2* and 0.05* mg/kg respectively. In the compound-specific method, the limit of determination was reported as 0.04 mg/kg in milk and 0.2 mg/kg in tissues. Therefore on the basis of the limits of determination in both specific and non-specific methods, MRLs of 0.05* mg/kg can be recommended for milk and 0.2* mg/kg for cattle tissues and offal; STMRs of 0 were estimated for both tissues and milk. Withdrawal of dosing at the 10 ppm level for 2-3 days led to residues below the limit of determination in all tissues.

Similarly in hens, the lowest residue level in the feed was 10 ppm. Continuous feeding at that level for 28 days resulted in residues below the limit of determination in all tissues and eggs. In the compound-specific method, the limit determination in eggs was reported as 0.05 mg/kg and in tissues as 0.2 mg/kg. However in the non-specific common moiety method used in the feeding study, the limits of determination were 0.15 mg/kg in both eggs and tissues. On the basis of the specific method, MRLs of 0.05* mg/kg are recommended for eggs and 0.2* mg/kg for poultry meat and offal. STMRs of 0 were estimated for eggs, poultry meat and poultry offal.

Processing studies on canola (rape seed), cotton, peanuts, soya beans, sugar beet, sunflowers and tomatoes were reported. Calculated processing factors were 0.22 and 0.1 for crude and edible cotton seed oil respectively, 0.4 and 0.09 for crude and refined peanut oil 0.32, for crude rape seed oil, and 0.09 and 0.002 for crude and refined soya bean oil respectively. STMRs for cotton seed, rape seed and soya beans had not previously been estimated, so STMRs for the processed products could not be calculated.

An STMR of 0.35 mg/kg was estimated for tomatoes in the 1997 review of clethodim. STMRs of 0.27, 1.2 and 0.77 were calculated for tomato juice, paste and purée respectively from the corresponding processing factors.

An STMR of 1.3 was estimated for peanuts in 1997. STMRs of 0.52 and 0.12 respectively were calculated for crude and edible peanut oil.

FURTHER WORK OR INFORMATION

Desirable

Data on residues occurring in commerce and/or at consumption (from 1994 and 1997 Meetings).

DIETARY RISK ASSESSMENT

Chronic intake

In the current evaluation, STMRs for 16 commodities have been estimated. Where consumption data were available these STMRs were used in the estimates of dietary intake together with existing STMRs and a revised estimated maximum residue level for potato.

Estimated Dietary Intakes for the five GEMS/Food regional diets, based on new and existing STMRs and a proposed MRL, were in the range of 3-30% of the ADI (Annex III). The Meeting concluded that the intake of residues of clethodim resulting from its uses that have been considered by the JMPR is unlikely to present a public health concern.

Acute intake

The Meeting concluded that an acute RfD for clethodim is unnecessary. This conclusion was based on a determination that the pesticide is unlikely to present an acute toxicological hazard, and residues are therefore unlikely to present an acute risk to consumers.

4.9 DIAZINON (022)

RESIDUE AND ANALYTICAL ASPECTS

Diazinon was evaluated by the 1993 JMPR as a periodic review for plant protection uses. The 1993 Meeting recommended an increase in the CXL for pome fruits and cabbages from 0.5 to 2 mg/kg and the withdrawal of the CXLs for animal commodities in the absence of animal processing studies and data from uses to control ectoparasites.

The 1996 Meeting considered new feeding studies with poultry and cattle, and new and previously reported data from supervised trials of ectoparasite control in cattle and sheep. That Meeting was able to estimate a number of maximum residue levels but considered additional information on GAP and modern trials at maximum GAP rates to be highly desirable.

The Meeting received reports of new residue trials on sheep (dipping) and pigs (spraying). Additional results for pome fruit and cabbage were also available.

The analytical methods that determine the parent compound as well as the metabolites diazoxon and hydroxydiazinon rely on acetone/water extraction and liquid-liquid partition, followed in extracts of animal products by clean-up on various cartridges, with determination by GLC with an FPD or NPD. The LODs of the three compounds were 0.005 mg/kg in pig blood, muscle, liver and kidney and 0.01 mg/kg in cabbage, apples, pears, pig skin and fat, and sheep tissues.

The 1993 JMPR noted that residues of diazinon *per se* are generally stable in crop samples (except strawberries) and processed commodities for a minimum of 26 months under freezer conditions (-27° to -12°C). Hydroxydiazinon was stable in crops except strawberries and apples. Residues of diazoxon however were unstable in all substrates tested except maize oil.

Residues of diazinon and hydroxydiazinon are stable in animal tissues and milk under deep frozen conditions (≤-18°C) for at least 9 months, but diazoxon is only stable in fat, of limited stability in milk and highly unstable in liver and muscle

Definition of the residue

The residue was defined by the 1993 JMPR as diazinon *per se*. The current Meeting discussed the relevance of metabolites to the dietary intake. Metabolism in plants progresses, as in animals, primarily by hydrolysis of the ester linkage, yielding 4-hydroxy-2-isopropyl-6-methylpyrimidine, followed by oxidation of the isopropyl group to primary and tertiary alcohols and/or oxidation of the methyl group to the alcohol. Diazoxon and hydroxydiazinon were not reported as significant plant metabolites by the 1993 JMPR but could play an intermediary role in the degradation of diazinon and so could be of concern for the assessment of acute dietary risk.

In all, 120 samples of pome fruit and 225 samples of cabbage were analysed with freezer storage of pome fruit for 4-7 months and cabbage for 4-12 months. Diazoxon was found in 8 samples of pome fruit (5.7%) and in 2 of cabbage (0.89%) with a maximum value of 0.02 mg/kg in both commodities. Hydroxydiazinon could not be determined in any sample. The disappearance of the metabolites under freezer conditions indicates that they will also be unstable under field conditions. Furthermore, the Meeting was informed that 19 trials with snap beans, apples, plums and carrots had been conducted to investigate the occurrence of diazoxon and hydroxydiazinon at harvest, without storage of the samples before analysis. The first results showed residues of the metabolites well below 10% of the parent. The Meeting therefore concluded that diazoxon and hydroxydiazinon would not be of concern for consumer exposure and that the residue in plants for dietary intake estimations should be defined as diazinon.

In animal products, residues of diazoxon and hydroxydiazinon were below the LODs in muscle, kidney, liver and blood samples at all periods after dosing. In the 32 sheep fat samples analysed no diazoxon could be determined, but hydroxydiazinon was found in 12 samples (37.5%) at two weeks after treatment (max. 0.02 mg/kg). At the slaughtering interval according to GAP of four weeks, no residues of either metabolite were found. The absence of diazoxon in samples of animal tissues (except fat) stored deep frozen could be due to its absence at slaughter or to its rapid degradation. However, no diazoxon residues were found in sheep fat (where it is stable), whereas diazinon and hydroxydiazinon were detected. Although the determination of diazoxon is limited by its instability in certain tissues, it can be assumed that it occurs at much lower levels than diazinon, and any remaining small amounts of diazoxon at the time of slaughter can reasonably be expected to be rapidly hydrolysed. The Meeting concluded that there is no need to include diazoxon or hydroxydiazinon in the residue definition for the assessment of dietary risk of animal products.

Definition of the residue for compliance with MRLs and for the estimation of dietary intake: diazinon.

The residue is fat-soluble.

The Meeting received data from supervised trials on apples, pears and head cabbages. New dipping and spraying studies were carried out on sheep and pigs.

Pome fruit. The 2 mg/kg MRL proposed by the 1993 JMPR was based on older US results and former US GAP (2–8 x 0.06 kg ai/hl, PHI 14 days). Recently US GAP for diazinon on pome fruit was changed to a maximum of 2.2 kg ai/ha, 0.235 kg ai/hl per application, and a maximum of 6.7 kg ai/ha per season, PHI 21 days. No other information on GAP was reported (obsolete uses reported by the 1993 JMPR were not considered).

Twelve supervised trials on apples and 14 on pears in the USA complied with the new US GAP. Samples were analysed for residues of diazinon, diazoxon and hydroxydiazinon.

The residues in apples and pears from trials according to current US GAP in rank order (median underlined) were <0.01 (7), 0.01, 0.02 (2), 0.04 (6), 0.06 (2), 0.08 (2), 0.10, 0.11 (2), 0,12, 0.13 and 0.24 mg/kg.

Hydroxydiazinon was not found in any of the samples. Diazoxon was detected in pears from two trials according to GAP at 0.01 and 0.02 mg/kg.

On the basis of the combined apple and pear data, the Meeting estimated an STMR of 0.04 mg/kg and a maximum residue level of 0.3 mg/kg for pome fruit to replace the existing CXL (2 mg/kg).

Diazinon residues were below the LOD of 0.01 mg/kg in washed, peeled and sliced apples. Processing factors of 1.43, <0.01, <0.01 and <0.01 for wet apple pomace, juice, canned slices and apple sauce respectively, were derived from a processing study reported by the 1993 JMPR. From the STMR of 0.04 mg/kg, the Meeting estimated STMRs of 0.0572 mg/kg for wet apple pomace, and 0.0004 mg/kg for apple juice, sauce and canned slices.

Head cabbages. The 2 mg/kg MRL for cabbages proposed by the 1993 JMPR was based on US data and former US GAP (4.4 kg ai/ha followed by >1 x 0.56 kg ai/ha, PHI 5–7 days). The US GAP was recently changed to an increased PHI of 21 days.

Eleven supervised trials on cabbages according to current US label use directions were reported. These directions allow for a single pre-plant treatment of 4.4 kg ai/ha followed by five post-emergence foliar applications of 0.55 kg ai/ha at 7-day intervals using ground equipment.

The samples analysed were described in the report as follows: “Untrimmed and trimmed cabbage heads were obtained from separate plants, ... in order to avoid contamination. Trimmed cabbage heads were obtained by removing the wrapper leaves consisting of the obviously decomposed outer leaves.” The Meeting noted that the term “trimmed heads” should be in accordance to the Codex definition for the commodity, but concluded that maximum residue levels should not be based on cabbages with outer leaves removed as there is so much uncertainty as to how many leaves would be removed in practice.

The diazinon residues in rank order were <0.01, <0.01, 0.01, 0.01, 0.05, 0.08, 0.24 and 0.35 mg/kg for untrimmed heads, <0.01 (11) mg/kg for trimmed heads and 0.04, 0.07, 0.1, 0.1, 0.11, 0.13, 0.86 and 1.0 mg/kg for wrapper leaves.

Diazoxon was detected (0.02 mg/kg) in only one trial, in trimmed heads at a PHI of 21 days. Hydroxydiazinon was not found at or above the LOD.

The Meeting estimated a maximum residue level of 0.5 mg/kg for diazinon in head cabbages, to replace the existing CXL (2 mg/kg). An STMR of 0.01 mg/kg was estimated on the basis of the results for trimmed heads,.

Animal products. An EW formulation of diazinon, which is planned to replace the former EC-type formulations, was used in new trials on sheep dipping and pig spraying, but GAP is only pending. However, bioequivalence studies have shown that the water-based EW formulation used in the new studies is equivalent to the EC formulations used in earlier studies.

Sheep. According to the use pattern reported by the 1996 JMPR, the most important treatment rates recommended are 250 mg ai/l for sheep dipping (uses range from100 to 600 mg ai/l). The new dipping trial was conducted according to New Zealand GAP (200-400 mg ai/l) using a bath concentration of 300 mg/l.

The highest residues of diazinon occurred at the earliest slaughtering interval of two weeks. Fat contained the highest residues (maximum 1.5, median 1.2, mean 1.16 mg/kg). Low residues were found in muscle (maximum 0.06, median 0.05, mean 0.0475 mg/kg) and kidney (maximum 0.03, median 0.02, mean 0.0225 mg/kg). No residues were detected in the liver. The residues in muscle and kidney dissipated quickly, with all samples being below the LOD of 0.01 mg/kg by 8 and 6 weeks respectively. In fat diazinon was more persistent, with low residues up to 0.03 mg/kg present 10 weeks after treatment. The data confirm the findings reported by the 1996 JMPR (evaluation p. 216) for sheep: muscle maximum 0.03, median 0.02; liver maximum 0.01, median <0.01; kidney maximum 0.02, median 0.02; omental fat maximum 1.3, median1.1; subcutaneous fat maximum 1.4, median 1.4 mg/kg.

Residues of diazoxon were not found in any of the sheep tissues tested. Low levels of hydroxydiazinon were found in four of eight animals in subcutaneous fat and in one of eight animals in renal fat from sheep slaughtered 2 weeks after treatment (maximum 0.02 mg/kg). The residues were below the LOD of 0.01 mg/kg by 4 weeks after treatment.

Pigs. Diazinon residues in the muscle of pigs sprayed twice decreased from 0.035 mg/kg one day after the 2nd treatment to 0.007 mg/kg after 21 days. In liver, a maximum of 0.027 mg/kg was found after 3 days which decreased to 0.006 mg/kg at day 21. The highest residues of 0.25 mg/kg in the fat and skin were found on day 1 and decreased to <0.01 mg/kg on day 14. In kidney and blood, residues were below the LOD of 0.005 mg/kg in all samples. Neither diazoxon nor hydroxydiazinon was detected in any samples.

No new studies were reported on cattle or goats.

The new data on dipped sheep and sprayed pigs reported to the Meeting do not differ from the data provided in earlier submissions.

The 1996 JMPR had noted that in practice some animals might be exposed to more than one type of treatment (e.g. spraying and dipping as well as ear tags or wound dressing), but the present Meeting was informed that multiple treatments are unlikely in practice.

The 1996 JMPR requested monitoring data on subcutaneous fat of sheep. The Meeting received the 1998 UK statutory surveillance results for kidney fat (231 samples from cattle, 330 from pigs, 610 from sheep). Only one sample of sheep kidney fat contained residues of diazinon (2.3 mg/kg).

The Meeting agreed to maintain the previous maximum residue level estimates for the liver, kidney and meat of cattle, goats, pigs and sheep of 0.03, 0.03 and 2 mg/kg in the fat respectively. The STMRs estimated on the basis of different uses (dip, ear tag, spray) on goats, pigs, cattle and sheep by the 1996 JMPR were confirmed.

FURTHER WORK OR INFORMATION

Desirable

Studies on fruits and vegetables to investigate the occurrence of diazoxon and hydroxy diazinon at harvest, without storage of samples before analysis.

DIETARY RISK ASSESSMENT

Chronic intake

STMRs have been estimated by the current Meeting for pome fruit and head cabbages as well as by the 1996 JMPR for tomatoes and animal products. Where consumption data were available these STMRs were used in the estimates of dietary intake together with the existing MRLs and draft MRLs for 38 other food commodities.

The dietary intakes for the five GEMS/Food regional diets, based on new and existing STMRs and MRLs, were in the range of 20% to 180% of the ADI. The Meeting concluded that the dietary intake of diazinon residues may exceed the ADI for two GEMS/Food regional diets (Annex III). Further refinements of dietary intake estimates will be undertaken during the next periodic review of residues.

Acute intake

The international estimate of short-term intake (IESTI) for diazinon was calculated for the commodities for which MRLs and STMRs were established and for which consumption data (large portion consumption and unit weight) were available (*see* Section 3). The results are shown in Annex IV. The IESTI varied from 0.004 to 0.008 mg/kg bw in the general population and from 0.016 to 0.028 mg/kg in children. As no acute reference dose has been established the acute risk assessment for diazinon was not finalized.

4.10 DIMETHIPIN (151)

TOXICOLOGY

Dimethipin was first evaluated by the 1985 Joint Meeting, when a temporary ADI of 0-0.003 mg/kg bw was established on the basis of a NOAEL of 100 ppm, equivalent to 2.5 mg/kg bw

per day, in a 90-day study in dogs treated in the diet. Dimethipin was evaluated again by the 1988 Joint Meeting, which reviewed additional data and established an ADI of 0-0.02 mg/kg bw on the basis of a NOAEL for increases in the absolute and relative (to body weight) weights of the liver in female rats fed dimethipin in the diet in a two-year study. Further new data have since been provided. The compound was re-evaluated within the periodic review programme of the Codex Committee on Pesticide Residues (CCPR).

After oral administration to rats, goats and hens, ^{14}C-dimethipin was extensively absorbed (69% within 24 h) and rapidly excreted (89% within 48 h), mainly in the urine. Unchanged dimethipin represented only a small fraction of the residue in animals. In one metabolic pathway, dimethipin undergoes glutathione conjugation and subsequent degradation to several metabolites, including its mercapturic acid. In another pathway, dimethipin is hydrated and then undergoes ring cleavage. Dimethipin also binds covalently to amino acids, peptides and proteins, although the extent to which this binding is catalysed by enzymes is unknown.

Dimethipin (purity, 98.5%) was moderately toxic to rats given single oral doses, with LD_{50} values of 460 mg/kg bw in males and 550 mg/kg bw in females, or after exposure by inhalation, with LC_{50} values of 1.5 mg/l in males and 0.88 mg/l in females. It showed little toxicity in rabbits exposed dermally, with an LD_{50} value greater than 5000 mg/kg bw. A recrystallized form of dimethipin was severely irritating to the eye in rabbits. Technical-grade dimethipin was not irritating to rabbit skin but weakly sensitized the skin of guinea-pigs.

WHO has classified dimethipin as “slightly hazardous”.

In 90-day and long-term tests for toxicity, the liver was the main target in rats at doses of 10 mg/kg bw per day and above. The clinical findings consisted of increased absolute and relative weights of the liver and increased serum cholesterol concentration and transaminase activity. At doses greater than 85 mg/kg bw per day, disruption of liver morphology was evident in 90-day studies as hepatocellular hypertrophy, whereas in long-term studies the hepatocellular effects included focal dilatation of bile ducts, biliary cysts and bile-duct hyperplasia.

The testis was identified as another target organ. In a one-year study in dogs given dimethipin, testicular changes were seen at all doses, the lowest dose being 300 ppm (equivalent to 7.5 mg/kg bw per day), but these were considered not to be related to treatment but to be a result of poor nutritional status or incidental findings, as they were similar to testicular lesions seen in other studies in dogs in the same laboratory. Additionally, no testicular lesions were seen in dogs in a 90-day study. In contrast, Sprague-Dawley rats fed diets containing technical-grade dimethipin for two years showed increased incidences and severity of seminiferous tubular degeneration at the two highest doses, 1750 and 3500 ppm (equal to 78 and 160 mg/kg bw per day), associated at the high dose with hypospermia in the epididymides. The NOAEL for testicular degeneration was 40 ppm (2 mg/kg bw per day).

In a 90-day study in dogs given dimethipin in the diet, the lowest dose of 100 ppm (equivalent to 2.5 mg/kg bw per day) was the NOAEL, on the basis of oesophageal lesions at the LOAEL of 300 ppm (equivalent to 7.5 mg/kg bw per day).

In the one-year study in dogs described above, the effects seen at 1000 and 3000 ppm (equal to 25 and 75 mg/kg bw per day) included ‘thinness’ and increased relative kidney

weights in animals of each sex. At this dose, males had decreased blood urea nitrogen and creatinine concentrations and females had increased relative liver weights. One male and three females at the highest dose died and animals of each sex had decreased body weights and food consumption, hypocellularity of the bone marrow, gastritis, oedema, ulceration of the gastrointestinal tract, thymic atrophy, nephritis, centrilobular degeneration of the liver, splenic hyperplasia and lymphadenitis. The NOAEL was 300 ppm (equal to 7.5 mg/kg bw per day) on the basis of increased relative liver weights, increased alanine aminotransferase and alkaline phosphatase activities, and hepatocellular degeneration in females at 1000 ppm (equal to 25 mg/kg bw per day).

In a 78-week study of carcinogenicity in mice, a statistically significant increase in the incidence of alveloar and bronchiolar carcinomas was seen in males at the highest dose (2000 ppm, equal to 300 mg/kg bw per day). The combined incidence of lung adenocarcinoma and adenoma was significantly greater than the mean for controls in five previous studies but not when compared with that for concurrent controls or with the mean maximum incidence in controls in previous studies. As lung adenomas and adenocarcinomas occur commonly in this strain of mice, this finding was not considered to be of toxicological relevance. The NOAEL for systemic toxicity was 800 ppm (equal to 12 mg/kg bw per day) on the basis of increased haematocrit at the LOAEL of 400 ppm (equal to 60 mg/kg bw per day).

In two two-year studies in rats, the NOAEL for systemic toxicity was 40 ppm (equal to 2 mg/kg bw per day) on the basis of decreased body weights, increased absolute and relative weights of the liver, an increased incidence of biliary hyperplasia, and testicular degeneration at higher doses. No increase in tumour incidence was observed in rats at any dose. The Meeting concluded that dimethipin is not carcinogenic in mice or rats and is unlikely to pose a carcinogenic risk to humans.

Dimethipin has been tested in an adequate range of tests for genotoxicity *in vitro* and *in vivo*. Negative results were obtained in most assays. It induced a weak mutagenic response in one test for forward mutation in mouse lymphoma cells in the presence of metabolic activation. The Meeting concluded that dimethipin is unlikely to be genotoxic.

In a two-generation study of reproductive toxicity in rats, the highest dose of 800 ppm (equivalent to 40 mg/kg bw per day) caused decreased body weights and food consumption in parental animals of each sex and decreased body weights in pups on days 7, 14 and 21 of lactation. The NOAEL for both systemic toxicity in the parental generation and developmental toxicity in the pups was 200 ppm (equivalent to 10 mg/kg bw per day).

In a study of developmental toxicity in rats, excess mortality occurred at doses of 400 and 800 mg/kg bw per day. The NOAEL for both maternal and developmental toxicity was 160 mg/kg bw per day. In rabbits, the NOAEL for both maternal and developmental toxicity was 20 mg/kg bw per day. Does at the maternal LOAEL of 40 mg/kg bw per day showed body-weight loss on days 6-12 of gestation and decreased weight gain on days 6-28 of gestation. The LOAEL for developmental toxicity was 40 mg/kg bw per day on the basis of an increased incidence of fetuses with skeletal malformations (scoliosis).

The present Meeting confirmed the ADI of 0-0.02 mg/kg bw established by the 1988 Joint Meeting on the basis of the NOAEL of 2 mg/kg bw per day in the two-year study in rats conducted in 1981 and a safety factor of 100. This ADI is supported by the NOAEL of

40 ppm, equivalent to 2 mg/kg bw per day, in the two-year study in rats conducted in 1996. The ADI provides a 1000-fold margin of safety with respect to the NOAEL of 20 mg/kg bw per day for developmental toxicity in rabbits, which showed skeletal malformations at the LOAEL of 40 mg/kg bw per day.

An acute reference dose of 0.02 mg/kg bw was established on the basis of the NOAEL of 20 mg/kg bw per day for skeletal malformations in the study of developmental toxicity in rabbits and a safety factor of 1000. This high safety factor was used because of the nature of the effect.

A toxicological monograph was prepared, summarizing the data received since the previous evaluation and including relevant data from the previous monographs.

TOXICOLOGICAL EVALUATION

Levels that cause no toxic effect:

Mouse: 80 ppm, equivalent to 12 mg/kg bw per day (toxicity in a 78-week study of toxicity and carcinogenicity)

Rat: 40 ppm, equivalent to 2 mg/kg bw per day (toxicity in two two-year studies of toxicity and carcinogenicity)
160 mg/kg bw per day (maternal and developmental toxicity in a study of developmental toxicity)
10 mg/kg bw per day (parental and reproductive toxicity in a two-generation study of reproductive toxicity)

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

Dog: 100 ppm, equivalent to 2.5 mg/kg bw per day (toxicity in a 90-day study of toxicity)

Estimate of acceptable daily intake for humans

0-0.02 mg/kg bw

Estimate of acute reference dose

0.02 mg/kg bw

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

Further observations in humans

List of relevant end-points for setting guidance values for dietary and non-dietary exposure

Absorption, distribution, excretion and metabolism in mammals

Rate and extent of oral absorption:	69% within 24 h, rats

Dermal absorption:	Low dermal penetration, rabbits
Distribution:	Widely distributed, rats
Potential for accumulation:	No evidence of accumulation
Rate and extent of excretion:	89% within 48 h mainly via urine
Metabolism in animals:	Parent <5%; metabolites consist of glutathione conjugates and degradates, rats
Toxicologically significant compounds(animals, plants and environment)	Parent compound
Acute toxicity	Oral toxicity is moderate, but only slightly toxic by dermal and inhalation routes of exposure
Rat LD_{50} oral	440 mg/kg bw (males) and 600 mg/kg bw (females)
Rabbit LD_{50} dermal	>5000 mg/kg bw
Rat LC_{50} inhalation	0.88 mg/l, 4 h (female) and 1.5 mg/l, 4 h (males)
Rabbit Skin irritation	Not irritating
Rabbit Eye irritation	Severely irritating
Guinea Pig Skin sensitization	Weakly sensitizing
Short-term toxicity	
Target/critical effect	Liver: hepatotoxicity, hepatic hypertrophy, rats
Lowest relevant oral NOAEL	2 mg/kg bw per day, rats
Lowest relevant dermal NOAEL	1000 mg/kg bw per day (highest dose tested), rats
Lowest relevant inhalation NOAEL	Not determined
Genotoxicity	Not genotoxic
Long-term toxicity and carcinogenicity	
Target/critical effect	Rat liver: increased weight, liver enzymes, bile-duct hyperplasia; rat testis: degeneration
Lowest relevant NOAEL	2 mg/kg bw per day in two two-year studies, rat
Carcinogenicity	Not carcinogenic in mice and rats
Reproductive toxicity	
Reproduction target/critical effect	None. Decreased pup body weight at days 7, 14 and 21 of lactation at maternally toxic doses, rats
Lowest relevant reproductive NOAEL	10 mg/kg bw per day
Developmental target/critical effect	Increased incidence of skeletal malformations, rabbit
Lowest relevant developmental NOAEL	Rabbit, 20 mg/kg bw per day
Neurotoxicity/Delayed neurotoxicity	No evidence of neurotoxicity

Other toxicological studies	None
Medical data	None
Summary	
ADI	0-0.02 mg/kg bw; based on NOAEL of 2 mg/kg bw per day in two two-year studies in rats and a safety factor of 100
Acute reference dose	0.02 mg/kg bw; based on NOAEL of 20 mg/kg bw per day for skeletal malformations in rabbits and a safety factor of 1000

DIETARY RISK ASSESSMENT

Estimated Theoretical Maximum Daily Intakes for the five GEMS/Food regional diets, based on existing MRLs, were in the range of 0–2% of the ADI (Annex III). The Meeting concluded that the intake of residues of dimethipin resulting from its uses that have been considered by the JMPR is unlikely to present a public health concern.

4.11 DINOCAP (087)

TOXICOLOGY

[*The toxicological section of the 1998 report on dinocap was inadvertently omitted and is now included here. References to the "present" Meeting are to be understood as referring to the 1998 Meeting.*]

Dinocap was evaluated by the JMPR in 1969, 1974 and 1989. An ADI of 0-0.001 mg/kg bw was allocated in 1989 on the basis of a NOAEL of 0.5 mg/kg bw per day in a study of developmental toxicity in rabbits and a safety factor of 500. At the present Meeting recent data on material of greater purity than that tested previously were evaluated. Dinocap consists of 2,4- and 2,6-dinitro-octylphenyl crotonates in which the octyl moiety is either 1-methylheptyl, 1-ethylhexyl, or 1-propylpentyl. A number of the studies that were reviewed were performed with the methylheptyl isomer used as a model for dinocap.

WHO has classified dinocap as "slightly hazardous".

Dinocap is well absorbed after oral exposure. 5-25% is absorbed after dermal exposure, varying with species and concentration. No conclusions were drawn about the degree of dermal absorption in humans from the results of a study in which mouse and human skin were compared; however, human skin is generally regarded as being less permeable to toxicants than that of mice.

The urinary metabolites of the methylheptyl isomer in rats and mice have been extensively characterized; characterization of the faecal metabolites was reported by the 1989

JMPR, which concluded that the pattern of metabolites in faeces seen by thin-layer chromatography was similar to that observed in squash and cucumbers.

The new data confirmed the generally low degree of acute toxicity of dinocap in rats; mice, however, appear to be more sensitive than rats to both acute and developmental effects. Dinocap is a skin irritant and sensitizer. The available studies did not address the uncoupling of oxidative phosphorylation, identified by the 1989 JMPR as a potentially significant mode of action.

In a carcinogenicity study in mice at 0, 15, 100 and 200 ppm no evidence of carcinogenicity was found. The NOAEL was 15 ppm, equal to 2.7 mg/kg bw per day. The lack of carcinogenicity in mice is consistent with the absence of carcinogenicity in rats reported by the 1989 JMPR. A multigeneration study of reproductive toxicity at dietary concentrations of 0, 40, 200 and 1000 ppm in rats showed no specific effect on any reproductive parameters; the NOAEL was 200 ppm equal to 13 mg/kg/day. The results of tests for genotoxicity (on the less pure form of dinocap) were negative.

In a study of developmental toxicity in mice dosed by gavage at 0, 4, 10 and 25 mg/kg bw per day, impaired otolith formation was seen at 25 mg/kg/bw per day. A dose-related increase in open eyelids and cleft palate extended down to 10 mg/kg bw per day in the absence of maternal toxicity. The NOAEL was 4 mg/kg bw per day. Dermal application of 50, 80 and 100 mg/kg bw per day to mice proved excessive for the evaluation of developmental toxicity. A further dermal study in mice at 0, 1, 4, 10 and 25 mg/kg bw per day showed malformations including impaired otolith formation at 25 mg/kg bw per day in the absence of maternal toxicity. The NOAEL for developmental toxicity following dermal application to mice was 10 mg/kg bw per day. The results of these recent studies of developmental toxicity confirmed the teratogenic potential of purified dinocap in mice, even when applied dermally. Impaired otolith development, characteristic of dinocap teratogenicity in mice, was also seen in hamsters at doses that cause maternal toxicity. Less specific malformations were seen in rabbits at maternally toxic doses. The present Meeting concluded that the NOAEL in the studies in rabbits described by the 1989 JMPR was 3 mg/kg bw per day rather than 0.5 mg/kg bw per day, since the findings on which the putative effect level was established do not appear to be repeatable or clearly dose-related. The methylheptyl isomer has been shown not to be teratogenic to mice. The reason for the species difference in the teratogenicity of dinocap in rats and mice therefore cannot be deduced from the data on the metabolism of the methylheptyl isomer.

The 2-year study in dogs that was evaluated at the 1989 Joint Meeting was also reassessed on the basis that the critical effect (retinal atrophy) was secondary to effects on the tapetum lucidum. Since the tapetum lucidum is not present in humans, or in rats and mice in which no retinal effect was seen, the Meeting concluded that it would be inappropriate to base the evaluation on this effect. The NOAEL was 60 ppm, equivalent to 1.5 mg/kg bw per day.

Teratogenic effects in mice were considered to be the toxicological end-point of greatest concern. Since dinocap was shown to be teratogenic in mice after either oral or dermal administration and since malformations were seen in at least three species, the Meeting considered a high safety factor to be appropriate. An ADI of 0-0.008 mg/kg bw was established on the basis of the NOAEL of 4 mg/kg bw per day in the developmental toxicity study in mice and a safety factor of 500.

Establishment of an acute RfD was considered to be appropriate since teratogenicity may occur after a single exposure. An acute RfD was established on the basis of the NOAEL of 4 mg/kg bw per day for teratogenicity in mice and a safety factor of 500, to give an acute RfD of 0-0.008 mg/kg bw, which is appropriate for women of child-bearing age.

An addendum to the toxicological monograph was prepared.

TOXICOLOGICAL EVALUATION

Levels that cause no toxic effect

Mouse: 15 ppm, equal to 2.7 mg/kg bw per day (toxicity in a study of carcinogenicity)
4 mg/kg bw per day (developmental toxicity)
10 mg/kg bw per day (maternal toxicity in a study of developmental toxicity)

Rat: 200 ppm, equal to 6.4 mg/kg bw per day (toxicity in a study of carcinogenicity)
50 mg/kg bw per day (maternal and developmental toxicity in a study of developmental toxicity)

Rabbit: 3 mg/kg bw per day (maternal toxicity in a study of developmental toxicity)

Dog: 60 ppm, equivalent to 1.5 mg/kg bw per day (study of toxicity)

Estimate of acceptable daily intake for humans

0-0.008 mg/kg bw

Estimate of acute reference dose

0.008 mg/kg bw

Information that would be useful for the continued evaluation of the compound

Further observations in humans

List of end points for setting guidance values for dietary & non-dietary exposure

Absorption, distribution, excretion and metabolism in mammals

Rate and extent of oral absorption:	60-69% absorbed, max. concentration at 2-6 hours
Dermal absorption:	5%-25%
Distribution	Widely distributed
Potential for accumulation:	Limited (<0.3% in tissue after 7 days)
Rate and extent of excretion:	Biphasic; $T_{1/2}$=3 h for 1st phase, 44 h for 2nd phase, oral administration, rabbit
Metabolism in animals	Extensive; >96% metabolized
Toxicologically significant compounds (animals, plants and environment)	Metabolites assumed to be of similar toxicity to parent

Acute toxicity	
Rat LD_{50} oral	3100 mg/kg bw
Rat LD_{50} dermal	>5000 mg/kg bw
Rat LC_{50} inhalation	3 mg/l
Skin irritation	Irritating
Eye irritation	Irritating
Skin sensitization	Sensitizing
Short-term toxicity	
Target/critical effect	General toxicity (dog 2-year study)
Lowest relevant oral NOAEL	1.5 mg/kg bw per day
Lowest relevant dermal NOAEL	10 mg/kg bw per day (mouse, teratogenicity)
Lowest relevant inhalation NOAEL	No data
Genotoxicity	Not genotoxic in an adequate battery of tests
Long term toxicity and carcinogenicity	
Target/critical effect:	Impaired weight gain
Lowest relevant NOAEL	2.7 mg/kg bw per day (mouse, carcinogenicity)
Carcinogenicity	Not carcinogenic
Reproductive toxicity	
Reproduction target/critical effect	No effect on fertility and ability to rear young
Lowest relevant reproductive NOAEL	13 mg/kg bw per day (rat, multigeneration study)
Developmental target/critical effect	Malformations in mouse
Lowest relevant developmental NOAEL	4 mg/kg bw per day
Neurotoxicity/Delayed neurotoxicity	No data, but no concern raised in other studies
Other toxicological studies	Inhibits oxidative phosphorylation; methyl heptyl isomer not teratogenic
Medical data	No significant dinocap-related effects reported

Summary	Value	Study	Safety factor
ADI	0-0.008 mg/kg bw	Mouse, developmental toxicity (4 mg/kg bw per day)	500
Acute reference dose	0.008 mg/kg bw	Mouse developmental toxicity (4 mg/kg bw per day)	500

RESIDUE AND ANALYTICAL ASPECTS

Dinocap was evaluated in 1998 when residue data on grapes, apples, cucurbits, strawberries, peppers, peaches, apricots and tomatoes were submitted. Maximum residue levels were estimated for all commodities except apricots and tomatoes. In view of new information on GAP in Spain provided by the manufacturer, the data on residues in tomatoes submitted in 1998 were re-evaluated.

Field trials in France, Italy and Spain according to Spanish GAP (0.0195-0.026 kg ai/hl, PHI 7 days) gave residues of <0.04 (4), <0.05 and 0.04 mg/kg at PHIs of 7 or 8 days. In two trials in glasshouses in Spain, the residues were 0.08 and 0.18 mg/kg. The residues in rank order were <0.04 (4), <0.05, 0.04, 0.08 and 0.18 mg/kg.

The Meeting estimated a maximum residue level of 0.3 mg/kg and an STMR of 0.045 mg/kg for dinocap in tomatoes.

DIETARY RISK ASSESSMENT

Chronic intake

An STMR for tomato was estimated for dinocap by the present Meeting. At the 1998 JMPR, dinocap was evaluated as a new compound and STMRs were estimated for apples, grapes, strawberries, peaches, peppers and cucurbits. The dietary intake was calculated for all the commodities (Annex III).

The International Estimated Daily Intakes (IEDIs) for the five GEMS/Food regional diets, based on new and existing STMRs, were in the range of 0 to 2% of the ADI. The Meeting concluded that the intake of residues of dinocap resulting from its uses that have been considered by the JMPR is unlikely to present a public heath concern.

Acute intake

The acute reference dose for dinocap established by the 1998 JMPR is 0.008 mg/kg bw. The international estimates of short-term intake (IESTIs) for tomatoes are shown in Annex IV. The IESTI was 0.008 mg/kg bw (100% of the acute RfD) for adults and 0.0087 mg/kg for children (*see* Section 3). For the general population the Meeting concluded that it is unlikely that the acute intake of dinocap residues would exceed the acute reference dose. The acute RfD is not relevant to children because it is based on a teratogenic effect. The Meeting recommended that the JMPR re-evaluate the acute toxicity of dinocap to consider the necessity for establishing an acute RfD relevant to children.

4. 12 ETHEPHON (106)

RESIDUE AND ANALYTICAL ASPECTS

Ethephon was evaluated in the CCPR Periodic Review Programme by the 1994 JMPR. Recommended MRLs for cantaloupe, grapes, peppers, pineapple and tomato were retained at

Step 7B by the 31st Session of the CCPR (1999) pending a review of new data by the 1999 JMPR.

The Meeting received information on analytical methods and GAP together with supplementary residue data on cantaloupes, grapes, peppers, pineapples and tomatoes.

A GLC analytical method involving derivatization to dimethyl ethephon with diazomethane has been used for many years and was reviewed by the 1994 JMPR. Another method depending upon the release of ethylene and its determination by headspace GLC has been developed to avoid the use of diazomethane. The LOD for fruits and vegetables is generally about 0.02 mg/kg. The method was validated for many commodities including tomatoes, pineapples, cantaloupes, peppers and grapes.

The current definition of the residue is ethephon. The Meeting agreed that this was a suitable definition for compliance with MRLs and for the estimation of dietary intake.

Ethephon is a systemic plant growth regulator, and when used on crops near maturity induces fruit ripening. It is generally inappropriate to set minimum pre-harvest intervals; it is preferable to harvest the crop at the proper stage of maturity. When a pre-harvest interval is specified it is normally shorter than necessary to avoid over-ripening.

The 1994 JMPR noted that ethephon residues were stable in the treated crops and that the PHI usually had little influence on the residue levels. Summary reports of two trials in The Netherlands in which ethephon was applied to the stems of tomato plants demonstrated rapid translocation and build-up in the fruits over 3-12 days.

The application rate (kg ai/ha) rather than the spray concentration is the prime determinant of GAP.

Supervised trials

Grapes. In France, ethephon may be used on grapes at 0.36-0.45 kg ai/ha. The residues in grapes harvested 35 and 38 days after treatment in two trials were 0.37 and 0.25 mg/kg. In both trials the levels in grapes harvested at the longer intervals were slightly higher than in fruit harvested 25 days after treatment.

Ethephon may be used at 0.56 kg ai/ha on grapes in the USA and harvesting is permitted 14 days later. The residues in grapes from three trials meeting these conditions were 0.17, 0.24 and 0.33 mg/kg.

Ethephon residues in grapes from 10 trials in the USA recorded in the 1994 JMPR Evaluations were <0.06, 0.15, 0.15, 0.24, 0.31, 0.35, 0.42, 0.46, 0.47 and 0.82 mg/kg, 14-47 days after treatment at 0.56 kg ai/ha.

The residues in grapes from the 2 French and 13 US trials according to GAP in rank order (median underlined) were <0.06, 0.15, 0.15, 0.17, 0.24, 0.24, 0.25, 0.31, 0.33, 0.35, 0.37, 0.42, 0.46, 0.47 and 0.82 mg/kg.

The Meeting estimated a maximum residue level of 1 mg/kg and an STMR of 0.31 mg/kg for ethephon in grapes. The maximum residue level supports the previous recommendation.

The processing factor for raisins (2.7) was applied to the estimated maximum residue level for grapes to produce an estimated maximum residue level, after rounding, for ethephon in dried grapes of 5 mg/kg. The same processing factor applied to the STMR (0.31 mg/kg) and HR (0.82 mg/kg) for grapes gave an STMR of 0.84 mg/kg and an HR-P of 2.2 mg/kg for dried grapes.

The processing factor for wine (1.76) was considered unrealistic. At the highest estimate, residues in wine should not exceed those in the grapes. The Meeting concluded that the STMR for wine should be the same as for grapes, 0.31 mg/kg.

Pineapples. Pineapples may be treated with ethephon at 1.2 kg ai/ha to induce ripening in Costa Rica, where residues were below the LOD (0.1 mg/kg) in pineapples harvested 7 days after treatment with 1.6 kg ai/ha in two trials.

The approved application rate on pineapples in the Ivory Coast is 1.9 kg ai/ha. The residue in pineapples treated at 1.4 kg ai/ha and harvested 3 days later was 0.28 mg/kg, and that in the pulp was below the LOD (0.1 mg/kg).

In Bolivia the approved treatment rate for pineapple ripening is 0.96 kg ai/ha with a PHI of 14 days. The residues in the pineapples were below the LOD (0.05 mg/kg) in 2 trials in Brazil, a neighbouring country, where the application rates were 0.96 and 1.9 kg ai/ha with harvest 14 days after treatment.

US trials were reported by the 1994 JMPR. The residues from 6 trials where the application rate was 2.2 kg ai/ha (the maximum GAP rate) were 0.09, 0.13, 0.59, 0.76, 0.86 and 0.97 mg/kg.

The US delegation to the CCPR drew attention to differences in interpretation of the data between the JMPR and the USA. For example, the USA adjusted the residue data for analytical recoveries, which converted one of the levels to 1.3 mg/kg, suggesting an MRL of 2 mg/kg. Generally, the JMPR practice is to use uncorrected results and to regard recoveries as a criterion of acceptability. The USA also drew attention to a residue of 1.1 mg/kg resulting from the low application rate of 0.56 kg ai/ha. However, it was a 1970 trial and its validity is uncertain; it seems inconsistent with the modern data and was disregarded by the 1994 JMPR. The Meeting noted the rationale for the different procedures, but agreed that the 1994 interpretations were consistent with usual JMPR practice.

Residues in pineapples from the 2 Costa Rica, 1 Ivory Coast, 2 Brazilian and 6 US trials according to GAP in rank order (median underlined) were <0.05, <0.05, 0.09, <0.1, <0.1, 0.13, 0.28, 0.59, 0.76, 0.86 and 0.97 mg/kg.

The Meeting noted that the highest residues were very close to 1 mg/kg and that residues above 1 mg/kg would be possible, and estimated a maximum residue level of 2 mg/kg and an STMR of 0.13 mg/kg for ethephon in pineapples. The maximum residue level is recommended to replace the draft MRL of 1 mg/kg.

The processing factors for juice (0.39) and canned slices (0.28) were applied to the STMR of 0.13 mg/kg to produce STMRs for ethephon in pineapple juice and canned pineapple of 0.051 and 0.036 mg/kg respectively. An HR-P of 0.27 mg/kg was estimated for canned pineapple from the highest residue in the trials of 0.97 mg/kg and the processing factor of 0.28.

Cantaloupes. US GAP permits the use of ethephon on cantaloupes at 0.84 kg ai/ha with a PHI of 2 days. In 7 US trials in 1994 according to GAP ethephon residues were 0.18, 0.25, 0.31, 0.35, 0.42, 0.54 and 0.63 mg/kg.

The 1994 JMPR evaluation reported residues in cantaloupes in 9 trials in 1969-72 and 1989 with application rates of 0.90-0.98 kg ai/ha and PHIs of 2-4 days, essentially according to current GAP, of 0.07, 0.11, 0.15, 0.16, 0.18, 0.23, 0.23, 0.30 and 0.44 mg/kg.

The residues in cantaloupes from the 16 US trials according to GAP in rank order (median underlined) were 0.07, 0.11, 0.15, 0.16, 0.18, 0.18, 0.23, 0.23, 0.25, 0.30, 0.31, 0.35, 0.42, 0.44, 0.54 and 0.63 mg/kg.

The Meeting estimated a maximum residue level of 1 mg/kg and an STMR of 0.24 mg/kg for ethephon in cantaloupes. The maximum residue level supports the previous recommendation.

Peppers. Ethephon is registered for use on peppers in the USA at 0.35-1.1 kg ai/ha with a 5 days PHI. In a series of 10 US trials in 1994 on sweet and hot peppers according to maximum US GAP the residues in rank order (median underlined) were 0.16, 0.52, 0.58, 0.76, 0.96, 1.0, 1.4, 1.8, 2.1 and 2.4 mg/kg.

The 1994 JMPR reviewed results from 12 US trials on peppers in 1973 where ethephon was applied at 1.12 kg ai/ha with harvest 5-8 days later, which is equivalent to current GAP. The residues in rank order (median underlined) were 3.5, 4.3, 4.5, 5.7, 6.8, 7.3, 8.9, 9.7, 10.6, 10.8, 22.3 and 26.2 mg/kg.

Clearly the two residue populations are different although the use pattern is the same; if the residues were from one population the probability of no overlap between the two sets of results would be very low. There is no explanation for the difference in terms of different analytical methods or agricultural practices. There is no direct reason to discard the 1973 data but the Meeting decided to accept the more recent results because the trials were situated in those States of the USA with major production of peppers, had better documentation, and perhaps better reflected current formulations and application equipment.

The Meeting estimated a maximum residue level of 5 mg/kg and an STMR of 0.98 mg/kg for ethephon in peppers. The maximum residue level is recommended to replace the draft MRL of 30 mg/kg.

Tomatoes. Ethephon is registered in the USA for application to tomatoes at 1.8 kg ai/ha with harvest no sooner than 3 days later. The residues in 5 US trials in 1991 according to GAP were 0.30, 0.55, 0.68, 1.2 and 1.7 mg/kg.

The 1994 JMPR reviewed 13 US residue trials in 1970-1990 where ethephon was applied at 1.75-2.1 kg ai/ha with PHIs of 3-16 days. The residues were <0.02, 0.10, 0.14, 0.15, 0.21, 0.23, 0.32, 0.37, 0.44, 0.50, 0.92, 1.14 and 1.41 mg/kg.

The Meeting received summary reports of trials on tomatoes in Europe: 6 in Belgium (1971, 1972), 4 in The Netherlands (1976, 1985), 2 in Portugal and 1 in the UK (1980). The trials were not evaluated because no field reports, analytical validation or residues from untreated control plots were available.

The residues in the 18 US trials according to GAP in rank order (median underlined) were <0.02, 0.10, 0.14, 0.15, 0.21, 0.23, 0.3, 0.32, 0.37, 0.44, 0.5, 0.55, 0.68, 0.92, 1.14, 1.2, 1.41 and 1.7mg/kg.

The Meeting estimated a maximum residue level of 2 mg/kg and an STMR of 0.41 mg/kg for ethephon in tomatoes. The maximum residue level supports the previous recommendation.

The processing factors for juice (0.34) and paste (0.75) were applied to the estimated STMR for tomatoes to produce STMRs for ethephon in tomato juice and paste of 0.14 and 0.31 mg/kg respectively.

Processing. A processing study on Syrah and Grenache grapes showed higher residues in wine than in the grapes: the calculated processing factors were 2.08 and 1.44 respectively, mean 1.76, which appeared somewhat unrealistic.

The following processing factors for products from grapes, pineapples and tomatoes were derived from processing information evaluated by the 1994 JMPR: raisins 2.7, canned pineapple juice 0.39, canned pineapple slices 0.28, tomato juice 0.34, tomato paste 0.75.

FURTHER WORK OR INFORMATION

Desirable

Information on the fate of ethephon during the processing of grapes to wine. The available studies suggested that ethephon was concentrated in the wine by factors of 1.4 and 2.1.

DIETARY RISK ASSESSMENT

Chronic intake

Maximum residue levels have been estimated for ethephon in canteloupes, dried grapes, peppers, pineapples and tomatoes to confirm or replace existing draft MRLs. STMRs have been estimated for the main commodities and some processed commodities. All the other values (16) used for the intake estimation are previously established CXLs. The dietary intakes of ethephon are shown in Annex III.

Estimated dietary intakes of ethephon for the 5 GEMS/Food regional diets were in the range of 2-20% of the ADI. The Meeting concluded that the intake of residues of ethephon resulting from its uses that have been considered by the JMPR is unlikely to present a public health concern.

Acute intake

The international estimate of short-term intake (IESTI) for ethephon was calculated for commodities for which MRLs were recommended and STMRs estimated and for which consumption data (large portion consumption, unit weight) were available (*see* Section 3). The results are shown in Annex IV. The IESTI ranged from 0.005 to 0.031 mg/kg bw in the total population and from 0 to 0.099 mg/kg bw in children. As no acute reference dose has been established, the acute risk assessment for ethephon was not finalized.

4.13 ETHOPROPHOS (149)

TOXICOLOGY

Ethoprophos was evaluated for toxicological effects by the 1983 Joint Meeting and in 1987, when an ADI of 0-0.0003 mg/kg bw was established on the basis of a NOAEL of 0.025 mg/kg bw per day in a one-year study in dogs. Since that time, several studies have been conducted on the metabolism, acute, short-term and long-term toxicity, reproductive and developmental toxicity, neurotoxicity and mutagenicity of ethoprophos. The compound was evaluated at the present meeting within the CCPR Periodic Review Programme.

After oral administration to rats, ^{14}C-ethoprophos was rapidly and virtually completely absorbed, metabolized and excreted. The main route of excretion was the urine (51-56%), but significant proportions were excreted in expired air (about 15%) and faeces (10-14%). Little radiolabel was found in tissues at 168 h, representing less than 2.5% of the dose, and the highest concentrations were found in excretory organs (liver, kidneys and lungs). There was no evidence that bioaccumulation would occur after repeated doses. The kinetics of the radiolabel and the biotransformation appeared to be independent of the route of administration (oral or intravenous), magnitude and frequency of dose and sex. Ethoprophos was metabolized by dealkylation of one or both S-propyl groups, followed by conjugation. The dermal absorption of ethoprophos has not been studied *in vivo*, but radiolabelled ethoprophos penetrated the skin *in vitro*, the greatest penetration being seen through mouse skin, lesser penetration through rat and rabbit skin (at equal rates), and the least penetration through human skin. In all of the species tested, the rate of penetration was greater with ethoprophos (emulsified concentrate) diluted 1:19 in water than with undiluted material.

Single oral doses of ethoprophos were toxic to rats, mice and rabbits (LD_{50} values, 31-62 mg/kg bw) and it was highly toxic to rats exposed once by inhalation (LC_{50}, 0.25 mg/l). Mice and rabbits were more sensitive to dermal exposure than rats and female rats were more sensitive than males, with LD_{50} values of 8.5 mg/kg bw for rabbits, 18 mg/kg bw for mice, 420 mg/kg bw for female rats and 1300 mg/kg bw for male rats. The toxic signs observed after exposure by any route were characteristic of cholinesterase inhibition.

WHO has classified ethoprophos as ‘extremely hazardous’.

Ethoprophos not only irritates the eyes of rabbits but is very toxic after administration into the eye, causing the death of tested animals within 1 h. In a test for dermal irritation, all treated animals died within 8 h of exposure to the undiluted compound. In a three-week study

in rabbits, the compound caused slight dermal irritation at all doses tested (0.03, 0.1 and 1 mg/kg bw per day), whereas no dermal irritation was observed in a three-week study in rats given doses of up to 10 mg/kg bw per day.

In studies in dogs (13, 20 and 52 weeks) and mice and rats (two years) given ethoprophos orally, inhibition of cholinesterase was the most sensitive parameter. In dogs, the NOAEL for inhibition of brain acetylcholinesterase activity was 1 mg/kg bw per day, the highest dose tested. In mice, brain acetylcholinesterase activity was inhibited at 30 ppm, resulting in a NOAEL of 2 ppm, equal to 0.25 mg/kg bw per day; in rats, the overall LOAEL was 30 ppm (equal to 1.3 mg/kg bw per day) and no effects were seen at 10 or 1 ppm (equal to 0.5 and 0.04 mg/kg bw per day, respectively). In a two-generation study of reproductive toxicity in rats, inhibition of brain acetylcholinesterase activity was seen in animals of each sex of both parent generations at 30 ppm, resulting in a NOAEL of 1 ppm, equal to 0.04 mg/kg bw per day. In a 13-week study of neurotoxicity in rats, the activity of brain acetylcholinesterase was inhibited in females at all doses tested, the lowest dose being 4 ppm, equal to 0.26 mg/kg bw per day. Clinical signs characteristic of cholinesterase inhibition were observed only in the two-year study in rats, in which the highest dose was reduced from 600 to 400 ppm because of clinical signs.

Inhibition of brain acetylcholinesterase activity was also demonstrated after dermal exposure of rabbits and rats to ethoprophos for three weeks, with NOAELs of 0.1 mg/kg bw per day (LOAEL, 1 mg/kg bw per day) in rabbits and 0.3 mg/kg bw per day (LOAEL, 1 mg/kg bw per day) in rats.

Ethoprophos was not carcinogenic in a long-term study in mice treated in the diet. The highest dose tested was 30 ppm, equal to 4.9 mg/kg bw per day. In three studies of chronic toxicity and carcinogenicity in rats, some evidence was obtained that ethoprophos may stimulate progression of C-cell tumours in the thyroid and adrenal neoplasms (phaeochromocytomas), but this effect was considered to have little relevance for human risk assessment. The highest dose tested was 400 ppm, equal to 26 mg/kg bw per day. The Meeting concluded that ethoprophos is unlikely to pose a carcinogenic risk to humans.

Ethoprophos was tested in an adequate set of assays for genotoxicity *in vitro* and *in vivo*. Positive results in studies for chromosomal aberrations and sister chromatid exchanges *in vitro* after metabolic activation indicate that the compound has intrinsic genotoxic activity. Chromosomal aberrations were not induced in rats in two assays and dominant lethal mutations were not induced in rats in another study, although a slightly positive or equivocal result was obtained in a further study for dominant lethality. The Meeting concluded that ethoprophos is unlikely to be genotoxic *in vivo*.

In a two-generation study of reproductive toxicity in rats, no effect was observed on reproductive parameters. Clinical signs were observed only in the F_0 parents at the highest dose (300 ppm). The NOAEL was 1 ppm, equal to 0.04 mg/kg bw per day, on the basis of reduced body-weight gain in F_0 males and inhibition of brain acetylcholinesterase activity in animals of each sex in both parental generations. The NOAEL for developmental toxicity was 30 ppm, equal to 1.3 mg/kg bw per day, on the basis of effects on body weight and body-weight gain in pups of both generations and deaths of pups in the F_2 litters at 150 ppm.

In studies of developmental toxicity, maternal toxicity was characterized by growth depression in rats in one study (NOAEL, 2 mg/kg bw per day) and in rabbits in one study (NOAEL, 0.125 mg/kg bw per day), whereas no maternal toxicity was observed in rabbits in

another study (NOAEL, 2 mg/kg bw per day, highest dose tested). Since in the first study in rabbits the effect was only marginal (not statistically significant), the overall NOAEL for maternal effects in rabbits was 2.5 mg/kg bw per day. No effects on the fetuses of either species were observed. Cholinesterase activity was not measured in these studies.

The relationship between neurotoxicity and cholinesterase inhibition was examined in rats in two studies. In rats exposed by gavage to single doses of 0, 20, or 40 mg/kg bw (females) or 0, 30, or 60 mg/kg bw (males), cholinesterase activity in plasma, erythrocytes and brain was inhibited, with a maximum effect 2 h after dosing. While cholinesterase inhibition was found in tissues at the lowest doses tested, clinical signs characteristic of cholinesterase inhibition were seen only at the highest doses (60 mg/kg bw for males and 40 mg/kg bw for females). In the second study, in which male rats were exposed to a single dose of ethoprophos at 5, 50, or 75 mg/kg bw and females at 5, 25, or 50 mg/kg bw, effects on motor activity were observed in animals of each sex at doses of 50 mg/kg bw and higher, and functional and behavioural effects were observed at 25 mg/kg bw and higher. These neurotoxic signs were seen only on the day of dosing. Significant inhibition of acetylcholinesterase activity in erythrocytes, measured one day after exposure, was observed in females at doses of 5 mg/kg bw and higher and in males at 50 mg/kg bw and higher. The inhibition in females was not dose-related, and there was a large standard deviation at 5 mg/kg bw . The Meeting concluded that the NOAEL in this study was 5 mg/kg bw.

In a 13-week study in rats, neurotoxicity was observed in tests for motor activity and for functional and behavioural abnormalities only at the highest dose (400 ppm). The NOAEL for neurotoxic effects was 40 ppm, equal to 2.6 mg/kg bw per day. The activity of brain acetylcholinesterase was inhibited in females at all doses tested; the lowest dose was 4 ppm, equal to 0.26 mg/kg bw per day.

A study of delayed neurotoxicity in hens was performed with doses of ethoprophos causing a high mortality rate despite antidotal treatment. Equivocal findings were reported in some of the treated birds; data on the effect of this compound on neuropathy target esterase activity in hens would be useful to fully assess the neuropathological potential of ethoprophos.

A study of occupational exposure to ethoprophos did not reveal any significant effects on human plasma or erythrocyte cholinesterase activity. The calculated rates of exposure of head and neck areas were 3.1-78 g/h (average, 34 g/h) and the rate of exposure of the hands was calculated to be 0.2-18 g/h (average, 6.3 g/h).

O-Ethyl *S*-propyl phosphorothioate, a metabolite in the rat, and *O*-ethyl *O*-methyl *S*-propyl phosphorothioate and *O*-ethyl *S*-methyl *S*-propyl phosphorodithioate, 2 metabolites that have been identified only in corn and potatoes (not in rats), were tested for toxicity and for their ability to inhibit cholinesterase activity in female rats given single oral doses. The two plant metabolites were of approximately the same toxicity as the parent compound, while the animal metabolite was less toxic (LD_{50} = 1600 mg/kg bw) than the parent.

The 1987 Meeting derived the ADI on the basis of a slight effect on the liver in a 52-week study in dogs at a dose of 1 mg/kg bw per day. The NOAEL for this effect was 0.025 mg/kg bw per day. Since this marginal effect was not observed in other studies in dogs or in other species and there is a 40-fold difference between the LOAEL and the NOAEL, this NOAEL was not used as the overall NOAEL to derive the ADI in the present evaluation.

The present Meeting established an ADI of 0-0.0004 mg/kg bw on the basis of the NOAEL of 1 ppm, equal to 0.04 mg/kg bw per day, for inhibition of brain acetylcholinesterase activity in the two-year study of toxicity and carcinogenicity in rats and in the study of reproductive toxicity in rats, and a 100-fold safety factor.

An acute reference dose of 0.05 mg/kg bw was established on the basis of the NOAEL of 5 mg/kg bw in the study of acute neurotoxicity in rats, in which functional and/or behavioural effects and inhibition of erythrocyte acetylcholinesterase were observed at the next highest dose, and a 100-fold safety factor.

A monograph was prepared, summarizing the data received since the previous evaluation and including all relevant data from the previous monograph and monograph addendum.

TOXICOLOGICAL EVALUATION

Levels that cause no toxic effect

Mouse 2 ppm, equal to 0.25 mg/kg bw per day (two-year study of carcinogenicity and toxicity)

Rat 1 ppm, equal to 0.04 mg/kg bw per day (two-year study of carcinogenicity and toxicity)
1 ppm, equal to 0.04 mg/kg bw per day (parental toxicity in a study of reproductive toxicity)
5 mg/kg bw (single dose, study of neurotoxicity by gavage)
2 mg/kg bw (maternal toxicity, study of developmental toxicity; acetylcholinesterase activity not determined);
18 mg/kg bw (fetotoxicity, highest dose tested, study of developmental toxicity; acetylcholinesterase activity not determined)

Rabbit 2.5 mg/kg bw (maternal toxicity and fetotoxicity, study of developmental toxicity; acetylcholinesterase activity not determined);

Dog 0.025 mg/kg bw per day (one-year study of toxicity)

Estimate of acceptable daily intake for humans

0-0.0004 mg/kg bw

Estimate of an acute reference dose

0.05 mg/kg bw

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

Information on effects on neuropathy target esterase activity in hens

Further observations in humans

List of relevant end-points relevant for setting guidance values for dietary and non-dietary exposure

Absorption, distribution, excretion and metabolism in mammals

Rate and extent of oral absorption	>70%, mainly within 12 h (rats)
Dermal absorption	Tested in vitro, no quantitative data. Penetration rate mouse skin>rat, rabbit skin>human skin
Distribution	Widely distributed, highest levels in organs of elimination (rats)
Potential for accumulation	No
Rate and extent of excretion	Excretion in urine (55%), expired air (13-17%) and faeces (7-9%) (rats)
Metabolism in animals	In rats, ethoprophos is metabolized via dealkylation of one or both S-propyl groups, followed by conjugation
Toxicologically significant compounds	Parent compound and plant metabolites (*O*-ethyl *O*-methyl *S*-propyl phosphorothioate and *O*-ethyl *S*-methyl S-propyl phosphorodithioate)

Acute toxicity

Rat LD_{50} oral	33-62 mg/kg bw (vehicle, corn oil)
Rat LD_{50} dermal	424 mg/kg bw, females
Rat LD_{50} inhalation	0.25 mg/l
Skin irritation	Not reported, but death occurred within 8 h of dermal exposure
Eye irritation	Yes, but also death within 1 h of ocular exposure
Sensitisation	Not tested

Short-term toxicity

Target/ critical effect	Acetylcholinesterase inhibition
Lowest relevant oral NOAEL	<0.26 mg/kg bw per day (LOAEL, 13-week study of neurotoxicity in rats)
Lowest relevant dermal NOAEL	0.1 mg/kg bw per day (three-week study of dermal toxicity in rabbits)
Lowest relevant inhalation NOAEL	Not tested

Genotoxicity	Not genotoxic in vivo

Long term toxicity and carcinogenicity

Target/critical effect	Acetylcholinesterase inhibition
Lowest relevant NOAEL	0.04 mg/kg bw per day (105-week study in rats treated in the diet)

Carcinogenicity	Not carcinogenic (mice, rats)
Reproductive toxicity	
Reproduction target/critical effect	Reduced body weight and survival at maternally toxic doses
Lowest relevant reproductive NOAEL	Maternal toxicity: 1 ppm, equal to 0.04 mg/kg bw per day; fetotoxicity: 30 ppm, equal to 1.3 mg/kg bw per day
Developmental target/critical effect	Only maternal toxicity (highest dose tested), no fetotoxicity.
Lowest relevant developmental NOAEL	Rabbit: maternal and fetotoxicity: 2.5 mg/kg bw per day (highest dose tested) Rat: maternal toxicity: 2 mg/kg bw per day; fetotoxicity: 18 mg/kg bw per day
Neurotoxicity/ Delayed neurotoxicity	5 mg/kg bw per day (acute study in rats) <4 ppm, equal to 0.26 mg/kg bw per day (13-week study in rats) No evidence for delayed neurotoxicity in hens, but some equivocal findings.
Other toxicological studies	No significant effects on erythrocte acetylcholinesterase activity in exposed workers
Medical data	-

Summary	value	Study	Safety factor
ADI	0-0.0004 mg/kg bw	Two-year study, rat; two-generation study of reproductive toxicity, rats	100
Acute reference dose	0.05 mg/kg bw	Acute neurotoxicity, rats	100

DIETARY RISK ASSESSMENT

Estimated Theoretical Maximum Daily Intakes for the five GEMS/Food regional diets, based on existing MRLs, were in the range of 20–40% of the ADI. The Meeting concluded that the intake of residues of ethoprophos resulting from its uses that have been considered by the JMPR is unlikely to present a public health concern.

4.14 ETHOXYQUIN (035)

RESIDUE AND ANALYTICAL ASPECTS

Ethoxyquin, an antioxidant preservative, was first evaluated in 1969 and re-evaluated for toxicology in the CCPR Periodic Review Programme in 1998. It was scheduled by the 1995 CCPR for a periodic review of residue chemistry in 1999. The deletion of the CXL for pears treated post-harvest, the only use with a Codex MRL, was postponed pending the toxicological and residue chemistry reviews.

Data on residues and environmental fate were provided by the Northwest Horticultural Council (USA) and additional information was reported by the governments of Germany and The Netherlands.

Animal metabolism

No studies were reported. Since the only use is for the post-harvest treatment of pears and pears are not a ruminant or poultry feed item, studies of metabolism in ruminants and poultry are not needed.

At the 1998 Meeting, the WHO Core Assessment Group reviewed the metabolism of ethoxyquin in rats. Parent ethoxyquin was not found in the urine and only traces were found in the faeces, liver, kidneys and adipose tissue of rats given an intravenous administration. Some metabolites were identified in the urine and bile. The main metabolic pathway was *O*-de-ethylation, yielding a phenol, and conjugation .

The metabolic products in rats are different from those in plants.

Plant metabolism

Anjou pears were dipped in a solution containing unlabelled and [^{14}C]ethoxyquin (ring-labelled) at a concentration of 20 mg/ml, 7.5 times the maximum label rate. The pears were dipped in the solution for 30 seconds, air-dried for 2 hours and stored in an incubator at –2°C and relative humidity >95% with constant air circulation. Eight pears were removed from storage at intervals of 0, 2, 7 and 14 days, and 6, 8, 10, 12, 16, 20, 24, 28 and 33 weeks.

The eight pears at each sampling were washed with methanol, two were sliced and ground at liquid nitrogen temperature, and the remaining six were peeled and the combined peels and pulps separately frozen and ground.

The whole pears, peel and pulp were each extracted with methanol/water/ chloroform (2.2:1:1). The post-extraction solids from the three 33-week samples were sequentially treated with cellulase and refluxing 0.1 N NaOH.

The samples were analysed by LSC, TLC, HPLC, GLC and GC-MS. The total radioactive residue (TRR) remained constant at 22 $\pm$ 3 mg/kg over the 14 sampling intervals, but the distribution among rinse, pulp and peel changed dramatically. The rinse contained 86% of the TRR on day 0 and this decreased to 50% on day 7 and 8.2% in week 33. The composition of the residue in the rinse changed from 58% ethoxyquin on day 0 to 0.49% in week 33. The residue in the peel increased from 14% on day 0 to 46% in week 10 and then fluctuated between 34 and 50% of the TRR. The residue in the pulp increased from 1.5% on day 0 to 16% on day 7 and to 49% in week 24. Thus, the radiolabelled residue was substantially translocated into both the peel and pulp.

The radiolabelled residue was readily isolated from the pear samples by a combination of solvent rinse, organic and aqueous solvent extractions, cellulase hydrolysis and base hydrolysis. In the pears stored for 33 weeks after treatment, 8% of the TRR was removed by a methanol rinse, 46% was extracted by chloroform, 27% was extracted by methanol/water, 2% was released by cellulase and 23% was released by mild base hydrolysis. The final post-extraction solid contained 9% of the TRR. Similar results were obtained at other storage intervals.

A significant proportion of the radiolabelled residue was identified by a combination of TLC, HPLC and GC-MS. In the pears stored for 33 weeks about 40% of the TRR (6.8 mg/kg as ethoxyquin) was identified as a mixture of C-N and N-N dimers. Only 0.5% (0.09 mg/kg) was identified as parent ethoxyquin. An additional 2% was characterized as released by cellulase and 27% of the TRR (4.6 mg/kg) was characterized by HPLC and TLC as a complex mixture of water-soluble polar compounds. Air oxidation of [^{14}C]ethoxyquin produced a residue that yielded TLC and HPLC chromatograms similar to those of rinses and extracts of [^{14}C]ethoxyquin-treated pears. The residue is composed of degradation products (dehydrodemethyl-ethoxyquin, *N*-methyl-ethoxyquin, dihydro-ethoxyquin) and this residue may constitute 7% of the TRR (1.2 mg/kg) in whole pears stored for 33 weeks.

The Meeting concluded that the metabolism and degradation of ethoxyquin on pears is adequately understood. Ethoxyquin is rapidly degraded or metabolized and the residue, but not ethoxyquin itself, is translocated into the pulp. Less than 0.5% of the total radioactive residue was ethoxyquin (in the methanol rinse) in treated pears stored frozen for 33 weeks.

No information was reported to the Core Assessment Group on the toxicology of the plant degradation products. They formed rapidly and were not observed in the rat metabolism study. The Meeting agreed not to recommend any MRLs, and recommended the withdrawal of the single existing CXL, until the toxicology of the degradation products in plants is known.

Environmental fate

No studies on environmental fate were reported, but none are required because ethoxyquin is used only in controlled indoor situations where entry into soil or water is very unlikely.

Analytical methods

The official US enforcement method consists in extraction of the whole fruit, peel, or pulp with iso-octane, clean-up by partition, and analysis with a photofluorimeter. The method was validated with labelled and unlabelled ethoxyquin, and used in pear trials at a limit of determination of 0.25 mg/kg.

The two official enforcement methods in The Netherlands are extraction and analysis by capillary column GLC (multi-residue method) and extraction with n-hexane and analysis by HPLC with a fluorescence detector. Acceptable recoveries were reported.

An AOAC HPLC method was validated at 0.5 mg/kg and used for data collection.

The Meeting concluded that adequate analytical methods exist for the determination of ethoxyquin in fruits for both enforcement and data collection.

Stability of residues in stored analytical samples

No studies were conducted, but the results of the metabolism study clearly indicate that ethoxyquin is unstable on pears stored frozen. Almost 50% of the ethoxyquin is lost on the day of application and 85% is lost by day 28 of frozen storage.

Definition of the residue

The current definition is ethoxyquin. The metabolism study has shown that ethoxyquin is readily degraded to dimers and probably to demethyl-ethoxyquin, methyl-ethoxyquin, dehydrodemethyl-ethoxyquin and dihydro-ethoxyquin.

The Meeting concluded that the residue for compliance with MRLs should be defined as ethoxyquin. The residue for the estimation of dietary exposure cannot be defined until the toxicities of the plant degradation products are known.

Residues resulting from supervised trials.

Fourteen trials on pears were conducted in the USA. GAP specifies post-harvest treatment with a 2700 mg/kg aqueous or wax spray on a brush bed or conveyor rolls. The trials were conducted at this rate, two with brush conveyor application of wax and twelve with an aqueous spray. Samples were frozen immediately and analysed within 14-18 days of treatment. The metabolism study indicates that a substantial loss of ethoxyquin (perhaps about 60%) may have occurred during storage.

The residues in rank order were 0.40, 0.66, 1.58, 1.72, 1.72, 1.79, 1.81, 1.90, 1.99, 2.03, 2.23, 2.26, 2.29 and 2.45 mg/kg. The Meeting estimated an STMR of 1.86 mg/kg and a maximum residue level of 3 mg/kg, but could not recommend the maximum residue level for use as an MRL.

Fate of residues in storage and processing

No storage or processing studies were reported, but ethoxyquin has been shown to be unstable on frozen pears and would be even more unstable on pears stored at temperatures above 0°C.

FURTHER WORK OR INFORMATION

Desirable

1. Studies of ruminant or poultry metabolism.

2. A study of the stability of residues in stored analytical samples, with samples taken at intervals of hours up to 24 hours and then on alternate days.

DIETARY RISK ASSESSMENT

Chronic intake

No intake could be estimated because the Meeting recommended withdrawal of the single existing CXL.

Acute intake

The 1998 JMPR concluded that an acute RfD for ethoxyquin is unnecessary. This conclusion

was based on a determination that the pesticide is unlikely to present an acute toxicological hazard, and residues are therefore unlikely to present an acute risk to consumers.

4.15 FENAMIPHOS (085)

RESIDUE AND ANALYTICAL ASPECTS

Fenamiphos was first reviewed by the JMPR in 1974, with subsequent residues evaluations in 1977, 1978 and 1980. The compound was scheduled for periodic review at the 27th Session of the CCPR (ALINORM 95/24A Appendix IV). At the 30th (1998) Session it was noted that the TMDI based on existing CXLs slightly exceeded the revised ADI of 0.0008 mg/kg body weight allocated by the 1997 Meeting.

The manufacturer submitted a comprehensive data package in support of the existing CXLs for bananas, Brussels sprouts, cabbages, coffee beans, cotton seed, grapes, melons, oranges, peanuts, pineapples and tomatoes. Additional data were reported to estimate new maximum residue levels for apples, cherries, lemons, limes, grapefruit, onions, peaches and peppers.

Physicochemical data for fenamiphos indicate that the compound is moderately soluble in organic solvents (10-20 g/l) and highly soluble in toluene and 2-propanol (>200 g/l at 20° C).

Animal metabolism

The metabolism of fenamiphos was investigated in rats, a lactating goat, a dairy cow and laying hens.

In a series of four experiments, rats were dosed with [*phenyl*-1-^{13,14}C]fenamiphos as a single low i.v. dose, a single low oral dose, repeated low oral doses and a single oral dose at 10 times the low dose rate. Similar patterns of elimination and transformation were observed in all cases. Urine was the main route of elimination, with 93-100% of the radioactivity recovered within 48 hours after administration. In the faeces 1.5-3.8% of the dose was eliminated during the first 48 hours. The total radioactivity in the tissues, including the GI tract, was 0.045-0.23% of the administered dose; the radioactivity in the tissues of all the animals was below the limit of quantification and was not examined further.

The identified radioactivity in the excreta accounted for more than 93% of the total recovered radioactivity. The main metabolites in the urine and faeces were fenamiphos sulfoxide phenol (FSOP) accounting for 4-22% and its sulfate conjugate (FSOP-sulfate), 40-54%. The presence of these compounds indicates that a major transformation pathway in rats involves oxidation of the methylthio group, with cleavage of the isopropyl chain on the amine and of the phosphate ester function.

The most recent toxicological review of fenamiphos by the JMPR was in 1997. The findings in the rat studies were identical, *i.e.* fenamiphos was rapidly excreted, with >96% of the radioactivity excreted renally by 48 hours after dosing. At 48 hours, most of the residues in the tissues were below the limits of quantification. The main urinary metabolites were fenamiphos sulfoxide phenol sulfate, fenamiphos sulfoxide phenol, fenamiphos phenol sulfate and fenamiphos sulfone phenol sulfate.

In a dairy cow study, [U-*phenyl*-^{14}C]fenamiphos sulfoxide was administered in a single dose of 0.8 mg/kg body weight. Blood, milk and urine samples were taken at hourly intervals and faeces were collected upon elimination. Four hours after administration, the animal was slaughtered and tissue samples including GI tract were taken for analysis. Approximately 88% of the administered dose was recovered, with 47% in the rumen contents, 39% in the urine, and 1.4% in the tissues.

Peak radioactivity in the blood of 0.24 mg/kg fenamiphos sulfoxide equivalents was observed 1 hour after dosing, with a steady decrease to 0.09 mg/kg 4 hours after administration. The main source of the recovered radioactivity in the blood was fenamiphos sulfoxide phenol at levels of 55 to 74%.

The radioactivity in the milk peaked in the 4 hour samples at a level of 0.061 mg/kg fenamiphos sulfoxide equivalents. The predominant radioactive components were fenamiphos sulfoxide phenol (37-40%) and fenamiphos phenol (<21%); 27-46% of the radioactivity remained unidentified.

In the urine, fenamiphos sulfoxide phenol was the main component of the total radioactive residue, at levels of 60-70% of the recovered radioactivity over the 4-hour period of the study.

Metabolites were identified in specific tissue samples, including muscle, fat, liver, kidney and heart. A large proportion of the radioactivity remained unidentified. Of the identified compounds, unchanged fenamiphos sulfoxide and fenamiphos sulfoxide phenol were the predominant compounds; fenamiphos was detected in the liver, fat, kidneys and heart.

[*Phenyl*-^{14}C]fenamiphos was administered to a lactating goat at a dose of 1 mg/kg body weight for 3 days. Samples of blood, urine, faeces and milk were taken at regular intervals. Peak plasma radioactivity equivalent to 0.6 μg/ml was observed 0.25 hours after the first dose and decreased steadily to 0.12 μg/ml at 6 hours after administration. A half-life of 4.5 hours was calculated for the elimination of the radioactivity from plasma during the 1-6 hours after administration of the first dose.

The total recovered radioactivity was 65.5%, with urine accounting for 61% of the dose. Additional elimination in the faeces and milk accounted for 3.6% and 0.06% of the dose respectively. Radioactivity in edible tissues and organs totalled 0.3% of the dose.

The main radioactive metabolites in milk were fenamiphos phenol sulfate, fenamiphos sulfoxide phenol sulfate and fenamiphos sulfone phenol sulfate. Conjugate formation increases the water-solubility of the metabolites, so similar metabolite patterns are found in urine and in milk.

In edible tissues, the highest radioactivity was present in the liver and kidneys, at levels of 0.13 and 0.04 mg/kg fenamiphos equivalents respectively, or 0.09 and 0.04% of the recovered radioactivity. The main radioactive components in liver were fenamiphos sulfoxide and fenamiphos sulfoxide phenol. In kidney however, the main metabolites were fenamiphos sulfoxide phenol sulfate and fenamiphos sulfone phenol sulfate, again indicating that conjugation is a necessary transformation before the elimination of the metabolites. The tissues were re-analysed 8 and 24 months after the initial extractions. At 8 months similar

results were found in both liver and kidney, but re-analysis of the liver samples at 24 months showed that the metabolites initially present had undergone some reductive transformation to fenamiphos and fenamiphos phenol sulfate.

Three types of muscle samples were analysed for metabolite composition: loin, flank and round. In round and loin muscle, the compounds present were fenamiphos sulfoxide, fenamiphos sulfoxide phenol sulfate and fenamiphos sulfone phenol sulfate. In flank muscle however, they were desisopropyl-fenamiphos sulfone, fenamiphos sulfoxide phenol and fenamiphos sulfone phenol sulfate, indicating incomplete transformation from fenamiphos sulfoxide to fenamiphos sulfoxide phenol sulfate in flank muscle, as cleavage of the isopropyl and phosphate ester groups are two of the main processes of metabolic degradation of fenamiphos.

Laying hens were dosed orally with [*phenyl*-1-^{13,14}C]fenamiphos at 1 mg/kg body weight for 3 days. Blood, excreta and eggs were collected at regular intervals. The birds were killed 0.5 hours after the third dose.

Peak radioactive levels of 0.44 µg/ml were found in plasma 0.5 hours after the third dose, and decreased to 0.03 µg/ml at 24 hours. An elimination half-life of 4.3 hours was calculated from samples taken over a 24-hour period after administration. The total recovered radioactivity in individual birds ranged from 64 to 73% of the administered dose with excreta contributing to 60-70% of the total radioactivity. The TRR in eggs amounted to 0.03% and in tissues from 1.74 to 4.85%. The highest levels of radioactivity, 0.23, 0.61 and 2.2 µg/g fenamiphos equivalents, were present in the kidneys, liver and gizzard respectively.

The predominant metabolites in the tissues and eggs were fenamiphos phenol, fenamiphos sulfoxide phenol, fenamiphos sulfone phenol and/or their sulfate conjugates. Unchanged fenamiphos was also present in all tissues and eggs. The main pathways of transformation in hens include oxidation of the methylthio group and cleavage of the phosphate ester group, followed by conjugation of the resulting phenols.

In summary, the primary processes of metabolism in rats, goats, cows and hens involve oxidation of the methylthio sulfur, cleavage of the isopropyl group leaving a primary amine, cleavage of the phosphate ester group and conjugation of the resulting phenols leading to ease of elimination. Evidence of cleavage of the isopropyl group was found only in the goat and hen studies, where desisopropyl-fenamiphos sulfoxide was identified as an additional metabolite.

Plant metabolism

Studies on beans, tomatoes, carrots, cabbage and pineapples were reported. Application methods included spray, stem injection, soil treatment and uptake from solution. Snap beans were treated with [*ethyl*-^{14}C] and [*methylthio*-^{3}H]fenamiphos by stem injection (1 mg/plant) or soil treatment (6.7 kg ai/ha). After 4 weeks the plants were sampled and extracted. After soil treatment most of the radioactivity was recovered from the soil, with the remainder present in plant solids and as volatiles caught in acid and base traps. Less than 1% of the applied ^{14}C was present in extracted plant material. After stem injection most of the radioactivity was trapped as volatile compounds or remained as unextracted plant material; 11% of the applied ^{14}C was extracted. The main extractable ^{14}C metabolites from both treatments were fenamiphos sulfoxide and fenamiphos sulfone.

In a subsequent study bean plants were treated by uptake from solution and stem injection. Uptake from solution resulted in a slower incorporation of the radiolabel into the plants, so the predominant extracted radioactive compound was parent fenamiphos instead of fenamiphos sulfoxide during the first 14 days.

[*Ethyl*-^{14}C] and [U-*phenyl*-^{14}C]fenamiphos were applied as soil treatments to tomatoes at a rate equivalent to 6.7 kg ai/ha, 20-30 days before fruit maturity. The distribution of radioactivity in the fruit was investigated up to 74 days after treatment. Most of the radioactivity was extracted, with less than 3% of the ^{14}C present in insoluble fractions from the ring label but up to 36% from the ethyl label. This difference is presumably because different fragments of fenamiphos are incorporated after cleavage into plant components. The predominant radioactive components of the residue in the organic extracts were fenamiphos sulfoxide and fenamiphos sulfone, confirming that oxidation of the methylthio group followed by cleavage of the phosphate ester function are the main transformation pathways in plant metabolism.

Carrots were transplanted into soil treated with [*ethyl*-^{14}C]fenamiphos at a rate equivalent to 10 kg ai/ha. Whole plants were harvested 53, 67 and 86 days after treatment. A large proportion of the radioactivity in both roots and foliage (34-66%) was present in unextracted solids and similar proportions of the radioactivity were extracted into aqueous and organic phases. Hydrolysis of the aqueous extracts showed that most of the water-soluble radioactivity was due to the phenol sulfoxide and phenol sulfone conjugates.

[*Ethyl*-^{14}C] or [U-*phenyl*-^{14}C]fenamiphos was applied as a soil treatment at a rate equivalent to 13.4 or 33.6 kg ai/ha before transplanting cabbage seedlings. Cabbage heads were harvested at intervals up to 90 days after treatment and samples of whole head, outer and inner leaves were analysed for radioactivity. The results indicated that as the crop matures the aqueous extractable radioactivity increases and the organic extractable radioactivity decreases. The total radioactivity and its distribution in outer and inner leaves after treatment with [*ethyl*-^{14}C]fenamiphos were similar at the same sampling intervals. The main identified radioactive components in the organic extractable fractions were generally fenamiphos sulfoxide and fenamiphos sulfone. Enzymic hydrolysis of the aqueous fractions indicated that the water-soluble metabolites were glucoside conjugates of phenol derivatives of fenamiphos. Acid digestion of the insoluble fraction yielded the metabolites found in the organic phase, *i.e.* fenamiphos sulfoxide and fenamiphos sulfone.

In a series of five experiments, pineapple plants were treated with [*ethyl*-^{14}C] or [U-*phenyl*-^{14}C]fenamiphos either as a soil treatment, spray or stem injection. Most of the radiolabel from the soil treatment was present in the soil, with a gradual increase in the radioactivity in the pineapple foliage up to 90 days after treatment. As in cabbages and carrots, there was an increase in the radioactivity in the aqueous and insoluble fractions with time compared to the proportion of organosoluble radioactivity, irrespective of the application method. The predominant radioactive components were fenamiphos sulfoxide and sulfone, with lower levels of the corresponding phenols. Similar metabolite patterns were observed after spray treatment and stem injection. Enzymatic hydrolysis of the aqueous fractions yielded 14-34% of the applied radioactivity as fenamiphos sulfoxide phenol and 6-14% as fenamiphos sulfone phenol after stem injections and spray applications.

Crop rotation studies were conducted with various crops including cereals, a root crop, an oilseed crop and leafy vegetables after treatment of the soil at 7.6 kg ai/ha. The results with the different crops were similar and in agreement with the plant metabolism studies, *i.e.* the radioactivity extracted into aqueous fractions and remaining in the plant solids increased with time owing to conjugation of fenamiphos sulfoxide and sulfone phenols. The soil radioactivity was measured at each cropping interval and the patterns of degradation observed in the soil and rotational crops were similar.

The maximum residues of fenamiphos sulfoxide and fenamiphos sulfone (as fenamiphos equivalents) were 0.08-6.55 mg/kg and 0.04-5.41 mg/kg respectively in the crops and crop fractions investigated after the first rotation (30 days). In the second rotation (120 days), fenamiphos sulfoxide and fenamiphos sulfone residues ranged from 0.02 to 2.82 mg/kg and 0.01 to 2.90 mg/kg respectively, and in the third rotation (269 days) the corresponding residues were <0.01-0.39 mg/kg and <0.01-0.62 mg/kg.

The additional metabolites desisopropyl-fenamiphos sulfoxide and desamino-fenamiphos sulfoxide were both identified in the rotational studies and provide evidence that cleavage of the isopropyl group and the resulting amino group are among the metabolic transformations that occur in plants.

In another crop rotation study, unlabelled fenamiphos was applied to the soil at a rate equivalent to 6.72 kg ai/ha and incorporated after application. Rotational crops of wheat, sorghum, turnips, spinach and mustard greens were planted 1, 4 and 8 months after the soil treatment. Soil samples were taken immediately after treatment and at planting and harvest of the rotational crops. The residues were <0.01 mg/kg at 4 months plant back in all samples except spinach leaves and sorghum forage and straw. The residues in sorghum forage were 0.44 and 0.68 mg/kg and in straw 0.02 mg/kg at one site, but <0.01 mg/kg at another site. After 8 months plant back the residues were <0.01 mg/kg in all sorghum plant fractions. The residues in spinach leaves were 0.03 mg/kg at 4 months plant back.

In summary, the conclusions from the plant metabolism studies were that fenamiphos sulfoxide and fenamiphos sulfone are the main metabolites formed after the application of fenamiphos by various methods. In crops with a substantial period from treatment to harvest fenamiphos sulfoxide phenol and fenamiphos sulfone phenol are also formed, as is apparent by the change in the extraction characteristics of the radioactivity with time. Overall, the metabolites of fenamiphos in plants and animals are similar and the existing definition of the residue as “sum of fenamiphos, its sulfoxide and sulfone, expressed as fenamiphos” is appropriate.

Environmental fate

The photodegradation of [U-*phenyl*-^{14}C]fenamiphos on soil proceeds via first order kinetics with measured half-life values of 1.6 hours under laboratory conditions (Hg vapour lamp) and 2.7 hours in natural sunlight. The main photolytic products are fenamiphos sulfoxide and fenamiphos sulfone.

The adsorption/desorption properties of fenamiphos were investigated in four types of soil ranging from sand to clay loam. Measured K_{oc} values for fenamiphos indicated low mobility in the sandy soil and medium mobility in sandy loam, silt loam and clay loam (K_{oc} 150-500 medium mobility; 500-2000 low mobility). In another study, the adsorption /

desorption characteristics of fenamiphos were investigated in 16 soils from different geographic locations, ranging from cool/moderate to sub-tropical climates. The highest adsorption capacity was measured in a soil with high clay and silt contents. In all the soils higher adsorption constants were found for fenamiphos than for fenamiphos sulfoxide phenol or fenamiphos sulfone phenol. Silt loam adsorbed a higher proportion than clay loam of both fenamiphos sulfoxide and fenamiphos sulfone.

Degradation half-lives of 15.7 and 30 days were reported for fenamiphos in aerobic conditions, with fenamiphos sulfoxide and fenamiphos sulfone the main degradation products. The half-life in anaerobic conditions was 87.9 days, with fenamiphos sulfoxide the main degradation product. In aerobic soil degradation studies conducted in 16 soils from different geographic locations, half-lives were reported as less than 15 days at 22º C. In an outdoor degradation study, the half-life of fenamiphos was reported as 19.9 and 18.2 days in predominantly sandy soils at two sites in California.

In leaching experiments with aged residues, [^{14}C]fenamiphos was applied to soil and the mixture aged for 63 days. The treated soil was applied to columns containing a sandy loam and a silt loam, which were eluted for 48 hours with water. Less than 1% of the applied radioactivity was found in the eluates; up to 16% was collected as volatiles. Fenamiphos was mainly converted to fenamiphos sulfoxide in the aged soil.

In two field dissipation studies degradation half-lives of 15 and of 15.9 days were reported for fenamiphos. Soil core samples were taken after 1 and 2 sprays of fenamiphos at 12.3 kg ai/ha. The maximum residues of fenamiphos were 1.5 and 2.7 mg/kg and 2.0 and 2.5 mg/kg after the 1st and 2nd sprays respectively, and of fenamiphos sulfoxide 3.3 and 4.1 mg/kg after the first applications and 2.0 and 2.5 mg/kg after the second; they decreased to <0.01 mg/kg at 90, 93 and 254, 361 days after the 1st and 2nd sprays, at all soil depths examined (down to 61 cm). The results indicate that fenamiphos is degraded rapidly, whereas fenamiphos sulfoxide dissipates at a relatively rapid rate after 1 spray and more slowly after 2 sprays.

Calculated half-lives for the hydrolysis of fenamiphos in buffer solutions at pH 3 and 9 were 3-10 and 22-230 days respectively. In pH 3 buffer solution, the main hydrolysis product was deaminated fenamiphos, with fenamiphos phenol and deaminated fenamiphos phenol present below 10% of the applied concentration. At pH 9 however, the main hydrolysis products were fenamiphos phenol, fenamiphos sulfoxide phenol and fenamiphos sulfoxide, presumably owing to base hydrolysis of the phosphate ester group. At elevated temperatures of 60, 70 and 80° C the half-lives ranged from 1.7-9.8 days, 14-67 days and 5-70 hours at pH 4, 7 and 9 respectively.

In sterile solutions at pH 5, 7 and 9 which were kept in the dark, the calculated half-lives for hydrolysis ranged from 235-301 days, with the longest at pH 7.

Aqueous solutions of fenamiphos in phosphate buffer were irradiated under laboratory conditions (Hg lamp) and samples were analysed at regular intervals up to 24 hours. The half-life was calculated as 3.6 hours and the main photolytic products at 24 hours were fenamiphos sulfoxide and fenamiphos sulfonic acid phenol.

In summary, the degradation of fenamiphos in soil and water proceeds via oxidation of fenamiphos to fenamiphos sulfoxide and fenamiphos sulfone, so the products

formed are similar to the metabolites formed in plants and animals. An additional product detected was fenamiphos phenol sulfonic acid, formed by oxidative demethylation of the methylthio group and hydrolysis of the phosphate ester.

Methods of residue analysis

Analytical methods for the determination of fenamiphos and its metabolites in various plant substrates, animal tissues, soil and water are based on the published method of Thornton (1971). The method was originally validated for citrus peel and pulp, pineapple fruit, bran and forage, peanut kernels, hulls and vines, and tobacco. Several modifications were subsequently reported. The basic procedure involves homogenization of the sample, filtering, and partitioning the solution with methyl chloride or other organic solvents. The organic extract is evaporated to dryness, and the residue is redissolved in acetone and oxidised with $KMnO_4$ solution. The oxidised residues are partitioned again into methyl chloride, which is evaporated before dissolution in acetone for quantification by GLC with an FPD in the phosphorus mode. Total residues of fenamiphos, fenamiphos sulfoxide and fenamiphos sulfone are quantified in a single sulfone peak. The limits of determination in various crops are reported as 0.01-0.1 mg/kg

Fenamiphos is included in multi-residue enforcement methods which were provided by the governments of Australia and The Netherlands. In the *Official Methods of Analysis in The Netherlands*, fenamiphos is quantified at a limit of 0.05 mg/kg in various crops; recoveries were reported for lettuce. In fatty foods the limit of determination is also 0.05 mg/kg. Inclusion of the sulfoxide and sulfone metabolites was not mentioned. Fenamiphos is quantified at a limit of 0.02 mg/kg in crops in the method provided by the Australian government.

Analyses of animal tissues involve quantification of total residues including fenamiphos sulfoxide, sulfone and sulfoxide phenol (FSO, FSO_2, and FSOP). The metabolites desisopropyl-fenamiphos and its sulfoxide and sulfone (DIF, DIFSO and $DIFSO_2$) are quantified in an additional peak containing the methylated residues. The work-up procedures for animal tissues and milk are similar to those for crops, but CH_3CN is used in the partitioning steps before oxidation. Reported limits of quantification in milk and tissues are 0.005 and 0.01 mg/kg respectively.

The limits of quantification in soil and water are 0.01 mg/kg and 0.1 μg/l respectively. An electrospray MS method was developed for the determination of fenamiphos and its degradation products in soil. Deuterated fenamiphos is introduced into the soil sample as an internal standard before work-up, followed by extraction in CH_3CN and analysis by LC-MS-MS. Aliquots are then analysed by HPLC/MS to determine fenamiphos and its sulfoxide and sulfone. The limit of determination for the individual compounds is 0.01 mg/kg.

Recoveries were determined by fortification with fenamiphos alone or a mixture of fenamiphos and its sulfoxide and sulfone.

The stability of residues was determined in stored samples of a number of crops including asparagus, banana, cotton seed (seed, meal, hulls and oil), garlic, and grapes (berries, juice, wet and dry pomace and raisins). Samples were fortified with a mixed standard composed of fenamiphos, FSO and FSO_2 at 1 mg/kg each (3 mg/kg total) and held

in frozen storage (≤-5° C) for up to 18 months. Some decrease of total residues (<10%) was observed in garlic and grape pomace after 12 months. At 18 months <10% decrease was found in most commodities and crop fractions except raisins and cotton seed hulls, which had decreased by <20%. The Meeting agreed that a decrease of <20% should not be considered significant, and that residues in the commodities examined were stable when stored frozen for 18 months.

In a study of the storage stability of residues in animal tissues, extracts of cattle fat, kidney, liver and muscle were fortified separately with 1 mg/kg fenamiphos, DIF, FSO, DIFSO, FSO_2 or $DIFSO_2$, and milk with 1 mg/kg fenamiphos, FSO or FSO_2. Tissues and milk were stored at -25° C for up to 2 and 3 months respectively. The results showed that fenamiphos, FSO and FSO_2 were stable in milk for 61 days, but fenamiphos was unstable in fat, liver, kidney and muscle, and was degraded within 83 days. As fenamiphos would have been converted to its sulfoxide and sulfone and the analytical method determines total residues as fenamiphos sulfone, the total fenamiphos residues in tissues are considered to be stable.

Use pattern

Fenamiphos is registered in many countries as a nematicide. Numerous labels from registered products were submitted by the manufacturer. For many crop uses, fenamiphos is applied pre- or post-planting as a soil treatment, in-furrow spray or by drip irrigation. To established crops, it is applied as a spray to individual plants or trees, with repeat treatments if necessary. Both fenamiphos sulfoxide and fenamiphos sulfone also exhibit nematicidal activity.

Supervised trials

Data were provided in support of the existing CXLs for bananas, Brussels sprouts, cabbages, carrots, coffee beans, cotton seed, grapes, melons, pineapples, potatoes and tomatoes. New data were reported on apples, cherries, lemons, limes, grapefruit, onions, peaches, peppers and zucchini.

The residues in the supervised crop trials were determined as the sum of fenamiphos, its sulfoxide and sulfone, expressed as fenamiphos.

Root, tuber and bulb vegetables. There are existing CXLs for fenamiphos in carrots, potatoes and sweet potatoes.

Trials on carrots were conducted in Australia, Italy and Spain. Fenamiphos was applied to soil before sowing in all the trials. The registered use pattern in Australia is for a single application at a maximum rate of 9-9.6 kg ai/ha and a PHI of 84 days. In Italy, a single application of 15 kg ai/ha is registered with a PHI of 90 days. The Spanish trials were not directly comparable to a registered use in Spain and were evaluated against GAP in Italy. Where higher rates of application gave residues below the limit of detection the results were also used in the estimation of the maximum residue level. The residues from trials according to GAP ranged from <0.02 to 0.08 mg/kg. The residues in rank order were <0.02 (8), 0.02, 0.024, 0.027, 0.05, 0.06 (2), 0.07 and 0.08 mg/kg. The Meeting estimated a maximum residue level of 0.2 mg/kg (the existing CXL) and an STMR of 0.02 mg/kg. (HR = 0.08 mg/kg).

Supervised trials on potatoes were conducted in Australia and Spain. Registered uses in Australia allow single applications at a maximum rate of 10 kg ai/ha with a PHI of 84 days. In Spain single applications of 8-10 kg ai/ha are allowed with a PHI of 120 days. The treatments were applied pre-planting. The residues in the tubers were <0.01-0.17 mg/kg in six trials. The Meeting considered that there were insufficient data to confirm the existing CXL of 0.2 mg/kg and recommended its withdrawal.

As no data were provided for sweet potatoes, the Meeting recommended withdrawal of the existing CXL of 0.1 mg/kg.

Trials on onions were conducted in Australia and South Africa. The product was applied to soil 4 or 5 days before sowing. The registered use in Australia is for a single application at 9.7 kg ai/ha with a PHI of 84 days. In South Africa the maximum rate is 3 kg ai/ha with a PHI of 80 days. Some samples in one of the South African trials were not fully mature although the reported PHIs in that trial were longer than in the other trials. The residues in onion bulbs ranged from <0.01 to 0.05 mg/kg in trials which complied with GAP. The Meeting considered that there were insufficient data to estimate a maximum residue level.

Brassica vegetables. There are existing CXLs for broccoli, Brussels sprouts, cabbages and cauliflower.

Data from 7 trials in the USA were provided for Brussels sprouts. The registered use pattern allows single applications of 6.7 kg ai/ha at planting with no specified PHI. The residues in 6 trials were <0.01 mg/kg; in the other trial a higher rate of 10 kg ai/ha was employed which resulted in residues of 0.02 mg/kg. The Meeting estimated a maximum residue level of 0.05 mg/kg and an STMR of 0.01 mg/kg, and recommended the withdrawal of the existing CXL of 0.05* mg/kg (HR = 0.01 mg/kg).

Trials on cabbages were conducted in Australia and the USA. The registered use pattern in Australia for crucifers is a single application up to 7 days before planting at a rate of 9-11 kg ai/ha and no specified PHI. GAP in the USA allows single applications at 6.7 kg ai/ha with no specified PHI. The residues in cabbage heads were <0.01-0.05 mg/kg in 12 trials which complied with GAP. The residues in rank order were <0.01 (10), 0.01, <0.02, 0.02 (3) and 0.05 mg/kg. The Meeting recommended the withdrawal of the existing CXL of 0.05* mg/kg and estimated a maximum residue level of 0.05 mg/kg and an STMR of 0.01 mg/kg (HR = 0.05 mg/kg).

In the US trials, wrapper leaves and field trash were also analysed for fenamiphos residues. The residues in the wrapper leaves were slightly higher than those levels found in the cabbage heads.

No data in support of the existing CXLs for broccoli and cauliflower were submitted. No information on specific GAP for cauliflower or broccoli was provided, although there are registered uses for brassicas in Costa Rica and crucifers in Australia. The Meeting agreed to recommend withdrawal of the existing CXLs for broccoli and cauliflower.

Fruiting vegetables. Supervised trials on peppers were conducted in Italy, Spain and Portugal in glasshouses and under field conditions. Applications ranged from several days before planting in the field trials to drip irrigation at flowering or early stages of fruiting in the

glasshouse trials. Data from trials with an encapsulated formulation (CS) have been recorded in the Tables, but registration of the product is only pending in Spain and Portugal and the data were therefore not used in the estimation of the maximum residue level and STMR. Current registered uses in Spain are single applications at planting at rates of 5-10 kg ai/ha with a PHI of 90 days.

The residues in peppers ranged from <0.02 to 0.35 mg/kg after treatment with GR and EC formulations, and from <0.02 to 0.31 mg/kg after treatment with the CS formulation. The range of residues was similar from treatment with the registered formulations and the CS product. The residues in rank order were <0.02, <0.05, 0.05 (2), 0.06 (2), 0.26 and 0.35 mg/kg. A maximum residue level of 0.5 mg/kg and an STMR of 0.055 mg/kg were estimated. (HR = 0.35 mg/kg).

Sixteen field and 11 glasshouse trials on tomatoes were conducted in Australia, Brazil, Italy, Portugal, South Africa and Spain with GR, EC, EW and CS formulations. In the field trials fenamiphos was applied at or shortly after planting, and in the glasshouse trials application was by drip irrigation pre-flowering or at early fruit formation. The registered use in Australia is for single applications at a maximum rate of 11 kg ai/ha with no specified PHI. In Brazil a single application at 3-4 kg ai/ha with a PHI of 90 days is registered. The Italian use pattern is for single applications at 10-15 kg ai/ha with a PHI of 20 days. In Portugal, a maximum of 3.4 kg ai/ha may be applied in a single treatment with a PHI of 20 days. On South African labels, application rates are expressed in g ai/m, allowing a maximum of 1 g ai/m and unspecified PHI. Spanish labels for the GR and EC products specify single applications at rates of 5-10 kg ai/ha with a PHI of 90 days.

The residues in tomatoes were <0.02-0.30 mg/kg after treatment with the GR and EC formulations and <0.02-0.15 mg/kg after treatment with the CS formulation. Although the CS product is a pending registration, the residues from the CS trials were within the range found for the currently registered formulations. The residues from the CS formulation were not considered in the estimation of the maximum residue level or STMR. The residues in rank order were <0.02 (4), <0.05 (5), <0.1, 0.15, 0.17, 0.27 and 0.30 mg/kg. The Meeting estimated a maximum residue level of 0.5 mg/kg and an STMR of 0.05 mg/kg, and recommended withdrawal of the existing CXL of 0.2 mg/kg (HR = 0.30 mg/kg).

Four glasshouse trials on zucchini were conducted in Italy in which the CS formulation was applied at the 3 to 5 leaf stage of growth. The proposed GAP for the CS product in Spain allows single applications at 10 kg ai/ha with a PHI of 90 days. The residues were <0.02 mg/kg in all the trials. As registration of the CS product is pending and there were no trials with registered formulations, a maximum residue level for zucchini could not be estimated.

Thirteen field and 9 glasshouse trials on melons were conducted in Australia, Brazil, Guatemala, Mexico and Italy with GR, EC and CS formulations. Application timings ranged from 14 days before sowing to flowering. In many trials residues were determined in the whole fruit and pulp; in some the residues in peel were reported separately. Registered use patterns in Australia are for single applications at a maximum rate of 9.6 kg ai/ha and no specified PHI. In Brazil, labels recommend single applications at 4 kg ai/ha with no specified PHI. The 10, 12 and 15 GR products are registered in Guatemala with single applications at a maximum rate of 5.1 kg ai/ha and a PHI of 60 days. In Italy the 5 GR product may be applied at rates of 5-10 kg ai/ha with a PHI of 20 days. In Spain GR and EC products are registered

with a maximum rate of 10 kg ai/ha and a PHI of 90 days. Registration of the CS formulation is pending. The trials in Mexico were evaluated against the registered uses in Guatemala.

The residues in the whole fruit after treatment with the GR and EC formulations were <0.01-<0.05 mg/kg. In trials with the CS formulation residues in the whole fruit were <0.02-0.03 mg/kg. The residues in the pulp were below the reported limit of detection or determination in all the trials. The residues in the whole fruit in rank order were <0.01 (6), <0.02 (3) and <0.05 (4) mg/kg. The Meeting estimated a maximum residue level of 0.05* mg/kg, the same as the existing CXL. The residues in the pulp in rank order were <0.01 (4) and <0.02 mg/kg. The Meeting estimated an STMR of 0.02 mg/kg for melon pulp (HR = 0.02 mg/kg).

Two trials on watermelons were carried out in Italy, where the registered use pattern is a single application of a GR product at 5-10 kg ai/ha with a PHI of 20 days. Sampling in the trials was at fruit maturity, 85-109 days after treatment, so the PHI was not observed although the application was made up to 20 days before planting. The residues in the whole fruit and pulp were below the limit of determination of 0.02 mg/kg. The Meeting agreed that as there were few trials for watermelons and Italian GAP for melons and watermelons is identical, the trials on melons could be used to support a recommended MRL for watermelon. A maximum residue level of 0.05* mg/kg was therefore estimated for watermelon, with an STMR of 0.02 mg/kg (HR = 0.02 mg/kg).

Citrus fruits. Many of the trials on citrus fruit were conducted in the USA at excessive treatment rates. In trials on grapefruit, lemons, limes and oranges, soil applications were made at rates of 2.4 and 4 times the registered label rates. The registered use patterns for citrus fruits in the USA prescribe single applications at a maximum rate of 8.4 kg ai/ha with a PHI of 30 days. In many trials, residues were reported in the whole fruit, pulp and peel.

Supervised trials on grapefruit in the USA were at rates equivalent to 4 times the maximum label rate. The residues were <0.01-0.29 mg/kg and <0.01-0.08 mg/kg in the whole fruit and pulp respectively, in samples taken at PHIs of 30-243 days. As the trials did not reflect GAP in the USA and application at excessive rates resulted in detectable residues, the data could not be used to estimate a maximum residue level for grapefruit.

Eight trials on lemons were conducted in Australia, South Africa and the USA. Again in the 6 US trials, the rates were equivalent to 2.6 or 4 times the maximum registered rate. The registered use pattern in Australia is single applications at 30 kg ai/ha with no specified PHI. In South Africa, GAP allows a maximum rate of 12 kg ai/ha or 2 g ai/m^2 to be applied with a PHI of 150 days. The residues from the Australian and South African trials were <0.05 mg/kg in the whole fruit, pulp and peel. The residues in the US trials were <0.01-0.03 mg/kg in the whole fruit and <0.01 mg/kg in the pulp. The Meeting considered that 6 of the 8 trials were not according to GAP and could not be used to estimate a maximum residue level for lemons.

In two US trials on limes the rates of application were 4 times the maximum GAP rate. The residues in the whole fruit 147 days after treatment were below the limit of detection of 0.01 mg/kg.

Trials were conducted in Australia, South Africa and the USA in support of the existing CXL of 0.5 mg/kg for oranges. All the trials in the USA were at rates of 2.6 or 4

times the maximum registered rate. GAP in Australia and South Africa is identical to that for lemons. The residues in the whole fruit were <0.02-0.08 mg/kg in the trials in Australia and South Africa. In the US trials the residues were <0.01-0.17 mg/kg in the whole fruit and <0.01-0.02 mg/kg in the pulp. As most of the trials were in the USA at excessive rates they could not be used to estimate a maximum residue level. The Meeting therefore recommended the withdrawal of the existing CXL for oranges.

In summary, the Meeting concluded that as exaggerated treatments were applied in most of the trials on citrus fruits and residues above the limit of determination were found at varying intervals after treatment, no maximum residue levels could be estimated.

Pome fruits. Numerous trials on apples were conducted in the USA where the registered use rates are 5.4-8.2 kg ai/ha with a PHI of 72 days. The trials were all at a rate of 22.4 kg ai/ha, 2.6 times the maximum rate. The residues in the whole fruit in all 33 trials were below the limit of detection of 0.01 mg/kg; the reported limit of determination was 0.05 mg/kg. Although the trials were not in accord with US GAP, the Meeting considered that as there were no detectable residues in any of the trials after exaggerated treatments, the data could be used to estimate a maximum residue level of 0.05* mg/kg and an STMR of 0.01 mg/kg (HR = 0.01 mg/kg).

Stone fruits. Nineteen supervised trials on cherries were conducted in the USA, 16 at 2.7 and 3 at 1.7 times the maximum registered rate (8.2 kg ai/ha with a PHI of 45 days). The residues in the whole fruit ranged from <0.01 to 0.18 mg/kg at PHIs of 45-52 days after treatment. The trials were not in accord with GAP in the USA or other countries, so no maximum residue level could be estimated.

Twenty nine trials on peaches were conducted in the USA and one in Italy at rates equivalent to 2.7 and 1.7 times the maximum national registered rates respectively. The residues in the whole fruit were <0.01-0.16 mg/kg at the earliest sampling intervals, after treatment at stages from pre-flowering to immature fruit. As the trials did not comply with GAP in either Italy or the USA, the Meeting could not estimate a maximum residue level.

Berries and other small fruits. Supervised trials on grapes were conducted in Chile, Mexico, South Africa and the USA. In the US trials, residues were determined in raisins and raisin trash as well as grapes. GAP in Chile specifies rates of 6-8 kg ai/ha (in-furrow) or 2.8-4.8 kg ai/ha (drip irrigation), with a PHI of 45 days. Registered use patterns in Mexico are for 4-6 kg ai/ha and no specified PHI. In South Africa, a maximum rate of 1 g ai/m^2 is registered with a PHI of 100 days, and in the USA 3.3-6.5 kg ai/ha with a PHI of 2 days.

The Chilean and US trials were at GAP rates and above, up to 3 and 1.5 times the maximum rates in Chile and the USA respectively. Sampling was at longer intervals than the GAP PHI in many of the US trials, but the earliest sampling is considered to accord with GAP if mature fruit were collected. The residues in the grapes were <0.01-0.09 mg/kg from a total of 49 trials. The residues from trials which were considered to comply with GAP in rank order were <0.01 (11), 0.01 (6), 0.02 (7), 0.03 (5), <0.05 (4), 0.07 (2) and 0.09 mg/kg. Although analytical recoveries of fenamiphos were determined at concentrations of 0.01, 0.02, 0.03 and 0.05 mg/kg, recoveries of all components of the defined residue (fenamiphos, FSO and FSO_2) were determined only at concentrations of 0.05 and 0.1 mg/kg, so the validated limit of determination in grapes is 0.05 mg/kg. The Meeting estimated a maximum

residue level of 0.1 mg/kg, confirming the existing CXL, and an STMR of 0.02 mg/kg (HR = 0.09 mg/kg).

Tropical fruits-inedible peel. Trials on bananas were conducted in Australia, Brazil, the Canary Islands (Spain), Costa Rica and the Windward Islands. Trials in the Canary Islands and the Windward Islands were evaluated against GAP for Spain and Costa Rica respectively. Rates at or above the registered use patterns were applied in the trials. In some cases rates of application were expressed both as kg ai/ha and as g ai/plant to allow for different cropping densities in different regions. For example the trials in Costa Rica allowed for cropping densities ranging from 416 to 833 plants/ha, and those in the Windward Islands for 412-1785 plants/ha. Although trials with the CS product were reported, the results were not used in the estimation of the maximum residue level or STMR because registration of the product was pending. The residues were determined separately in the pulp and peel or on a whole fruit basis; where residues in the pulp and peel were below the limit of detection or determination, the residues in the whole fruit were considered to have the same value.

The residues in the whole fruit in rank order were <0.01 (7) and <0.02 (3) mg/kg. The Meeting estimated a maximum residue level of 0.05* mg/kg, based on the routine limit of quantification of fenamiphos, and recommended withdrawal of the existing CXL of 0.1 mg/kg. The residues in banana pulp in rank order were <0.02 (6) and <0.025 (3) mg/kg. An STMR of 0.02 mg/kg was estimated (HR = 0.025 mg/kg).

Trials on pineapples were mainly in Hawaii, with a few trials in Australia and Puerto Rico. Registered use patterns in Australia allow a maximum of 5 applications at 2.4 kg ai/ha to the main plant crop and ratoon crop and a maximum of 2 applications at 4.8 kg ai/ha to the ratoon crop alone; PHIs are not specified. Registered labels in the USA specify two use patterns, one for Puerto Rico and the other for Hawaii. For Puerto Rico, a pre-plant application of 10 kg ai/ha with additional applications at 5.4-9.8 kg ai/ha post-planting and to the first ratoon crop, with total applications of 20 kg ai/ha per ratoon crop are recommended, with a PHI of 225 days for the post-planting applications. In Hawaii the total applications are 26.2 kg ai/ha per plant crop and 9.8 kg ai/ha per ratoon crop, made up of a pre-planting application of 9.8 kg ai/ha for the plant crop and post-planting sprays at 0.5-3.3 kg ai/ha. A PHI of 30 days is recommended for the post-planting applications.

In the Hawaiian trials the rates were equivalent to 2.3 times the pre-planting application, 1.2-2.3 times the total plant crop treatment and up to 2.3 times the ratoon crop treatment. The residues were <0.01-0.03 mg/kg in the whole fruit and <0.01-0.05 mg/kg in the pulp. Residues were determined in bran, foliage, forage, crowns and stumps in addition to whole fruit and pulp.

In two Puerto Rican trials, twice the pre-plant rate and up to 1.1 times the post-plant rates were applied to the plant crop.

The residues in the whole fruit in the 3 Australian trials were <0.01 mg/kg, but only 1 trial complied with GAP. The residues in the pulp were <0.01 mg/kg in the Puerto Rican trials. Although the residues in the Hawaiian trials were from exaggerated treatments, the number of post-planting applications to the plant and ratoon crops are not always specified on the label, and multiple applications may be required at these stages depending upon pest pressure. Total application rates per plant crop and ratoon crop are indicated however. The Meeting considered that although treatments were exaggerated the residues in

the whole fruit and pulp were below the limit of detection in most of the trials, so the results were acceptable for estimating a maximum residue level and an STMR. The residues in the whole fruit in rank order were <0.01 (8), 0.02 and 0.03 mg/kg, and in the pulp <0.01 (26), 0.01 (2), 0.02 (2), 0.05 and 0.14 mg/kg. The Meeting included the figure of 0.14 mg/kg in the data set, as the conditions of the trial (PHI, application rate and application timing) did not differ from other instances where residues in the pulp were <0.01 mg/kg. The validated limit of determination in pineapple pulp, bran, foliage and crowns was 0.05 mg/kg. The Meeting estimated a maximum residue level of 0.05* mg/kg, confirming the existing CXL for pineapples, and an STMR of 0.01 mg/kg for pineapple pulp (HR = 0.14 mg/kg).

The residues in wet bran were <0.01-0.25 mg/kg, in dry bran <0.01-2.3 mg/kg and in unspecified bran <0.01-0.13 mg/kg.

Oilseeds. Supervised trials on peanuts were conducted in the USA and South Africa. The residues were determined in nuts, shells, foliage and vines. In the US trials, up to 7 times the maximum registered rate was applied and nuts were sampled at normal harvest. Residues in all samples of nuts were below the limit of detection or determination. The residues in vines were <0.01-3.19 mg/kg at rates of 4.7-7 times the label rate and PHIs of 94-154 days after planting. GAP in the USA allows single applications at rates of 1.6-2.9 kg ai/ha, with no specified PHI. In South Africa, the registered use pattern is a single application at 1.6-3.2 kg ai/ha and a PHI of 63 days. Although exaggerated treatments were applied, no residues were detectable in the nuts and the Meeting therefore concluded that the existing CXL of 0.05* mg/kg could be supported. The Meeting estimated an STMR of 0, as no residues were detectable in any samples. It was considered that owing to the high oil content of peanuts residues might accumulate in the nuts, but this was not found (HR = 0.01 mg/kg for peanut).

In trials on cotton seed in Brazil, South Africa and the USA fenamiphos was applied before or shortly after planting. In the US trials the rates were 0.6-1.7 times the maximum registered rate. GAP in the USA requires application at 0.82-3.27 kg ai/ha with no specified PHI, in Brazil 3-5 kg ai/ha with a PHI of 98 days, and in South Africa 15 g ai/100m of row with no specified PHI. Residues were determined in seed (delinted and fuzzy) and ginned trash. The residues in the cotton seed in all the relevant trials (25) were <0.01 mg/kg. The Meeting estimated a maximum residue level of 0.05* mg/kg, confirming the existing CXL, as this was the validated limit of determination. An STMR of 0.01 mg/kg was estimated (HR = 0.01 mg/kg).

The residues in the cotton gin trash were <0.01 mg/kg in 7 trials which were considered to conform to US GAP.

Coffee. Supervised trials were conducted in Brazil, Guatemala and Mexico. In all the trials a single soil application was made to mature trees at the pre-bloom or fruit formation stage. Residues were determined in the fruit (berries) and the beans. The MRL applies to the seed only; the bean and other parts of the fruits are not included.

GAP in Brazil is 1-7 g ai/plant with a PHI of 45 days, in Guatemala 2.4-5 kg ai/ha and a PHI of 60 days, and in Mexico 1-1.5 g ai/plant with a PHI of 45 days. The Mexican trials were not considered, as the prescribed GAP could not be compared with the application rate as expressed in the supervised trials. The residues in the two relevant samples of beans were <0.1 and <0.2 mg/kg. The residues in the berries in rank order were 0.01 (3), 0.02, 0.03,

0.04, <0.05 (4), 0.06 and 0.11 mg/kg. The Meeting did not estimate a maximum residue level as there were insufficient data for beans, and recommended withdrawal of the existing CXLs of 0.1 mg/kg for coffee beans and coffee beans, roasted.

Dietary burden of livestock and animal feeding studies

Tables of dietary burden were compiled for dairy cattle and hens, in which maximum and median residues in various feed items were listed together with an indication of the percentage dry matter, percentage of the item in the diet, and the intake expressed as mg/animal/day. Commodities in which the dry matter was above 85% as received were not corrected for dry matter.

For dairy cattle, a dry matter intake of 15 kg/day for a 500 kg animal was assumed. An exposure of 0.13 ppm in the feed (1.88 mg/animal/day; 0.004 mg/kg body weight/day) was estimated on the basis of the consumption of dry apple pomace, raisin trash, peanut vines and dry tomato pulp, which provided the highest median residues. As a typical diet would not consist only of these items the estimate is probably exaggerated. The lowest level in the diet in the cattle feeding study was 2 ppm fenamiphos sulfoxide or about 15 times the calculated exposure. After feeding at 2 ppm for 28 days residues in the milk, liver, kidney, muscle (flank and loin) and fat (omental, subcutaneous and renal) were below the limits of detection of 0.001 mg/kg in milk and 0.01 mg/kg in tissues. The limits of determination were reported as 0.005 mg/kg in milk and 0.01 mg/kg in tissues. On the basis of these limits the Meeting estimated maximum residue levels of 0.005* mg/kg in milk and 0.01* mg/kg in the tissues. STMRs of 0 were estimated for milk, meat and edible offal, since no residues were detectable in any tissues after feeding at 15 times the calculated exposure level for a dairy animal.

For hens, an intake of 150 g dry matter/day and 2 kg body weight were assumed. An estimated maximum exposure of 0.01 ppm in the feed was based on 100% peanut meal as a worst-case situation, as only peanut meal and cotton meal were included in the dietary burden table. The lowest feeding levels in two studies with labelled fenamiphos were 0.06 and 2 ppm for 14 consecutive days. The total radioactivity from the 0.06 ppm level in eggs or tissues was not reported. With feeding at 2 ppm the maximum radioactivities in the tissues were below the minimum quantifiable limits of 7 to 20 ng/g (ppb) as fenamiphos. On the assumption that the limit of determination reported in cattle tissues is also applicable to poultry tissues and eggs, the Meeting estimated maximum residue levels of 0.01* mg/kg for poultry meat, poultry offal and eggs. It should be noted that the calculated exposure of 0.002 ppm in the hen diet is probably exaggerated as feeding 100% peanut or cotton meal would not be considered typical. STMRs of 0 were estimated for eggs, poultry meat and poultry offal.

Processing

Processing studies on tomatoes, oranges, apples, grapes and pineapples were reported.

Tomatoes containing residues of 0.5 mg/kg fenamiphos were subjected to commercial processing into canned tomatoes, juice and ketchup. Total fenamiphos residues were concentrated in tomato pulp solids (wet and dry) and tomato pomace, as well as other commodities that may be used as animal feed items. Calculated processing factors for tomato juice, pasteurised tomato juice, ketchup and canned tomatoes were 0.74, 0.88, 0.58 and 0.72

respectively. As an STMR of 0.05 mg/kg was estimated for whole tomatoes, an STMR of 0.05 mg/kg was also estimated for tomato juice (HR-P = 0.27 for tomato juice).

Tomatoes fortified with [U-*phenyl*-^{14}C]fenamiphos at 0.8 mg/kg were allowed to stand at room temperature for 24 hours then blanched, peeled, cored, and cooked for 40 minutes. Blanching and cooking led to a reduction of residues by almost 50%, with 27% of the radioactivity present in the cooking water. There was negligible loss of radioactivity (1.5%) by peeling and coring.

Orange trees were treated at a rate equivalent to 100 kg ai/ha and fruit were harvested and processed when residues had reached maximum levels in the leaves, which were sampled at monthly intervals after treatment. The residues in the whole fruit ranged from <0.01 to 0.13 mg/kg, with average residues of 0.07 mg/kg. The residues were concentrated in unwashed and washed peel, peel bits, clear oil (produced from the peel), chopped peel, pressed dry peel, press liquor and molasses, with processing factors of 6.71, 8.57, 3.28, 64, 1.86, 5.71, 2.86 and 7.0 respectively. Processing factors for juice and pulp were 0.28 and 0.14 respectively. STMRs were not calculated for the processed fractions as no maximum residue level was estimated for oranges or citrus fruits.

Apple trees were treated with a soil application at 33.6 kg ai/ha. Fruit were harvested 66 days after treatment and processed into juice and pomace. The residues in the apples were 0.14 mg/kg and were concentrated in wet and dry pomace with processing factors of 4.86 and 17.7 respectively. A processing factor of 0.78 was calculated for apple juice. As an STMR of 0.01 mg/kg was estimated for apple an STMR of 0.0078 mg/kg was calculated for juice.

Grapes were processed after treatment at rates of one and 5 times the maximum registered rate in the USA. The residues in fruit were 0.07, 0.02 and 0.02 mg/kg at 55, 56 and 7 days after treatment respectively at 1, 1 and 5 times rates. Fenamiphos residues were concentrated in raisins, raisin trash and dry pomace, with processing factors of 1.57, 8.3 and 5 respectively. Processing factors for juice and wet pomace were <1. An STMR of 0.009 mg/kg was calculated for juice (HR-P for raisins = 0.14 mg/kg; grape juice = 0.04 mg/kg).

Pineapples were processed into raw juice, canned juice, raw bran and dried bran. The residues in the whole fruit were 0.67 mg/kg after 7 applications at 5 times the registered US rate for Hawaii. The residues were concentrated in canned juice, raw bran and dried bran with calculated processing factors of 1.2, 2.1 and 2.5 respectively. STMRs of 0.006 and 0.012 mg/kg were calculated for raw and canned juice (HR-P = 0.17 mg/kg for pineapple juice, canned).

Peanuts were treated with 5 times the maximum registered US rate at the mid to late pegging stage. The residues in the kernels were 0.01 mg/kg. The peanuts were processed into meal, soapstock, crude oil and refined oil. The residues were ≤0.01 mg/kg in all the fractions except crude oil which contained 0.02 mg/kg. This was not considered to be a concentration effect as the refined oil contained <0.01 mg/kg. An STMR of 0 was estimated for peanuts, so the STMR for peanut oil is the same. The Meeting estimated a maximum residue level of 0.05* mg/kg for peanut oil, crude.

The residues in cotton seed were 0.01 mg/kg after a single exaggerated application at planting. Cotton bolls were harvested at maturity 153 days after treatment. The seed was processed into meal, hulls, soapstock, crude oil and refined oil. The residues in all the

processed fractions were ≤0.01 mg/kg, except in crude oil which contained 0.02 mg/kg. This was not considered to be a concentration effect. The Meeting estimated a maximum residue level of 0.05* mg/kg and an STMR of 0.01 mg/kg for cotton seed oil, crude.

The Meeting recommended withdrawal of the following existing CXLs which were not supported by data: broccoli, cauliflower, kiwifruit, soya beans, sugar beet and sweet potato.

DIETARY RISK ASSESSMENT

Chronic intake

STMRs were estimated for all commodities included in the dietary intake assessment. International Estimated Daily Intakes for the five GEMS/Food regional diets were in the range of 3-14% of the ADI (Annex III).

The Meeting concluded that the intake of residues of fenamiphos resulting from its uses that have been considered by the JMPR is unlikely to present a public health concern.

Acute intake

The acute reference dose for fenamiphos is 0.0008 mg/kg bw , as the available data did not permit the 1997 Meeting to establish an acute reference dose different from the ADI. The calculated short-term intakes ranged from 15 to 2900% of the acute reference dose for children and 8 to 863% of the acute reference dose for the general population (Annex IV). It should be noted that for commodities such as apples, bananas, melons, peanuts and watermelons, residues in the edible portion in all supervised trials were below the limit of detection of the method used, but for the purposes of the short-term risk assessment figures at the limit of detection were used in the calculation. The current method does not allow any further refinement of the acute intake assessment.

The Meeting concluded that all commodities should be considered further when an acute reference dose is established from new data or when new data on unit weight, variability factor etc. become available.

4.16 FENPROPIMORPH (188)

RESIDUE AND ANALYTICAL ASPECTS

Fenpropimorph was first evaluated for residues by the 1995 JMPR. That Meeting estimated maximum residue levels which were recommended for use as MRLs for cereals (barley, oats, rye, wheat), cereal straw and fodder (dry), sugar beet and fodder beet leaves and tops.

Conventional livestock and poultry feeding studies with determination of fenpropimorph and the main metabolites identified in metabolism studies, and validated analytical regulatory methods (including representative chromatograms) for the determination of fenpropimorph and its main metabolites in animal products were listed as desirable.

A dairy cattle feeding study and an analytical method for animal products as well as information on GAP, a metabolism study and residue data on bananas have been reported to the present Meeting.

Plant metabolism

Banana plants were treated four times at the twofold application rate of 0.9 kg ai/ha with morpholine-2,6-^{14}C- and phenyl-U-^{14}C-labelled fenpropimorph.

On a whole fruit basis, bananas treated with morpholine-labelled fenpropimorph had a maximum TRR as fenpropimorph of about 0.67 mg/kg in unripe, and 0.61 mg/kg in ripe, unbagged fruit. The corresponding values for bagged fruit were 0.35 and 0.32 mg/kg. Bananas treated with the phenyl-labelled compound had significantly lower TRR levels: 0.11 mg/kg (unripe, unbagged) and 0.09 mg/kg (ripe, unbagged). The corresponding values for bagged bananas were 0.025 and 0.026 mg/kg.

Most of the total ^{14}C was extractable with methanol: 83 to 88% from ripe fruit and 27% to 72% from unripe fruit. The extract of bananas treated with the morpholine-labelled compound showed two main HPLC peaks. One was non-polar and identified by MS as unchanged fenpropimorph. The other peak was polar and was identified by HPLC after acetylation as a mixture of natural assimilation products (glucose, fructose, saccharose). Bananas treated with phenyl-labelled fenpropimorph showed only one prominent HPLC peak which was identified as fenpropimorph.

In contrast to the metabolism in cereals (1995 JMPR), the metabolites 4-{3-[4-(2-hydroxy-1,1-dimethyl)ethylphenyl]-2-methylpropyl}-*cis*-2,6-dimethylmorpholine (BF 421-1), 2-methyl-2-{4-[2-methyl-3-(*cis*-2,6-dimethylmorpholin-4-yl)propyl]phenyl}propionic acid (BF 421-2), methyl 2-methyl-2-{4-[2-methyl-3-(*cis*-2,6-dimethylmorpholin-4-yl)propyl] phenyl} propionate (BF 421-2-Me), [3-(4-*tert*-butylphenyl)-2-methylpropyl](2-hydroxypropyl)amine (BF 421-7), *cis*-2,6-dimethylmorpholine (BF 421-10), 4-[3-(4-*tert*-butylphenyl)-2-methyl-1-oxopropyl]-*cis*-2,6-dimethylmorpholine (BF 421-13) and 4-[3-(4-*tert*-butylphenyl)-2-methyl propyl]-*cis*-2,6-dimethylmorpholine-3-one (BF 421-15) were not reported.

Farm animal metabolism

In goats fenpropimorph acid, BF 421-2, is the main component of the residue. BF 421-2 would not be expected to concentrate in lipid-rich tissues and products, but it can occur at detectable levels. In liver, the data suggested that the residues of BF 421-2 plus its conjugates would almost certainly be no more than twice the level of BF 421-2 alone. In hens BF 421-2 is probably also the main metabolite but, since residues were only characterized in plasma, liver and kidneys, there was no information on the nature of the residue in poultry meat, fat or eggs (1995 JMPR).

Methods of residue analysis

BASF method 241/1 was developed to determine residues of fenpropimorph in bananas. Fenpropimorph was distilled from the fruit using Bleidner apparatus after mixing with aqueous sodium bicarbonate solution and the distillate was collected in dichloromethane. After clean-up by liquid/liquid partition and a cation-exchange column, the final residues were quantified by GLC with an NPD. The LOD for whole fruit and pulp was 0.05 mg/kg.

The official multi-residue method of analysis in The Netherlands describes the determination of fenpropimorph residues in fatty and non-fatty foods by GLC with an ion trap detector. The LOD is 0.05 mg/kg.

BF 421-2, the main metabolite of fenpropimorph in animal products, is extracted from fat with hexane, from meat liver and kidney by maceration with methanol/aqueous pH 9 buffer, and from milk and eggs with acetonitrile/aqueous pH 9 buffer. After liquid-liquid partition and further clean-up on a C-18 bonded silica gel column, the BF 421-2 is determined by HPLC with a UV detector. LODs are 0.01 mg/kg for animal tissues and eggs, and 0.002 mg/l for milk. No conjugates of BF 421-2, other metabolites or the parent compound are determined by the method.

Under frozen storage, fenpropimorph residues are stable for at least 7.5 months in bananas. Recoveries of BF 421-2 when stored frozen for 7-8 months were muscle 66%, fat 74%, blood 76%, milk 81%, liver 92% and kidney 95%.

Definition of the residue

The 1995 JMPR concluded that for enforcement and dietary intake purposes the residue in plants should be defined as fenpropimorph. No residue definition was proposed for animal products.

The present Meeting agreed that the definition of the residue for compliance with MRLs for plant commodities should be fenpropimorph *per se*. On the basis of the metabolism in bananas, the same definition should be acceptable for the estimation of the dietary intake in bananas.

On the basis of the metabolism studies on rats and lactating goats reviewed by the 1995 JMPR, the Meeting agreed that BF 421-2 can be used as a marker compound for enforcement purposes. The definition of the residue for compliance with MRLs for animal products should therefore be 2-methyl-2-{4-[2-methyl-3-(*cis*-2,6-dimethylmorpholin-4-yl)propyl]phenyl}propionic acid (BF 421-2), expressed as fenpropimorph. The same definition should be used for animal products to estimate the dietary intake.

In view of the residues found in animals in the tissues and organs in the metabolism and feeding studies, the Meeting concluded that BF 421-2 should not be categorised as fat-soluble.

The Meeting concluded that the following residue definitions are appropriate.

Commodities of plant origin for compliance with MRLs and for the estimation of dietary intake: fenpropimorph

Commodities of animal origin for compliance with MRLs and for the estimation of dietary intake 2-methyl-2-{4-[2-methyl-3-(*cis*-2,6-dimethylmorpholin-4-yl)propyl]phenyl}propionic acid.

Residues resulting from supervised trials

Bananas. Fenpropimorph is registered in Cuba for 4–12 applications of 0.44 kg ai/ha and 2.2 kg ai/hl. In view of the fungicide resistance management strategy for morpholine products, the four applications used in the supervised trials have been considered to be the maximum number of treatments.

Eight supervised trials were conducted in 1994 in Martinique: 4 x 0.53 kg ai/ha (20 l water/ha, 2.6 kg ai/hl) were applied to bagged bananas as a simulated aerial treatment. On day 0, the residues in the whole fruit were <0.05 (6), 0.07 and 0.13 mg/kg.

A further 15 trials were conducted in 1996 in Costa Rica (4), Ecuador (4), Columbia (3), Honduras (2), Guatemala (1) and Mexico (1), all with 4 applications at the nominal application rate of 0.545 kg ai/ha (20 l water/ha, 2.7 kg ai/hl). In each plot 50% of the trees were bagged. Twelve trials were with ground and three with aerial applications. Residues in the ground-sprayed trials on the day of treatment were as follows.

Unbagged bananas, whole fruit: 0.1, 0.12, 0.16, 0.26, 0.32, 0.36, 0.43, 0.65, 0.7, 0.75, 1.2, 1.4 mg/kg
Unbagged bananas, pulp: <0.05 (4), 0.06, 0.08, 0.14, 0.18, 0.28, 0.29, 0.3, 0.43 mg/kg
Bagged bananas, whole fruit: <0.05 (7), 0.13, 0.16, 0.17, 0.33, 0.4 mg/kg
Bagged bananas, pulp: <0.05 (7), 0.07, 0.07, 0.08, 0.2 mg/kg

The residues from aerial application were significantly lower. One sample of unbagged whole fruit contained 0.11 mg/kg. Residues in all the other samples were below the LOD.

The Meeting estimated a maximum residue level of 2 mg/kg based on the residues in ground-sprayed unbagged whole fruit and an STMR of 0.11 mg/kg from the corresponding residues in the pulp.

Animal products. Assuming worst-case feeding situations, the maximum theoretical fenpropimorph levels in animal feed were estimated by the 1995 JMPR to be 1.3 ppm for beef cattle, 1.7 ppm for dairy cattle and 0.35 ppm for poultry.

Groups of 3 cows were fed for 28 days with 26 kg maize silage containing 5.2 ppm, 15.7 ppm or 52.4 ppm fenpropimorph. For an average body weight of 600 kg the calculated daily dose rates were 0.23, 0.68 and 2.3 mg fenpropimorph per kg body weight. Milk samples were collected from all cows on days 1, 4, 7, 9, 14, 17, 21, 23 and 28. At the end of the test period the animals were slaughtered and their tissues and milk analysed for residues of the metabolite BF 421-2.

There was hardly any difference in the residues of BF 421-2 in the milk or tissues between the two lower dose groups. No clear explanation for this was suggested. As the ratios of the high/mean residues in the 52.4 to 5.2 ppm dose group in milk were 8.8/8.3, in liver 9.1/7.5, in kidney 8.4/8.3, in muscle 7.8/6.3 and in fat 11/7.8, indicating near linearity, further calculations assuming a more realistic dietary burden of 1.7 ppm were based on the residues in these groups only. The following Table shows the highest and the mean measured and extrapolated residues. Since the residues reached a plateau in the milk slowly (in 2

weeks), maximum residue levels were estimated from the highest extrapolated residues. STMRs were estimated from the mean extrapolated residues.

Dose group ppm	BF 421-2 residues, calculated as fenpropimorph, mg/kg									
	Milk, day 14 high mean		Liver high mean		Kidney high mean		Muscle high mean		Fat high mean	
1 x rate, 5.2 (1.7) [1]	0.017 (0.006)	0.012 (0.004)	0.86 (0.28)	0.68 (0.22)	0.1 (0.033)	0.08 (0.026)	0.036 (0.012)	0.027 (0.009)	0.018 (0.006)	0.018 (0.006)
3 x rate, 15.7 (1.7)	0.022 (0.0024)	0.017 (0.0018)	0.67 (0.073)	0.52 (0.056)	0.11 (0.012)	0.091 (0.01)	0.036 (0.004)	0.027 (0.003)	0.027 (0.003)	0.018 (0.002)
10 x rate, 52.4 (1.7)	0.16 (0.005)	0.1 (0.003)	7.8 (0.25)	5.1 (0.17)	0.84 (0.027)	0.66 (0.021)	0.28 (0.009)	0.17 (0.006)	0.2 (0.006)	0.14 (0.005)

[1]Values in parenthesis: calculated, assuming 1.7 ppm intake

The Meeting estimated maximum residue levels of 0.01 mg/kg for milk, 0.3 mg/kg for liver, 0.05 mg/kg for kidney, 0.02 mg/kg for meat and 0.01 mg/kg for fat and STMR levels of 0.004 mg/kg for milk, 0.22 mg/kg for liver, 0.026 mg/kg for kidney, 0.009 mg/kg for meat and 0.006 mg/kg for fat.

As the metabolism is similar in rats and cows, these levels are estimated for cattle, goats, sheep and pigs.

The Meeting noted that the nature of the residue in poultry meat, fat and eggs is unknown and no feeding study was carried out. Nevertheless, taking into account the results of the poultry metabolism study reviewed by the 1995 JMPR, with doses of 51.5 ppm in the diet with the phenyl label and 39.3 ppm with the morpholine label compared with the low estimated maximum dietary burden of 0.35 ppm, the Meeting concluded that no residues are to be expected in poultry products.

DIETARY RISK ASSESSMENT

Chronic intake

STMRs have been estimated by the current Meeting for bananas and animal products. Where consumption data were available these STMRs were used in the estimates of dietary intake together with the draft MRLs for 5 other food commodities.

The estimated dietary intakes for the five GEMS/Food regional diets, based on these MRLs and STMRs, were in the range of 10-90% of the ADI. The Meeting concluded that the intake of residues of fenpropimorph resulting from its uses that have been considered by the JMPR is unlikely to present a public heath concern.

Acute intake

The international estimate of short-term intake (IESTI) for fenpropimorph was calculated for the only commodity for which an MRL and STMR was established and for which consumption data (large portion consumption and unit weight) were available (*see* Section 3). The results are shown in Annex IV. The IESTIs were 0.0045 mg/kg bw for the general population and 0.018 mg/kg bw for children. As no acute reference dose has been established, the acute risk assessment for fenpropimorph was not finalized.

4.17 FENPYROXIMATE (193)

RESIDUE AND ANALYTICAL ASPECTS

Fenpyroximate was first evaluated for toxicity and residues by the 1995 JMPR, which allocated an ADI of 0-0.01 mg/kg bw. That Meeting estimated a maximum residue level of 0.2 mg/kg for apples but this could not be recommended for use as an MRL owing to the lack of critical supporting data.

The Meeting received information on analytical methods with supplementary residue data on oranges, grapes and hops, animal metabolism studies on goats and rats, and an animal feeding study on cows.

Animal metabolism

The metabolism of fenpyroximate in goats was rapid. Small traces of fenpyroximate were found in fat, kidney, muscle and milk. Ten metabolites were identified or characterized. The main compounds found were G-4 *((*E)-α-(1,3-dimethyl-5-phenoxypyrazol-4-ylmethylene-amino-oxy)-*p*-toluic acid*)* and G-7 *((E)*-α-(3-methyl-5-phenoxypyrazol-4-ylmethyleneamino-oxy*)*-*p*-toluic acid*)* in the liver and kidneys, fenpyroximate, G-2 (1-hydroxylmethyl-1-methyl- ethyl *(E)*-α-(1,3-dimethyl-5-phenoxypyrazol-4-ylmethyleneamino-oxy*)*-*p*-toluate) and G-4 in muscle and fat, fenpyroximate, G-2 and G-9 (4-cyano-1-methyl-5-phenoxy pyrazole-3-carboxylic acid) in milk and M-8 (1,3-dimethyl-5-phenoxypyrazole-4-carboxylic acid) and G-9 in urine. The faeces contained fenpyroximate and G-2.

Analytical methods

Analytical methods for fenpyroximate and its isomer were described in the 1995 evaluation. They were based on extraction with methanol and acetone, partitioning with hexane and acetonitrile and clean-up with some combination of C-18 cartridges, gel permeation, silica gel and alumina columns. Determination was by GLC and HPLC. The limits of determination were 0.01 mg/kg for green peppers by HPLC, and 0.1 and 0.2 mg/kg for fruit and tea by GLC.

In the analytical method used for the supervised field trials homogenized orange pulp, orange peel and grapes are extracted with acetone/water twice and centrifuged to separate the phases. The supernatants are collected and adjusted to a volume with acetone/water. An aliquot of the extract is partitioned with dichloromethane (oranges) and ethyl acetate (grapes) after addition of sodium chloride. The organic layer is collected and evaporated. The residue is dissolved in diethyl ether/hexane (1:19) and cleaned up on a silica solid phase extraction (SPE) cartridge, eluted with acetone/hexane (1:1). The eluate is reconstituted in acetonitrile/water (7:3) for quantification by LC-MS. The limits of determination in orange pulp, orange peel and grapes are 0.01, 0.05 and 0.01 mg/kg.

Dried hops are homogenized and extracted with ethyl acetate twice after the addition of water and centrifuged to separate the phases. The organic phases are collected and evaporated. The residue is dissolved in methanol. An aliquot of the extract is partitioned twice with 2,2,4-trimethylpentane after the addition of water and saturated sodium carbonate

solution. The organic layer is collected and evaporated. The residue is dissolved in acetonitrile/water (3:10) and cleaned up on a C-18 SPE cartridge, eluted with acetonitrile. The eluate is reconstituted in acetone/water (7:3) for quantification by LC-MS. The limit of determination is 0.01 mg/kg.

In the analytical method used for the processing study on apples homogenized samples of apples, apple juice or apple pomace are extracted by blending with aqueous ethyl acetate and celite. After filtration the extract is evaporated nearly to dryness. The sample is dissolved in ethyl acetate/cyclohexane mixture and cleaned up by GPC. The GPC eluate is further cleaned up on an SPE cartridge eluted with toluene/acetone(95:5). The eluate is concentrated and analysed by gas chromatography with a mass selective detector. The limits of determination are approximately 0.05 mg/kg.

In the analytical methods for animal products used in the animal processing study milk and muscle samples are extracted with acetone and then acetone/water (2:1). The combined extracts are acidified and concentrated to remove acetone, the aqueous solution is extracted with ethyl acetate and the extract partitioned with aqueous sodium carbonate. The ethyl acetate fraction contains fenpyroximate and G-2, while the aqueous fraction contains G-4 and G-9. The ethyl acetate fraction is concentrated and the residue extracted with acetonitrile. The acetonitrile extract is reconstituted in hexane/diethyl ether (9:1) and cleaned up on a silica SPE cartridge, eluted with diethyl ether. Fenpyroximate and G-2 in the eluate are hydrolysed to the common product G-4 which is subsequently methylated with diazomethane. The reaction solution is evaporated and the residue dissolved in hexane/diethyl ether (9:1) and cleaned up on a silica SPE cartridge, eluted with diethyl ether. The eluate is reconstituted in acetone for analysis by GLC with an NPD. The aqueous fraction containing G-4 and G-9 is acidified and extracted with ethyl acetate. The ethyl acetate extract is methylated with diazomethane. The reaction solution is reconstituted in hexane/diethyl ether (9:1) and cleaned up on a silica SPE cartridge eluted with diethyl ether. The eluate is reconstituted in acetone for GLC analysis.

Fat samples are extracted twice with acetonitrile. The combined extracts are concentrated and dissolved in hexane. The hexane solution is partitioned with aqueous sodium carbonate and ammonium hydroxide. The hexane fraction contains fenpyroximate and G-2, while the aqueous fraction contains G-4. The hexane and aqueous fractions are cleaned up and analysed as described for milk and muscle.

Liver and kidney samples are homogenized twice with acetonitrile/water (4:1). The combined supernatant fractions are made up to a volume. An aliquot is partitioned with acetic acid and the aqueous fraction is extracted with acetonitrile. The acetonitrile fraction contains fenpyroximate, G-3 ((E) - 2 - [4-(1, 3-dimethyl -5- phenoxypyrazol -4-ylmethyleneamino-oxymethyl)benzoyloxy]-2-methylpropionic acid), G-4 and G-7. The acetonitrile fractions are reconstituted in ethyl acetate. The ethyl acetate solution is cleaned up by GPC and the eluate is methylated with diazomethane and reconstituted in acetonitrile for LC-MS-MS analysis. The limits of determination in the milk and tissues are 0.005 and 0.01 mg/kg.

Stability of residues in stored analytical samples

Animal commodities. Samples were fortified separately with fenpyroximate and various metabolites at 0.1 mg/kg.

Milk was stored frozen for 73-79 days. Recoveries of fenpyroximate, G-2 and G-9 were 89, 83 and 65%. Recoveries of fenpyroximate, G-2 and G-4 were 60, 68 and 47% from muscles stored for 51-56 days, and 67, 37 and 54% from fat stored for 49-54 days. Liver and kidney samples were stored frozen for 53 and 55 days. Recoveries of fenpyroximate, G-7, G-4 and G-3 were 105, 99, 121 and 107% from liver and 86, 88, 81 and 89% from kidneys.

Plant commodities. The storage stability of fenpyroximate in plant commodities was reported in the 1995 monograph. After about 3 years approximately 65% of the initial residue remained on apples and grapes stored at -20°C. In citrus samples fortified with fenpyroximate 65% remained in the pulp stored for 140 days and 72% in peel stored for 188 days. About 100% of the fenpyroximate remained in hops stored at -18°C for 2 years, about 100% of the residues remaining. No new studies were reported.

Definition of the residue

The current residue definition is "fenpyroximate". In new animal metabolism and feeding studies the metabolite G-4 was found in the liver and kidneys and G-2 was found in muscle, fat and milk. However, since toxicity studies on fenpyroximate would include these metabolites they indicate that the metabolites would have little or no potential for toxicity.

The Meeting concluded that the current residue definition is suitable both for compliance with MRLs and for the estimation of dietary intake.

The octanol-water partition coefficient and the results of the animal feeding studies indicate that fenpyroximate is fat-soluble.

Use pattern

Fenpyroximate is an acaricide. National registrations specify only one application per season to avoid the development of resistance.

For tree crops, spray concentration (kg ai/hl) rather than application rate (kg ai/ha) is the prime determinant of GAP for the use of fenpyroximate.

Results from supervised trials

Oranges. Fenpyroximate may be used at 0.005 kg ai/hl (0.1 kg ai/ha) on oranges in Italy with a PHI of 30 days. The residues in whole oranges in four trials in Italy under these conditions were all 0.04 mg/kg and in one trial in Greece in accordance with Italian GAP the residue was 0.07 mg/kg. The residues in the pulp in all five trials were <0.01 mg/kg.

Fenpyroximate may be used at 0.005-0.0075 kg ai/hl on oranges in Spain with a PHI of 14 days. The residues in whole oranges from four trials in Spain and one in Greece under these conditions were 0.04 (2), 0.05 (2) and 0.09 mg/kg. The residues in the pulp were all <0.01 mg/kg.

In Japan, fenpyroximate may be used on mandarins at 0.003-0.005 kg ai/hl with a PHI of 14 days. The residues in mandarins in two trials 14 or more days after treatment according to GAP were 0.04 and 0.21 mg/kg (1995 JMPR).

The residues in oranges from Italy, Spain and Greece were within the same population.

The residues in the whole oranges from 4 Italian trials, 4 Spanish trials and 1 Greek trial according to GAP in rank order were 0.04 (6), 0.05 (2) and 0.09 mg/kg. All the 9 residues in the pulp were <0.01 mg/kg.

The Meeting estimated a maximum residue level and an STMR level for fenpyroximate in oranges of 0.2 mg/kg and 0.01 mg/kg respectively.

Apples. Fenpyroximate may be used at 0.008 kg ai/hl (0.06-0.08 kg ai/ha) on apples in France with a PHI of 21 days. The residues in apples from five French trials, ten German trials and one Belgian trial in accordance with French GAP were 0.03, 0.09, 0.06, 0.11, 0.16, 0.1, 0.09 (2), 0.12, 0.16, 0.12, 0.06, 0.15, 0.08 and <0.05 mg/kg.

Fenpyroximate may be used at 0.005 kg ai/hl (0.075-0.175 kg ai/ha) on apples in Australia with a PHI of 14 days. The residues in apples from four Australian trials were 0.18, 0.14, 0.12 and 0.17 mg/kg and from seven trials in New Zealand in accordance with Australian GAP were 0.05, 0.04, 0.03, 0.08 and 0.06 (3) mg/kg.

Fenpyroximate may be used at 0.0025 kg ai/hl (0.05-0.075 kg ai/ha) on apples in New Zealand with a PHI of 28 days. The residues in apples from seven trials in New Zealand meeting these conditions were <0.01 (2), 0.01, 0.03 and 0.02 (3) mg/kg.

The residues from France and Australia, and those from New Zealand complying with Australian GAP, were in a single population, but those from trials according to New Zealand GAP cannot be combined with the others since the PHI is longer and the spray concentration is lower.

The fenpyroximate residues in trials according to French and Australian GAP in rank order (median underlined) were <0.05, 0.03 (2), 0.04, 0.05, 0.06 (5), 0.08 (3), 0.09 (3), 0.1, 0.11, 0.12 (3), 0.14, 0.15, 0.16 (2), 0.17 and 0.18 mg/kg

The Meeting estimated a maximum residue level of 0.3 mg/kg and an STMR of 0.09 mg/kg for fenpyroximate in apples.

Grapes. Fenpyroximate may be used at 0.005 kg ai/hl (0.05 kg ai/ha) on grapes in Italy with a PHI of 28 days. The residues in the grapes from four trials in Italy meeting these conditions were 0.02, 0.03 and 0.04 (2) mg/kg. Fenpyroximate is not registered in France but one trial at the spray concentration of 0.006 kg ai/hl was considered to be in accordance with Italian GAP. The residue was <0.02 mg/kg.

Fenpyroximate may be used at 0.0075-0.01 kg ai/hl (0.1 kg ai/ha) on grapes in Spain with a PHI of 14 days. The residues in grapes from four trials in Spain meeting these conditions were 0.06 and 0.04 (3) mg/kg. Two trials in France at 0.006 and 0.008 kg ai/hl and five trials in Italy at 0.0062-0.013 kg ai/hl were considered to be in accordance with Spanish GAP. The residues were <0.02, 0.07, 0.08, 0.17, 0.19, 0.47 and 0.57 mg/kg.

In Japan, fenpyroximate may be used at 0.003-0.005 kg ai/hl on grapes with a PHI of 14 days. The residues in grapes from four trials meeting these conditions were 0.41, 0.45, 0.53 and 0.51 mg/kg.

The residues from the trials in Spain, France, Italy and Japan were in the same population.

The fenpyroximate residues in the combined Spanish, French, Italian and Japanese trials according to GAP in rank order (median underlined) were <0.02, 0.02, 0.03, 0.04(5), 0.06, <u>0.07</u>, 0.08, 0.17, 0.19, 0.41, 0.45, 0.47, 0.51, 0.53 and 0.57 mg/kg.

The Meeting estimated a maximum residue level and an STMR level for fenpyroximate in grapes of 1 mg/kg and 0.07 mg/kg respectively.

<u>Hops</u>. Fenpyroximate may be used at 0.0075 kg ai/hl (0.225-0.263 kg ai/ha) on hops in Germany with a PHI of 21 days. The residues in hops from twelve trials in Germany meeting these conditions in rank order were <1, 1.2, 2.1(2), 3.7, <u>4.3</u>, <u>4.4</u>, 5.0, 5.9, 6.2, 7.4 and 8.4 mg/kg.

The Meeting estimated a maximum residue level of 10 mg/kg and an STMR of 4.4 mg/kg for fenpyroximate on hops.

Processing

<u>Apples</u>. In four processing studies the mean processing factor from fresh apples to apple juice was 0.42 and that from apples to wet pomace was 5.1. The 1995 JMPR evaluated a processing study in which the residues in the fruit were 0.06 and 0.15 mg/kg and those in apple purée were <0.05 (2) mg/kg, giving processing factors for apple purée of <0.83 and <0.24 (mean <0.54). Since the estimated STMR for apples is 0.09 mg/kg, the calculated STMRs for apple juice and purée are 0.09 × 0.42 = 0.038 and 0.09 × 0.54 = 0.049.

The Meeting estimated STMRs for apple juice of 0.04 mg/kg and for apple purée of 0.05 mg/kg.

<u>Grapes</u>. The processing study reported in the 1995 JMPR monograph showed residues in wine of <0.01 mg/kg from residues in fresh grapes of 0.15, 0.13 and 0.14 mg/kg, giving processing factors for wine of <0.07, <0.08 and <0.07 (mean <0.07). The STMR for grapes is 0.07 mg/kg, so the calculated STMR for wine is 0.07 × 0.07 = 0.0049 mg/kg.

<u>Hops</u>. In the processing study reported in 1995, beer containing residues of <0.01 mg/kg was brewed from dried hops containing residues of 6.4, 9.0, 11.4 and 37.4 mg/kg giving processing factors for beer of <0.0016, <0.0011, <0.0009 and <0.0003 (mean <0.001).

The Meeting estimated an STMR for beer of 0.0044 mg/kg from the STMR for hops of 4.4 mg/kg.

Animal feeding studies

Dairy cattle dosed at a level equivalent to 1, 3 or 10 ppm in the feed showed mean total residues of fenpyroximate and its metabolite G-2 of <0.01, 0.015 and 0.038 mg/kg in muscle,

0.015, 0.056 and 0.11 mg/kg in fat, <0.003, <0.003 and <0.01 mg/kg in liver, and <0.003, <0.01 and 0.014 mg/kg in kidney. The residues in the milk of the high-dose group were 0.007 to 0.017 mg/kg.

The concentration factors for wet apple pomace from processing studies were 4.0 to 6.0 (mean 5.1).

Assuming a dry matter content of 40% in wet apple pomace and maximum incorporation rates of dry apple pomace of 20 and 40% in dairy and beef cattle diets respectively, the maximum feed intakes will be approximately 0.25 and 0.5 ppm.

$$0.09 \text{ mg/kg} \times 5.1/40\% \times 20\% \ (40\%) = 0.25 \text{ ppm } (0.5 \text{ ppm})$$

The residues were below the LOD in muscle at the 1 ppm feeding level, in kidneys at 1 and 3 ppm, and in liver at 1, 3 and 10 ppm. Residues were detected in the fat and milk at the 1, 3 and 10 ppm feeding levels. The Meeting noted that the calculated dietary burdens of 0.5 ppm for beef cattle and 0.25 ppm for dairy cattle were close the lowest feeding level of 1 ppm.

In the animal feeding study, the lowest feeding level showed <0.01 mg/kg in muscle, 0.018 mg/kg in fat and <0.003 mg/kg in kidney and liver. Milk from the low-dose group was not analysed. The calculated maximum dietary burden was 1/6th of the 3 ppm feeding level, in which the highest milk residue was 0.011 mg/kg. The calculated milk residue from the estimated dietary burden is therefore 0.002 mg/kg. Liver and kidney may contain residues of the polar metabolite G-4 at an estimated maximum of 0.1 mg/kg from the calculated dietary level.

The Meeting estimated maximum residue levels of 0.02 mg/kg for cattle meat (fat), 0.01* mg/kg for cattle kidney and liver and 0.005* mg/kg for cattle milk, and STMRs of 0.01 mg/kg for cattle meat, 0 mg/kg for cattle liver and kidney, and 0.002 mg/kg for cattle milk.

FURTHER WORK OR INFORMATION

Desirable

An additional study of processing grapes to wine and raisins.

The Meeting was informed that the results of a study of processing grapes to raisins, pomace, forage and juice would be available in the year 2000.

DIETARY RISK ASSESSMENT

Chronic intake

STMRs have been estimated for 9 commodities. The International Estimated Daily Intakes for the five GEMS/Food regional diets were in the range of 0-1% of the ADI. The Meeting concluded that the intake of residues of fenpyroximate resulting from its uses that have been considered by the JMPR is unlikely to present a public health concern.

Acute intake

The international estimated short-term intake (IESTI) for fenpyroximate was calculated as described in Section 3 for the commodities for which maximum residue levels and STMRs were estimated and for which consumption data (large portion consumption, unit weight) were available. The results are shown in Annex IV. The IESTI varied from 0 to 0.008 mg/kg bw in the general population and from 0 to 0.032 mg/kg bw in children (*see* Section 3). As no acute reference dose has been established, the risk assessment for fenpyroximate was not finalized.

4.18 FOLPET (41)

RESIDUE AND ANALYTICAL ASPECTS

Folpet was evaluated in 1998 for residues in the CCPR Periodic Review Programme. The 1998 Meeting did not receive information on the environmental fate of folpet in soil and in water/sediment systems and (1) agreed that its estimates of maximum residue levels should not be recommended for use as MRLs and (2) recommended withdrawal of existing draft MRLs until these critical supporting studies could be evaluated.

The 1998 Meeting noted that farm animal feeding studies had not been provided, but would be needed before MRLs could be recommended for cereal grain, fodder and forage. The Meeting re-examined this requirement in the light of the results of a metabolism study in which goats had been dosed with [^{14}C]folpet at the equivalent of 24 ppm in the feed for 6 days. Folpet itself was not present in the milk and tissues, but metabolites were identified at levels of 0.001-0.02 mg/kg.

The FAO Manual (Chapter 3.1.5.1) states that livestock processing studies are required where significant residues (>0.1 mg/kg) occur in commodities fed to animals and where significant residues (>0.01 mg/kg) may occur in edible tissues. The Meeting agreed that the metabolism study satisfied the need for a ruminant feeding study up to the feed level tested because no significant residues occurred in the tissues. The Meeting noted that no studies of poultry metabolism had been evaluated.

The Meeting received information on the environmental fate of folpet in soil and on aqueous hydrolysis and photolysis which satisfied the requirements for these critical supporting studies. A study of potato metabolism was also made available.

The metabolism of folpet applied to the foliage of potatoes was similar to that in other plants with the main metabolites in the tubers identified as phthalic and phthalamic acids. Folpet itself was not translocated into the tubers.

The disappearance of folpet incubated with soil under aerobic conditions was biphasic, with initial half-lives of below 10 days but with extended half-lives in the longer term. Phthalimide was the only major degradation product. Half of the folpet was mineralized in the first month.

The estimated half-life of folpet in anaerobic soil was 15 days.

In a field dissipation study folpet and phthalimide were detected mainly in the surface soils and had disappeared within one week of the final treatment. Folpet and its soil degradation products showed low mobility in a soil column leaching study.

The half-lives of folpet dissolved at 1 mg/l in sterile aqueous buffered solutions at 25°C in the dark were 2.6 hours, 1.1 hours and 67 seconds at pH 5, 7 and 9 respectively. Hydrolysis at pH 3 was not accelerated by exposure to natural sunlight or a UV lamp, showing that photolysis played little part in breakdown.

Folpet itself disappeared very quickly from a water/sediment system incubated in the dark, as would be expected from its rate of abiotic hydrolysis. The study was recently completed and a brief summary was provided.

Residue trials were reviewed in 1998. New information has now been provided on GAP, which has assisted re-evaluation. Current GAP and relevant data from the supervised trials are summarized in an interpretation table in the 1999 Evaluation.

Apples. Folpet is registered in Argentina for use on apples with a spray concentration of 0.12 kg ai/hl and a PHI of 15 days. The residues in apples from 2 trials where the spray concentration matched GAP but the PHI was 10 days (sufficiently close for a persistent residue) were 1.4 and 2.6 mg/kg.

In two trials in Chile where the conditions corresponded to Chilean GAP (2.0 kg ai/ha and PHI 7 days) the residues were 2.0 and 3.7 mg/kg.

In a Hungarian trial according to GAP (application at 1.6 kg ai/ha and a PHI of 10 days) the folpet residue on apples was 8.0 mg/kg. In a Swiss trial according to GAP (spray concentration 0.10 kg ai/hl and a PHI of 21 days) the residue was 3.4 mg/kg, and in a Spanish trial also according to GAP (spray concentration 0.16 kg ai/hl and a PHI of 10 days) the residue was 3.1 mg/kg.

Folpet may be sprayed at 0.13 kg ai/hl on 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 recorded in the 1993 Evaluations folpet was applied 10 times at a concentration of 0.13 kg ai/hl and the resulting residue 21 days after the final application was 1.8 mg/kg

In summary, the residues in apples from trials according to GAP were Argentina 1.4, 2.6 mg/kg, Chile 2.0, 3.7 mg/kg, Hungary 8.0 mg/kg, Switzerland 3.4 mg/kg, Spain 3.1 mg/kg and Portugal 1.8, 3.2 mg/kg. The residues in rank order (median underlined) in the 9 trials were 1.4, 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 of 10 mg/kg and an STMR of 3.1 mg/kg for folpet on apples. The estimated maximum residue level supports the existing draft MRL.

Grapes. In two trials in Chile corresponding to Chilean GAP (2.0 kg ai/ha and PHI 14 days) the residues were 2.6 and 3.0 mg/kg, and in a Mexican trial according to GAP (1.0 kg ai/ha, PHI 10 days) the residue was <0.05 mg/kg.

In 12 French trials according to GAP (1.5 kg ai/ha and 21 days PHI) the residues were 1.6, 1.9, 1.9, 2.2, 2.4, 2.8, 3.1, 3.5, 4.6, 5.7, 5.8 and 5.9 mg/kg.

The 1993 JMPR reported 4 trials according to national GAP, 2 French (1.5 kg ai/ha, PHI 21 days), 1 Italian (0.16 kg ai/hl, 10 days PHI) and 1 Spanish (0.20 kg ai/hl, 21 days PHI). The residues were 1.2, 1.3, 0.58 and 2.0 mg/kg respectively.

The trial in Mexico may have been from a different population and was excluded from the evaluation.

In summary, the residues in grapes from trials according to GAP were Argentina 1.6 mg/kg, Chile 2.6, 3.0 mg/kg, France 1.2, 1.3, 1.6, 1.9, 1.9, 2.2, 2.4, 2.8, 3.1, 3.5, 4.6, 5.7, 5.8 and 5.9 mg/kg, Italy 0.58, 3.3 mg/kg and Spain 2 mg/kg. The residues in rank order (median underlined) in the 20 trials were 0.58, 1.2, 1.3, 1.6, 1.6, 1.9, 1.9, 2.0, 2.2, <u>2.4</u>, <u>2.6</u>, 2.8, 3.0, 3.1, 3.3, 3.5, 4.6, 5.7, 5.8 and 5.9 mg/kg.

The Meeting estimated a maximum residue level of 10 mg/kg and an STMR of 2.5 mg/kg for folpet on grapes. The estimated maximum residue level supports the existing draft MRL.

<u>Strawberries</u>. Folpet is registered in Spain at a spray concentration of 0.15 kg ai/hl and a PHI of 21 days. The residues were <0.01, 0.04 and 0.09 mg/kg in three trials in Italy and 1.1 mg/kg in one Spanish trial (1993 JMPR) according to Spanish GAP.

Mexican GAP permits application of folpet to strawberries at 1.3 kg ai/ha 2 days PHI. The residues in 3 Mexican trials complying with GAP were 1.6, 1.8 and 2.2 mg/kg.

In 3 trials in plastic tunnels according to glasshouse GAP in The Netherlands (spray concentration of 0.13 kg ai/hl and 14 days PHI) the residues were 1.4, 1.6 and 1.9 mg/kg.

In summary, the residues in strawberries from trials according to GAP were Italy <0.01, 0.04 and 0.09 mg/kg, Mexico 1.6, 1.8 and 2.2 mg/kg, The Netherlands 1.4, 1.6 and 1.9 mg/kg and Spain 1.1 mg/kg. The Meeting agreed that the residues in Italy appeared to be a different population from the others and should be excluded. The residues in rank order (median underlined) in the remaining 7 trials were 1.1, 1.4, 1.6, <u>1.6</u>, 1.8, 1.9 and 2.2 mg/kg.

The Meeting estimated a maximum residue level of 5 mg/kg and an STMR of 1.6 mg/kg for folpet on strawberries. The estimated maximum residue level supports the existing draft MRL.

<u>Onions</u>. The residue in onions from a trial in Chile in accordance with GAP (application of 2 kg ai/ha and 7 days PHI) was 0.36 mg/kg. The residues in 2 trials in Mexico (application at 1.5 kg ai/ha) were 0.41 and 0.41 mg/kg with conditions complying with GAP (1.4 kg ai/ha and 7 days PHI).

Portuguese GAP for onions allows a folpet spray concentration of 0.13 kg ai/hl and a 7 days PHI. The residues in one trial in Portugal and one in Spain (0.16 kg/hl, PHI 10 days) complying with this were 5.0 and 2.5 mg/kg respectively. Two trials in Greece (0.12 kg

ai/hl and 20 days PHI) were acceptably close to Greek GAP (0.16 kg ai/hl with a 20 days PHI) and produced no detectable residues (<0.05 mg/kg).

Four Hungarian trials according to Hungarian GAP (0.13 kg ai/hl and 14 days PHI) produced residues of <0.05, 0.05, 0.07 and 0.21 mg/kg.

In summary, the residues in onions from trials according to GAP were Chile 0.36 mg/kg, Greece <0.05, <0.05 mg/kg, Hungary <0.05, 0.05, 0.07 and 0.21 mg/kg, Mexico 0.41, 0.41 mg/kg, Portugal 5.0 mg/kg and Spain 2.5 mg/kg. The Meeting agreed that the residues in the Portuguese and Spanish trials appeared to be from a different population from the remainder and that only 9 trials would be used for the evaluation. The residues in onions in rank order (median underlined) in the 9 trials were <0.05 (3), 0.05, <u>0.07</u>, 0.21, 0.36, 0.41 and 0.41 mg/kg.

The Meeting noted that the three highest values suggested that residues would sometimes exceed 0.5 mg/kg and estimated a maximum residue level of 1 mg/kg and an STMR of 0.07 mg/kg level for folpet in onions.

<u>Cucumbers</u>. In Cyprus folpet is registered for use on cucumbers at 1.0 kg ai/ha with a 2 days PHI. The residues in cucumbers were 0.11 mg/kg in a Cyprus trial sufficiently close to GAP (1.2 kg ai/ha and 3 days PHI).

In Hungary the residues in cucumbers were <0.02 mg/kg in a trial according to Hungarian GAP (0.13 kg ai/hl and 14 days PHI).

Folpet may be used on cucumbers in Mexico at 1.7 kg ai/ha with a 3 days PHI. In the 4 trials in Mexico according to GAP the residues were 0.11, 0.36, 0.56 and 0.70 mg/kg.

A Canadian trial could not be used because the trial conditions (application rate 1.0 kg ai/ha and spray concentration 0.10 kg ai/hl) did not match maximum GAP (2.0 kg ai/ha, 0.20 kg ai/hl)

In summary the residues in cucumbers from trials according to GAP were Cyprus 0.11 mg/kg, Hungary <0.02 mg/kg and Mexico 0.11, 0.36, 0.56 and 0.70 mg/kg. The trial in Hungary may have been from a different population and was excluded from the evaluation. The residues in rank order (median underlined) in the 5 trials were 0.11, 0.11, <u>0.36</u>, 0.56 and 0.70 mg/kg.

The Meeting estimated a maximum residue level of 1 mg/kg and an STMR of 0.36 mg/kg for folpet in cucumbers. The estimated maximum residue level is recommended to replace the draft MRL of 0.5 mg/kg.

<u>Melons</u>. In Greece folpet is registered for use on melons with a spray concentration of 0.16 kg ai/hl and a PHI of 20 days. The residues were below the LOD (<0.05 mg/kg) in melons from 2 Greek trials meeting these conditions (0.12 kg ai/hl and 20 days PHI).

Honduras permits a spray concentration of 0.16 kg ai/hl and harvest 3 days after the final application. Melons were harvested 3 days after the final application in one trial in Guatemala (0.10 kg ai/hl) and 2 trials in Honduras (0.13 kg ai/hl) where the residues were 0.23, 0.32 and 0.41 mg/kg.

Mexican GAP permits application of folpet to melons at 1.8 kg ai/ha and harvest 7 days later. The residues were 0.40, 0.89 and 2.2 mg/kg in melons from 3 Mexican trials according to GAP.

In summary, the residues in melons from relevant trials were Greece <0.05, <0.05 mg/kg, Guatemala 0.23 mg/kg, Honduras 0.32, 0.41 mg/kg and Mexico 0.40, 0.89, 2.2 mg/kg. The trials in Greece may have been from a different population and were excluded from the evaluation. The residues in rank order (median underlined) in the 6 trials were 0.23, 0.32, 0.40, 0.41, 0.89 and 2.2 mg/kg.

The Meeting estimated a maximum residue level of 3 mg/kg and an STMR of 0.41 mg/kg for folpet in melons. The estimated maximum residue level supports the draft MRL.

Tomatoes. Data were available from supervised trials according to GAP in Chile, Hungary, Italy, Mexico, Portugal and Spain. Trials in the USA and The Netherlands and trials in plastic greenhouses in Italy could not be evaluated because no relevant GAP was reported. The evaluated trials were as follows.

The residue in a trial in Chile (application rate 1.7 kg ai/ha, GAP 1.9 kg ai/ha and 7 days PHI) was 2.4 mg/kg.

In Hungary folpet is registered for use on tomatoes at a spray concentration of 0.13 kg ai/hl with harvest permitted 14 days after the final application. In 4 Hungarian tomato trials reported in 1998 and 1 reported in 1993, the residues were all below the LOD (<0.02 and <0.05 mg/kg).

Mexican GAP permits application of folpet to tomatoes at 1.9 kg ai/ha and harvest 2 days later. The residues from 5 Mexican trials were 0.45, 1.0, 1.3, 1.6 and 1.8 mg/kg.

In 2 Portuguese trials (0.16 kg ai/hl and 7 days PHI) in compliance with Portuguese GAP (0.13 kg ai/hl and 7 days PHI) the residues were 0.34 and 0.58 mg/kg.

The registered use in Spain permits a spray concentration of 0.15 kg ai/hl and a 10 days PHI. The residues in 2 Spanish and 4 Italian trials in substantial agreement with Spanish GAP were 1.2 and 1.3 mg/kg in Spain and 0.43, 0.60, 0.70 and 0.80 mg/kg in Italy.

In summary, the residues in tomatoes from the relevant trials were Chile 2.4 mg/kg, Mexico 0.45, 1.0, 1.3, 1.6, 1.8 mg/kg, Hungary <0.02, <0.05 4 mg/kg, Portugal 0.34, 0.58 mg/kg, Spain 1.2, 1.3 mg/kg and Italy 0.43, 0.60, 0.70, 0.80 mg/kg. The residues in tomatoes in rank order in the 19 trials were <0.02, <0.05 (4), 0.34, 0.43, 0.45, 0.58, 0.6, 0.7, 0.80, 1.0, 1.2, 1.3, 1.3, 1.6, 1.8 and 2.4 mg/kg

The residues from the Hungarian trials appear to be a different population from the others. The residues in the remaining 14 trials (median underlined) were 0.34, 0.43, 0.45, 0.58, 0.6, 0.7, 0.80, 1.0, 1.2, 1.3, 1.3, 1.6, 1.8 and 2.4 mg/kg

The Meeting estimated a maximum residue level of 3 mg/kg and an STMR of 0.90 mg/kg for folpet in tomatoes. The estimated maximum residue level supports the draft MRL.

Head lettuce. Eight trials according to national GAP were reported.

Four trials in plastic tunnels in Hungary (0.13 kg ai/hl and 14days PHI) produced residues of 12, 24, 29 and 39 mg/kg. The residues in 3 Mexican trials (1.3 kg ai/ha and 7 days PHI) were 4.5, 9.8 and 16 mg/kg. The residue from a trial in Portugal in accordance with GAP (0.13 kg ai/hl spray and 14 days PHI) was 4.3 mg/kg.

In summary, the residues in head lettuce from the 8 trials were Hungary 12, 24, 29 and 39 mg/kg, Mexico 4.5, 9.8 and 16 mg/kg and Portugal 4.3 mg/kg. The residues in rank order (median underlined) were 4.3, 4.5, 9.8, 12, 16, 24, 29 and 39 mg/kg.

The Meeting estimated a maximum residue level of 50 mg/kg and an STMR of 14 mg/kg for folpet in head lettuce.

Potatoes. Supervised trials on potatoes were reported from Italy, Mexico, Poland, Russia and South Africa. Translocation of folpet to the tubers from foliar application would not be expected from such a water-insoluble compound as folpet, and this was borne out by the potato metabolism study. Occasional residues could occur if a tuber is exposed above the soil surface to direct spray.

Spanish GAP (spray concentration 0.15 kg ai/hl and PHI 10 days) was used to evaluate 4 Italian trials (0.13 kg ai/hl, 10 days PHI) where the residues were 0.08 and <0.01 (3) mg/kg.

Mexican GAP specifies application at 1.9 kg ai/ha with harvest 30 days later. The residues in potatoes were below the LOD (0.01 mg/kg) in 2 trials with application rates of 2.5 and 4.8 kg ai/ha and were 0.01 mg/kg in 2 trials with application rates of 2.4 and 5.2 kg ai/ha. Trials with exaggerated rates can be included in the evaluation because the chance of residues occurring depends more upon spray contacting exposed tubers than upon the application rate.

GAP in the Ukraine allows application of 1.5 kg ai/ha with 20 days PHI. Trials in Poland and Russia were evaluated against Ukrainian GAP. The residues in one Polish and 4 Russian trials where application was at 1.5-1.6 kg ai/ha with harvest 12-21 days later were <0.01, <0.04 (2) and <0.1 mg/kg.

In summary, the residues in potatoes from the 13 trials effectively according to GAP were Italy <0.01 (3), 0.08 mg/kg, Mexico <0.01 (2), 0.01 mg/kg (2), Poland <0.01 mg/kg and Russia <0.04 (2), <0.1 mg/kg (2). The residues in rank order (median underlined) were <0.01 (6), 0.01 (2), 0.04 (2) 0.08 and <0.1 (2) mg/kg.

The Meeting estimated a maximum residue level of 0.1 mg/kg and an STMR of 0.01 mg/kg for folpet in potatoes.

Processing

The 1998 JMPR reported processing factors of 2.6 and 0.035 for wet apple pomace and apple juice respectively. The Meeting estimated STMRs of 8.1 mg/kg (2.6 x 3.1) for wet pomace and 0.11 mg/kg (0.035 x 3.1) for juice.

The 1998 Meeting reported a processing factor of 3.2 for producing dried grapes (raisins) and estimated a maximum residue level of 40 mg/kg for folpet residues in dried grapes. The Meeting confirmed this estimate, which agrees with the existing draft MRL. By applying the processing factor (3.2) to the STMR for grapes (2.5 mg/kg) the Meeting estimated an STMR of 8.0 mg/kg for dried grapes. The same processing factor applied to the HR found in the trials on grapes (5.9 mg/kg) produced an HR-P of 18.9 mg/kg for dried grapes (raisins).

The calculated processing factor for grape juice was 0 (<0.003); folpet was not detected in the juice. The Meeting estimated an STMR for grape juice of 0.0075 mg/kg (0.003 x 2.5).

Folpet was not detected (<0.05 mg/kg) in wine in 10 processing trials, providing good evidence that the residues do not occur in wine, which is implied by the rapid hydrolysis of folpet in solution and the removal of insolubles in the process and that the processing factor for wine is 0. The Meeting estimated an STMR of 0 mg/kg for folpet residues in wine.

The calculated processing factor for the transfer of the residues from tomatoes to purée and paste is 0 (<0.028); residues in the processed commodities were below the LOD, 0.05 mg/kg. The Meeting estimated STMRs of 0.025 mg/kg (0.028 x 0.90) for tomato purée and paste.

DIETARY RISK ASSESSMENT

Chronic intake

New and revised MRLs for folpet have been recommended for apples, cucumbers, dried grapes, grapes, head lettuce, melons, onion, potato, strawberry and tomato. STMRs have been estimated for the primary commodities and some processed commodities. The dietary intake of folpet is shown in Annex III.

International Estimated Daily Intakes for folpet for the 5 GEMS/Food regional diets, based on estimated STMRs, were in the range of 0-9% of the ADI. The Meeting concluded that the intake of residues of folpet resulting from its uses that have been considered by the JMPR is unlikely to present a public health concern.

Acute intake

The international estimate of short-term intake (IESTI) for folpet was calculated as described in Section 3 of this report for commodities for which MRLs were recommended and STMRs estimated and for which consumption data (large portion consumption, unit weight) were available. The results are shown in Annex IV. The IESTI ranged from 0 to 0.15 mg/kg bw in

the total population and from 0 to 0.49 mg/kg bw in children. As no acute reference dose has been established, the acute risk assessment for folpet was not finalized.

4.20 GLUFOSINATE-AMMONIUM

TOXICOLOGY

Glufosinate-ammonium was evaluated toxicologically by the 1991 Joint Meeting, when an ADI of 0–0.02 mg/kg bw was established based on the NOAEL in a long-term toxicity study in rats and a 100-fold safety factor. The 1991 Meeting also requested additional observations in humans and information on the biological significance of the increased renal glutamine synthetase activity observed in rats. The (-) isomer of *N*-acetyl-glufosinate is a major metabolite when glufosinate-ammonium is applied to glufosinate-tolerant crops. The 1998 JMPR considered residues issues arising from applications of glufosinate-ammonium to tolerant crops. The 1998 Meeting proposed that the residue be defined as the "sum of glufosinate-ammonium, 3-[hydroxy(methyl)phosphinoyl]propionic acid and *N*-acetyl-glufosinate" but could not adopt this definition until *N*-acetyl-glufosinate had been evaluated toxicologically. The present Meeting reviewed additional data on human exposure, glutamine synthetase activity, the toxicity of repeated doses, and the toxicokinetics of glufosinate-ammonium, together with an extensive dossier on *N*-acetyl-glufosinate and a summary of the results of studies on 3-[hydroxy(methyl)phosphinoyl]propionic acid, another metabolite of glufosinate-ammonium.

Glufosinate-ammonium

Orally administered [^{14}C]glufosinate-ammonium is rapidly but sparingly (~10%) absorbed. Excretion of the absorbed dose was rapid. The kidney and liver contained the highest concentrations of residue, which were significantly higher than those in plasma. The concentrations in brain were lower than those in plasma, indicating limited penetration of the blood-brain barrier. There were no marked differences between the sexes. Administration of 500 mg/kg bw resulted in more prolonged absorption and excretion than with 20 or 2 mg/kg bw. Metabolism of glufosinate-ammonium was limited (~ 30% of the absorbed dose) and the main urinary and tissue residues were 3-[hydroxy(methyl)phosphinoyl]propionic acid, methylphosphinico-butanoic acid and 2-hydroxy-4-methylphosphinicobutanoic acid. In faeces, significant concentrations (up to 10%) of *N*-acetyl-glufosinate were detected, indicating that acetylation was performed by the gut microflora. Metabolites were also found in tissues.

Glutamine synthetase (E.C.6.3.1.2) is a key enzyme involved in the metabolism of nitrogen and glutamate. Inhibition of glutamine synthetase resulting in high levels of ammonia is the mechanism of action of glufosinate-ammonium in plants. The activity of glutamine synthetase varies with tissues and species. The Meeting considered reports on the relevance of glutamine synthetase activity in the liver and kidney of experimental animals and humans, including data reviewed by the 1991 JMPR. Because of the presence of alternative pathways for the homeostatic control of ammonia, <50% inhibition of glutamine synthetase in rat liver was not associated with increased ammonia concentrations and was not considered to be adverse. Glutamine synthetase activity in the kidney shows considerable variation between species, with relatively high activity in rodents and negligible activity in

dogs and humans. Inhibition of kidney glutamine synthetase in the absence of pathological findings was considered not to be relevant to human risk assessment.

In the central nervous system, ammonia homeostasis is maintained by a number of enzymes, including glutamine synthetase and glutamate dehydrogenase. Under normal conditions, the flux through glutamine synthetase in brain is reported to be approximately 2-10% of its theoretical capacity and for glutamate dehydrogenase it is approximately 0.1% of its capacity. With such excess capacity, inhibition of brain glutamine synthetase will not necessarily result in significant increases in brain ammonia concentrations; this is confirmed by data showing that animals with decreased glutamine synthetase activity do not have increased brain ammonia levels. However, the 'glutamine-glutamate shunt', between GABA and glutamate in neurones and glutamine in astrocytes, plays a role in both excitatory and inhibitory neurotransmission. The results of studies considered by the 1991 Meeting indicate that significant changes in a range of biogenic amines in regions of the brain in dogs are associated with $\geq$8% changes in glutamine synthetase activity after administration of glufosinate-ammonium at 8 mg/kg bw for 28 days, a dose that produced 'increased gait activity'. Thus, it has been proposed that any statistically significant inhibition of glutamine synthetase activity in brain by >10% be considered a marker of potentially adverse effects on brain biochemistry and behaviour.

Studies *in vitro* and *in vivo* showed that glufosinate-ammonium inhibits glutamine synthetase in the brain, kidney and liver of rats. With 100 ppm glufosinate-ammonium in the diet (equivalent to 10 mg/kg bw per day), glutamine synthetase activity was inhibited in liver and kidney but not in brain, and the Meeting concluded that the NOAEL was 10 mg/kg bw per day. The inhibition in liver and kidney was evident by day 6, did not increase markedly up to day 90, and showed significant reversal during a 31-day recovery period. The finding of increased renal glutamine synthetase activity in a previous long-term study in rats was considered to be a rebound response to continued inhibition and to be of no relevance to human risk assessment.

New studies in which rats and mice received repeated, high doses (270-1400 mg/kg bw per day) in the diet for 90 days were designed to determine the maximum tolerated doses rather than NOAELs. There was no evidence of specific toxicity or of irreversible neurobehavioral effects in the rats. The LOAEL in rats was 7500 ppm, equal to 560 mg/kg bw per day. A new carcinogenicity study in rats showed that glufosinate-ammonium had no significant carcinogenic potential at doses up to 10 000 ppm, equal to 470 mg/kg bw per day. A significant increase in retinal atrophy was seen in this study in females at doses >5000 ppm (equal to 280 mg/kg bw per day) and in males at 10 000 ppm (equal to 470 mg/kg bw per day) but not in either sex at 1000 ppm (equal to 45 mg/kg bw per day), the NOAEL. The results of these three studies were consistent with those of previous studies and supported the overall NOAEL of 40 ppm (2 mg/kg bw per day) identified previously in a long-term study in rats that included a more extensive range of investigations.

No adverse findings were reported in workers in glufosinate-ammonium production plants, but their exposure was stated to be low. A number of cases of attempted suicide in Japan have involved a glufosinate-ammonium-based formulation, but it was not clear whether the effects reported were due to glufosinate-ammonium or other constituents. The most significant effect was delayed neurological symptoms. The available evidence indicates that exposure to glufosinate-ammonium under normal conditions of use does not present a significant risk to humans.

N-Acetyl glufosinate

Oral doses of [^{14}C]*N*-acetyl-glufosinate are absorbed to a limited extent (5-10%), but the absorption is rapid, with peak plasma levels found 1 h after dosing with 3 mg/kg bw. Excretion of the absorbed dose is also rapid and occurs predominantly in the urine as the parent compound. The excretory half-life for the initial phase is <1 h and for the second phase approximately 7 h. The residue concentrations in the liver and particularly kidneys four days after dosing were significantly greater than those in the plasma. Absorbed *N*-acetyl-glufosinate undergoes limited biotransformation, but a significant proportion (11%) of a low oral dose (3 mg/kg bw) was de-acetylated to glufosinate-ammonium in the intestine. It is not clear what proportion of the glufosinate-ammonium present in the tissues after oral administration of *N*-acetyl-glufosinate is absorbed from the intestine as glufosinate-ammonium. The toxicokinetics of *N*-acetyl-glufosinate after repeated administration have not been investigated.

N-Acetyl-glufosinate is of low acute toxicity after oral administration to mice and rats (LD50s >2000 mg/kg bw) and is not a skin sensitizer. Because *N*-acetyl-glufosinate is a plant metabolite and is not present in pesticide formulations, it has not been studied for acute toxicity *via* dermal and inhalation routes or for eye or skin irritancy.

N-Acetyl-glufosinate has not been classified for toxicity by WHO.

N-Acetyl-glufosinate is of low toxicity after repeated oral administration to mice, rats, or dogs. Some and possibly all of the inhibition of glutamine synthetase activity evident in all 3 species was attributable to glufosinate-ammonium. The NOAEL, in the most sensitive species, for inhibition of glutamine synthetase in the brain, was 500 ppm (equal to 19 mg/kg bw per day) in a 90-day toxicity study in dogs (glutamine synthetase activity was not measured in a 1-year toxicity study in dogs). In a 2-year toxicity study in rats there was evidence of chronic progressive nephropathy and urolithiasis. The Meeting noted the absence of pathological changes in the 90-day study, the lack of a dose-response relationship of the kidney lesions, the high sodium concentrations associated with administration of *N*-acetyl-glufosinate, and the high prevalence of renal lesions in aged rats, and concluded that the renal lesions seen in the long-term study in rats were not relevant to human risk assessment. Increased incidences of adrenal cortical hyperplasia, adrenal necrosis and polyarteritis nodosa were seen in males receiving doses $\geq$2000 ppm (equal to $\geq$91 mg/kg bw per day) and an increased incidence of extramedullary haematopoiesis of the spleen was seen in females at those doses. The NOAEL in rats, the most sensitive species, for pathological findings was 200 ppm, equal to 9 mg/kg bw per day.

The Meeting concluded that *N*-acetyl-glufosinate is not carcinogenic at the highest doses tested (equal to 1200 mg/kg bw per day in mice and 1000 mg/kg bw per day in rats).

N-acetyl-glufosinate has been studied in an adequate range of tests for genotoxicity. The Meeting concluded, on the basis of the results, that *N*-acetyl-glufosinate is not genotoxic.

Reproductive performance and outcome in a 2 generation study of reproductive toxicity in rats were not affected by administration of *N*-acetyl-glufosinate at doses up to 700

mg/kg bw per day. The compound was not teratogenic to either rats or rabbits and was not fetotoxic to rats. An increased incidence of supernumerary thoracic ribs was found in fetuses from rabbits exposed to *N*-acetyl-glufosinate at ≥160 mg/kg bw per day, a finding that may be secondary to the maternal toxicity seen at such doses. The NOAEL for fetotoxicity and maternal toxicity was 64 mg/kg bw per day.

3-[hydroxy(methyl) phosphinoyl]propionic acid

Summaries of a range of studies on the genotoxicity, acute toxicity, the toxicity of repeated doses, and teratogenicity of the glufosinate-ammonium metabolite 3-[hydroxy(methyl)phosphinoyl]propionic acid were available. The lowest NOAEL seen in these studies (50 mg/kg bw per day) is 25-fold higher than the NOAEL used to derive the ADI for glufosinate-ammonium.

Overall evaluation

The present Meeting compared the toxicity profiles of *N*-acetyl-glufosinate and 3-[hydroxy(methyl)phosphinoyl]propionic acid with that of glufosinate-ammonium and concluded that the toxicity of the metabolites was comparable to or less than that of the parent compound. The present Meeting established a group ADI of 0-0.02 mg/kg bw for glufosinate-ammonium, *N*-acetyl-glufosinate and 3-[hydroxy(methyl) phosphinoyl]propionic acid (alone or in combination). This is the same value as the ADI established for glufosinate-ammonium by the 1991 JMPR on the basis of the NOAEL in the long-term study in rats given technical-grade glufosinate-ammonium and applying a 100-fold safety factor.

The present Meeting concluded that it was unnecessary to establish an acute reference dose because glufosinate-ammonium, *N*-acetyl-glufosinate and 3-[hydroxy(methyl) phosphinoyl]propionic acid are of low acute toxicity.

A monograph addendum was prepared.

TOXICOLOGICAL EVALUATION

Levels that cause no toxic effect

Glufosinate-ammonium
From 1991 JMPR evaluation

Mouse: 80 ppm, equal to 11 mg/kg bw per day (toxicity in a two-year study of toxicity and carcinogenicity)

Rat: 40 ppm, equal to 2.1 mg/kg bw per day (toxicity in a two-year study of toxicity and carcinogenicity)
120 ppm equal to 6 mg/kg bw/d (toxicity in a study of reproductive toxicity)
10 mg/kg bw per day (developmental effects, highest dose tested in a study of developmental toxicity)
2.2 mg/kg bw per day (maternal and fetotoxicity in a study of developmental toxicity)

Rabbit: 6.3 mg/kg bw per day (maternal and fetotoxicity in a study of developmental toxicity)
20 mg/kg bw per day (developmental effects, highest dose tested in a study of developmental toxicity)

Dog: 4.5 mg/kg bw per day (toxicity in a one-year study)

N-Acetyl-glufosinate

Mouse: 1000 ppm, equal to 150 mg/kg bw per day (toxicity in a two-year study of toxicity and carcinogenicity)

Rat: 200 ppm, equal to 9 mg/kg bw per day (toxicity in a two-year study of toxicity & carcinogenicity)
2000 ppm, equal to 140 mg/kg bw per day (parental toxicity in a study of reproductive toxicity)
10 000 ppm equal to 700 mg/kg bw per day (reproductive effects, highest dose tested in a study of reproductive toxicity)
1000 mg/kg bw per day (highest dose tested in a study of developmental toxicity)

Rabbit: 400 mg/kg bw per day (developmental effects, highest dose tested in a developmental toxicity study)
64 mg/kg bw per day (maternal and fetotoxicity in a study of developmental toxicity)

Dog: 500 ppm, equal to 19 mg/kg bw per day (toxicity in a 90 day study)

Estimate of acceptable daily intake for humans

0-0.02 mg/kg bw (for glufosinate-ammonium, *N*-acetyl-glufosinate and 3-[hydroxy(methyl) phosphinoyl]propionic acid, alone or in combination)

Estimate of acute reference dose

Unnecessary

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

Further observations in humans

Summary of critical end-points for *N*-acetyl-glufosinate and glufosinate-ammonium

Absorption, distribution, excretion and metabolism in mammals

	Glufosinate-ammonium (1991 JMPR)	*N*-Acetyl-glufosinate
Rate and extent of oral absorption:	Rapid but limited (5-10%)	Rapid but limited (5-10%)
Distribution:	Wide. Higher concentration in kidney and liver	Wide. Higher concentration in kidney and liver

Potential for accumulation:	Minimal	Minimal
Rate and extent of excretion:	Rats, rapid, >92% of 30 mg/kg bw in 24 h, primarily in faeces	Rats, rapid, >95% of 3 mg/kg bw in 24 h, primarily in faeces
Metabolism in animals	Main metabolite is 3-[hydroxy(methyl) phosphinoyl] propionic acid (rat, goat, hen)	Limited. Some de-acetylation to glufosinate-ammonium (rat, goat, hen)
Toxicologically significant compounds	Parent	Parent and glufosinate-ammonium
Acute toxicity	glufosinate-ammonium	*N*-acetyl-glufosinate
Rat LD_{50} oral	1660 mg/kg bw	>2895 mg/kg bw
Rat LD_{50} intraperitoneal	~100 mg/kg bw	>1185 mg/kg bw
Mouse LD_{50} oral	420 mg/kg bw	>2895 mg/kg bw
Skin sensitization in guinea pigs	Negative - Buehler	Negative - M&K
Short-term toxicity		
Target/critical effect	Glutamine synthetase inhibition. Behaviour in dogs. Kidney weights and urinary parameters in rats.	Glutamine synthetase inhibition in brain of dogs, mice, rats.
Lowest relevant oral NOAEL	5 mg/kg bw per day in dogs	19 mg/kg bw per day in dogs
Genotoxicity	Not genotoxic	Not genotoxic
Long-term toxicity and carcinogenicity		
Target/critical effect	Glutamine synthetase inhibition increased kidney weight in rats	Adrenal necrosis and hyperplasia; spleen haematopoiesis in rats
Lowest relevant NOAEL	2 mg/kg bw per day in rats	9 mg/kg bw per day
Carcinogenicity	Not carcinogenic	Not carcinogenic
Reproductive toxicity		
Reproduction target/critical effect	Reduced litter size, rats	None
Developmental target/critical effect	General maternal /fetotoxicity	Extra ribs/maternal toxicity in rabbits
Lowest relevant reproductive NOAEL	12 mg/kg bw per day in rats	137 mg/kg bw per day - general toxicity in rats
Lowest relevant developmental NOAEL	2 mg/kg bw per day in rats	64 mg/kg bw per day in rabbits
Neurotoxicity	Possibly behavioural, but no pathological findings	No evidence of specific effects.
Medical data	Suicidal poisonings - producing coma, delayed neurological effects, death. No findings in work force	No data, not produced commercially.

Summary	Value	Study	Safety factor
ADI (*N*-acetyl-glufosinate)	Combined with glufosinate-ammonium	-	-

ADI (glufosinate-ammonium)	0-0.02 mg/kg bw	2 years, rat	100
Acute reference dose	Unnecessary	-	-

RESIDUE AND ANALYTICAL ASPECTS

The 1998 JMPR evaluated glufosinate-ammonium for its uses on glufosinate-tolerant crops. It estimated a number of maximum residue levels, but could not generally recommend them for use as MRLs or propose a revised residue definition until the toxicological evaluation of the metabolite *N*-acetyl-glufosinate (NAG) had been completed. It suggested a provisional revised definition of the residue to take into account the nature of the residue occurring in both conventional and glufosinate-tolerant crops: Sum of glufosinate-ammonium, and *N*-acetyl-glufosinate calculated as glufosinate (free acid).

When glufosinate is used on genetically modified glufosinate-tolerant crops *N*-acetyl-glufosinate is produced. It should be included in the residue definition for enforcement because (1) it is sometimes the main residue component, and (2) the same GLC derivative is produced in the analytical method for both glufosinate itself and NAG, so unless the compounds are separated before derivatisation they both appear as their common derivative. The revised definition is also suitable for commodities from conventional crops because if NAG is absent it will not contribute to the analytical result and if present at low levels it is necessarily already included in the analytical result. NAG is a minor metabolite or degradation product in animals, soils and water/sediment systems.

In the light of the current toxicological evaluation of NAG the Meeting confirmed the suggested residue definition as suitable for both compliance with MRLs and for the estimation of dietary intake.

The residue reported in the supervised trials consists of three components: glufosinate, NAG and 3-[hydroxy(methyl)phosphinoyl]propionic acid (MPP). The method of calculating the total residue was described by the 1998 JMPR and is illustrated by example:

Glufosinate	MPP	NAG	Total
<0.05	<0.05	<0.05	<0.05
<0.05	<0.05	0.06	0.06
0.05	<0.05	0.09	0.14

Canadian GAP for canola specifies treatment at ‘early bolting’. The 1998 JMPR was informed that the 10-leaf stage is very close to bolting, but subsequent advice from Canada is that under Canadian conditions and practices a 4-6-leaf growth stage corresponds to early bolting.

Twelve Canadian trials on canola were essentially in accord with Canadian GAP (0.60 kg ai/ha, treatment at early bolting) and produced residues of <0.05 (8), 0.07, 0.12, 0.17 and 0.24 mg/kg.

The Meeting estimated a maximum residue level for glufosinate-ammonium on rape seed of 0.3 mg/kg, but noted that the residues arising from this new use were within the

existing CXL of 5 mg/kg, which was based on uses on susceptible rape. It is not possible to estimate an STMR on only part of the residue data.

The dietary burden of glufosinate-ammonium for estimating MRLs for animal commodities is 8.1 and 9.3 ppm for beef and dairy cattle respectively and 4.4 ppm for poultry, calculated from MRLs and proposed MRLs for feed commodities.

The levels of 8.1 and 9.3 ppm are comparable to the 9.1 ppm feeding level in the lactating cow feeding study reported in 1998. Residues were not detected in milk (<0.02 mg/kg) or tissues (<0.05 or <0.1 mg/kg) at this feeding level. Occasional residues were detected in milk (0.02, 0.03 mg/kg) at the next feeding level of 27 ppm, but not in the tissues. The Meeting estimated maximum residue levels at the LODs for meat, offal and milk.

The level of 4.4 ppm is equivalent to the nominal 3.6 ppm feeding level in the feeding study on laying hens. No residues were detected in the tissues or eggs at this feeding level. The Meeting estimated maximum residue levels at the LODs for poultry meat, offal and eggs.

The dietary burdens for estimating STMRs for beef and dairy cattle products are 3.5 and 3.6 ppm respectively, derived from the STMR for maize forage and MRLs for the other feed commodities.

The residues were below the LOD in the muscle, liver and kidneys at feeding levels of 9.1 and 27 ppm. The Meeting noted that the dietary burden of 3.5-3.6 ppm was much less than the feeding level of 27 ppm and as an approximation assumed that tissue residues would be proportional to dietary intake:

STMR for animal commodity = LOD × (STMR dietary burden) ÷ (feeding level)

STMR for meat = 0.05 × 3.6 ÷ 27 = 0.007 mg/kg (no detections at 27 ppm feeding level)

STMR for edible offal = 0.1 × 3.6 ÷ 27 = 0.014 mg/kg (no detections at 27 ppm feeding level)

STMR for milk = 0.02 × 3.6 ÷ 27 = 0.003 mg/kg (no detections at 27 ppm feeding level)

The Meeting agreed that the calculated STMRs were low enough to be treated as effectively zero and estimated STMRs of 0 for meat, edible offal and milks.

STMRs for poultry feed commodities were not produced in this evaluation. Eggs, poultry meat and poultry edible offal were assigned STMRs equivalent to the LODs.

DIETARY RISK ASSESSMENT

Chronic intake

A revised maximum residue level for glufosinate-ammonium in soya beans and new maximum residue levels in animal commodities together with corresponding STMRs were

estimated and combined with existing CXLs and draft MRLs to estimate the dietary intakes shown in Annex III.

Estimated Dietary Intakes for the 5 GEMS/Food regional diets, based on estimated STMRs and existing MRLs, were in the range of 3-10% of the ADI. The Meeting concluded that the intake of residues of glufosinate-ammonium resulting from its uses that have been considered by the JMPR is unlikely to present a public health concern.

Acute intake

The Meeting concluded that an acute RfD for glufosinate-ammonium is unnecessary. This conclusion was based on a determination that the pesticide is unlikely to present an acute toxicological hazard and residues are therefore unlikely to present an acute risk to consumers.

4.20 MALATHION (049)

RESIDUE AND ANALYTICAL ASPECTS

Malathion is an insecticide and acaricide which was originally scheduled for periodic re-evaluation by the 1995 JMPR. The review was postponed by the 1994 CCPR and re-scheduled for periodic re-evaluation of residue aspects in 1999. The manufacturer provided residue data, information on GAP and studies to support existing CXLs. Other data on use patterns, methods of residue analysis, residues in food in commerce or at consumption and national residue limits were provided by the governments of Australia, The Netherlands, Thailand, Poland and the UK.

Metabolism

Studies of metabolism in animals and plants were with [^{14}C]malathion labelled at the 2 and 3 position of the succinate moiety.

In laying hens dosed with the equivalent of 25 ppm in the feed for 4 days, malathion was metabolised within 24 hours. The highest concentration of radioactivity was in the faeces, with a total radioactive residue (TRR) of 14 mg/kg as malathion at day 2. In the egg yolks radioactivity was detected by the fourth day, with a TRR of 0.96 mg/kg. In egg whites the TRR was 0.33 mg/kg on days 1 and 4. The highest concentration of radioactivity in the tissues was in the kidneys and liver (1.08 and 0.77 mg/kg respectively) and the lowest levels were in light and dark muscle (0.11 mg/kg). No malathion or any products of immediate metabolism exceeded 0.05 mg/kg in any of the samples except the white from one egg (day 1), where significant activity from malathion carboxylic acid was detected. This result, however, was attributed to contamination by faeces, which had been shown to contain the metabolite. Incorporation of ^{14}C was found in carboxylic acids, proteins and triglycerides. The extensive metabolism of malathion in hens results in low residues in the eggs and tissues.

In goats dosed with the equivalent of 115 ppm malathion in the diet for five days, the highest concentration of radioactivity was found at day 5, with fat, kidney and liver samples showing 1.42-2.23 as malathion. The TRR in heart and muscle samples ranged from 0.26 to 0.39 mg/kg. Radioactivity in the milk increased from 1.42 mg/kg at day 1 to 2.46 mg/kg at day 4 then decreased to 2.14 mg/kg on day 5. In the kidneys, the monocarboxylic acid was

detected at 0.06 mg/kg. No malathion or any immediate metabolites were observed at levels above 0.05 mg/kg in any other sample analysed. [^{14}C]Malathion was found to be a carbon source for the production of triglycerides, which were incorporated in the tricarboxylic acid cycle and lactose. The extensive metabolism of malathion in goats again results in low residues in the milk and tissues

Metabolism studies on rats evaluated by the 1997 JMPR also showed that malathion was rapidly absorbed, biotransformed and excreted within 24 h. Most of the administered dose was recovered in the urine (76-90% of the TRR) and faeces (6.6-14%), with below 1% in the tissues. The main metabolites were malathion monocarboxylic and dicarboxylic acids .

Plant metabolism studies on cotton, wheat, alfalfa and lettuce showed that the metabolism of malathion in plants proceeds via malathion dicarboxylic acid to succinic acid which is incorporated into plant constituents such as starch, proteins, pectin, lignin, hemicellulose and cellulose.

Cotton plants were treated at 1.46 kg ai/ha and leaves and mature and immature bolls collected approximately 18 h after the last application. The TRR in immature bolls, lint and gin trash was 55.6, 217 and 428 mg/kg malathion equivalents respectively. The main component identified in organic solvent extracts of the seed was malathion, representing 33% of the total radioactive residue (49.4 mg/kg). Malathion monocarboxylic acid and malaoxon were at 2.6% and 0.2% of the total radioactivity in the residue respectively. Polar extracts contained 12.9% of the TRR of which 9.6% was characterized, with succinate the main component (2.0% of the TRR). Approximately 67% of the radioactivity was recovered in the experiment.

In wheat plants treated three times at 1.68-1.8 kg ai/ha, malathion was the main component of the organic solvent extracts, representing 13%, 27% and 11% of the TRR in forage, grain and straw respectively. Malathion monocarboxylic acid (6% of the TRR in forage 0.5% in grain, 7.3% in straw) and malathion dicarboxylic acid (4.9% of the TRR in forage, 1.1% in grain and 0.1% in straw) were the main metabolites. Malaoxon was present at low levels (<0.01-0.4% of the TRR). From 82 to 89% of the radioactivity was recovered from each wheat fraction.

When alfalfa plants were treated twice with malathion at 2.0-2.1 kg ai/ha, samples harvested 18 h after the last application contained malathion as the main residue (42% of the TRR in forage and 16.4% in hay), followed by malathion monocarboxylic acid (9.8% and 2.7% in forage and hay) and malaoxon (0.8% of the TRR in hay). More than 80% of the radioactivity was recovered in the experiment.

Malathion was applied at 6 x 2.0 kg ai/ha to lettuce and the plants were harvested 14 days after the last treatment. Malathion represented 36.8%, malathion monocarboxylic acid 12.8% and malaoxon 1.2% of the total radioactivity in the residue. Aqueous extracts contained 44% of the TRR and organic extracts 58% of the TRR.

In summary, the metabolism of malathion in animals and plants is qualitatively similar. Malathion is hydrolysed to mono and dicarboxylic acids and these metabolites are further degraded and incorporated into animal and plant constituents. A major quantitative difference is that no parent compound or primary metabolite was detected in animal tissues,

eggs or milk, whereas in plants malathion was the main residue with up to 12.8% of the TRR representing its monocarboxylic acid metabolite.

Environmental fate

All the studies were with malathion labelled at the 2 and 3 positions of the succinate moiety.

Adsorption/desorption

Malathion was adsorbed in moderate amounts by sandy loam, sand, loam and silt loam soils with K_d varying from 0.83 to 2.47 and K_{oc} from 151 to 308. Adsorption generally increased as soil organic matter, clay content and cation exchange capacity increased. The ß-substituted monocarboxilic acid was the main degradation product representing 0.1 to 8.6% of the TRR in adsorption solutions and 0.3 to 9% of the TRR in desorption solutions. The experiment lasted approximately 3 h and the samples were flushed with nitrogen initially. Malathion was fairly stable under the experimental conditions, accounting for 74.2 to 98.6% of the TRR.

When [^{14}C]malathion was applied to 2 non-sterile soils at 6.88-8.86 mg/kg dry weight kept in the dark at 22 °C, the half life was 4.9 h. After 1 day malathion represented on average 2.6% of the TRR. The main extractable product was malathion dicarboxylic acid (13.8 and 1.1% of the TRR after 6 h and 4 days respectively). Bound residues and $^{14}CO_2$ represented >50% of the TRR at day 7. Dissipation of ^{14}C residues by volatilization was insignificant. No degradation of malathion was observed after 4 days in the sterile control sample.

A study of aerobic and anaerobic degradation of malathion on a loamy sand soil was conducted at 25°C in the dark. The main degradation products in both systems were malathion dicarboxylic acid (up to 62.3% of the TRR on day 7 under aerobic conditions), $^{14}CO_2$, and bound residues. Malathion was degraded with a half-life of 1 day under aerobic conditions and <30 days under anaerobic conditions.

The dissipation of malathion was studied in bare soil and in a cotton field after six applications at 1.13 kg ai/ha. No residues were found below a 30 cm depth in the crop plot or below 15 cm in the bare ground plot. Malathion was not detected in any soil samples later than one day after the last application (up to 0.14 mg/kg dry weight). Malathion dicarboxylic acid was detected in only two samples (at 0.11 mg/kg in bare soil one day after the last application and at 0.016 mg/kg in the cotton plot after the second application). No malaoxon was detected in any sample analysed (<0.01 mg/kg).

Photodegradation does not appear to be a major mechanism of degradation of malathion. In a study with sandy loam fortified on the surface with 10 mg/kg [^{14}C]malathion and kept at 25^{o}C under a 12-hour light/12-hour dark cycle over a 30-day period, the rate constant and extrapolated half-life of malathion were 0.00399 day^{-1} and 173 days respectively. A shorter half-life of 63.5 days found in the control sample (24 h dark) is believed to be a result of increased microbial activity.

The leaching potential of [^{14}C]malathion and its degradation products was evaluated in 4 types of soil aged for approximately one half-life (14.3, 2.1, 0.5 and 0.9 h for sand, sandy loam, loam and silty clay respectively). Two flasks of each soil were sampled after dosing, two at the ageing period and two mixed thoroughly and added to the top of

replicate columns containing untreated soil of each type. Five to 74.4% of the radioactivity was found in the leachate. Malathion was found to leach only from the sand column (1.9% of the TRR). The dicarboxylic acid was the main compound, with up to 47.5% of the TRR in the leachates, followed by the monocarboxylic acid (0.1 to 13.3% of the TRR).

The volatility of malathion was evaluated in a silt loam soil spiked with the "Ready to use", ULV and EC formulations at the recommended field rate, with air flows of 100 and 300 ml/min and 50% and 75% soil field capacity. Volatile ^{14}C was found only with the EC formulation (50% soil moisture and 100 ml/min), where 26.5% of the applied dose was recovered as CO_2.

The aquatic degradation of malathion in a water/sediment system fortified with 1.108-1.02 mg/kg was evaluated under aerobic and anaerobic conditions at 22°C in the dark. The two monocarboxylic acids, demethyl-monocarboxylic acids, dicarboxylic acid and demethyl-dicarboxylic acid were mainly associated with the water, with maximum concentrations from 20.9 to 46.4% of the TRR. In the sediment the concentrations ranged from 3.6 to 8.1%. Dissipation by volatilization was minimal, with <0.5 and <0.1% of the TRR in aerobic and anaerobic conditions respectively. Half-lives of malathion in water and sediment in aerobic conditions were 1.09 and 2.55 days respectively and in anaerobic conditions 2.49 and 2.45 days.

Analytical methods for malathion and malaoxon in plants and processed commodities were submitted by the manufacturer. The analytes are extracted with acetonitrile and acetonitrile/water (80:20), the organic extract is cleaned up on activated carbon and silica gel extraction cartridges and the analytes are quantified by gas chromatography with a flame photometric detector in the phosphorus mode. Recoveries of malathion and malaoxon averaged 89.6% and 98.2% respectively. The LOD is 0.01 mg/kg for all raw and processed human food analysed and 0.05 mg/kg for raw and processed animal feed. For dry samples a hydration step is included before the extraction. Lipids are removed from the extracts with hexanes and the analytes are partitioned 3 times with dichloromethane.

In a multi-residue method reported by The Netherlands for non-fatty samples, no clean-up is necessary and the analytes are determined by GLC with and NPD or ion-trap detector. The LOD for both malathion and malaoxon is 0.02 mg/kg. In an Australian method for organophosphorus insecticides, clean-up was by gel-permeation chromatography and dialysis from a semi-permeable membrane followed by alumina column. The analytes are determined by GLC with an NPD or FPD with an LOD of 0.01 and 0.02 mg/kg.

The stability of residues in stored analytical samples was determined in various raw and processed agricultural commodities. Duplicate samples were fortified with 0.50 mg/kg malathion and malaoxon and stored at <-5°C for 12 months. The analytes were stable for 12 months, with 69 to 105% of malathion and 91 to 109% of malaoxon remaining at the end of the study.

Definition of the residue

In plants, malathion was the main residue. The highest metabolite concentration (monocarboxylic acid) was 13% of the labelled residue. This metabolite is rapidly metabolized further in animals. The Meeting agreed that the residue should be defined as malathion *per se* for compliance with MRLs and for the estimation of dietary intake.

Residues resulting from supervised trials

All the trials were in the USA during the years 1990 to 1997.

Oranges. In six trials in California and Florida with ground applications of EC formulations below the maximum GAP for citrus (28.4 kg ai/ha), residues of malathion at 7 days PHI varied from 0.42 to 1.9 mg/kg. Eight other trials with ULV formulations with aerial and ground application at the proposed or higher rates gave residues ranging from <0.01 to 2.9 mg/kg.

As no data from trials at the maximum GAP rate were reported the Meeting could not recommend an MRL for oranges and as no data were reported for other citrus fruits, the Meeting recommended withdrawal of the existing MRL.

Apples. In three trials in Tennessee, California and Michigan below the maximum GAP rate (20 kg ai/ha), residues at 3 days PHI varied from 0.05 to 2.6 mg/kg. Three other trials at shorter PHIs or higher rates showed residues ranging from 0.19 to 2.5 mg/kg and as no data from trials at the maximum GAP rate were reported, the Meeting recommended withdrawal of the existing MRL.

Pears. In three trials below maximum GAP rate (20 kg ai/ha) in California, New York and Washington, residues at a PHI of 1 day were 0.34 to 1.9 mg/kg. As there were no trials at the maximum GAP rate, the Meeting recommended withdrawal of the existing MRL for pears.

Cherries. In one trials on sweet cherries in California with ground application at maximum GAP (10 kg ai/ha, 3 days PHI), the residues were 1.8 mg/kg. Other trials with ground application at a lower rate gave residues ranging from 0.26 to 2.6 mg/kg. In another six trials in California, Oregon, Michigan, Montana and New York with aerial ULV application at GAP rate (1.0-1.3 kg ai/ha, 1-day PHI), the residues were 0.02, 0.03, 0.08, 0.17, 0.34 and 0.47 mg/kg.

It is clear that ground application gives higher residues than aerial application, even when the application rate is not the maximum allowed by GAP.

The Meeting concluded that insufficient data from trials with ground application at the maximum GAP rate had been reported and recommended withdrawal of the existing MRL for cherries.

Apricots and peaches. In one trial on apricots and four on peaches in New Jersey, Michigan, California and Georgia with 4-5 applications of 4.2 kg ai/ha, residues after 6 or 7 days varied from 0.16 to 1.4 mg/kg. GAP rate for these commodities is 1.6 to 12 kg ai/ha. As no data from trials at the maximum GAP rate were reported, the Meeting could not recommend an MRL for apricot and recommended withdrawal of the existing MRL for peaches.

Grapes. In six trials in California, Washington and New York at 2.1 kg ai/ha (the GAP rate is 2.3-3.1 kg ai/ha), residues at a PHI of 3 days ranged from 0.33 to 2.7 mg/kg. As no data from trials at the maximum GAP rate were reported, the Meeting recommended withdrawal of the existing MRL for grapes.

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Strawberries. In seven trials in Pennsylvania, Oregon, California and Florida with EC or WP formulations within the range of EC GAP rates (1.2-2.7 kg ai/ha), residues at 3 days PHI were 0.09, 0.16, 0.19, 0.25, 0.39, 0.53 and 0.59 mg/kg.

The Meeting estimated a maximum residue level of 1 mg/kg, the same as the previous MRL, and an STMR of 0.25 mg/kg for strawberries.

Blueberries. In seven trials in Michigan, Oregon and Maine, with ground applications of EC formulations at 0.75 and 1.4 kg ai/ha (GAP 1.7-2.8 kg ai/ha), residues at a 1-day PHI varied from 0.26 to 7.1 mg/kg. In another four trials with aerial applications of a ULV formulation close to the GAP rate (0.8 kg ai/ha) residues at a 0-day PHI were 0.06, 0.55, 4.0 and 7.5 mg/kg.

The Meeting estimated a maximum residue level of 10 mg/kg and an STMR of 2.27 mg/kg for blueberry.

Blackberries and raspberries. In six trials in California and Oregon on blackberries and four in Washington on raspberries with WP and EC formulations within the EC GAP range at 2.1-2.27 kg ai/ha (GAP is 1.3-4.6 kg ai/ha), residues at 1 day varied from 1.3 to 11 mg/kg.

As no data from trials at the maximum GAP rate were reported, the Meeting recommended withdrawal of the existing MRLs for blackberries and raspberries.

Avocado. In two trials in California at 5.3 kg ai/ha (GAP rate is 5.4-12 kg ai/ha), residues were 0.07 and 0.08 mg/kg at 7 days PHI. As no data from trials at the maximum GAP rate were reported, the Meeting could not estimate a maximum residue level for avocado.

Figs. In two trials in California within the GAP range (2.7–3.3 kg ai/ha) samples harvested at a longer PHI than the proposed GAP interval contained malathion residues of 0.32 and 0.36 mg/kg. As no trials were conducted according to GAP, the Meeting could not estimate a maximum residue level or an STMR.

Guavas. Three trials in Hawaii and Florida were at a higher rate than the proposed GAP (1.0 kg ai/ha, 2 days PHI). Malathion residues 1 or 2 days after the last application were 0.10, 0.24 and 0.30 mg/kg. As no trials were according to GAP, the Meeting could not estimate a maximum residue level or an STMR.

Mangoes and sugar apples. In one trial on each in Florida at the proposed GAP rate for mangoes (1.4-11.2 kg ai/ha) the residues were 0.31mg/kg at 3 days and 0.07 mg/kg at 1 day. As no trials were according to approved GAP, the Meeting could not estimate a maximum residue level or an STMR.

Papayas. In three trials in Hawaii and Florida according to the proposed GAP (1.4-14 kg ai/ha), malathion residues (PHI 1 day) ranged from <0.05 to 0.56 mg/kg. As no trials were according to approved GAP, the Meeting could not estimate a maximum residue level.

Onions. In six trials on bulb onions and six on green onions in California, Oregon, New York, Texas and Nebraska within the GAP range (1.2-2.4 kg ai/ha), residues of malathion at 3 days PHI were 0.02, 0.08, 0.11, 0.35, 0.37 and 0.59 mg/kg in bulb onions and 0.18, 0.19, 0.35, 0.69, 2.5, 5.0 mg/kg in green onions.

The Meeting estimated a maximum residue level of 1 mg/kg and an STMR of 0.23 mg/kg for bulb onions and a maximum residue level of 5 mg/kg and an STMR of 0.52 mg/kg for green onions,

Broccoli. In five trials in New York, Tennessee, Washington and California at 1.4 kg ai/ha (GAP is 0.1-3.4 kg ai/ha)), the residues at 3-5 days PHI varied from 0.02 to 9.3 mg/kg. As no trials were at the maximum GAP rate, the Meeting recommended withdrawal of the existing MRL for broccoli.

Cabbage. In fourteen trials on head cabbages in Wisconsin, Ohio, New York, Florida, Washington, California, Indiana and Texas at 1.4 kg ai/ha (GAP is 0.1-3.4 kg ai/ha), samples with or without the wrapper leaves at 7 days PHI had malathion residues of <0.05 (13) and 0.10 mg/kg. As no trials were at the maximum GAP rate, the Meeting could not estimate a maximum residue level.

Cucumbers. Nine trials were conducted in Florida, New Jersey, Texas, North Carolina, California and Michigan. GAP allows up to 1.6 kg ai/ha with PHI of 1 day and up to 2.3 kg ai/ha with PHI of 3 days. Trials carried out at 2.1 kg ai/ha gave residues at a PHI of 1 day of <0.01, 0.01, 0.02 (3), 0.03 (2), 0.06 and 0.10 mg/kg.

The Meeting estimated a maximum residue level of 0.2 mg/kg and an STMR of 0.02 mg/kg.

Cantaloupes and watermelons. In two trials on cantaloupes and one trial on watermelons in Georgia, California and Texas at 6 x 1.12 kg ai/ha (GAP for melons is 1.2-2.3 kg ai/ha), residues at a 1-day PHI were <0.05 (2) and 0.80 mg/kg. As there were so few trials and none was at maximum GAP, the Meeting could not estimate a maximum residue level or STMR.

Mushrooms. In one trial in Pennsylvania at the GAP rate of 4 x 1.9 kg ai/ha, malathion residues were <0.05 mg/kg at a PHI of 1 day. There were insufficient data from trials according to GAP to estimate a maximum residue level or an STMR.

Peppers. In seven trials in New Jersey, Florida, North Carolina, California, Michigan and Texas close to maximum GAP (2.0 kg ai/ha), malathion residues at 3 days PHI were <0.01 (4), 0.02, 0.05 and 0.08 mg/kg. The Meeting estimated a maximum residue level of 0.1 mg/kg and an STMR of 0.01 mg/kg.

Tomatoes. The maximum GAP for tomatoes in the USA is 2.3 kg ai/ha with a PHI of 1 day and up to 4.9 kg ai/ha with a PHI of 5 days. In seven trials in New Jersey, Florida, Michigan and California at 1.74 kg ai/ha, malathion residues at a 1 day PHI were 0.10, 0.14, 0.17, 0.21, 0.27, 0.33 and 0.41 mg/kg. In seven other trials at 3.84 kg ai/ha, residues varied from 0.13 to 1.2 mg/kg 3 days after application. These trials did not comply with GAP and were not used for evaluation.

The Meeting estimated a maximum residue level of 0.5 mg/kg and an STMR of 0.21 mg/kg.

Sweet corn. In six trials in Wisconsin, Washington, Montana, California, Florida and New York with ground applications of an EC formulation close to the maximum GAP rate (1.6 kg

ai/ha) residues in the kernels + cobs at 5 days PHI were <0.01 (5) and 0.02 mg/kg. In six trials with aerial application of a ULV formulation the residues were <0.01 mg/kg. There is no approved use of aerial application on sweet corn in the USA.

The Meeting estimated a maximum residue level of 0.02 mg/kg and an STMR of 0.01 mg/kg for sweet corn (grain).

The residues in the forage from the 12 trials were also determined. Those from the ground applications are evaluated with the residues in field corn (maize) forage.

Okra. In two trials in South Carolina and Texas within the GAP range (1.2-2.0 kg ai/ha), malathion residues at a 1-day PHI were <0.05 and 2.1 mg/kg.

There were insufficient data to estimate a maximum residue level or an STMR.

Lettuce. In two trials in California on leaf lettuce according to GAP (1.6-2.7 kg ai/ha), the residues at a PHI of 14 days were 0.99 and 3.1 mg/kg. In four other trials at the same rate in New Jersey, Florida, Washington and Arizona, wrapper leaves were removed from the samples before analysis. In 3 trials in California on head lettuce at the same rate, residues ranged from 0.01 to 0.17 mg/kg after 14 days.

The Meeting concluded that there were insufficient data from trials according to GAP to estimate a maximum residue level for leaf lettuce. As there were no trails according to GAP on head lettuce the Meeting recommended withdrawal of the existing MRL.

Mustard greens. In seven trials in South Carolina, North Carolina, Indiana, Washington, California, Georgia, Texas and Arizona according to GAP (0.8-1.6 kg ai/ha), malathion residues at 7 days PHI were <0.05 (2), 0.07 (2), 0.46, 0.52 and 1.1 mg/kg. In seven other trials conducted at nearly twice the higher GAP rate the residues ranged from <0.05 to 5.9 mg/kg.

The Meeting estimated a maximum residue level of 2 mg/kg and an STMR of 0.07 mg/kg.

Spinach. In five trials in New Jersey, Texas, South Carolina, Washington and California within the GAP range (1.3-2.7 kg ai/ha.), malathion residues at a PHI of 7 days were <0.05, 0.16, 0.35, 1.1 and 2.2 mg/kg. One trial under the same conditions gave a residue of 36 mg/kg. As all the other residues in spinach and other leafy vegetables were in a much lower range, this value was not considered for estimation.

The Meeting estimated a maximum residue level of 3 mg/kg and an STMR of 0.35 mg/kg.

Watercress. In three trials in Florida and Hawaii at 0.5 and 1.4 kg ai/ha (GAP is 1.3-2.7 kg ai/ha), residues of malathion were <0.05 mg/kg in samples taken after 7 days. As there were no trials at maximum GAP, the Meeting could not estimate a maximum residue level.

Beans. Five trials were conducted on lima beans in Wisconsin, Florida, Pennsylvania, North Carolina and California, and five on snap beans in Wisconsin, Oregon and New York with

aerial applications according to GAP (0.7 kg ai/ha). At a PHI of 1 day, the residues were <0.01, 0.05, 0.12, 0.13, 0.21, 0.41, 0.49, 0.56, 0.71 and 0.90 mg/kg.

The Meeting estimated a maximum residue level of 1 mg/kg and an STMR of 0.31 mg/kg for beans, except broad beans and soya beans. The Meeting also recommended withdrawal of the existing MRL of 2 mg/kg for common beans.

Peas. In two trials in California and Wisconsin close to the maximum GAP rate (3.3 kg ai/ha) malathion residues at 3 days were 0.38 and 0.96 mg/kg in peas with pods and 2.9 and 32 mg/kg in dry forage. One other trial gave residues of 0.34 mg/kg in peas with pods 2 days after the last application.

The Meeting concluded that there were too few trials according to GAP and recommended withdrawal of the existing MRL.

Beans, dry. In ten trials in Michigan, California, Idaho, New York and Nebraska with aerial applications according to GAP (0.7 kg ai/ha), malathion residues at 1 day were 0.07, 0.10 (2), 0.16, 0.36, 0.39, 0.42, 0.62 and 1.2 mg/kg.

The Meeting noted that the existing MRL was based on post-harvest treatment and estimated a maximum residue level of 2 mg/kg and an STMR of 0.36 mg/g for dry beans.

Potatoes. In fifteen trials in Idaho, Maine, Florida, Wisconsin and Nebraska at 2 x 1.74 kg ai/ha (GAP is 0.8-3.3 kg ai/ha), malathion residues at day 0 were <0.01(14) and 0.02 mg/kg. As no data from trials at the maximum GAP rate were reported, the Meeting could not recommended a maximum residue level.

Turnips. In six trials in Georgia, Indiana, Ohio, California, South Carolina, Washington and Texas near the maximum GAP rate (1.6 kg ai/ha), malathion residues in the tops at 7 days were <0.05 (2), 0.99, 1.4, 1.8 and 3.4 mg/kg, and in the roots ≤0.05 (4), 0.09 and 0.13 mg/kg. In one trial at the higher rate, residues in the tops were 15 and 10 mg/kg and in the roots 0.11 mg/kg.

The Meeting estimated a maximum residue level of 0.2 mg/kg and an STMR of 0.05 mg/kg for turnips roots, and a maximum residue level of 5 mg/kg and an STMR of 1.195 mg/kg for turnips tops.

Carrots. In six trials in Wisconsin, New Jersey, Florida, Washington, California and Texas at 1.4 kg ai/ha (GAP is 1.2-2.4 kg ai/ha) residues ranged from <0.05 to 0.54 mg/kg after 7 days. As no data from trials at the maximum GAP rate were reported, the Meeting could not estimate a maximum residue level.

Celery. In two trials in Florida and California within the GAP range (1.2-2.0 kg ai/ha), residues at 7 days were 0.91 and 1.2 mg/kg. There were insufficient data from trials according to GAP reported and the Meeting recommended withdrawal of the existing MRL.

Asparagus. In four trials in California, New Jersey, Washington and Wisconsin close to maximum GAP (1.7 kg ai/ha), residues at 1 day were 0.10, 0.13, 0.48 and 0.69 mg/kg.

The Meeting estimated a maximum residue level of 1 mg/kg and an STMR of 0.305 mg/kg.

Wheat. Twenty trials were conducted in Oklahoma, Kansas, Ohio, Washington, ND and Montana on winter and spring wheat according to GAP with either ground application of an EC formulation (GAP is 1.2-1.7 kg ai/ha) or aerial application of a ULV formulation (GAP is 0.3-0.7 kg ai/ha). The residues at a PHI of 7 days in grain from the trials with ground applications were <0.01, 0.02, 0.03, 0.04 (3), 0.08, 0.10 and 0.14 mg/kg and from trials with aerial applications <0.01 (2), 0.03, 0.04 (2), 0.08, 0.09, 0.10, 0.20, 0.22 and 0.28 mg/kg. The residues from the two applications constitute a single population with residues of <0.01 (3), 0.02, 0.03 (2), 0.04 (5), 0.08 (2), 0.09, 0.10(2), 0.14, 0.20, 0.22 and 0.28 mg/kg.

In a single trial with post-harvest application of dust formulation according to GAP, the residue in the grain after 59 days of storage was 7.5 mg/kg. This trial was not considered in the estimation as one trial in not enough to reflect residues from post-harvest applications.

The Meeting estimated a maximum residue level of 0.5 mg/kg and an STMR of 0.04 mg/kg for wheat grain.

In forage the residues on a fresh weight basis from ground applications were <0.05 (9) and 0.09 mg/kg and from aerial application <0.05, 0.19, 0.23, 0.27, 0.49, 1.3, 1.8, 1.9, 2.3 and 2.4 mg/kg. The two residue populations are distinct so the higher residues from the aerial applications were used for estimation. The range of the moisture contents of the analysed samples was stated to be 70-85%, with a mean of 78.4%. Applying this value to the median and highest residues from aerial application (0.895 and 2.4 mg/kg respectively) gives values on a dry weight basis of 4.14 and 11 mg/kg.

The Meeting estimated a maximum residue level of 20 mg/kg and an STMR of 4.14 mg/kg for wheat forage.

In straw the residues from ground applications were <0.05, 0.66, 0.68, 0.81, 1.6, 2.2, 2.5, 3.2, 3.8 and 9.4 mg/kg, and from aerial applications 1.0, 1.4, 3.2, 5.1, 6.5, 7.2, 8.4, 12, 18 and 34 mg/kg. As in forage, the residues in straw were higher from ground applications and were used for estimation. The Meeting estimated a maximum residue level of 50 mg/kg and an STMR of 6.85 mg/kg for wheat straw (fodder).

Sorghum. In four trials in Texas and Nebraska with ground applications of EC formulations close to the GAP rate (1.2 kg ai/ha) the residues in the grain at 7 days PHI were 0.02, 0.07, 0.12 and 0.49 mg/kg. In four other trials with aerial applications of a ULV formulation according to GAP (0.7-1.0 kg ai/ha) residues were 0.13, 0.34, 2.0 and 2.2 mg/kg at 7 days. The residues from both modes of application, considered to be a single population, were 0.02, 0.07, 0.12, 0.13, 0.34, 0.49, 2.0 and 2.2 mg/kg.

The Meeting estimated a maximum residue level of 3 mg/kg and an STMR of 0.235 mg/kg for sorghum (grain).

Maize. Twenty one trials on field corn in Indiana, Illinois, Nebraska, Ohio, Texas and Wisconsin at GAP rate were with either ground applications of EC formulations (GAP is 1.2-1.6 kg ai/ha, 5 days PHI) or aerial applications of ULV formulations (GAP is 0.266-0.533 kg ai/ha, 5 days PHI). In the grain the residues 7 days after the last application from the ground

trials were <0.01 (5), 0.01, 0.02 (3) mg/kg and from the aerial trials <0.01 (11) and 0.02 mg/kg. The residues from both applications form a single population with the rank order <u><0.01</u> (16), 0.01, 0.02 (4) mg/kg.

In a post-harvest trial according to GAP the residue in the grain after 60 days of storage was 6.9 mg/kg. This trial was not considered in the estimation as one result is not enough to reflect residues from post-harvest applications.

The Meeting estimated a maximum residue level of 0.05 mg/kg and an STMR of 0.01 mg/kg for maize (grain).

The residues in the forage from the ground applications were <0.05 (7), 0.12 and 0.19 mg/kg and from the aerial applications <0.05, 0.06, 0.07, 0.09 (2), 0.15, 0.24, 0.34, 0.22, 0.25, 0.76 and 1.2 mg/kg. The residues in the sweet corn forage from ground applications according to GAP were <0.05 (2), 0.20, 0.33, 1.7 and 2.4 mg/kg. The three populations can be combined, giving residues in rank order of <0.05 (10), 0.06, 0.07, <u>0.09</u> (2), 0.12, 0.15, 0.19, 0.20, 0.22, 0.24, 0.25, 0.33, 0.34, 0.76, 1.2, 1.7 and 2.4 mg/kg. Applying a moisture content of 56% (specified for sweet corn and corn forage in the FAO Manual) to the median and the highest residues in the three populations (0.09 and 2.4 mg/kg respectively) gives values on a dry weight basis of 0.20 and 5.4 mg/kg respectively.

The Meeting estimated a maximum residue level of 20 mg/kg and an STMR of 0.45 mg/kg for maize forage.

In straw, the residues from ground applications were 1.3, 1.8, 2.3, 3.2, 3.4, 4.5, 4.6, 4.7, 11 and 13 mg/kg and from aerial applications 1.4, 5.0, 6.6, 6.7, 6.9, 8.0, 11, 12 (2), 19, 22, 24 mg/kg. The two applications give the single population of residues in rank order 1.3, 1.4, 1.8, 2.3, 3.2, 3.4, 4.5, 4.6, 4.7, 5.0, <u>6.6</u>, <u>6.7,</u> 6.9, 8.0, 11 (2), 12 (2), 13, 19, 22 and 24 mg/kg.

The Meeting estimated a maximum residue level of 50 mg/kg and an STMR of 6.65 mg/kg for maize fodder.

<u>Nuts</u>. In two trials in Florida on chestnuts close to the maximum GAP rate (6.8 kg ai/ha), the residues at 2 days were 0.08 and 0.58 mg/kg. In two trials on macadamia nuts in Hawaii far below maximum GAP rate (16.7 kg ai/ha) the residues were <0.05 mg/kg at 1 day. In two trials on walnuts in California near the maximum GAP rate (3.14 kg ai/ha), no residues were detected at 7 days. For the three uses on nuts the labels state that application may be at the time of harvest.

As the data from trials at the maximum GAP rate were limited, the Meeting could not estimate a maximum residue level for malathion in chestnuts, macadamia nuts or walnuts, and recommended the withdrawal of the existing MRL for tree nuts.

<u>Cotton</u>. Seventeen trials were conducted in Texas, Arizona, California and Louisiana according to GAP with either ground applications of EC formulations (GAP is 0.4-3.14 kg ai/ha) or air applications of ULV and Ready-to-use formulations (ULV GAP is 0.3-1.4 kg ai/ha). The residues in the cotton seed at a 0-day PHI from EC formulations were 3.0, 3.8, 4.1, 7.1, 7.8 and 14 mg/kg, and from Ready-to-use formulations 2.3, 4.2, 4.3, 4.8, 4.9 and 5.4 mg/kg and from ULV formulations 2.1, 2.7, 5.4, 5.9 and 6.4 mg/kg. The residues from the

three formulations, which constitute a single population, were 2.1, 2.3, 2.7, 3.0, 3.8, 4.1, 4.2, 4.7, 4.8, 4.9, 5.4 (2), 5.9, 6.4, 7.1, 7.8 and 14 mg/kg.

The Meeting estimated a maximum residue level of 20 mg/kg and an STMR of 4.8 mg/kg for cotton seed.

Flax. In one trial in Nevada at a proposed GAP rate of 1 x 0.56 kg ai/ha, no residues were found in samples of straw, seed or meal after 52 days (the LOD is 0.05 mg/kg). There were insufficient data to estimate a maximum residue level or an STMR for flax.

Mint. In three trials on peppermint and spearmint in Wisconsin and Idaho below the maximum GAP rate (1.6 kg ai/ha), the residues in fresh mint at a PHI of 7 days were 0.51, 1.2 and 1.4 mg/kg and in mint oil 5.7, 8.0 and 9.1 mg/kg. In four trials at about 3 times the maximum GAP the residues were 13-56 mg/kg in fresh mint and 140-460 mg/kg in oil.

As there were no trials at the maximum GAP rate, the Meeting could not estimate a maximum residue level for mint.

Clover. Twenty six trials were conducted in Wisconsin, Michigan, Idaho, Oklahoma, Georgia, New York and Minnesota with either ground application of an EC formulation at 1.4 kg ai/ha (GAP is 1.2-1.6 kg ai/ha) or aerial application of a ULV formulation at 0.68 kg ai/ha (GAP is 0.7-1.0 kg ai/ha). Two applications were made before each cutting (up to 3 cuts) and each cut was considered to be one trial. Samples were taken after 0 to 14 days (GAP allows application at harvest).

The residues in the forage at day 0 from trials with the EC formulation were 14, 17, 18, 31, 20, 37, 39, 40, 57, 71, 73, 88 and 95 mg/kg, and from trials with the ULV formulation 2.8, 3.2, 8.7, 9.5, 14, 16, 25, 33, 38, 39, 46, 56 and 60 mg/kg. The residues from the two modes of application constitute one population with residues of 2.8, 3.2, 8.7, 9.5, 14 (2), 16, 17, 18, 20, 25, 31, 33, 37, 38, 39 (2), 40, 46, 56, 57, 60, 71, 73, 88 and 95 mg/kg. The range of moisture contents of the analysed sample was stated to be 71-85%, with a mean of 81%. Applying this value to the median and highest residues (32 and 95 mg/kg respectively) gives values on a dry weight basis of 168 and 500 mg/kg.

The Meeting estimated a maximum residue level of 500 mg/kg and an STMR of 168 mg/kg for clover forage.

In hay, the residues from foliar applications were 9.2, 9.7, 16, 21, 34, 35, 36, 53, 64, 86 90 and 120 mg/kg, and from aerial applications 4.4, 5.0, 12, 15, 18, 19, 20, 26, 33, 49, 58, 90, 93 and 98 mg/kg. These formed a single population with residues of 4.4, 5.0, 9.2, 9.7, 12, 15, 16, 18, 19, 20, 21, 26, 33, 34, 35, 36, 49, 53, 58, 64, 86, 90 (2), 93, 98 and 120 mg/kg.

The Meeting estimated a maximum residue level of 150 mg/kg and an STMR of 33.5 mg/kg for clover hay.

Alfalfa. Two series of eleven trials each were conducted in Pennsylvania, Wisconsin, Michigan, South Dakota, Iowa, Washington, California, Minnesota, Idaho and Nebraska either with ground application of 1.4 kg ai/ha of an EC formulation (GAP is 1.2-1.96 kg ai/ha) or aerial application of 0.68 kg ai/ha of an ULV formulation (GAP is 0.5-1.1 kg ai/ha).

Two applications were made before each cutting (up to 3 cuts) and samples were taken after 0 to 14 days (GAP allows application at harvest).

Malathion residues in forage at day 0 from trials with the EC formulation were 19, 22, 23, 28, 29, 34, 35, 37, 40, 42, 45, 45, 47, 51 (2), 53, 54, 60, 64, 65, 68, 70, 81, 92, 95 and 98 mg/kg, and from aerial application 0.99, 1.8, 4.5, 5.2, 5.7, 8.7, 9.0, 9.7, 10, 12, 17, 20, 21, 22, (3), 23, 25, 29, 32, 36, 38, 41, 43, 72 and 95 mg/kg, forming a single population with residues of 0.99, 1.8, 4.5, 5.2, 5.7, 8.7, 9.0, 9.7, 10, 12, 17, 19, 20, 21, 22 (4), 23 (2), 25, 28, 29 (2), 32, 34, 35, 36, 37, 38, 40, 41, 42, 43, 45, 46, 47, 51 (2), 53, 54, 60, 64, 65, 68, 70, 72, 81, 92, 95 (2) and 98 mg/kg. The Meeting was informed that the moisture contents of the forage samples varied from 71-85%, with a mean of 78%. This value was used to calculate the median and highest residues in forage on a dry weight basis: 157 and 445 mg/kg.

The Meeting estimated a maximum residue level of 500 mg/kg and an STMR of 157 mg/kg for alfalfa forage.

In hay, the residues at day 0 after EC treatment were 1.5, 2.0, 3.2, 3.9, 6.1, 6.5, 7.7, 11, 16, 17 (2), 20 (2), 27, 43, 46, 52, 85, 140 and 175 mg/kg and after aerial treatment 2.1 (2), 2.8, 2.9, 3.3, 3.5, 4.4, 4.6, 5.6, 6.2, 8.6, 9.7, 12, 14, 19, 20, 21, 25, 26 (2), 33, 38, 45, 52, 56, 67 and 135 mg/kg, forming a single population with residues of 1.5, 2.0, 2.1 (2), 2.8, 2.9, 3.2, 3.3, 3.5, 3.9, 4.4, 4.6, 5.6, 6.1, 6.2, 6.5, 7.7, 8.6, 9.7, 11, 12, 14, 16, 17 (2), 19, 20 (3), 21, 25, 26 (2), 33, 38, 43, 45, 46, 52 (2), 56, 67, 85, 135, 140 and 175 mg/kg.

The Meeting estimated a maximum residue level of 200 mg/kg and an STMR of 17 mg/kg for alfalfa fodder (hay).

Grasses. Twenty trials in Montana, Virginia, Oklahoma, South Dakota, Kansas, Tennessee, Arkansas, Pennsylvania, Kentucky and New York were with either ground application of an EC formulation (GAP is 1.2-1.6 kg ai/ha) or aerial application of a ULV formulation (GAP is 0.5-0.8 kg ai/ha). The residues at day 0 (GAP allows application at harvest) in grass forage were 2.0, 19, 10, 22, 25, 29, 30, 34, 38, 44, 55, 68 (2), 72, 74, 75, 80, 83, 130 and 190 mg/kg and in hay 1.9, 4.0, 6.0, 24, 27, 30, 33, 34, 36, 42, 46, 54, 55, 58, 61, 66, 68, 100, 130 and 260 mg/kg.

The Meeting estimated a maximum residue level of 200 mg/kg and an STMR of 49.5 mg/kg for grass forage and a maximum residue level of 300 mg/kg and an STMR of 44 mg/kg for grass hay.

Fate of residues in processing

In a processing study on oranges, malathion was applied at 8 times the label rate and oranges were harvested 7 days after the last application. Malathion was concentrated in oil (processing factor 219), dried pulp (processing factor 10) and molasses (processing factor 1.4). The residues in the juice were decreased considerably (processing factor <0.05).

In a processing study with grapes, malathion was applied at 5 times the label rate and grapes were harvested 3 days after the last application. Malathion was concentrated in wet pomace (processing factor 2.5), dry pomace (processing factor 11) and raisin waste (processing factor 6). The residues in juice and raisins were decreased considerably with processing factors of 0.08 and 0.43 respectively.

Tomatoes were treated with malathion at 5 times the maximum label rate and harvested 1 day after the last application. Malathion residues were concentrated in the wet pomace (processing factor 1.7) and dry pomace (processing factor 13.3), and decreased in juice, purée and ketchup with processing factors of 0.03, 0.58 and 0.75 respectively.

In a processing study on snap beans in Oregon, malathion was applied at 5 times the maximum label rate and beans were harvested 1 day after the last application. The beans were washed in water, the debris, stems and blossom ends were removed and the beans mechanically cut to give cut beans. Residues were concentrated in the removed parts (cannery waste) with a processing factor of 8.3, and residues in cut beans decreased considerably with a processing factor of<0.02.

Potatoes were treated at 5 times the maximum label rate and harvested on the day of the last application. Residues in whole potato tubers, granules, wet peel and chips were <0.01 mg/kg. Malathion was detected only in the dry peel at a level of 0.06 mg/kg.

Malathion was applied at 5 times the maximum label rate to field corn and the grain harvested 7 days after the last application. Whole grain, grain dust, grits, meal, flour, crude and refined oil (dry milling and wet milling), bleached and deodorised oil (dry milling and wet milling) and starch were analysed. Malathion was detected only in grain dust at levels of 0.99 and 0.74 mg/kg in dust >2540 μm and ≤2540 μm respectively.

In a post-harvest trial according to GAP, the residues were concentrated in the aspirated grain by processing factors (PF) of 70 and 97 in >2540 μm and ≤2540 μm fractions respectively, meal (PF = 1.7), flour (PF 2.0), dry milled crude oil (PF 4.5), dry milled refined oil (PF 1.4), wet milled crude oil (PF 6.2) and wet milled refined oil (PF 3.5). The residues were decreased in grits, dry and wet milled bleached/deodorized oil and wet milled starch, by processing factors of 0.7, 0.016, 0.02 and 0.002 respectively. The Meeting concluded however that it was unlikely that malathion would be concentrated in flour, and agreed not to estimate a maximum residue level for maize flour.

In a processing study on rice, malathion was applied at 5 times the maximum rate and grain was harvested 7 days after the last application. The residues were concentrated in grain dust (PF 1.7 in dust >2540 μm and 2.5 in dust <2540 μm) and in hulls (PF 5.5). The residues were decreased in polished rice and bran by processing factors of 0.02 and 0.67 respectively. The Meeting concluded that it was unlikely that malathion would be decreased after processing to bran.

In a processing study on wheat, malathion was applied at 5 times the maximum label rate and grain was harvested 7 days after the last application. Malathion residues were concentrated after processing in grain dust, with a factor of 36 in dust >2540 μm and of 56 in dust ≤ 2540 μm and in middlings (between 240 and 730 μm) with a processing factor of 2.2. In bran, shorts (>240 μm) and patent flour (<132 μm), residues were reduced with processing factors of 0.41, 0.39 and 0.23 respectively. The Meeting concluded however that it was unlikely that malathion residue in wheat would be decreased after processing to bran. In another study with post-harvest treatment conducted according to GAP, residues in grain were concentrated in the aspirated grain fraction, with PF 1.25 and 35 for dust >2540 μm and ≤2540 μm respectively.

In a processing study on cotton, malathion was applied at 3.3 times the maximum label rate and cotton seed was harvested on the day of the last application. The residues of malathion decreased in all fractions analysed, with processing factors of 0.77 in hull, 0.07 in meal, 0.67 in crude oil, 0.65 in refined oil and 0.008 in bleached and deodorized oil.

Residues in food in commerce or at consumption

Monitoring by the governments of Australia and The Netherlands from 1994 to 1998 showed that malathion residues were undetectable (LOD 0.02 and 0.05 mg/kg) in most of the samples of fruit, grain and vegetables analysed. In a market survey in Australia malathion was detected only in psyllium husk (maximum 0.02 mg/kg), silver beet (maximum 0.50 mg/kg) and strawberries (maximum 0.10 mg/kg). In enforcement monitoring of 289 samples, malathion was detected only in one celery sample. In monitoring in The Netherlands from 1994 to 1996 12% of the 19828 samples analysed had detectable residues, with a mean of <0.02 mg/kg.

FURTHER WORK OR INFORMATION

Desirable

1. Farm animal feeding studies

2. Processing studies on wheat, rice and maize (corn) treated pre-harvest.

DIETARY RISK ASSESSMENT

Chronic intake

Thirty six STMRs were estimated for malathion. There were consumption data for 20 commodities which were used with the STMRs for the dietary intake calculation. The results are shown in Annex III.

International Estimated Daily Intakes for the five GEMS/Food regional diets, based on estimated STMRs, were 0% of the ADI. The Meeting concluded that the intake of residues of malathion resulting from its uses that have been considered by the JMPR is unlikely to present a public heath concern.

Acute intake

The international estimate of short-term intake (IESTI) for malathion was calculated for the commodities for which maximum residue levels and STMRs were estimated and for which consumption data (large portion consumption, unit weight) were available (*see* Section 3). The results are shown in Annex IV. The IESTI varied from 0 to 0.017 mg/kg body weight in the general population and from 0 to 0.058 mg/kg body weight in children. As no acute reference dose has been established, the acute risk assessment for malathion was not finalized.

4.21 METHIOCARB (132)

RESIDUE AND ANALYTICAL ASPECTS

Methiocarb was identified by the 1995 CCPR as a candidate for periodic review (ALINORM 95/24A, Annex 1). The periodic review of toxicology was in 1998 and the present evaluation is a periodic review of residue aspects. The most recent extensive residue reviews were in 1981 and 1983.

Animal metabolism

The metabolism of [*phenyl*-1-^{14}C]methiocarb was studied in rats, dairy cows and chickens.

[*Phenyl*-1-^{14}C]methiocarb was administered at dose levels of 20 and 0.25 mg/kg body weight to rats. Most of the administered radioactivity was excreted with the urine in 48 hours, >90% in the high-dose group and >70% in the low-dose group. The main metabolites in the organic extracts of urine were methiocarb phenol and methiocarb sulfoxide phenol. The same study was evaluated in the 1998 review of the toxicology.

A dairy cow (500 kg) was dosed by capsule with radiolabelled methiocarb at 0.14 mg/kg bw/day for 5 consecutive days. The residue in the milk peaked at 0.062 mg/kg as methiocarb on day 3. The total residues in the meat and fat were not quantifiable, <0.01 mg/kg. The total residues in the kidneys and liver were 0.108 and 0.073 mg/kg respectively. The following metabolites were identified, by TLC only, in milk: methiocarb sulfoxide phenol and conjugates 27% of the TRR; methiocarb sulfone phenol and conjugates 26% of the TRR; methiocarb sulfoxide 3% of the TRR; in kidney: methiocarb phenol and conjugate 55% of the TRR; methiocarb sulfoxide phenol 7% of the TRR; methiocarb sulfone phenol 17% of the TRR; in liver: methiocarb phenol and conjugate 25% of the TRR; methiocarb sulfoxide phenol and conjugate, 9% of the TRR; methiocarb sulfone phenol and conjugate 6% of the TRR; methiocarb and conjugate 14% of the TRR. Methiocarb was found only in the liver.

Eight hens were dosed with [^{14}C]methiocarb for 5 consecutive days at 4.4 mg/kg bw/day. All eggs contained <0.1 mg/kg methiocarb equivalents. The total residues were 0.45 mg/kg in the muscle, 0.7 mg/kg in fat, 2.0 mg/kg in liver and 3.3 mg/kg in kidney.

Tissue extracts were analysed by two-dimensional TLC only. The main residues in fat were methiocarb 41% of the TRR, methiocarb phenol and conjugate 26%, methiocarb sulfoxide phenol and conjugate 9%, and *N*-hydroxymethyl-methiocarb 7% of the TRR. The main radioactive compounds in the muscle were methiocarb 7% of the TRR, methiocarb phenol and conjugate 16%, methiocarb sulfoxide phenol and conjugate 28% and *N*-hydroxymethyl-methiocarb sulfoxide 17%. The main residue in the liver were methiocarb phenol and conjugate 17% of the TRR, methiocarb sulfoxide phenol and conjugate 24%, methiocarb sulfone phenol and conjugate 11% and *N*-hydroxymethyl-methiocarb sulfoxide 6% of the TRR.

The Meeting concluded that the livestock metabolism studies were marginally acceptable and that the metabolism of methiocarb in ruminants and poultry was sufficiently understood. Critical data, such as feed consumption to determine the concentration of the administered pesticide on a feed basis, were not provided. Identifications were based only on

TLC and should have been confirmed by other techniques. No detailed information was supplied on the periods of storage of the samples and extracts before analysis or of the stability of methiocarb and its metabolites under the storage conditions.

Methiocarb is extensively metabolized in ruminants and poultry by ester cleavage, followed by oxidation of the resulting phenol to the sulfoxide and sulfone. A competing pathway observed only in hens is hydroxylation of the carbamate methyl and oxidation of the sulfur to sulfoxide. The metabolites found in rat urine suggest a similar metabolism.

Plant metabolism

Studies were on rice, tomatoes, lettuce and apples.

In the apple study, [*phenyl*-1-^{14}C]methiocarb was applied directly to the surface of apples on a tree with a syringe, with both single and multiple applications. The total residue on the apples after the last of 8 treatments was 4.52 mg/kg as methiocarb, of which 0.67 mg/kg was in the pulp. Of the total radioactive residue, 24% was in the benzene wash of the whole apple, 60% in the peel and 15% in the pulp. The residue in the whole apple consisted of 61% methiocarb, 6.5% methiocarb sulfoxide, 4.6% methiocarb phenol, 22% methiocarb sulfoxide phenol and 1.1% methiocarb sulfone phenol.

In a study of the translocation of [*phenyl*-1-^{14}C]methiocarb from soil to lettuce and tomato seedlings the methiocarb was applied at 1.12 kg ai/ha to the sandy soil in which the plants were growing. Translocation was rapid. Seven days after the application, 45% of the applied radioactivity was in the lettuce plants and 26% was in the tomato plants.

Rice at the soft dough stage was sprayed with [*phenyl*-1-^{14}C]methiocarb at 2.24 kg ai/ha. Some plants were sprayed again at the same rate 9 days later. The plants were harvested 0, 6, 14, 21 or 28 days after the first or second application and separated into grain heads and stalks. In both rice grain and stalks, 95–98% of the recovered radioactivity was organosoluble on the day of application, but this decreased to 63–72% 28 days after both single and double applications. The organic extracts of grain and stalks were analysed only by TLC. The composition of the residue in the organic extracts on the day of the single application was 94% methiocarb, 2% methiocarb sulfoxide and about 1% each of methiocarb sulfone phenol and methiocarb sulfoxide phenol in the stalks. *N*-hydroxymethyl-methiocarb sulfoxide was also detected in later samples. After 28 days the organic extract contained 11% methiocarb, 32% methiocarb sulfoxide, 11% methiocarb sulfoxide phenol and 3% each of *N*-hydroxymethyl-methiocarb sulfoxide and methiocarb sulfone in the grain and 20% methiocarb, 36% methiocarb sulfoxide, 10% methiocarb sulfoxide phenol and 2% methiocarb sulfone phenol in the stalks.

The Meeting concluded that the plant metabolism studies were marginally satisfactory and adequately defined the metabolism of methiocarb in plants. Only the studies on apples and rice determined the nature of the residues in the edible portions and the overall ^{14}C balance could not be determined from the information provided. Identifications were by TLC only: other techniques should have been used to confirm identities and to investigate unidentified compounds. No information was provided on the periods of storage of the samples and extracts or the stability of methiocarb and its metabolites under the storage conditions. The studies are not representative of such major uses as seed treatment and application to the soil as a bait or by incorporation.

Methiocarb is readily translocated. Metabolism is by ester cleavage and oxidation of the resulting phenols to sulfoxides and sulfones. The parent compound may also undergo conversion to the sulfoxide and sulfone and *N*-hydroxymethyl compounds. The metabolic products in livestock and plants are similar.

Environmental fate

Rotational crops. Two studies were conducted. In the first, radiolabelled methiocarb was incorporated into sandy loam soil at 5.6 kg ai/ha. Sweet corn was planted as the main crop and harvested at normal maturity. The land lay fallow until the following year when rotational crops of wheat, sugar beet and spinach were planted. At 399 days after application wheat forage contained 0.15 mg/kg methiocarb equivalents and sugar beet tops contained 0.108 mg/kg. At 450 days after application, sugar beet tops contained 0.071 mg/kg methiocarb equivalents, roots contained 0.252 mg/kg and spinach contained 0.225 mg/kg. Spinach taken 450 days after application and wheat heads (0.066 mg/kg), stalks (0.141 mg/kg) and forage (0.323 mg/kg) from 551 days after application were extracted and the extracts analysed by TLC. The main residue component in spinach was methiocarb sulfoxide phenol, 26% of the total radioactive residue (0.058 mg/kg). The main compounds in wheat forage were methiocarb sulfoxide at 12% (0.039 mg/kg) and methiocarb sulfone at 10%, in wheat stalks methiocarb sulfoxide phenol at 7% and methiocarb sulfone at 8% (0.011 mg/kg), and in the wheat heads *N*-hydroxymethyl-methiocarb 12% (0.008 mg/kg), methiocarb sulfoxide phenol at 14% and methiocarb sulfone at 11%.

In the second study, unlabelled methiocarb was applied to bare soils in the USA at rates of 1.4–11.2 kg ai/ha. Rotational crops (sorghum, wheat, snap beans, peas, carrots, radishes, maize, corn, black-eyed-peas, turnips) were planted at intervals of 30 days during 365 days after the application. Samples were analysed for combined residues of methiocarb, methiocarb sulfone and methiocarb sulfoxide. No residues were detected (<0.02 mg/kg total) in any edible portion of the vegetables or grain planted 30 or more days after application of the methiocarb at rates up to 11.2 kg ai/ha. Green vines and green forage contained total residues after treatment at 11.2 kg ai/ha of 0.14 mg/kg in corn forage (30 day plantback), 0.15 and 0.07 mg/kg in black-eyed pea vines at 30 and 90 day plantbacks respectively, and 0.29 mg/kg in turnip tops (30 day plantback).

Degradation in soil

Soil was treated with 7 mg/kg [*phenyl*-1-^{14}C]methiocarb, equivalent to 11.5 kg ai/ha and watered weekly. Samples were taken at intervals up to 16 weeks, extracted and analysed by TLC. The proportion of organic- and water-extractable radioactivity decreased from 76% at week 4 to 67% at week 16. The distribution of radioactivity changed slightly during the period. Methiocarb accounted for 49% of the applied radioactivity at 4 weeks and 30% at 16 weeks. Methiocarb sulfoxide and its conjugate remained constant at 20–22% of the applied radioactivity. Methiocarb sulfoxide phenol increased from 5.3% to 15%.

A more detailed study under aerobic conditions with dry sandy loam soil at an application rate of 1.44 mg/kg showed that extractable residues decreased from 100% of the applied radioactivity on day 0 to 27% on day 217 and bound residues increased to 43% over the same period. Radioactive carbon dioxide appeared on day 29 and increased to 30% of the applied radioactivity on day 217. Methiocarb decreased from 96% of the residue on day 0 to

3% on day 217. On day 29 the main radioactive compounds as a percentage of the applied radioactivity were methiocarb 24%, methiocarb sulfoxide 30%, methiocarb sulfoxide phenol 16%, methiocarb sulfone 1% and methiocarb sulfone phenol 3%. The degradation followed biphasic first-order kinetics, with half lives of 17.7 days and 111 days.

A soil sample from the above experiment was taken after 14 days and the conditions made anaerobic by covering the sample with water (pH 5) and purging continuously with nitrogen. The system was sampled 0–64 days after conversion to the anaerobic environment. The extractable proportion decreased only slightly, from 87 to 76%. Methiocarb decreased from 55% to 27% and methiocarb phenol increased from 0 to 47%. Methiocarb sulfoxide was readily hydrolysed to methiocarb sulfoxide phenol. Volatile compounds accounted for <4% of applied radioactivity.

A more recent study with radiolabelled methiocarb applied to soil at a rate of 100 g ai/ha was not made available to the Meeting, but new half-lives based on first order kinetics were calculated in various types of soil. Under aerobic conditions, methiocarb had a half-life of 1–2 days and methiocarb sulfoxide a half-life of 2–6 days.

The photolysis of [*phenyl*-1-^{14}C]methiocarb on the surface of sandy loam soil exposed to natural sunlight was compared with controls maintained in the dark. After 30 days methiocarb accounted for 47% of the radiolabelled residue on irradiated soil and 75% on control soil. The main product was methiocarb sulfoxide, 23% of the radiolabelled residue on irradiated soil at 30 days and 3.1% on the control soil. Both photolytic and non-photolytic degradation was occurring. Calculated half-lives were 28 days for irradiated samples and 81 days for dark controls.

Adsorption and desorption constants for various soils were determined for [*phenyl*-1-^{14}C] methiocarb, [*phenyl* -1-^{14}C] methiocarbphenol, [*phenyl*-1-^{14}C] methio carbsulfoxide and [*phenyl*-1-^{14}C]methiocarb sulfoxide phenol. Methiocarb sulfoxide was rapidly degraded and was not adsorbed by soil; within 24 hours of application the soil contained only methiocarb sulfoxide phenol. Methiocarb showed moderately high K_d values, suggesting significant adsorption to all types of soil. The K_d for adsorption ranged from 4.3 ml/g in sandy loam to 9.0 ml/g in silt loam and for desorption from 6.7 in sandy loam to 16.2 in silt loam. The K_d for adsorption of methiocarb sulfoxide phenol ranged from 0.19 in sand to 0.66 in sandy loam and for desorption from 0.74 in sand to 1.6 in silty clay. Methiocarb sulfoxide phenol showed low adsorption to all the soils.

In a leaching experiment [*phenyl*-1-^{14}C]methiocarb was added to sandy loam soil at 37 mg/kg. The soil was aged aerobically for 30 days and an aliquot was extracted and analysed. The residues in the aged soil consisted of 80% methiocarb, 7% methiocarb sulfoxide, 6% methiocarb sulfoxide phenol and 6% insoluble. The leaching rate with 0.01 N aqueous calcium chloride solution through sand, sandy loam and silty loam was compared. Over a 5-day period 1.1 l of the aqueous solution was passed through columns of soil topped with the treated soil (20 g). The leachate from sand, sandy loam and silty loam contained 23%, 7% and 3% of the applied radioactivity respectively. Sand retained 71% of the applied radioactivity, sandy loam 92% and silty loam 93%. The sand leachate contained 2% methiocarb and 12% methiocarb sulfoxide and the sandy loam and silty loam contained more methiocarb sulfoxide than methiocarb, although the concentrations were very low. The results indicate that methiocarb sulfoxide is more readily leached than methiocarb.

Fate in water/sediment systems. The degradation of [*phenyl*-1-^{14}C]methiocarb in aerobic and anaerobic aquatic systems was investigated. The radiolabelled material was added to pond water at 2 mg/l in glass jars. For the anaerobic study, preconditioned soil was also added. The jars were wrapped in black plastic and maintained in a greenhouse. Jars were removed at intervals of 0–112 days and the contents radio-analysed, extracted and the extracts analysed by TLC. In the aerobic system methiocarb disappeared in 3 days, and in the anaerobic system 5% remained after 7 days. By day 56 42% of the radioactivity was bound to the soil in the anaerobic system. The main products in the aerobic system (water phase) were methiocarb phenol and methiocarb sulfoxide phenol. The main product in the anaerobic system was methiocarb phenol.

The half-lives of [*phenyl*-1-^{14}C]methiocarb in buffered aqueous solutions were determined in the dark at 25°C. On the basis of first-order kinetics, the half-lives were 320, 21 and 0.21 days at pH 5, 7 and 9 respectively. Methiocarb is unstable under alkaline conditions. At pH 5 the main product was methiocarb sulfoxide (1-9%), and at pH 7 methiocarb phenol, 46% at day 30. At pH 9 after 7 days, the main compounds were methiocarb phenol 78%, and methiocarb sulfoxide phenol 10%. At pH 5 and 7 about 1% of *N*-hydroxymethyl-methiocarb was found, and at pH 9 about 1% of *N*-hydroxymethyl-methiocarb sulfone.

The photochemical degradation of [*phenyl*-1-^{14}C]methiocarb in pH 5.0 aqueous solution at 25°C exposed in quartz tubes to natural sunlight for 30 days. Controls were maintained in the dark. The only product identified was methiocarb sulfoxide, 13% of the applied radioactivity when irradiated and 1% in the dark. The photolysis half-life was calculated as 88 days, and 128 days corrected for non-photolytic degradation.

The Meeting concluded that the environmental fate of methiocarb is adequately known. In both soil and aqueous environments, methiocarb is degraded to the sulfoxide or loses the carbamate group, yielding methiocarb phenol. The half-life of methiocarb in soil has been variously determined as 1–2 days and 18 days, with the former more reflective of typical concentrations of methiocarb in soil. Methiocarb is relatively stable to sunlight, both on soil and in water. It is adsorbed by soils of various types and is not readily leached, whereas methiocarb sulfoxide is leached. Methiocarb sulfoxide phenol is formed by the rapid degradation of methiocarb sulfoxide in soil and is not adsorbed by a range of soils. Methiocarb is unstable in alkaline aqueous solutions with a half-life of 0.21 days.

The degradation products found in soil and water do not differ from those found in plant metabolism studies, except methiocarb sulfone quinone, which accounted for 8% of the extractable radioactivity in sandy loam soil incubated under aerobic conditions in the dark for 217 days.

Analytical methods

Numerous analytical methods are available both for data collection and for enforcement. Generally, the GLC methods determine the sum of methiocarb, methiocarb sulfoxide and methiocarb sulfone as methiocarb sulfone after a potassium permanganate oxidation step. The HPLC methods determine methiocarb, methiocarb sulfone and methiocarb sulfoxide as individual compounds.

In the GLC methods, such as Bayer Method 171 and DFG method 79-A-1, plant samples are extracted with acetone and 0.5 N HCl. The filtrate is extracted with chloroform, and the chloroform solvent changed to acetone. The acetone solution is precipitated with ammonium chloride and phosphoric acid, the filtrate extracted with chloroform and the chloroform again changed to acetone. This solution is oxidized with 0.1 M potassium permanganate for 15 minutes at room temperature. The residues are silylated and determined by GLC with a flame photometric detector. Variations of the sample preparation are available for milk and animal tissues. Calibration is with external standards, using a log-log calibration curve. The validated limit of determination is 0.05 mg/kg except for milk, for which it is 0.005 mg/kg.

In Bayer Method 172 basic hydrolysis follows the permanganate oxidation. The resulting sulfones and sulfone phenols are cleaned up, derivatized and determined as before. The limit of determination is 0.01 mg/kg. Recoveries are generally >80%.

Method I340 is a modification of Bayer Method 172 for poultry commodities. The ground tissue sample is extracted with acetonitrile and partitioned with hexane. Eggs are blended with acetone and partitioned with methylene chloride. The solvent is changed to acetonitrile and the solution is partitioned with hexane. The acetonitrile extracts of tissues and eggs are evaporated, redissolved in acetone and precipitated with ammonium chloride solution. The mixture is filtered and oxidized as in Method 171. The methylene chloride extract of the oxidation mixture is hydrolysed with sodium hydroxide, 2.5 N at 60°C for 30 min. The hydrolysis products are derivatized with BSTFA and determined as in Method 171. A capillary column is specified. The limit of determination is 0.02 mg/kg.

HPLC methods, such as Bayer Method 00014 and its many modifications, employ specific extraction procedures for green foliage of grain, fatty substrates (nuts) and fat-free materials (cucumber). Modification M004 is specifically designed for strawberries, melons, tomatoes, leek, lettuce and bell peppers. Plant material is macerated with methylene chloride and the extract is concentrated to an aqueous residue, to which is added salt, HCl (for strawberries, leeks and melons only) and water. The solution is cleaned up on a solid-phase extraction column and the methylene chloride eluate is analysed by HPLC.

HPLC includes post-column hydrolysis (0.05 N caustic soda, 90°C) and derivatization with *o*-phthalaldehyde and mercaptoethanol in borate buffer. The methylamine released by the basic hydrolysis of the carbamate reacts with the derivatizing agent to form 1-hydroxyethylthio)-2-methylisoindole, detected by fluorescence. Fortified recoveries indicate limits of determination of 0.04 or 0.02 mg/kg for each analyte, with limits of detection of about 0.006 mg/kg.

The Meeting concluded that adequate analytical methods exist for enforcement and data collection for methiocarb, methiocarb sulfoxide and methiocarb sulfone.

Stability of residues in stored analytical samples

Methiocarb and methiocarb sulfoxide were stable in blueberries stored frozen for 118 days at–23^{o}C. The study was performed with samples fortified at 2.8 mg/kg and 3.3 mg/kg with radiolabelled methiocarb and methiocarb sulfoxide respectively. The percentage remaining was approximately 99% after the storage interval.

Summary information only was supplied on the stability (at 0 to –10°C) of methiocarb, methiocarb sulfoxide and methiocarb sulfone in beans, grapes, cabbage, rice, tomatoes, broccoli, Brussels sprouts and cauliflower. Except for Brussels sprouts and broccoli, the data indicated that methiocarb and the metabolites are stable for up to 380 days. Details were not provided and concurrent method recoveries were not performed at each storage interval.

Samples from field trials were stored frozen for 1 month to 2 years before analysis.

The Meeting concluded that the information on storage stability is inadequate, except for berries and that the residues reported from field trials might be understated if methiocarb and its sulfone and sulfoxide metabolites are unstable under the storage conditions used for the samples. Understated residues will give rise to the estimation of erroneous maximum residue limits and STMRs. The Meeting therefore concluded that the validity of the trials (except on berries) could not be assured and recommended the withdrawal of all existing MRLs. The Meeting could not recommend MRLs except for strawberries, pending the review of adequate data on storage stability. Maximum residue levels were provisionally estimated however.

Definition of the residue

Plant and animal metabolism studies indicate that methiocarb is extensively metabolized to phenolic derivatives by cleavage of the carbamate, and by oxidation of methiocarb and the phenolic derivatives to sulfoxides and sulfones. A minor metabolic path involves hydroxylation of the carbamate methyl group and oxidation to the corresponding sulfoxide. The analytical methods determine methiocarb, methiocarb sulfoxide and methiocarb sulfone, either as methiocarb sulfone or individually. The current definition of the residue is “sum of methiocarb, methiocarb sulfoxide and methiocarb sulfone, expressed as methiocarb”.

The 1998 toxicology review established both a chronic ADI and an acute reference dose for methiocarb. It was noted that methiocarb sulfoxide, as well as methiocarb, is of acute dietary concern.

The Meeting concluded that the residue should be defined both for enforcement of MRLs and for the estimations of dietary intake as “the sum of methiocarb, methiocarb sulfoxide and methiocarb sulfone, expressed as methiocarb”.

Residues resulting from supervised trials

Residues reported as below the LOD (limit of determination) for the individual components of the residue were assigned the value of the LOD. For example if methiocarb, methiocarb sulfoxide and methiocarb sulfone were each <0.02 mg/kg on cabbage, the value used for deriving the MRL and the STMR would be 0.02 mg/kg.. If the method determined the three compounds as one derivative and the result was reported as below the LOD, the value of the LOD was again used, for example <0.05 mg/kg total residue would be taken as 0.05 mg/kg. For residues with individual component(s) exceeding the LOD, the residue was taken as being the sum of the residues exceeding the LOD. For example if the residue on cabbage was reported as 0.15 mg/kg methiocarb, <0.02 mg/kg methiocarb sulfoxide and 0.06 mg/kg

methiocarb sulfone, the residue would be taken to be 0.21 mg/kg. This procedure is appropriate, as the residue in many cases is predominantly (60%) one compound.

Potatoes. Two trials were reported from the UK. GAP is 3 ground applications of an RB formulation at 0.22 kg ai/ha with no specified PHI. The UK trials complied with GAP with PHIs of 18 and 20 days. The residues were not quantifiable (<0.02 mg/kg).

The Meeting could not estimate a maximum residue level or STMR because two trials were an inadequate number.

Leeks. Eleven field trials were reported from France and The Netherlands. GAP for France was not reported. In The Netherlands, up to 2 foliar applications of an SC formulation, 500 g/l, may be made at rates of 0.5-0.75 kg ai/ha, with a 14-day PHI. GAP is similar for Belgium, but the PHI is 21 days. The trials in France were evaluated against Belgian GAP. One trial in The Netherlands did not comply with GAP, because the PHI was 21 days.

The residues in rank order were 0.02, 0.03, 0.08, 0.14, 0.18, 0.25, 0.29 (2), 0.30 and 0.39 mg/kg. The Meeting estimated a provisional STMR of 0.22 mg/kg and a maximum residue level of 0.5mg/kg.

Cabbages. Fifteen field trials were reported from Austria, Belgium, Germany and The Netherlands. GAP for Austria specifies 2 foliar applications of a WP formulation at 0.5 kg ai/ha with a 14-day PHI or a spreading application of an RB formulation at 0.12 kg ai/ha with a 14-day PHI. GAP for Belgium allows 3 foliar applications of an SC formulation at 0.75 kg ai/ha with a 14-day PHI or 2 spreading applications of an RB formulation at 0.12 kg ai/ha with a 14-day PHI. In Germany GAP requires 2 applications of an RB formulation at 0.12 kg ai/ha with a 14-day PHI, and in The Netherlands one foliar application of a WP formulation at 1.5 kg ai/ha with a 14-day PHI.

Six trials in Germany complied with maximum GAP for the RB formulation, and eight in Germany, Belgium and The Netherlands with Belgian GAP for the SC formulation.

The residues in rank order were 0.02 (4), 0.03 (4) and 0.05 (6) mg/kg. The Meeting estimated a provisional STMR of 0.03 mg/kg and a maximum residue level of 0.1 mg/kg.

Cauliflowers. Four trials were reported from Germany, where GAP is two baiting applications of an RB or GB formulation at 0.12 kg ai/ha with a 14-day PHI. Four trials were conducted under maximum GAP conditions, but the incorrect commodity was analysed in one trial. The three relevant residues were all 0.05 mg/kg.

The Meeting agreed that four trials were inadequate for the estimation of a maximum residue level and STMR, but concluded that the data on cabbages could be extrapolated to cauliflowers since the GAP is identical and the application is ground, not foliar where differences in plant habit might lead to different residue levels. The Meeting estimated a provisional maximum residue level and STMR for cauliflower of 0.1 mg/kg and 0.03 mg/kg respectively.

Artichokes. Two trials were reported from Italy. The only reported GAP is for Israel: one foliar application of a WP formulation at 1.75 kg ai/ha, no PHI specified. The Italian trials did not comply with this GAP.

No maximum residue level or STMR could be estimated.

Peas. Eight trials were reported from Germany. GAP is a seed treatment at 0.5 l of a 500 g/l FS formulation per 100 kg of seed. The eight trials were under maximum GAP conditions and quantifiable residues were found in only one trial.

The residues in the peas were 0.05 (7) and 0.08 mg/kg. The residues in the pea vines were 0.05 (7) and 0.04 mg/kg. The Meeting estimated a provisional STMR for peas and vines of 0.05 mg/kg each and maximum residue levels of 0.1 mg/kg and 0.05 mg/kg respectively.

Pepper. Five trials were reported from Spain and 2 glasshouse trials from Portugal. GAP for Spain is 3 foliar applications of a WP formulation, each 1.0 kg ai/ha, with a 7-day PHI. GAP for Portugal is the same, but with a 14-day PHI. The more demanding PHI of Spain was applied to the trials in Portugal. Six trials were at maximum GAP and one was at an application rate more than 30% above the maximum.

The residues in the six trials in rank order were 0.27, 0.49, 0.84, 0.92, 1.33 and 1.53 mg/kg. The Meeting estimated an STMR of 0.88 mg/kg and a maximum residue level of 2 mg/kg.

Tomatoes. Eight trials were reported: 1 from Portugal and 7 from Spain. GAP for both Spain and Portugal specifies 2 foliar applications of a WP formulation at 1.0 kg ai/ha, with a 7-day PHI, for both field and glasshouse applications. Two glasshouse trials in Spain were at more than 30% above GAP rate, with residues at 7 days of 0.22 and 0.59 mg/kg. The remaining six trials were under maximum GAP conditions.

The residues in rank order were 0.04 (2), 0.11, 0.17 (2) and 0.81 mg/kg, the last from a glasshouse trial. The Meeting estimated a provisional STMR of 0.14 mg/kg and a maximum residue level of 1 mg/kg.

Cucumbers. Six trials were reported: 4 from France and 2 from Spain. The French trials were in glasshouses. GAP for France was not reported. GAP for Spain, against which the trials in France were evaluated, is 2 foliar applications of a WP formulation at 1.0 kg ai/ha, with a 7-day PHI. The six trials were at or within 30% of maximum GAP.

The residues in rank order were 0.04 (2), 0.07, 0.09, 0.11 and 0.12 mg/kg. The Meeting estimated a provisional STMR of 0.08 mg/kg and a maximum residue level of 0.2 mg/kg.

Melons. Seven trials were reported: 3 from France, 2 glasshouse from Portugal and 2 from Spain. No GAP was provided for France and Spain, but the trials can be covered by GAP in Portugal and Italy (two foliar applications of a WP formulation at 1.0 kg ai/ha, with a 7-day PHI). Six trials were at or within 30% of maximum GAP, but the analyses in Spain and Portugal were of the pulp and peel, not whole melons. The residue in the whole melons was calculated from the reported weights of peel and pulp. In 1 trial in France the PHI was more than 30% below GAP.

The residues in the whole melons in rank order were 0.07, 0.17, 0.18, 0.19, 0.26 and 0.49 mg/kg, and in the pulp 0.02 (4) and 0.06 (2) mg/kg. The Meeting estimated a provisional STMR of 0.02 mg/kg and a maximum residue level of 1 mg/kg.

Strawberries. Fourteen trials were reported: 6 from Spain, 2 from Portugal, 1 from Germany, 1 from Denmark, 1 from Belgium, 1 from The Netherlands and 2 from the UK. GAP in Portugal and Spain calls for 2 foliar applications of a WP formulation at 0.8 and 1.0 kg ai/ha respectively, with 7- and 15-day PHIs respectively. The shorter PHI of Portugal was applied to evaluate the trials in Spain. GAP in northern Europe requires the ground application of an RB formulation: in Belgium 2 applications, each 0.20 kg ai/ha, no PHI; in Germany 2 applications, each 0.12 kg ai/ha, 14-day PHI; in the UK 1 application, 0.22 kg ai/ha, 7-day PHI, and in Sweden 1 application, 0.2 kg ai/ha, no PHI. GAP in Denmark and The Netherlands was not reported. German GAP was applied to evaluate the trials in The Netherlands and Denmark. All trials were at or within 30% of maximum GAP.

The residues from the application of a granular formulation to the ground in rank order were 0.02 (2), 0.04 and 0.05 (3) mg/kg; and from foliar applications of a WP formulation 0.17, 0.29, 0.36, 0.43, 0.45, 0.54, 0.71 and 0.83 mg/kg. The latter is the critical GAP. The Meeting estimated an STMR of 0.44 mg/kg and a maximum residue level of 1 mg/kg.

Cereal grains. Two trials on wheat were reported from the UK, where GAP for cereal grains requires application of an RB formulation at 0.15 kg ai/ha–0.20 kg ai/ha, with a 7-day PHI. The number of applications is not specified. In the field trials two applications were made, one at drilling and one on the ground 94 and 98 days before harvest of grain and straw and 0 days before the harvest of forage. Three barley trials were reported from Germany. GAP for barley, oats, rye, wheat and triticale specifies up to 2 applications of an RB formulation at 0.1 kg ai/ha. The PHI is not specified, although the practical PHI is governed by the growth stage, up to growth stage 29. The trials were at or within 30% of maximum GAP. No quantifiable residues were found in the grain, straw, and fodder of wheat or barley. The residues in the grain, straw and fodder in rank order were <0.04 (2), <0.05 (3) mg/kg, <0.05 (3), <0.1 (2) mg/kg, <0.05 (3) and <0.1 (2) mg/kg respectively.

The Meeting concluded that the use of a bait formulation applied to the surface of the ground and not incorporated into the soil is unlikely to leave methiocarb residues in the grain commodities. The Meeting therefore judged five trials to be adequate for this GAP and estimated provisional maximum residue levels of 0.05*, 0.1* and 0.1* mg/kg for the grain, straw and fodder respectively of barley, oats, rye, wheat and triticale. The Meeting also estimated STMRs of 0 mg/kg for the grain, straw and fodder of these cereals.

Ten trials on maize in Germany were according to GAP: seed treatment or application at drilling with an FS formulation at 0.5 kg ai/100 kg seed.

The residues in maize grain (kernel and cob) in rank order were <0.05 (5) and <0.1 (4) mg/kg. The residues in the forage were all <0.1 mg/kg (6 samples).

The Meeting estimated provisional STMRs of 0 mg/kg and maximum residue levels of 0.1* mg/kg for maize grain and forage.

Rape seed. Seven trials were reported from Germany, where GAP specifies two applications of an RB formulation at 0.1 kg ai/ha with no specified PHI. The practical PHI is at growth stage 29–30. Three trials were with foliar application of a WP formulation for which no GAP in Germany was reported, but the trials were evaluated against GAP in The Netherlands (one foliar application of the WP formulation at 0.5 kg ai/ha with no specified PHI). These three trials were within 30% of the maximum GAP conditions. The remaining four trials were with a GR formulation, not RB. Residues from the granular formulation were found in rape forage on the day of application in two of the four trials at 0.54 and 2.6 mg/kg.

The Meeting regarded three trials with a foliar application as too few for the estimation of a maximum residue level or an STMR and recommended withdrawal of the existing MRL.

Hazelnuts. Five trials were conducted in Turkey where GAP is one foliar application of a WP formulation at 0.6 kg ai/ha, with a 90-day PHI. Nuts without shells were analysed. All the trials were at maximum GAP and all 5 residues were below the LOD of 0.05 mg/kg.

The Meeting estimated a provisional STMR of 0.05 mg/kg and a maximum residue level of 0.05* mg/kg.

No residue trials were reported for artichokes, broccoli, Brussels sprouts, citrus, lettuce, sugar beet or sweet corn. The Meeting recommended the withdrawal of the existing MRLs.

Animal feeding studies

In a poultry feeding study hens were fed a diet containing methiocarb and methiocarb sulfoxide (9:1) for 28 days, at rates ranging from 0 to 360 ppm in the feed. At 120 ppm residues were below the limit of determination (<0.02 mg/kg) in muscle, skin and fat, 0.03 mg/kg in eggs and 0.13 mg/kg in giblets (liver, etc.). At 360 ppm residues were <0.02 mg/kg in the muscle and fat, 0.02 mg/kg in skin, 0.06 mg/kg in eggs and 0.13 mg/kg in giblets.

A dairy cow feeding study was reported in which the animals were dosed daily for 29 days with the equivalent of 0, 10, 30, and 100 ppm methiocarb in the feed. Maximum total methiocarb residues in milk on day 29 were 0.007 mg/kg at the 10 ppm feeding level, 0.020 mg/kg at the 30 ppm level and 0.033 mg/kg at the 100 ppm level. No residues (<0.05 mg/kg total methiocarb) were found in any tissue at any feeding level, except 0.1 mg/kg total methiocarb in liver at 30 and 100 ppm.

The livestock feed items for which provisional maximum residue levels were estimated were maize grain, maize forage (ruminant feed only), pea vines (ruminant only), cereal grains and cereal forages (ruminant only). The residues in all these except pea vines were below the limits of determination. From the estimated maximum residue levels, 0.1* mg/kg for maize grain and forage, 0.05* mg/kg for cereal grains, 0.1* mg/kg for cereal forages and 0.05 mg/kg for pea vines, the diets were calculated to contain methiocarb residues 0.1 ppm for poultry, 0.24 ppm for beef cattle and 0.30 ppm for dairy cattle.

The 0.1 ppm diet for poultry is at least a factor of 1000 below the concentration at which residues were detected in poultry products in the feeding study. The Meeting concluded that poultry maximum residue levels could be estimated at the practical limit of

determination of the analytical methods, 0.05* mg/kg and STMRs at 0 mg/kg for poultry meat and eggs.

The estimated low concentrations of methiocarb and metabolites in the ruminant diet, about 0.3 ppm, might be expected to yield residues below the enforcement limits of determination (0.005 mg/kg for milk, 0.05 mg/kg for tissues). Assuming a 600 kg animal and a dietary intake of 20 kg/day, the intake can be estimated at 0.000010 g methiocarb/kg bw/day. This is an order of magnitude below the dosing level in the metabolism study (0.00014 g/kg bw/day). In that study, the total fat and muscle residues were each <0.01 mg/kg and the total milk residue was 0.06 mg/kg. In the ruminant feeding study, no residues (<0.05 mg/kg) were found in any commodity after 29 days at a 10 ppm feeding level (30 times the maximum theoretical intake), except in milk at 0.007 mg/kg. The metabolism and feeding studies both indicate that total methiocarb residues in ruminant commodities will below be the limits of determination of the analytical methods (<0.02–0.05 mg/kg, 0.005 mg/kg for milk). The Meeting estimated provisional maximum residue levels for ruminant commodities at the practical limit of determination, 0.05* mg/kg for tissues, 0.01 mg/kg for milk and STMRs for milk and ruminant tissues at 0 mg/kg..

Fate of residues in storage and processing

No relevant studies were reported. Processing studies for the preparation of strawberry jam and preserves and for the canning of peppers were reported to the Meeting. A potato processing study was reported, but the residue on the potatoes was below the limit of determination.

FURTHER WORK OR INFORMATION

Desirable

1. A study of the stability of residues in stored analytical samples covering the crops and storage conditions of the trials reported in support of MRLs. The residue trials data reviewed above may be used after adequate storage stability has been demonstrated.

2. Metabolism studies, plant and livestock, including a demonstration of the stability of methiocarb and its metabolites in the samples and extracts.

DIETARY RISK ASSESSMENT

Chronic intake

The Meeting recommended withdrawal of the existing CXLs, but recommended an MRL and estimated an STMR for strawberry. The International Estimated Daily Intakes (IEDIs) for the 5 GEMS/Food regional diets, based on the single STMR, were 0% of the ADI. The Meeting concluded that the intake of residues of methiocarb resulting from the one use that has been considered by the JMPR is unlikely to present a public health concern. The Meeting agreed that a new assessment of chronic dietary risk should be carried out if new MRLs are recommended.

Acute intake

The International Estimate of Short Term Intake (IESTI) was 23% of the acute RfD for the general population and 38% for children for the one food commodity, strawberries, considered (*see* Section 3). The Meeting concluded that the intake of residues of methiocarb resulting from the use that has been considered by the JMPR is unlikely to present a public health concern.

4.22 OXYDEMETON-METHYL (166)

DEMETON-S-METHYL (073)

The 1992 JMPR carried out a complete re-evaluation of oxydemeton-methyl and this compound and demeton-S-methyl were also the subject of a periodic review by the 1998 JMPR. At the 31st Session of the CCPR (ALINORM 99/24A, para. 98), the JMPR was asked to clarify whether demeton-S-methyl and demeton-S-methylsulphon should remain in the residue definition of oxydemeton-methyl since it was believed that registrations of these compounds would not be retained in the future.

Both demeton-S-methyl and oxydemeton-methyl are used as insecticides. Extensive information was provided for the periodic review of oxydemeton-methyl but the only information reported for demeton-S-methyl was on its metabolism in wheat. Residues were defined as the sum of demeton-S-methyl, oxydemeton-methyl and demeton-S-methylsulphon expressed as oxydemeton-methyl, both for compliance with MRLs and for the estimation of dietary intake.

Oxydemeton-methyl is the sulfoxide of demeton-S-methyl. It is metabolised similarly in plants and mammalian systems to form demeton-S-methylsulphon, which is commonly known as oxydemeton-methyl sulfone or ODM sulfone. In studies with radiolabelled compounds ODM sulfone formed a major part of the identified radioactivity in goat kidneys, muscle and fat, and wheat straw and grain, and was a minor metabolite in cabbages and rats. ODM sulfone is considered to be significantly more toxic than demeton-S-methyl or oxydemeton-methyl.

Numerous methods of analysis were reviewed. These were similar and all determined the combined residue of demeton-S-methyl, oxydemeton-methyl and demeton-S-methylsulphon after an oxidation step that converted demeton-S-methyl and oxydemeton-methyl to the sulfone. All supervised trials were with formulations containing oxydemeton-methyl, analyses were by methods which oxidised the residues to ODM sulfone, and all residues were expressed as the sum of oxydemeton-methyl and ODM sulfone.

The Meeting concluded that if demeton-S-methyl were no longer supported, its residues should no longer contribute to the total demeton-S-methylsulphon. However, its exclusion from the defined residue could lead to difficulties in enforcement situations where the misuse of demeton-S-methyl might have occurred.

The Meeting therefore recommended that additional information should be sought from the CCPR. Member governments should be asked to comment on their national situations relating to current enforcement methods and possible difficulties which might arise

as a result of amending the residue definition. Also, the registrants and national governments should be asked to comment on the registration status of demeton-S-methyl.

4.23 PERMETHRIN (120)

TOXICOLOGY

Permethrin is a synthetic pyrethroid insecticide. It is an ester of the dichloro analogue of chrysanthemic acid, chemically identified as (3-phenoxyphenyl)-methyl-(+-)-*cis*-*trans*-3-(2,2-dichloroethyenyl)-2,2-dimethylcyclopropanecarboxylate. The technical materials are mixtures of four stereoisomers, although the 1R, *cis* isomer is the most active insecticide. Permethrin is effective against a wide range of insect pests in agriculture, animal husbandry and public health and is used to control residential insects and dust mites. The insecticidal action of synthetic pyrethroids such as permethrin is due to interaction with ion channels on axons of the nervous systems of target species.

Permethrin was evaluated toxicologically by the 1979, 1981 and 1982 Joint Meetings. The 1982 Meeting established an ADI of 0-0.05 mg/kg bw for the 40:60 *cis:trans* mixture of permethrin stereoisomers, since it recognized that mixtures of permethrin stereoisomers in different isomeric ratios would require independent evaluation. The 1987 Meeting included permethrin mixtures in which the *cis:trans* ratio is nominally 25:75 in the ADI of 0–0.05 mg/kg bw. Permethrin was reviewed by the present Meeting within the Codex Committee on Pesticide Residues (CCPR) periodic review programme.

The metabolism of ^{14}C-permethrin was studied in rats, lactating goats and cattle, and laying hens. Permethrin was rapidly absorbed, distributed and excreted in these species after oral administration. Metabolism of the pyrethroid was extensive, yielding a vast number of polar degradates. Ester cleavage, hydroxylation, oxidation, and ultimately conjugation are the critical biological mechanisms in the metabolism of permethrin in the species studied. The metabolites that were common to all species were 4$^{\circlearrowleft}$-hydroxypermethrin, dichlorovinyl acid and phenoxybenzyl alcohol. Dichlorovinyl acid and phenoxybenzoic acid have also been identified in human urine after dermal application of permethrin.

In rats, 96% of the administered dose was recovered in urine and faeces within 12 days, while the total radiolabelled residues in tissues accounted for 0.3-0.8% of the dose. Recovery in urine and faeces within 24 h accounted for about 40% and 25% of the dose of *cis*-isomer and 65% and 10% of the dose of *trans*-isomer respectively. Repeated exposure resulted in temporary accumulation in fat tissue, but the chemical dissipated rapidly once exposure ceased.

In lactating goats and cows dosed orally with permethrin, recovery in urine and faeces accounted for at least 65% of the dose and the total radiolabelled residues in liver and milk samples represented 0.2-0.5%. Permethrin was extensively metabolized and readily eliminated after oral administration to laying hens, $\geq$90% of the administered oral dose being excreted, while the total radiolabel in egg and liver samples accounted for 0.1-0.2% of the dose.

The toxicity of permethrin is influenced by many factors including the *cis:trans* isomer ratio, carrier or vehicle, and strain of animal used. The *cis* isomer is considerably

more toxic than the *trans* isomer. The oral LD_{50} values in rats ranged from 6000 mg/kg bw for the 20:80 *cis:trans* isomeric mixture to 225 mg/kg bw for the 80:20 *cis:trans* isomeric mixture. Undiluted technical-grade permethrin (25:75 to 40:60 *cis:trans* isomeric mixtures) has low acute toxicity after oral, dermal and inhalation administration. It was mildly irritating to the eyes and slightly irritating to skin. It was not a skin sensitizer when tested by the Magnusson and Kligman method.

WHO has classified permethrin as 'moderately hazardous'.

Studies of repeated administration by inhalation, orally and dermally to rats, mice, rabbits, guinea-pigs and dogs showed that the main effects of technical-grade permethrin were on clinical signs, especially tremor and hyperexcitability, body weight and liver weight. In these short-term studies, the NOAEL values were 250 mg/m^3 (NOAEC) in a 13-week study in rats exposed by inhalation; 5 mg/kg bw per day in a 52-week study in which dogs received the compound in gelatine capsules orally; and 1000 mg/kg bw per day in a 21-day study in rabbits treated dermally.

In two long-term studies in rats in different laboratories with different strains, permethrin was not carcinogenic, but the evidence for carcinogenicity in mice was conflicting. In two studies conducted in same strain in the same laboratory, permethrin increased the incidences of lung and liver tumours in one study but not in the other. The spontaneous background incidence of both these tumour types is known to be extremely variable. A third study, conducted in a different mouse strain, gave negative results. Thus, the weight of evidence supports the conclusion that permethrin has very weak oncogenic potential and the probability that it has oncogenic potential in humans is remote. The NOAEL for long-term toxicity in rats was 100 ppm, equivalent to 5 mg/kg bw per day, on the basis of clinical signs and changes in body and organ weights and blood chemistry at 500 ppm. The NOAEL for long-term toxicity in mice was 500 ppm, equivalent to 75 mg/kg bw per day, on the basis of changes in organ weights at 2000 ppm.

No genotoxic activity was observed in an adequate battery of tests for DNA damage and mutagenicity *in vitro*, but there was evidence that permethrin can induce chromosomal aberrations in mammalian cells *in vitro.* No tests have been carried out in mammals for DNA damage, mutagenicity, or clastogenicity *in vivo*. A test for dominant lethal effects in male mice showed no activity.

In a multigeneration study of reproductive toxicity in rats, the NOAEL for systemic and reproductive toxicity was 180 mg/kg bw per day. In a second multigeneration study in rats, there a NOAEL was not identified for systemic toxicity, as effects were seen at 500 ppm, equivalent to 33 mg/kg bw per day, the lowest dose tested; the NOAEL for reproductive toxicity in the same study was 2500 ppm, equivalent to 110 mg/kg bw per day, the highest dose tested.

In a study of developmental toxicity in rabbits, the NOAEL for maternal effects was 600 mg/kg bw per day and that for developmental toxicity was 1200 mg/kg bw per day. In three studies of developmental toxicity in rats, the NOAEL for maternal toxicity was 83 mg/kg bw per day and the NOAEL for developmental toxicity was 225 mg/kg bw per day, the highest dose tested. In a study of developmental toxicity in mice, no NOAEL was identified for maternal toxicity, whereas the NOAEL for developmental effects was 400 mg/kg bw per day, the only dose tested. The Meeting concluded that technical-grade permethrin is not a reproductive or developmental toxin.

The results of acute and 90-day studies of neurotoxicity in rats and of an acute delayed neurotoxicity study in hens showed that technical-grade permethrin does not induce neuropathological changes. The NOAEL for neurotoxicity in a study in rats given a single dose was 150 mg/kg bw, on the basis of clinical signs of neurotoxicity and significant changes in measurements in a functional observational battery of tests at 300 mg/kg bw. The NOAEL for neurotoxicity in a 13-week study in rats was 15 mg/kg bw per day, on the basis of clinical signs of neurotoxicity and significant changes in measurements in the functional observational battery of tests at 90 mg/kg bw per day.

An ADI of 0–0.05 mg/kg bw for technical grade permethrin with *cis:trans* ratios of 25:75 to 40:60 was established on the basis of the NOAEL of 100 ppm, equivalent to 5 mg/kg bw per day, in the two-year study in rats, on the basis of clinical signs and changes in body and organ weights and blood chemistry at 500 ppm and the NOAEL in a one-year study in dogs of 5 mg/kg bw per day on the basis of reduced body weight at 100 mg/kg bw per day and applying a safety factor of 100.

The Meeting concluded that the establishment of an acute reference dose was not necessary because of the low acute toxicity of technical permethrin.

A toxicological monograph was prepared.

TOXICOLOGICAL EVALUATION

Levels that cause no toxic effect (relevant for technical permethrin with cis:trans ratios ranging from 25:75 to 40:60)

Mouse: 500 ppm, equivalent to 75 mg/kg bw per day (two-year study of toxicity and carcinogenicity)

Rat: 100 ppm, equivalent to 5 mg/kg bw per day (two-year study of toxicity and carcinogenicity)
180 mg/kg bw per day (for reproductive toxicity, highest dose in a three-generation study of reproductive toxicity)
225 mg/kg bw per day (for maternal and developmental toxicity, the highest dose in a study of developmental toxicity)
150 mg/kg bw (single dose in a study of neurotoxicity)
15 mg/kg bw per day (13-week study of neurotoxicity)

Rabbit: 400 mg/kg bw per day (maternal toxicity in a study of developmental toxicity)
1200 mg/kg bw per day (developmental toxicity in a study of developmental toxicity)

Dog: 5 mg/kg bw per day (one-year study of toxicity)

Estimate of acceptable daily intake for humans

0–0.05 mg/kg bw (for technical-grade permethrin with *cis:trans* ratios of 25:75 to 40:60)

Estimate of acute reference dose

Unnecessary

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

(1) Clarification of the *in vitro* test results for chromosomal aberrations and their potential significance *in vivo*.

(2) The Meeting was aware of other studies, in particular studies of acute toxicity, skin/eye irritation, sensitisation, and developmental toxicity in rats, that had been made available to regulatory entities by other sponsors. The continuing support of permethrin would benefit from the submission of these studies for review by the Joint Meeting.

End-points relevant for establishing guideline values for permethrin

Absorption, distribution, excretion and metabolism in mammals

Rate and extent of absorption:	Rapid and extensive (rat, lactating caprine and bovine, hen)
Distribution:	Mainly to fat (rat, lactating caprine and bovine, hen)
Potential for accumulation:	Some accumulation in fat on repeated dosing (rat)
Rate and extent of excretion:	*cis*-isomer: 40% in urine, 25% in faeces in 24 h in rat *trans*-isomer: 65% in urine, 10% in faeces in 24 h in rat
Metabolism in animals	Extensive; hydrolysis, hydroxylation, oxidation and conjugation (rat, lactating caprine, bovine, hen)
Toxicologically significant compounds (animals, plants and environment)	Parent compound

Acute toxicity

Rat LD_{50} oral	225 (*cis:trans* 80:20); 6000 (*cis:trans* 20:80) mg/kg bw
Rat LD_{50} dermal	No data
Rabbit LD_{50} dermal	2000 mg/kg bw (*cis:trans* 55:45 or 40:60) (highest dose)
Rat LC_{50} inhalation	>23.5 mg/l, 4 h (*cis:trans* 40:60)
Skin irritation	Slightly irritating to rabbit skin
Eye irritation	Mildly irritating to rabbit eyes
Skin sensitization	No sensitizing potential demonstrated in guinea-pigs

Short-term toxicity

Target/critical effect	Nervous system (rat); liver (mouse, rat, dog)
Lowest relevant oral NOAEL	5 mg/kg bw per day in dog (*cis:trans* content 32%:52%)

Lowest relevant dermal NOAEL	1000 mg/kg bw per day in rabbit
Lowest relevant inhalation NOAEL	250 mg/m^3 in rat (*cis:trans* ratio 40:60)

Genotoxicity

No DNA damage or mutagenicity *in vitro*; clastogenic *in vitro*; not studied *in vivo* in mammals

Long-term toxicity and carcinogenicity

Target/critical effect	Nervous system (rat)Liver (mouse, rat)
Lowest relevant NOAEL	Rat, 5 mg/kg bw per day; mouse, 75 mg/kg bw per day
Carcinogenicity	Not carcinogenic to mouse and rat

Reproductive toxicity

Reproduction target/critical effect	None identified
Lowest relevant reproductive NOAEL	180 mg/kg bw per day in rat
Developmental target/critical effect	Rat, none identified; rabbit, fetotoxicity
Lowest relevant developmental NOAEL	Rat, 225 mg/kg bw per day (*cis:trans* content 38%:58%); rabbit, 1200 mg/kg bw per day (*cis:trans* ratio 40:60)

Neurotoxicity/Delayed neurotoxicity

NOAEL, 150 mg/kg bw, single dose, rats; NOAEL ,15.5 mg/kg bw per day in a 90-day study, rats No acute delayed effect in hens (9050 mg/kg bw)

Other toxicological studies

Medical data

Paraesthesia

Summary	Value	Study	Safety factor
ADI	0-0.05 mg/kg bw	Rat, chronic toxicity, 5 mg/kg bw per day Dog, one year, toxicity, 5 mg/kg bw per day	100
Acute reference dose	Unnecessary		

DIETARY RISK ASSESSMENT

Estimated Theoretical Maximum Daily Intakes for the five GEMS/Food regional diets, based on existing MRLs, were in the range of 20-30% of the ADI. The Meeting concluded that the intake of residues of permethrin resulting from its uses that have been considered by the JMPR is unlikely to present a public health concern.

4.24 2-PHENYLPHENOL (056)

TOXICOLOGY

2-Phenylphenol and its sodium salt were evaluated by the 1969, 1983, 1985, 1989 and 1990 Joint Meetings. A temporary ADI of 0-0.02 mg/kg bw was allocated in 1983, which was extended in 1985 and 1989. An ADI of 0-0.02 mg/kg bw was established in 1990. Since that Meeting, studies have become available on biochemical aspects, biotransformation, effects on enzymes and other biochemical parameters, acute toxicity, short-term toxicity, long-term toxicity, genotoxicity, reproductive toxicity, dermal and ocular irritation and dermal sensitization, and on the mechanism of the carcinogenic effect in the rat urinary bladder. The compound was reviewed by the present Meeting within the CCPR periodic review programme.

The toxicological data for the sodium salt of 2-phenylphenol was not used to establish the ADI, since it rapidly dissociates to 2-phenylphenol. These data were, however, considered of value for the review and were therefore included.

After oral administration to mice and rats, 2-phenylphenol and its sodium salt are rapidly and extensively absorbed (95%) and distributed. Excretion is also rapid in these species, being almost complete within 48 h, and occurs mainly in urine (about 90%) and in faeces (about 5%). Little radiolabel (<1%) is retained in organs and tissues, including the urinary bladder. After dermal application of 2-phenylphenol to humans, about 43% of the applied dose was absorbed through the skin and about 58% was recovered in skin rinse and protective enclose. Most of the absorbed radiolabel was recovered in urine (99%) and only 1% was recovered in faeces. The absorption half-life was 10 h and the elimination half-life was 0.8 h. The rapid excretion of the radiolabel into urine indicates that 2-phenylphenol is unlikely to accumulate in humans exposed repeatedly. The metabolic profiles for both compounds were similar in mice, rats and humans at the various doses tested. The main metabolic pathways are conjugation of 2-phenylphenol or hydroxylation at the 5-position of the phenol ring, followed by conjugation with glucuronide or sulfate. The parent compound was detected in only very small amounts (0.4%) in urine. The metabolic profile in plants raised no toxicological concern, since about 90% of the residue found in oranges and pears is 2-phenylphenol or its conjugates.

2-Phenylphenol and its sodium salt have low acute oral toxicity in mice and rats, the LD_{50} values ranging from 600 to 3500 mg/kg bw.

Neither 2-phenylphenol nor its sodium salt has been classified by WHO for acute toxicity.

2-Phenylphenol and its sodium salt caused severe dermal irritation in rabbits, and the sodium salt caused severe dermal irritation in humans. 2-Phenylphenol irritated the eye of rabbits, whereas the sodium salt caused only moderate ocular irritation. Neither substance caused delayed contact hypersensitivity in guinea-pigs or humans.

In medium- and long-term tests for toxicity, the urinary bladder was regarded as the main toxicological target organ of both 2-phenylphenol and its sodium salt in male and female rats. At doses of 200 mg/kg bw per day and above, hyperplasia, papillomas, and

transitional-cell carcinomas were seen with both compounds in male rats. Increased mitosis was observed in the bladder epithelium three days after the start of dosing and thickening, i.e. simple hyperplasia, at 14 days. In female rats, hyperplasia and papillomas were observed, but to a far lower degree than in the males. In male and female mice, the liver was the primary target organ. Increased relative liver weights and an increased incidence of hepatocellular adenomas were seen with 2-phenylphenol at doses of 500 mg/kg bw per day and above. Reduced body-weight gain was a common finding in mice and rats. In 90-day studies, the NOAELs for 2-phenylphenol were 6300 ppm, equal to 760 mg/kg bw per day in rats and 300 mg/kg bw per day (highest dose tested for up to one year) in dogs, and the NOAEL for the sodium salt was 5000 ppm, equivalent to 550 mg/kg bw per day, in mice and 2500 ppm, equal to 180 mg/kg bw per day, in rats. In a one-year toxicity study, the NOAEL for 2-phenylphenol was 800 ppm, equal to 39 mg/kg bw per day, in rats. In two-year studies of carcinogenicity, the NOAEL for 2-phenylphenol was 250 mg/kg bw per day in mice and 800 ppm, equal to 39 mg/kg bw per day, in rats. In two-year carcinogenicity studies with the sodium salt, the NOAEL for carcinogenicity was 20 000 ppm, equal to 3000 mg/kg bw per day in mice and 2500 ppm, equivalent to 95 mg/kg bw per day, in rats. The Meeting concluded that both 2-phenylphenol and its sodium salt are carcinogenic in male rats and that 2-phenylphenol is carcinogenic in male mice.

2-Phenylphenol has been more extensively tested for genotoxic activity than its sodium salt. Within that limitation, the results for the two compounds were similar. Data were conflicting regarding covalent binding to DNA in the urinary bladder of rats dosed with either compound, and 2-phenylphenol induced chromosomal aberrations in cultured mammalian cells. Negative results were obtained for chromosomal aberrations *in vivo*. The Meeting concluded that there are unresolved questions on the genotoxic potential of 2-phenylphenol.

Several studies have been conducted to elucidate the mechanism of the carcinogenic action of 2-phenylphenol and its sodium salt on the male rat urinary bladder, since neither compound has a carcinogenic effect on the urinary bladder of female rats or in mice, guinea-pigs, or hamsters of either sex. No clear mechanisms have been found, although raising the urinary pH or sodium concentration has a promoting effect. There was some evidence from studies with the sodium salt that initial irritation followed by hyperplasia might be involved in the bladder carcinogenicity in male rats. In addition, ^{32}P-postlabelling has shown binding of 2-phenylphenol and its sodium salt to DNA in the male rat urinary bladder in some but not in other studies. The genotoxicity of the metabolites phenylhydroquinone and dihydroxybiphenyl appears to be similar to that of the parent molecules.

The Meeting concluded that the urinary bladder tumours observed in male rats and the liver tumours observed in male mice exposed to 2-phenylphenol were threshold phenomena that were species- and sex-specific, and that 2-phenylphenol was therefore unlikely to represent a carcinogenic risk to humans. In coming to this conclusion, the Meeting was aware that a working group convened by IARC had classified 2-phenylphenol, sodium salt, in Group 2B (possibly carcinogenic to humans) and 2-phenylphenol in Group 3 (not classifiable as to its carcinogenicity to humans). The Meeting noted, however, that the IARC classification is based on hazard identification, not on risk assessment, and is furthermore limited to published literature, with the exclusion of unpublished studies on toxicity and carcinogenicity.

In two two-generation studies of reproductive toxicity in rats, 2-phenylphenol had no reproductive toxicity, even at 460 mg/kg bw per day, the highest dose tested. The overall NOAEL for carcinogenicity was 92 mg/kg bw per day, since urinary bladder tumours were found in male rats at doses of 125 mg/bw per day and above.

In a study of developmental in mice with 2-phenylphenol and its sodium salt, the NOAELs for 2-phenylphenol were below 1500 mg/kg bw per day (lowest dose tested) for maternal toxicity and fetotoxicity and 2100 mg/kg bw per day (highest dose tested) for teratogenicity and the NOAELs for the sodium salt were below 100 mg/kg bw per day (lowest dose tested) for maternal toxicity, 100 mg/kg bw per day for fetotoxicity, and 400 mg/kg bw per day (highest dose tested) for teratogenicity.

In two studies of developmental toxicity in rats, the overall NOAELs for 2-phenylphenol were 150 mg/kg bw per day for maternal toxicity, 300 mg/kg bw per day for fetotoxicity, and 700 mg/kg bw per day (highest dose tested) for teratogenicity.

In two studies of developmental toxicity in rabbits, the overall NOAELs for 2-phenylphenol were 100 mg/kg bw per day for maternal toxicity, 500 mg/kg bw per day for fetotoxicity and 750 mg/kg bw per day (highest dose tested) for teratogenicity.

The Meeting established an ADI of 0-0.4 mg/kg bw for 2-phenylphenol, on the basis of the NOAEL of 39 mg/kg per day in the two-year study of toxicity (based on decreased body-weight gain and hyperplasia of the urinary bladder) and carcinogenicity of the urinary bladder in male rats and a safety factor of 100.

The Meeting determined that an acute RfD was unnecessary because of the low acute toxicity of 2-phenylphenol.

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

TOXICOLOGICAL EVALUATION

Levels of 2-phenylphenol that cause no toxic effect

Mouse: <250 mg/kg bw per day for carcinogenicity (lowest dose tested; two-year study of toxicity and carcinogenicity)
<1500 mg/kg bw per day (lowest dose tested; study of developmental toxicity; maternal toxicity)
2100 mg/kg bw per day (highest dose tested; study of developmental toxicity; not teratogenic)

Rat: 800 ppm, equal to 39 mg/kg bw per day (two-year study of toxicity and carcinogenicity)
460 mg/kg bw per day (two-generation study of reproductive toxicity; no reproductive toxicity; highest dose tested)
92 mg/kg bw per day (two-generation study of reproductive toxicity; urinary bladder tumours)
150 mg/kg bw per day (study of developmental toxicity; maternal toxicity; not teratogenic)

300 mg/kg bw per day (study of developmental toxicity; developmental toxicity)
700 mg/kg bw per day (study of developmental toxicity; teratogenicity)

Rabbit: 100 mg/kg bw per day (two studies of developmental toxicity; maternal toxicity)
500 mg/kg bw per day (two studies of developmental toxicity; fetotoxicity)
750 mg/kg bw per day (two studies of developmental toxicity; teratogenicity)

Dog: 750 mg/bw per day (highest dose tested; one-year toxicity study)

Estimate of acceptable daily intake for humans

0-0.4 mg/kg bw

Estimate of acute reference dose

Unnecessary

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

1. Mechanistic studies on urinary bladder tumours in male rats

2. Further observations in humans

List of relevant endpoints for setting guidance values for dietary and non-dietary exposure to 2-phenylphenol (unless otherwise specified)

Absorption, distribution, excretion and metabolism in mammals

Rate and extent of oral absorption:	Rapid (24 h) and complete (95-100%), mice and rats
Dermal absorption	Rapid and well absorbed (43%), humans
Distribution	Small concentrations (<1%) in tissues, mice and rats
Potential for accumulation	No accumulation, mice, rats and humans
Rate and extent of excretion	Rapid and complete (95-100%), mice, rats and humans
Metabolism in animals	Glucuronide and sulfate of *2*-phenylphenol and phenylhydroquinone, mice and rats
Toxicologically significant compounds (animals, plants and environment)	*2*-Phenylphenol

Acute toxicity

Rat LD_{50} oral	2800 mg/kg bw
Rabbit LD_{50} dermal	>5000 mg/kg bw
Rabbit LC_{50} inhalation	>36 mg/m3 air (aerosol, 4 h)
Skin irritation	2-Phenylphenol and its sodium salt: Severe skin

	irritation, rabbits
Eye irritation	2-Phenylphenol: Eye irritation, rabbits Sodium salt: Slightly eye irritation, rabbits
Skin sensitization	2-Phenylphenol and its sodium salt: No skin sensitization, guinea-pigs and humans

Short-term toxicity

Target/critical effect	Body-weight decrease, mice and rats and urinary bladder tumours, male rats
Lowest relevant oral NOAEL	300 mg/kg bw per day, dogs
Lowest relevant dermal NOAEL	No NOAEL, 1000 mg/kg bw per day, highest dose tested, rats
Lowest relevant inhalation NOAEL	Not investigated

Genotoxicity	Unresolved questions

Long term toxicity and carcinogenicity

Target/critical effect	Urinary bladder, male rats Liver, male and female mice
Lowest relevant NOAEL	39 mg/kg bw per day, male rats
Carcinogenicity	Urinary bladder tumours, male rats Liver tumours, male and female mice

Reproductive toxicity

Reproduction target/critical effect	No reproductive toxicity, rats
Lowest relevant reproductive NOAEL	460 mg/kg bw per day, highest dose tested, rats
Developmental target/critical effect	Developmental toxicity at maternally toxic doses, mice
Lowest relevant developmental NOAEL	300 mg/kg bw per day, rabbits

Neurotoxicity/Delayed neurotoxicity	No evidence of developmental neurobehavioral toxicity in rats. No evidence of neurotoxicity or neuropathology in medium- and long-term studies, mice, rats, dogs, or in developmental toxicity studies, mice, rats and rabbits

Other toxicological studies

Medical data	Skin irritation with the sodium salt, not with 2-phenylphenol

Summary	Value	Study	Safety factor
ADI	0-0.4 mg/kg bw	Long-term study of toxicity and carcinogenicity, rat	100
Acute reference dose	Not established (unnecessary)		

Acute reference dose	Unnecessary

RESIDUE AND ANALYTICAL ASPECTS

The 1969 JMPR recommended MRLs for 2-phenylphenol (OPP) and its sodium salt (SOPP) in several fruits. 2-Phenylphenol was originally scheduled for periodic re-evaluation of residues by the 1994 JMPR, but was withdrawn because the manufacturer indicated that it was not supporting the existing CXLs and the data base was considered insufficient to support a periodic review. OPP was rescheduled for periodic re-evaluation of residues by the 1999 JMPR (ALINORM 95/24A, Appendix IV). The California Citrus Quality Council (CCQC) and the Pear Bureau Northwest provided information in support of the periodic review. Additional information was supplied by the governments of Australia and The Netherlands.

Animal metabolism

Two lactating Nubian goats 2 to 4 years of age were dosed orally by capsule with [^{14}C]2-phenylphenol, labelled in the phenoxy ring daily for 5 consecutive days at an average dose level of 13.7 and 53.3 mg/kg b w/day. The doses were equivalent to 11.3 ppm and 32.1 ppm of the test material in the diet, based on actual feed consumption during the test period. Milk, urine and faeces were collected daily from each animal. The goats were slaughtered about 23 hours after the last dose.

All samples were radioanalysed. In both goats >90% of the administered radioactivity was eliminated, mainly in the urine. The radioactivity in the milk reached a plateau on day 1 or 2 for both animals at 0.03% of the administered dose, 0.008 µg OPP equivalents/g from the low dose and 0.043 µg/g from the high dose. Radioactive residues from the low dose were $\leq$0.005 mg/kg in the fat, kidney, liver and muscle, and from the high dose 0.003 mg/kg in the fat, 0.020 mg/kg in kidney, 0.014 mg/kg in liver and <0.001 mg/kg in muscle.

The extracts of kidneys and liver were analysed by HPLC. The organic solvent extracts of milk was not analysed because of the very low levels of radioactivity. Reference standards included phenyl-1,4-benzoquinone (PBQ), OPP and phenylhydroquinone (PHQ). No peak corresponded to a reference standard in any extract. The largest single component detected was 0.007 mg/kg as OPD in the acetonitrile extract of kidney. In general, no other component accounted for more than 0.002 mg/kg. Extracts were not hydrolysed to release possible conjugates because of the low radioactivity.

The metabolism of OPP in rats, mice and humans was summarized without supporting details. Metabolism studies have shown that OPP is well absorbed and rapidly excreted in the urine. The main metabolite excreted by rats was OPP sulfate with lesser amounts of glucuronide conjugates of OPP and its hydroxylated metabolite phenylhydroquinone (PHQ). Trace amounts of phenyl-1,4-benzoquinone (PBQ) were also detected in urine These metabolites were also found in the urine of mice given 5 daily doses of OPP at 25 and 1000 mg/kg bw and in human male volunteers given a dermal application of [^{14}C]OPP at 0.006 mg/kg bw. The sulfate conjugate of 2,4'-dihydroxybiphenyl (DHB) was also identified. Little or no free OPP and no free PHQ or PBQ was found in mice, rats and humans.

The Meeting concluded that the metabolism of OPP in ruminants is adequately understood. OPP and/or its metabolites are eliminated in the urine and do not accumulate in

any tissues or milk. OPP, PBQ and PHQ were not found in milk or tissues. Studies with rats and mice indicate that OPP is converted directly to the glucuronide and sulfate conjugates, and via a postulated 2,4'-DHB to a sulfate and via a postulated PHQ to PHQ glucuronide and sulfate.

Plant metabolism

The metabolism of OPP applied post-harvest to oranges and pears was reported. Oranges were dipped in either a 0.1% or 0.5% solution of radiolabelled OPP and were then stored for intervals from 2 hours–12 weeks under commercial storage conditions for pears at 1–4°C. Upon removal from storage, the oranges were rinsed with methanol to remove surface residues and then peeled. Pulp containing 6.2 mg/kg as OPP and juice 7.0 mg/kg as OPP from the 0.5% treatment after 12 weeks were extracted and analysed by HPLC. Peels taken at intervals were subjected to sequential extraction and enzyme, acid, and base hydrolysis.

The calculated total radioactive residue on whole oranges was 9–12 mg/kg from the 0.1% dip and 16 mg/kg from the 0.5% dip. Most of the radiolabelled residue (>95% of the TRR) remained in the rinse or the peel at all intervals. The main compound in the juice and pulp samples was OPP, 75% of the radioactivity in the pulp extract (0.14% of the TRR, 0.01 mg/kg) and about 51% of that in the juice extract (0.12% of the TRR, 0.01 mg/kg). Orange peel contained OPP and OPP conjugates (89% of the TRR) and phenylhydroquinone (3.6%).

Bosc pears were treated with an aqueous dipping solution of 40 g/kg unlabelled and (U-*phenoxy*-^{14}C]OPP. The pears were rinsed after treatment and stored at 1-4°C and 90% humidity for various periods (2 h–28 weeks). Pears taken from storage were rinsed with methanol to remove surface residues and peeled. Peels and pulp were extracted separately. Extracts were analysed by HPLC and GC-MS and LC-MS were used for qualitative identifications.

The pears sampled 28 weeks after treatment contained 42.2 mg/kg OPP equivalents. About 66% of the TRR was in the peel and 26% in the pulp. About 57% of the TRR in the peel and 23% in the pulp was identified as OPP and OPP conjugates, one a glucose conjugate. The rinse contained 4% of the TRR

The Meeting concluded that the metabolism of OPP in plants is adequately understood. Most of the residue in oranges and pears is OPP and OPP conjugates. PHQ (4% of the TRR) was found in orange peel. OPP did not translocate beyond the peel of oranges, but migrated substantially into the pulp of pears.

Environmental fate

Information was presented on the biodegradation of OPP in river water, activated sludge and municipal waste-water with a microbial inoculum (OECD Method 301B). In river water radiolabelled OPP at concentrations ranging from 1.2 to 120 µg/l was degraded to about 50% of the initial concentration in one week. The addition of $HgCl_2$ to inhibit biological activity reduced the decrease to only 10% after 30 days. In activated sludge, radiolabelled OPP at 9.6 mg/l was degraded to 50% of the initial concentration in 24 hours. OPP meets the criteria to be classed as readily biodegradable. Mineralization to $^{14}CO_2$ accounted for about 66% of the radioactivity after 11 days. In $HgCl_2$-treated controls <1% of the radioactivity was evolved as $^{14}CO_2$.

The Meeting concluded that OPP is readily degraded in surface waters and municipal waste mixtures and that the degradation is biologically mediated. The Meeting also concluded that information on the fate in soil is not required because OPP is used only as a post-harvest treatment in packing houses and similar indoor structures. Contamination of the soil is highly unlikely.

Analytical methods

Numerous methods exist for the determination of 2-phenoxyphenol and sodium 2-phenylphenate in crops. No methods are available for livestock commodities. The official enforcement method in the USA is a photometric method with an estimated limit of detection of 3 mg/kg. The chopped sample is steam distilled in aqueous phosphoric acid, the distillate is derivatized, and the absorbance at 500 nm is measured. Many laboratories now measure absorption after HPLC. With this variation the limit of determination is about 0.025 mg/kg.

Several HPLC methods that do not require distillation are described in the literature. One such method is routinely applied to citrus fruit by a major US citrus grower. A composite fruit sample is slurried and extracted with ethyl acetate. The extract is analysed by HPLC with fluorescence detection. The limit of detection is estimated to be 0.05 mg/kg OPP.

A GLC method is used industrially to measure residues in citrus fruit, kiwifruit and cantaloupes. Elf Atochem Method 415B involves reflux distillation with HCl and hexane. The distillate is extracted and analysed by GLC with a flame ionization detector and a capillary column. The limit of determination is 0.1 mg/kg.

The method used for trials and a processing study and proposed for enforcement in the USA is a GC-MS procedure. The blended fruit sample is simultaneously acid-hydrolysed, steam distilled and extracted in a micro-Nielson-Kryger apparatus. The extract is derivatized with BSTFA. The resulting trimethylsilyl ether is analysed by GC-MS in the selected ion mode. Ions monitored for OPP were 227, 242, 170 and 141, with m/z 227 used for quantification ion. The method can be adapted to determine PHQ. The limit of determination for OPP was 0.05 mg/kg in all citrus products except oil, in which it was 1 mg/kg.

The Meeting concluded that adequate methods exist for data collection and for MRL enforcement for OPP in fruit and fruit products.

Stability of residues in stored analytical samples

In storage stability studies on citrus OPP was stable at freezer temperatures in grapefruit for 6 months, lemons for 8 months, oranges for 7 months, orange juice for 5 months and orange oil for 9 months. PHQ was stable in grapefruit for 5 months and orange juice for 5 months, but unstable in oranges and orange oil. The PHQ data for lemons could not be interpreted.

A storage stability study on pears was conducted concurrently with the residue trials. OPP was stable in pears stored frozen for about 4 months.

The Meeting concluded that adequate storage stability data had been presented for OPP in citrus and processed citrus commodities and in pears.

Definition of residue

In studies of metabolism in oranges and pears OPP and its conjugates constituted 90% of the total radioactive residue (TRR) in oranges and 84% of the TRR in pears. PHQ was found in orange peel at low concentrations (<4% of the TRR). It is therefore appropriate to define the residue for both enforcement and for the estimation of dietary exposure as the sum of 2-phenylphenol and sodium 2-phenylphenate, free and conjugated, expressed as 2-phenylphenol. This applies to plant commodities only.

Residues resulting from supervised trials

Citrus fruits. US GAP encompasses only post-harvest fruit treatments. The trials complied with a foamer cleaning with brushes and spray for 10–60 sec at 1.45 kg sodium *o*-phenylphenate (SOPP) per hl or a waxing with brushes and spray at 0.97 kg SOPP per hl, with an application rate of the final mixture at 0.83 ml/kg fruit (1 gal/10,000 lbs.). Additional GAP not covered by the trials specifies (1) a dip/wash for 2–5 minutes with 0.36 kg SOPP per hl, followed by a fresh water rinse; and (2) a bin drench at 0.87 g SOPP per hl, with no rinse. The foamer cleaning would give the highest exposure to OPP.

Supervised trials were reported on lemons, oranges and grapefruits, two each on lemons and oranges in California, two on California grapefruit and two on Florida grapefruit. In each trial the fruit were subjected to a foamer cleaning with brushes using 1.45% anhydrous SOPP with a 30-second exposure. This was followed by the application of shipping wax containing 1.0% anhydrous SOPP, at 1 l of wax solution per 1200 kg of fruit, corresponding to maximum GAP; only one application of OPP is usually made. Some control samples contained OPP above the limit of determination (0.05 mg/kg), the range being <0.05–0.08 mg/kg. The concentration in the controls was at most about 2% of that in the treated samples and was not considered significant.

The residues in the whole fruit in rank order were 2.4 (3), 2.7, 5.2. 5.4, 6.5 and 6.7 mg/kg. The median is 3.95 mg/kg. The pulp samples were not analysed separately from peel, but the study of orange metabolism indicated that no more than 5% of the radioactive residue was likely to be found in the pulp. The STMR for pulp may be estimated as 0.05 x 3.93 mg/kg, and 0.20 mg/kg.

The number of trials is inadequate for any individual commodity, but 8 trials are acceptable for the citrus group. The Meeting estimated an STMR of 3.9 mg/kg and a maximum residue level of 10 mg/kg, confirming the existing MRL for citrus fruits.

Pears. US GAP specifies the post-harvest treatment of pears as (1) foamer and spray cleaning with 1.3 kg SOPP/hl for 15–30 seconds followed by a rinse, or (2) dipping in 0.35 kg SOPP/hl solution for 1.5–4 minutes, followed by a rinse.

In two trials in the USA, pears were dipped in a 0.49% solution of SOPP for 2 minutes, followed by a water rinse. The trials were according to maximum GAP and the residues were highest on the day of treatment. The residues were 0.82 and 1.4 mg/kg.

The Meeting could not estimate an STMR or maximum residue level as there were only two trials, and recommended the withdrawal of the existing MRL.

Apples. No trials were reported. The Meeting recommended the withdrawal of the existing MRL.

Animal feeding studies

No studies were reported. Orange pulp is used in cattle feed. The ruminant metabolism study showed no detectable residues of OPP or PHQ. Conjugates were not determined. The high-dose rate, equivalent to 32 ppm in the feed, represents approximately 6 times the theoretical maximum intake of OPP by cattle. This is based on the highest residue found in citrus trials according to GAP, 6.7 mg/kg, the average processing factor for converting citrus to dried pulp, 3.6 and the percentage of citrus pulp in the diet, 20%, and 6.7 mg/kg x 3.6 x 0.2 = 4.8 ppm. At the sixfold rate, more than 90% of the residue was eliminated. There was no propensity for the residue to accumulate in fat and muscle. Low levels of residues were found in the milk (0.04 mg/kg), kidney (0.02 mg/kg) and liver (0.01 mg/kg). These residues consisted of multiple components, none of which exceeded 0.007 mg/kg. Neither OPP nor PHQ was found. Measurable residues from the ingestion of OPP would not be expected from current treatments according to GAP. This assumes that additional bioaccumulation does not occur with exposure periods greater than 5 days.

The Meeting concluded that maximum residue levels need not be estimated for animal commodities.

Processing

Studies of the conversion of treated oranges into orange juice, orange oil and dried pulp were reported. Oranges were treated by a foamer cleaning with a 14.5 g/kg solution of SOPP for 120 seconds, followed by application of shipping wax containing 10 g SOPP per kg. The oranges were scarified before treatment to increase the uptake of OPP. The treatments represented maximum GAP, but the scarification would be expected to produce higher residues. Oranges were processed on the day of treatment and 28 and 56 days later. Two independent trials were conducted on each day, giving a total of six trials.

The residues decreased in converting oranges to juice. The processing factors were 0.018, 0.021, 0.034, 0.035, 0.037 and 0.040, an average processing factor of 0.031. The Meeting estimated an STMR for orange juice of 0.12 mg/kg, based on the STMR for citrus of 3.9 mg/kg and the average processing factor. The Meeting also estimated a maximum residue level for orange juice of 0.5 mg/kg, based on the maximum residue level for citrus of 10 mg/kg and the maximum processing factor of 0.040.

The residues increased in orange oil. The processing factors were 66, 77, 81, 88, 97 and 105, an average of 86. The Meeting estimated an STMR for orange oil of 340 mg/kg from the STMR for citrus of 3.9 mg/kg and the average processing factor, and a maximum residue level of 1000 mg/kg from the maximum residue level for citrus of 10 mg/kg and the maximum processing factor of 105.

The residues were increased slightly in dried pulp, an animal feed item. The processing factors were 2.2, 2.9, 3.0, 3.7, 4.4 and 5.4. The Meeting estimated a maximum residue level for dried orange pulp of 60 mg/kg, based on the citrus maximum residue level and the maximum processing factor, 10 x 5.4 = 54 mg/kg.

FURTHER WORK OR INFORMATION

Desirable

A ruminant feeding study at the level of the estimated dietary intake based on citrus pulp consumption and at 10 and 100 times that level. Milk and tissues should be analysed for OPP and PHQ, free and conjugated.

DIETARY RISK ASSESSMENT

Chronic intake

STMRs for one raw commodity and one processed commodity were used for a chronic dietary intake assessment. The International Estimated Daily Intakes for the 5 GEMS/Food regional diets, based on these STMRs, were all 0% of the ADI. The Meeting concluded that the intake of residues of 2-phenylphenol resulting from its uses that have been considered by the JMPR is unlikely to present a public health concern.

Acute intake

The Meeting concluded that an acute RfD for 2-phenylphenol is unnecessary. This conclusion was based on a determination that the pesticide is unlikely to present an acute toxicological hazard, and residues are therefore unlikely to present an acute risk to consumers.

4.25 PHOSALONE (060)

RESIDUE AND ANALYTICAL ASPECTS

Phosalone was the subject of a periodic review of residues by the 1994 JMPR. That Meeting concluded that the existing CXLs for phosalone should be withdrawn, owing to inadequacies in the available information. The CCPR decided to maintain the CXL for 4 years. A periodic review of the toxicology carried out by the 1997 JMPR, which allocated an ADI of 0-0.02 mg/kg bw.

The Meeting received new or revised information on physical and chemical properties, metabolic and environmental fate, analytical methods, stability of analytical samples, use patterns, supervised trials, apple processing, and national MRLs. A new determination of the octanol/water partition coefficient gave a value of log P_{ow} = 4.01 at 20°C.

Plant metabolism

Phosalone was typically the main residue; phosalone oxon and 6-chlorobenzoxazolone were found at low levels in apples. In grapes, phosalone was the main residue in the juice and constituted more than 95% of the residue in the pulp.

Environmental fate

Photolysis. In water at pH 5, decomposition is very rapid (half-life 15-20 minutes). The quantum yield at 300 nm for phosalone in aqueous solution was determined to be 0.19. In the troposhere the estimated reaction constant at 298° K is 9.34×10^{-3} s^{-1} which corresponds to a half life of about 74 daylight seconds.

Biodegradability. In active sludge about 20% of the initial radioactivity of [^{14}C]phosalone was detected as $^{14}CO_2$ after six weeks.

Aerobic degradation in soil. Phosalone was degraded rapidly with half-life of 2.9 days. Unextracted radiocarbon increased to an average of 85% by 30 days. The product phenoxazone was observed but did not exceed 1.5% of the applied radioactivity.

Anaerobic degradation in soil. In the water phase, phosalone was rapidly degraded to 2-amino-5-chlorophenol which reached a maximum of 20% of the applied radioactivity after 3 days, then decreased. In the soil phase phosalone was also rapidly degraded, producing chloroaminophenol which reached a maximum of 8% of the applied radioactivity after 14 days.

Soil adsorption/desorption was studied in sandy loam, silty clay loam, loam and clay. The average K_{oc} value for adsorption on the three loam soils was 2060. Degradation on clay was too rapid to measure adsorption. Phosalone is predicted to have slight to low mobility in soils.

Environmental fate in water/sediment systems. In river and ditch systems at 68% and 65% of the applied radioactivity was bound after 12 weeks. In the aqueous phases four degradation products were found but not identified. They did not exceed 10% of the applied radioactivity. In the sediment phosalone was the main residue, but did not exceed 6% of the applied radioactivity.

Bioaccumulation. A dynamic 42-day study was conducted to determine the uptake of radiolabelled phosalone by bluegill sunfish. The uptake rate constant for whole fish was 0.18 (± 0.02) mg/kg fish/mg/l water /day. The bio-concentration factors were 280 to 300 for viscera, 78 to 85 for edible tissue and 190 to 200 for whole fish.

Analytical methods. In general residues are extracted with acetone/water and cleaned up by liquid-liquid partition with dichloromethane. The final extract is concentrated and analysed by GLC with EC, NP or FP detection. There are several variants.

A number of residue analytical methods were described in the 1994 JMPR monograph. The method LODs for plants were generally 0.05 mg/kg with an ECD, FPD or NPD.

In a more recent method for phosalone and phosalone oxon the residues are extracted with acetone and cleaned up by partitioning between water and dichloromethane. Quantification is with an FPD. The LODs are 0.02 mg/kg for both compounds.

Stability of residues on stored analytical samples. Fortified peaches and almonds were stored frozen at -18 °C for 1 and 3 months. Recoveries after storage were 94 to 102% from peaches and 79 to 81% from almonds. Almonds, apples and cherries with incurred residues were stored at -18 °C for 19 to 24 months. The recovery of phosalone was 66 to 77% from almonds, 67 to 70% from apples and 113 to 133% from cherries.

Definition of the residue

The current definition of phosalone is "phosalone". A metabolism study on apples showed that phosalone was the predominant residue (75%-92%) and oxo-phosalone with only 2%-7% of the oxon. In grapes phosalone was about 90% or more of the residue with only 1-2% of the oxon. The Meeting concluded that the current residue definition is suitable both for compliance with MRLs and for the estimation of dietary intake.

The octanol-water partition coefficient (log P_{ow} = 4.01) suggests fat-solubility. The Meeting concluded that phosalone is fat-soluble.

Residues resulting from supervised trials

Pome fruits. Phosalone may be used at 0.06 kg ai/hl (0.6 kg ai/ha, standard orchard spray volume: 1000 l/ha) on apples and pears in France with a PHI of 14 days for EC, 15 days for SC. The residues in apples and pears from 5 French, 1 German, 1 Italian and 1 Spanish trials meeting these conditions were 1.1, 0.38, 0.74, 0.66, 1.5, 1.0, 0.46 and 0.38 mg/kg.

In Italy, phosalone may be used at 0.05-0.07 kg ai/hl on apples and pears with a PHI of 21 days. Several of the trails complied with both French and Italian GAP. The residues from 5 Italian, 3 French and 1 Spanish trials meeting these conditions were 0.6, 0.65, 0.85, 0.96, 0.74, 0.52, 1.5, 1.0, 0.91 and 0.36 mg/kg.

Phosalone residues in apples and pears from the 5 Italian, 5 French, 1 German and 1 Spanish trials in rank order (median underlined) were 0.38 (2), 0.46, 0.65, 0.66, 0.74, 0.85, 0.91, 0.96, 1.0, 1.1 and 1.5 mg/kg.

The Meeting estimated a maximum residue level of 2 mg/kg and an STMR of 0.8 mg/kg for phosalone in pome fruits.

Stone fruits. Phosalone may be used on cherries and peaches in France at 0.06 kg ai/hl (0.6 kg ai/ha) with a PHI of 14 days. The residues from 16 trials on cherries and 4 on peaches meeting these conditions were 0.18-1.6 mg/kg and 0.16-1.5 mg/kg respectively. The trials on peaches also complied with Italian GAP: 0.06-0.07 kg ai/hl with a PHI of 21 days. The residues in peaches from 2 Italian and 4 French trials meeting these conditions were 0.13, 0.68, 1.4, 0.45, 0.63 and 0.31 mg/kg.

The Meeting concluded that the residues in cherries and peaches belonged to the same population.

The residues in cherries and peaches from the French and Italian trials in rank order (median underline) were 0.16, 0.18, 0.23, 0.26(2), 0.29, 0.3, 0.35, 0.36, 0.42, 0.45 (2), 0.46, 0.47, 0.59, 0.6, 0.63, 0.72, 0.73, 1.4, 1.5 and 1.6 mg/kg.

Apricots. Phosalone may be used at 0.02 kg ai/hl on Japanese apricots in Japan with a PHI of 45 days. The residues in Japanese apricots from 2 trials in Japan meeting these conditions were 0.005 and 0.009 mg/kg.

The Meeting estimated a maximum residue level of 2 mg/kg and an STMR of 0.45 mg/kg for phosalone on stone fruits.

Tree nuts. Phosalone may be used on almonds in France at 0.06-0.075 kg ai/hl (0.60-0.75 kg ai/ha) with a PHI of 70 days. The residues in almonds from 6 French trials meeting these conditions in rank order (median underlined) were <0.02 (2), <0.05 (3) and 0.074 mg/kg.

The Meeting estimated a maximum residue level of 0.1 mg/kg and an STMR of 0.05 mg/kg for phosalone in almonds.

Phosalone may be used on hazelnuts and walnuts in France at 0.06 kg ai/hl (0.60 kg ai/kg) with a PHI of 21 days. The residues in hazelnuts from 4 French trials and in walnuts from 1 French trial meeting these conditions were all <0.05 mg/kg.

The Meeting estimated a maximum residue level of 0.05* mg/kg and an STMR of 0.05 mg/kg for phosalone in hazelnuts and walnuts.

Processing

Apples were processed to compote with a processing factor of 0.14. As the STMR for pome fruits is 0.8 mg/kg the Meeting estimated an STMR of 0.1 mg/kg for phosalone in apple compote.

DIETARY RISK ASSESSMENT

Chronic intake

Six STMRs were estimated for phosalone. There were consumption data for the 5 main commodities which were used for the dietary intake calculation. The results are shown in Annex III.

The International Estimated Daily Intakes for the 5 GEMS/Food regional diets, based on estimated STMRs, were in the range of 0-4% of ADI. The Meeting concluded that the intake of residues of phosalone from uses that have been considered by the JMPR is unlikely to present a public health concern.

Acute intake

The international estimated short-term intake (IESTI) for phosalone was calculated for the commodities for which maximum residue levels and STMRs were estimated and for which consumption data were available. The results are shown in Annex IV. The IESTI varied from 0 to 0.034 mg/kg bw for the general population and from 0 to 0.118 mg/kg bw for children (*see* Section 3). As no acute reference dose was established, the acute risk assessment for phosalone was not finalized.

4.26 PROPARGITE (113)

TOXICOLOGY

Propargite is an acaricide which has been used on a wide variety of food crops since its introduction in 1967. Toxicological assessments of the compound were performed by the 1977, 1980 and 1982 Joint Meetings. The 1977 Meeting established a temporary ADI of 0-0.08 mg/kg bw on the basis of a NOAEL of 300 ppm (equivalent to 15 mg/kg bw per day) in a three-generation reproductive toxicity study. Because a long-term toxicity study in rats reported in 1966 was considered by the Meeting to be inadequate, a safety factor of 200 was used. The results of a long-term study of carcinogenicity in mice were made available to the Meeting in 1980; no carcinogenic effects were observed. In a study of teratogenicity in rats, delayed maturation was observed and the 1980 Meeting concluded that this effect should be clarified. The 1982 Meeting re-evaluated the results of this study and concluded that propargite was not teratogenic in rats. That Meeting established an ADI of 0-0.15 mg/kg bw on the basis of a NOAEL of 15 mg/kg bw per day in the earlier multigeneration study of reproductive toxicity and a safety factor of 100. Propargite was re-evaluated by the present Meeting in the context of the CCPR periodic review programme.

The results of various studies of the pharmacokinetics of single oral doses of propargite in CD rats showed that gastrointestinal absorption was inversely related to the administered dose. After administration of a single oral dose of [^{14}C-phenyl]ring-labelled propargite to rats, 20-50% of the administered dose was excreted in the urine and 40-75% in faeces; about 1.5% of the administered dose was found in tissues, with slightly higher urinary excretion and correspondingly smaller faecal elimination in males. Roughly similar results were found in CD mice treated in the same way.

In rats, dermal absorption of propargite occurred mainly within the first 4 h after application. The absorption amounted to up to 33% of the administered dose of technical material and 3-17% of the administered doses of various formulations.

The metabolism of propargite has been elucidated in a series of studies in rats and mice. The compound was rapidly degraded to polar metabolites, metabolism of the cyclohexyl ring predominating. Most of the radiolabel in rat faeces was associated with unchanged parent compound and with a few metabolites, which were also found in urine. In comparative studies in rats and mice, no parent compound was found in the bile of either species, whereas the plasma contained small amounts of unchanged propargite; six metabolites were found in rat and mouse bile. The metabolites are formed as a result of hydrolysis of the propynyl sulfite side-chain, subsequent oxidation and conjugation of the *tert*-butyl moiety, and hydroxylation of the cyclohexyl moiety. No consistent quantitative and qualitative species differences in bile and plasma metabolite profiles were found.

In further studies of metabolism with propargite with a radiolabel located in the propynyl sulfite side chain and radiolabelled propargyl alcohol an additional metabolic pathway was identified which involved metabolism of the side chain by glutathione conjugation.

Propargite is of low acute toxicity with an oral LD_{50} in rats of 2800 mg/kg bw, but it irritates the skin and eyes. Propargite did not show dermal sensitizing potential in the Buehler test using guinea pigs.

WHO has classified propargite as ‘slightly hazardous’.

In short-term studies in rats, mice and dogs, the signs of systemic toxicity included effects on body weight and on haematological and clinical chemical parameters. In a study in which CD rats were fed propargite for three months, the NOAEL was 100 ppm, equivalent to 5 mg/kg bw per day. In dogs, dietary administration of propargite for one year resulted in a NOAEL of 160 ppm, equivalent to 4 mg/kg bw per day, on the basis of effects on body weight, on various haematological parameters and histopathological changes in the thymus and bone marrow. In a 21-day study in rabbits treated dermally, the NOAEL for systemic toxicity was ≤100 mg/kg bw per day, whereas no NOAEL for local irritation was found.

In long-term studies, the most significant toxicological finding was the occurrence of jejunal sarcomas in CD (Crl:CDBR) rats, whereas no carcinogenic effect was observed in CD-1 mice and Wistar (FDRL) rats. In a 78-week study in CD-1 mice dated 1979, the NOAEL was 50 ppm, equivalent to 7.5 mg/kg bw per day, on the basis of changes in organ weights. In the study in Wistar (FDRL) rats dated 1966, the NOAEL was 100 ppm, equivalent to 5 mg/kg bw per day, also on the basis of changes in organ weights.

In a two-year study reported in 1991 in which CD (Crl:CDBR) rats were given diets containing propargite at concentrations of 0, 50, 80, 400, or 800 ppm (equal to 0, 2, 4, 19 and 39 mg/kg bw per day in males and 0, 3, 5, 24 and 49 mg/kg bw per day in females), males at 400 and 800 ppm showed a dose-related increase in the incidence of undifferentiated sarcomas in the jejunum, a very rare tumour. Females also showed a clear tumorigenic response but with a different dose-response relationship, since a high incidence (21%) of jejunal tumours in the smooth muscle was observed at the highest concentration of 800 ppm but low incidences (one animal in each group) at 50, 80 and 400 ppm. Given the rarity of sarcomas arising at this site (0% in concurrent and historical female controls, 0% in concurrent male controls and 0.2% in historical male controls), a NOAEL for tumorigenicity could not be identified in this study. In a subsequent 20-month study with CD rats reported in 1998 at dietary concentrations of 0, 80, 400, or 800 ppm (equal to 0, 4, 21 and 42 mg/kg bw per day) for males and 0, 40, 400 or 800 ppm (equal to 0, 6, 28 and 55 mg/kg bw per day) for females, the appearance of jejunal masses at 400 and 800 ppm in males and at 400 ppm in females suggested that the tumorigenic response is a reproducible effect. Reduced cell proliferation in jejunal smooth muscle layers and decreased jejunal cell division were found at various times during the study. After 20 months, cell division and cell proliferation were found to be increased only in males at 800 ppm, with no corresponding response in females or in males at lower doses. No hyperplasia, cytotoxicity, or inflammation was found in the jejunal epithelium.

Several short-term (one or four weeks) studies of cell proliferation were conducted in male and female CD rats at concentrations of up to 800 ppm, in Wistar rats (WKY strain) at 900 ppm and in male CD-1 mice at 1000 ppm. The NOAEL for cell proliferation in the CD rat was 40 ppm (equal to 2 mg/kg bw per day) in females and 80 ppm (equal to 4 mg/kg bw per day) in males, both being the lowest doses tested. A proliferative response was observed at 800 ppm in both male and female rats after one week of treatment, whereas the response was observed only in males after four weeks of treatment at this concentration; no cell proliferation was observed at 40 and 80 ppm. No cell proliferation was found in Wistar rats (WKY) treated with 900 ppm or in CD-1 mice at 1000 ppm using the same study design.

The results of the long-term studies in CD rats and the short-term studies of cell proliferation indicate that the cell proliferation induced by propargite in the jejunum is characterized by an initial transient proliferative response, lasting for at least four weeks in males and for only about one week in females. This profile of cell proliferation suggests that the underlying mechanism for tumour formation in the jejunum of CD rats may be related to the mitogenic activity of the compound. The finding of consistently negative results in numerous tests for genotoxicity provide further support for the conclusion that propargite causes tumours by a non-genotoxic mechanism.

The observed dose-response relationship for tumour formation, with a greater increase in tumour incidence in males than in females, correlates with the duration and degree of jejunal cell proliferation. The prolonged duration of cell proliferation in male rats was associated with a more pronounced tumorigenic response than in females. Furthermore, propargite did not induce cell proliferation in species and strains in which no carcinogenic activity was observed. The available database does not further illuminate the causal relationship between cell proliferation and tumorigenicity, and no explanation was offered to explain the species, strain and sex specificity, or the association between the presence of an early, transient cell proliferation response and the occurrence of jejunal tumours in CD rats and the consistent absence of these findings in Wistar rats and CD-1 mice. Nevertheless, the association between proliferation and tumorigenic activity was recognized by the Meeting. The Meeting also noted that the NOAEL for cell proliferation of 40 ppm is very close to the lowest tumorigenic concentration in female rats of 50 ppm. The available database did not, however, clarify the dose-response relationship at low tumorigenic doses found in females and offered no further scientific evidence to support use of cell proliferation as a marker of potential carcinogenicity.

An adequate range of studies for genotoxicity was conducted and the results were consistently negative. Therefore the Meeting concluded that propargite is not genotoxic.

In a three-generation study of reproductive toxicity, reduced body-weight gain was seen at concentrations of 400 ppm (equivalent to 20 mg/kg bw per day) and above in parental animals and in pups during lactation. The results of a subsequent cross-fostering study showed that the growth retardation of the pups was reversible and was due to maternal toxicity. The NOAEL was 80 ppm, equivalent to 4 mg/kg bw per day, on the basis of reduced body-weight gain in parental animals and pups.

Two studies of developmental toxicity were conducted in rats and two in rabbits. In a study in Sprague-Dawley rats reported in 1979, fetal effects such as increased incidences of incomplete vertebral ossification and missing sternebrae and hyoids were observed in treated animals. Not all of the findings were dose-related and they were not reproduced in a study reported in 1990. The NOAEL was 25 mg/kg bw per day on the basis of reduced body-weight gain in dams and a slight increase in the postnatal mortality rate at the highest dose in the latter study. In the two studies in rabbits, dated 1983 and 1989, fetal effects indicative of developmental retardation were observed at maternally toxic doses of 6 mg/kg bw per day and above and an increased incidence of hydrocephaly was seen at higher doses in the first study. Most of the fetal effects, including hydrocephaly, were not confirmed in the second study, in which effects were observed only at doses of 8 mg/kg bw per day and higher. The overall NOAEL in rabbits was 4 mg/kg bw per day. No evidence for teratogenicity was found in these studies.

The Meeting allocated an ADI of 0-0.01 mg/kg bw on the basis of the LOAEL of 50 ppm (equal to 3 mg/kg bw per day) for tumorigenicity in female CD rats, with a safety factor of 300. This safety factor was chosen to account for the lack of a NOAEL in this study and the nature of the end-point (tumorigenesis), and to encompass the NOAEL in the same rat strain for increased cell proliferation in the jejunum, the site of tumour formation.

The Meeting concluded that it was unnecessary to determine an acute reference dose because of the low acute toxicity of propargite.

TOXICOLOGICAL EVALUATION

Levels that cause no toxic effect

Mouse: 50 ppm, equivalent to 7.5 mg/kg bw per day (effects on organ weights in a 78-week study of toxicity and carcinogenicity)

Rat: <50 ppm, equal to 3 mg/kg bw per day (lowest concentration tested; tumorigenicity in a two-year study)
80 ppm, equivalent to 4 mg/kg bw per day (maternal and fetal toxicity in a three-generation study)
25 mg/kg bw per day (maternal and fetal toxicity in studies of developmental toxicity)

Rabbit: 4 mg/kg bw per day (maternal and fetal toxicity in studies of developmental toxicity)

Dog: 160 ppm, equivalent to 4 mg/kg bw per day (toxicity in a one-year study)

Estimate of acceptable daily intake for humans

0-0.01 mg/kg bw

Estimate of acute reference dose

Unnecessary

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

1. Further studies on the mechanism of tumorigenic activity

2. Further observations in humans

List of relevant end-points for setting guidance values for dietary and non-dietary exposure to propargite

Absorption, distribution, excretion and metabolism in mammals

Rate and extent of oral absorption	Rapid and incomplete (50% in rats and mice)
Dermal absorption	Rat: *in vivo*, 30%

Distribution	Highest concentrations in intestine, liver (rats and mice)
Potential for accumulation	None
Rate and extent of excretion	Rapid excretion in rats and mice (urinary: approx. 50%; faecal 50%)
Metabolism in animals	Rapid degradation to numerous polar metabolites, no parent compound in bile and urine; hydrolysis of propynyl sulfite side-chain and subsequent oxidation of *tert*-butyl moiety and hydroxylation of cyclohexyl moiety, conjugation
Toxicologically significant compounds (animals, plants and environment)	Parent compound; animal and plant metabolites similar

Acute toxicity

Rat LD_{50} oral	2800 mg/kg bw
Rabbit LD_{50} dermal	>4000 mg/kg bw
Rat LC_{50} inhalation	0.89 mg/l (4 h)
Skin irritation	Irritating to rabbit skin
Eye irritation	Irritating to rabbit eye
Skin sensitization	Not sensitizing in guinea pigs (Buehler)

Short-term toxicity

Target/critical effect	Haematological system
Lowest relevant oral NOAEL	Dog: 1 year, 160 ppm (4 mg/kg bw per day)
Lowest relevant dermal NOAEL	Rabbit: 21 days, ≤ 100 mg/kg bw per day (systemic toxicity)
Lowest relevant inhalation NOAEL	

Genotoxicity

Not genotoxic

Long term toxicity and carcinogenicity

Target/critical effect	Intestine (jejunal tumours in CD rats), haematological system
Lowest relevant NOAEL	Rat (CD): 50 ppm (females; 3 mg/kg bw per day), two-year study
Carcinogenicity	Carcinogenic in CD rats, but not in FDRL rats and CD-1 mice

Reproductive toxicity

Reproduction target/critical effect	Reduced pup weight at maternally toxic doses
Lowest relevant reproductive NOAEL	Rat: 80 ppm (4 mg/kg bw per day), three-generation study
Developmental target/critical effect	Rat: fetotoxicity at maternally toxic doses Rabbit: fetotoxicity at maternally toxic doses
Lowest relevant developmental NOAEL	Rabbit: 4 mg/kg bw per day

Neurotoxicity/Delayed neurotoxicity

No evidence of neurotoxicity

Other toxicological studies

Transient cell proliferation in jejunal smooth muscle cells in CD rats

Medical data

Dermatitis in field workers

Summary

	Value	Study	Safety factor
ADI			
	0-0.01mg/kg bw	CD rats, two-year study	300
Acute RfD	unnecessary		

DIETARY RISK ASSESSMENT

Estimated Theoretical Maximum Daily Intakes for the five GEMS/Food regional diets, based on existing MRLs, were in the range of 30–210% of the ADI. Further refinements of dietary intake estimates will be undertaken during the periodic review of residues scheduled for 2001.

4.27 PROPYLENETHIOUREA (PTU, 150)

TOXICOLOGY

Propylenethiourea is a plant and animal metabolite and also a degradation product of propineb and therefore forms part of the residue to which consumers of propineb-treated produce may be exposed. The 1977 Joint Meeting expressed concern about the thyrotoxicity and carcinogenicity of propylenethiourea and allocated a temporary ADI of 0-0.005 mg/kg bw to propineb; this temporary ADI was reaffirmed by the 1980 and 1983 Meetings. The 1993 Meeting allocated a temporary ADI for propylenethiourea of 0-0.0002 mg/kg bw on the basis of the LOAEL in a two year study in mice and a safety factor of 1000.

The 1993 Meeting requested another long-term study of carcinogenicity in mice, clarification of the embryotoxicity, fetotoxicity and teratogenicity of propylenethiourea in rodents, and elucidation of its genotoxic potential. Studies to meet the above requests have now been supplied and were evaluated at the present Meeting.

Propylenethiourea was administered in the drinking-water of mice for 108 weeks. The NOAEL was 0.89 mg/kg bw per day, because of effects on body-weight gain of males at the next higher dose. Propylenethiourea was not carcinogenic in this study.

In a study of developmental toxicity in rats in which propylenethiourea was administered by gavage in deionized water to groups of inseminated dams, a NOAEL was not

identified for fetal toxicity at the lowest dose tested (1 mg/kg bw per day). In a supplemental study of developmental toxicity with a very similar protocol, the NOAEL for maternal effects was 1.2 mg/kg bw per day and that for fetal effects (skeletal variations) was 0.3 mg/kg bw per day.

Propylenethiourea did not induce reverse mutation in *Salmonella typhimurium* and did not induce chromosomal aberration or forward mutation at the *hrpt* locus in Chinese hamster V79 cells. The Meeting concluded that propylenethiourea was unlikely to have genotoxic potential.

In a study *in vitro* of the mechanisms of the toxicity to the thyroid of propylenethiourea, ethylenethiourea, tetramethylthiourea and propylthiouracil in a partially purified fraction of pig thyroid and a 10,000 x *g* supernatant from rat liver homogenate, propylenethiourea appeared to be only a weak inhibitor of iodothyronine deiodinase. The Meeting concluded that propylenethiourea (and ethylenethiourea) was unlikely to interfere with the formation of triiodothyronine from thyroxine *in vivo* and that the thyroid lesions seen were due to depression of thyroid hormone synthesis and consequent stimulation of the hypothalamic-pituitary-thyroid axis.

An ADI of 0-0.0003 mg/kg bw was allocated on the basis of a NOAEL of 0.3 mg/kg bw per day in a study of developmental toxicity in rats, using a 1000-fold safety factor. The 1000-fold safety factor was considered necessary since a multi-generation study of reproductive toxicity was not available. In fact, the Meeting noted that the NOAEL in a multi-generation study of reproductive toxicity of propineb, which generates propylenethiourea as a main metabolite, was about one tenth of the NOAEL for developmental toxicity and there is no evidence that a similar difference does not exist for propylenethiourea itself.

An acute reference dose of 0.003 mg/kg bw was established, on the basis of the NOAEL in the study of developmental toxicity in rats and a 100-fold safety factor.

An addendum to the toxicological monograph was prepared.

TOXICOLOGICAL EVALUATION

Levels that cause no toxic effect

Mouse: 6 ppm in drinking water; equal to 0.890 mg/kg bw per day (two- year study)

Rat 10 ppm in the diet, equivalent to 0.56 mg/kg bw per day (two-year study; evaluated by the 1993 JMPR)
1.2 mg/kg bw per day (maternal effects in a study of developmental toxicity)
0.3 mg/kg bw per day (fetal effects in a study of developmental toxicity)

Estimate of acceptable daily intake:

0-0.0003 mg/kg bw

Estimate of acute reference dose

0.003 mg/kg bw

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

Studies of reproductive toxicity

4.28 PYRETHRUM EXTRACT (PYRETHRINS, 063)

TOXICOLOGY

Extracts derived from chrysanthemum flowers of the genus *Chrysanthemus* have been used as insecticides for a long time. The insecticidal neurotoxic activity of these extracts is due to a mixture of three naturally occurring, closely related insecticidal esters of chrysanthemic acid (pyrethrins I) and three closely related esters of pyrethric acid (pyrethrins II). Selection of varieties of chrysanthemum rich in pyrethrins and extraction techniques have improved over the years. Currently available refined pyrethrum extract contains 45–55% total pyrethrins and 23-25% other phytochemical extracts containing triglyceride oils, terpenoids and carotinoid plant colours. Flavonoids, which have been associated with skin allergies, are not found in the refined extracts. The extracts usually also contain 20-25% light isoparaffins and 3-5% butylated hydroxy-toluene (BHA), which are usually added during and after processing respectively, for extraction or as antioxidants. The pyrethrin product used in the studies that were evaluated by the present Meeting was a blend of refined pyrethrum extract from the four main growing areas with a total pyrethrin content of 57.6%. The ratio of pyrethrins I to pyrethrins II in this sample was 1.85. In this document, the product used in the current series of studies is usually referred to as ‘pyrethrins’ in order to differentiate it from the pyrethrum extract used earlier.

Pyrethrum, the active principle containing pyrethrin isomers, was evaluated toxicologically by the 1965, 1966, 1967, 1968, 1969, 1970 and 1972 Joint Meetings. An ADI of 0-0.04 mg/kg bw was allocated by the 1972 Meeting. The compound was reviewed at the present meeting within the CCPR periodic review programme. This report summarizes new data on pyrethrins and data that were not reviewed previously.

Absorption, distribution and excretion in rats were investigated only for pyrethrins I. After oral administration, more than 90% of a low dose of pyrethrins I was absorbed, and the concentration of radiolabel in blood peaked between 5 and 8 h. The radiolabelled residues were widely distributed in the organs analysed, with the highest concentrations in fat in females. The elimination half-life of pyrethrins I for males and females was approximately 6 h. The mean percentage of administered radiolabel found in the urine ranged from 32 to 47% in males and from 50 to 57% in females, the remainder being excreted in faeces.

The substance is extensively metabolized, the residues of the parent compound in faeces and urine representing only 10%. Six metabolites were identified and two major metabolic pathways were suggested, the first involving oxidation of the double-bond and/or the methyl groups and the second involving hydrolysis of the ester bond. Pyrethrins I are

metabolized mainly through oxidative processes, while pyrethrins II are metabolized through a combination of hydrolytic and oxidative processes.

Pyrethrins show little acute toxicity, with an oral LD_{50} in rats of >1200 mg/kg bw and NOAELs for clinical signs of 710 mg/kg bw for males and 320 mg/kg bw for females, a dermal LD_{50} in rabbits of >2000 mg/kg bw and an inhalation LC_{50} in rats of 3.4 mg/l. They are minimally irritating to the skin and eye and show no potential for skin sensitization.

Pyrethrum extracts have not been classified by WHO for acute toxicity.

In short-term tests for toxicity in mice, rats and dogs, the lowest relevant NOAELs after oral administration were 1000, 1000 and 600 ppm, equal to 160, 57 and 18 mg/kg bw per day, respectively, for the three species. Statistically significant decreases in mean body weight or body-weight gain were observed at the high doses throughout most or all of the studies.

The liver is the main target organ in mice, rats and dogs, and an increased liver weight was frequently accompanied by changes in serum transaminase activity. In mice, increased liver weights were associated with a higher incidence of hepatocellular hypertrophy. In the livers of rats and dogs, generally unremarkable histopathological changes were observed. At doses of 85 mg/kg bw per day and above, a pyrethrum extract containing 20% pyrethrins induced microsomal enzymes in rats. Furthermore, anaemia was observed in rats and dogs at doses of 3000 ppm and above. The kidney was another target, but only in rats. In a 13-week study, rats at doses greater than 1000 ppm had increased kidney weights, associated with tubular degeneration and regeneration in the renal cortex.

In a 13-week study in rats exposed by inhalation, the NOAEL for systemic toxicity was 0.011 mg/l. The increases in liver weight were clearly related to exposure and were accompanied by changes in serum transaminase activity. Nonregenerative anaemia was also observed. The weights of the kidney and lung were increased in relation to body weight. The morphological abnormalities observed in the larynx, nasoturbinates, nasopharynx and lungs by light microscopy were considered to be localized responses indicative of a treatment-related effect.

Dermal administration of pyrethrins at doses up to 1000 mg/kg bw per day for 21 days caused no systemic toxicity in rabbits.

In a two-year study of toxicity and carcinogenicity in rats and an 18-month study of carcinogenicity in mice, the NOAEL was 100 ppm in both species, equal to 14 and 4 mg/kg bw per day in mice and rats respectively. The liver was the main target. A treatment-related effect on the incidence of lung tumours was seen in mice and increased incidences of benign tumours of the skin, liver and thyroid were observed in rats. The increased incidences of hepatocellular adenomas were associated with persistent induction of P450 enzymes and hepatocellular hypertrophy, suggesting that pyrethrins are rodent-specific hepatoproliferative carcinogens. Enzyme induction leading to increased clearance of thyroid hormones would also be consistent with the higher incidence of follicular hyperplasia and follicular adenomas. However, additional studies on the mechanism of formation of the liver and thyroid tumours are required. The meeting concluded that the increased tumour incidences caused by

pyrethrins are threshold phenomena of negligible relevance to the low doses to which humans are exposed[3].

Pyrethrins did not induce reverse mutagenicity in *Salmonella typhimurium* with metabolic activation, did not induce chromosomal aberration in Chinese hamster ovary cells, and did not induce unscheduled DNA synthesis in rat primary hepatocytes. The Meeting concluded that pyrethrins have no genotoxic or mutagenic potential, but, a test for gene mutation in mammalian cells is required.

Pyrethrins did not show developmental toxicity in rats or rabbits at the highest maternally toxic doses tested, which were 75 and 250 mg/kg bw per day respectively. The only effects on the offspring, observed in a two-generation study of reproductive toxicity in rats, were reduced body weights at the parentally toxic doses of 1000 and 3000 ppm, with a NOAEL of 100 ppm, equivalent to 10 mg/kg bw per day.

In a study of neurotoxicity in rats given single oral doses, acute neurological disorders (tremors, wetness of the urogenital area, salivation, perinasal encrustation, exaggerated startle response, decreased grip strength, and hind-leg splay) and behavioural effects (increased motor activity and decreased rearing and ambulation) were noted, with a NOAEL of 20 mg/kg bw.

The available data on humans did not show a causal relationship between exposure to modern pyrethrin-containing products and significant adverse health effects.

An ADI of 0-0.04 mg/kg bw was established for the tested blend of refined pyrethrum extract, which was based on the NOAEL of 100 ppm, equal to 4 mg/kg bw per day, observed in the long-term study of toxicity and carcinogenicity in rats and a safety factor of 100. This figure is identical to the ADI derived by the 1972 Meeting, which was based on a NOAEL of 200 ppm, equivalent to 10 mg/kg bw per day, in a long-term study in rats and a safety factor of 250.

The acute and long-term toxicity of the pyrethrins differs significantly. The acute toxicity of orally administered pyrethrins is expressed as neurotoxic effects. The longer-term toxicity was based principally on effects on the liver. Therefore, an acute reference dose of 0.2 mg/kg bw was allocated for the tested blend of refined pyrethrum, which was based on the NOAEL of 20 mg/kg bw for acute neurotoxicity in rats and a safety factor of 100.

A toxicological monograph was prepared, summarizing data received since the previous evaluation.

TOXICOLOGICAL EVALUATION

Levels that cause no toxic effects

Mouse: 100 ppm, equal to 14 mg/kg bw per day (18-month study of carcinogenicity)

Rat: 20 mg/kg (study of acute neurotoxicity)
100 ppm, equal to 4 mg/kg bw per day (104-week study of carcinogenicity)

[3] The ‘conceptual framework for cancer risk assessment’ developed by an IPCS working group, but not yet published, was applied for the evaluation of postulated modes of action.

100 ppm, equivalent to 10 mg/kg bw per day (parental and reproductive toxicity in a two-generation study of reproductive toxicity)
75 mg/kg bw per day (maternal toxicity in two teratogenicity studies, no developmental toxicity in a study of teratogenicity at the highest dose tested)

Rabbit: 25 mg/kg bw per day (maternal toxicity in a study of teratogenicity, no developmental toxicity in a study of teratogenicity at the highest dose tested)

Dog: 500 ppm, equal to 14 mg/kg bw per day (toxicity in a 52-week study)

Estimate of acceptable daily intake for humans

0-0.04 mg/kg bw

Estimate of acute reference dose

0.2 mg/kg bw

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

1. Gene mutation test in mammalian cells (required for submission to WHO by 2001)

2. Mechanistic study on liver and thyroid tumorigenesis (required for submission to WHO by 2001)

3. Further observations in humans

List of end-points relevant for setting guidance values for dietary and non-dietary exposure

Absorption, distribution, excretion and metabolism in mammals

Rate and extent of oral absorption:	Immediately (peak between 5 and 8 h) and nearly complete (>90%) in rats
Distribution:	Widely distributed in rats, highest concentrations in fat
Potential for accumulation:	None
Rate and extent of excretion:	Nearly complete excretion in urine (32-47% and 50-57% in male and female rats) and in faeces
Metabolism in animals	Extensively metabolized in rats, six metabolites identified; two major metabolic pathways.
Toxicologically significant compounds (animals, plants and environment)	Parent compound and metabolites

Acute toxicity

Rat LD_{50} oral	>1200 mg/kg bw
Rabbit LD_{50} dermal	>2000 mg/kg bw
Rat LC_{50} inhalation	>3.4 mg/l (4 h)
Skin irritation	None in rabbits
Eye irritation	None in rabbits
Skin sensitization	Not a sensitizer (Buehler test in guinea pigs)

Short-term toxicity	
Target/critical effect	Liver (mice, rat, dog), erythrocytes (rat, dog), kidney (rat)
Lowest relevant oral NOAEL/NOEL	90-day, dog: 600 ppm (18 mg/kg bw per day)
Lowest relevant dermal NOAEL/NOEL	3-week, rabbit: >1000 mg/kg bw per day
Lowest relevant inhalation NOAEL/NOEL	Three-month, rat: 0.01 mg/l
Genotoxicity	
	In an incomplete range of studies, no genotoxic or mutagenic potential identified
Long term toxicity and carcinogenicity	
Target/critical effect	Liver
Lowest relevant NOAEL/NOEL	Two-year, rat: 100 ppm (4 mg/kg bw per day)
Carcinogenicity	Increased tumour incidences in liver, thyroid, skin (rats) and lungs (mice)
Reproductive toxicity	
Reproduction target/critical effect	Reproductive effects (reduced pup body weights) at parentally toxic doses
Lowest relevant reproductive NOAEL/NOEL	Rat: 100 ppm (10 mg/kg bw per day)
Developmental target/critical effect	No developmental effects at maternally toxic doses
Lowest relevant developmental NOAEL/NOEL	Rat: 75 mg/kg bw per day
Neurotoxicity/Delayed neurotoxicity	
	Acute clinical disorders and behavioural effects
Acute neurotoxic NOAEL/NOEL	Rat: 20 mg/kg bw
Other toxicological studies	
	Induction of hepatic microsomal activity
Medical data	
	Available human data do not show any causal relationships between exposure to modern pyrethrin-containing products and significant adverse health effects.

Summary	Value	Study	Safety factor
ADI	0-0.04 mg/kg bw	Long-term toxicity, rats	100
Acute reference dose	0.2 mg/kg bw	Acute neurotoxicity, rats	100

DIETARY RISK ASSESSMENT

Estimated Theoretical Maximum Daily Intakes for the five GEMS/Food regional diets, based

on existing MRLs, were in the range of 30–60% of the ADI. The Meeting concluded that intake of residues of pyrethrum extract resulting from its uses that have been considered by JMPR is unlikely to present a public health concern.

4.29 PYRIPROXYFEN (200)

4-phenoxyphenyl (*RS*)-2-(2-pyridyloxy)propyl ether

Pyriproxyfen is a 2-phenoxy phenoxy oxime, an insecticide that acts as an insect growth regulator. It is intended for use as a spray in the control of arthropods, including cockroaches and fleas, on crops, dumps and indoors. Pyriproxyfen was evaluated for the first time by the present Meeting.

TOXICOLOGY

After oral administration to rats, [^{14}C]pyriproxyfen is slowly (T_{max} for plasma radiolabel, 8 h) and incompletely (≤50% of the dose) absorbed, but is then rapidly eliminated, predominantly in the faeces (90%), with only 4-11% in the urine, after 48 h. Absorbed pyriproxyfen is excreted mainly via the bile (34-37% of the administered dose in 48 h). The metabolism of pyriproxyfen is qualitatively similar in rats, mice, lactating goats and laying hens. A large number of metabolites have been detected, the main route of biotransformation being 4$^{\circlearrowleft}$-hydroxylation. Other pathways include hydroxylation of the pyridyl ring, ether cleavage and conjugation. Mice conjugate a much greater proportion of the dose than rats. The concentration of pyriproxyfen in tissues, other than fat, was very low (generally <0.01 µg equivalent per g after 72 h; fat <0.1µg equivalent per g). The half-lives of the radiolabel in tissues, including blood and fat, were 8-36 h. The dermal absorption of pyriproxyfen has not been studied.

The acute oral toxicity of pyriproxyfen is low, with LD_{50} values >5000 mg/kg bw in mice, rats and dogs. The acute dermal toxicity is also low, with LD_{50} values >2000 mg/kg bw in mice and rats and after exposure by inhalation, with an LC_{50} value >1.3 mg/l air in mice and rats.

WHO has classified pyriproxyfen as “unlikely to present acute hazard in normal use”.

Pyriproxyfen was mildly irritating to the eye but not to the skin of rabbits. It did not sensitise the skin of Hartley guinea-pigs (maximisation test).

In short- and long-term studies of the effects of pyriproxyfen in mice, rats and dogs, the liver was the main toxicological target, with increases in liver weight and changes in plasma lipids, particularly cholesterol at doses of 120 mg/kg bw per day and above in the rat. There was some evidence that the compound might cause modest anaemia in mice, rats and dogs at high doses. In mice treated with pyriproxyfen in the diet for three months, additional effects seen included increased mortality, histopathological changes in the kidney and decreased bodyweight. The NOAEL was 150 mg/kg bw per day in mice, 23 mg/kg bw per day (two studies) in rats and 100 mg/kg bw per day in dogs fed pyriproxyfen in the diet for three months. In long-term toxicity studies in mice, pyriproxyfen also caused a dose-dependent increase in the occurrence of systemic amyloidosis, which was associated with

increased mortality. The NOAEL was 120 ppm, equal to 16 mg/kg bw per day. In rats, the only additional effect was reduced body-weight gain. The NOAEL was 600 ppm, equal to 27 mg/kg bw per day. In two one-year studies in dogs, pyriproxyfen was administered in capsules. The overall NOAEL was 10 mg/kg bw per day on the basis of increased relative liver weight and increased total plasma cholesterol in males. There was some evidence that pyriproxyfen can act as an hepatic enzyme inducer, at least in the dog. Pyriproxyfen showed no toxicity when administered dermally to rats for 21 days, at doses of up to 1000 mg/kg bw per day. On inhalation for 28 days for 4 h per day, pyriproxyfen caused only minor effects in rats (initial salivation, sporadically reduced body-weight gain, slightly increased serum LDH activity) at 10000 mg/m^3. The NOAEL was 480 mg/m^3.

Pyriproxyfen was not carcinogenic at doses up to 420 mg/kg bw per day in a long-term dietary study of carcinogenicity in mice or at doses of up to 140 mg/kg bw per day in a long-term dietary study of toxicity and carcinogenicity in rats. Pyriproxyfen showed no evidence of carcinogenicity in a one-year toxicity study in dogs at doses of up to 1000 mg/kg bw per day. The Meeting concluded that pyriproxyfen does not pose a carcinogenic risk to humans.

Pyriproxyfen was not genotoxic in an adequate range of tests for mutagenicity and cytogenicity *in vitro* and *in vivo*. The Meeting concluded that pyriproxyfen is not genotoxic.

The reproductive toxicity of pyriproxyfen in the rat has been investigated in a two-generation study of reproductive toxicity, a segment 1 study (compound administration to males and females before and in the early stages of gestation) and a segment 3 study (compound administration during the prenatal and lactation periods). The NOAEL for maternal toxicity was 1000 ppm, equal to 98 mg/kg bw per day in the two-generation study and 100 mg/kg bw per day in the segment 3 study. Reproductive toxicity was observed only in the segment 3 study, in which there was an increase in the number of stillborns in the F_0 generation and a reduction in the number of implantations and mean number of live fetuses in the F_1 generation, at 500 mg/kg bw per day. The NOAEL for reproductive toxicity was 300 mg/kg bw per day. No reproductive toxicity was observed in the two-generation study, the NOAEL being 5000 ppm, equal to 340 mg/kg bw per day, the highest dose tested, or in the segment 1 study, the NOAEL being 1000 mg/kg bw per day, the highest dose tested.

The developmental toxicity of pyriproxyfen has been studied in rats and rabbits. In rats, a NOAEL for maternal toxicity was not identified, the lowest dose being 100 mg/kg bw per day at and above which decreased body-weight gain was observed. Pyriproxyfen caused little developmental toxicity and was not teratogenic. In a segment 3 study, the F_1 offspring were subjected to a series of developmental tests for possible neurotoxicity, including physical indices, tests of behaviour, motor and sensory functions and learning ability. Although there were some effects on growth at doses of 300 mg/kg bw per day and above, there was no developmental neurotoxicity up to 500 mg/kg bw per day, the highest dose tested. Visceral anomalies (dilatation of the renal pelvis) were found at 300 mg/kg bw per day and above. The NOAEL for developmental toxicity was 100 mg/kg bw per day, based on retarded physical development and visceral anomalies associated with this. In a more conventional developmental toxicity study in rats, no evidence of growth retardation or of developmental neurotoxicity was found at doses up to and including 1000 mg/kg bw per day, the highest dose tested. There was an increased frequency of skeletal variations (opening of the foramen transversalium of the 7th cervical vertebra) in fetuses at 300 mg/kg bw per

day. The frequency of visceral anomalies was significantly increased in F_1 offspring some weeks after birth. The NOAEL for developmental toxicity was 300 mg/kg bw per day, based on an increased frequency of skeletal variations with visceral anomalies in F_1 offspring at 1000 mg/kg bw per day. In a developmental study in rabbits, signs of maternal toxicity (abortion and premature delivery) were evident at 300 mg/kg bw per day and above (NOAEL 100 mg/kg bw per day). No developmental toxicity was observed, the NOAEL being 1000 mg/kg bw per day, the highest dose tested.

The Meeting established an ADI of 0-0.1 mg/kg bw per day on the basis of the NOAEL of 10 mg/kg bw per day in the one-year study of toxicity in dogs and a safety factor of 100.

The Meeting concluded that it was not necessary to establish an acute RfD because of the low acute toxicity of pyriproxyfen.

A toxicological monograph was prepared, summarising the data that were reviewed at the present Meeting

TOXICOLOGICAL EVALUATION

Level that cause no toxic effect

Mouse: 120 ppm, equal to 16 mg/kg bw per day (18-month study of carcinogenicity)

Rat: 600 ppm, equal to 35 mg/kg bw per day (24-month study of toxicity and carcinogenicity)
5000 ppm, equal to 345 mg/kg bw per day (reproductive toxicity, two-generation study of reproductive toxicity, highest dose tested)
100 mg/kg bw per day (developmental toxicity in a segment 3 study of developmental toxicity)
<100 mg/kg bw per day (maternal toxicity in a developmental toxicity study in rats, lowest dose tested)

Rabbit: 100 mg/kg bw per day (maternal and reproductive toxicity in a study of developmental toxicity)
1000 mg/kg bw per day (developmental toxicity in a study of developmental toxicity, highest dose tested)

Dog: 10 mg/kg bw per day (12-month study of toxicity)

Estimate of acceptable daily intake for humans

0-0.1 mg/kg bw

Estimate of acute reference dose

Unnecessary

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

Observations in humans.

List of end-points relevant for setting guidance values for dietary and non-dietary exposure

Absorption, distribution, excretion and metabolism in mammals

Rate and extent of oral absorption:	Slow, incomplete absorption (≤ 50%), rat
Dermal absorption:	No data (no systemic toxicity up to 1000 mg/kg bw per day by dermal route, rat)
Distribution of total residues:	highest concentrations of radiolabel in fat and, to lesser extent, liver, rat
Potential for accumulation:	Possibility of limited accumulation in fat, rat
Rate and extent of excretion:	Rapid, complete, 88-96% within 48 h, primarily in faeces; 4-11% in urine, rat
Metabolism in animals	Extensive. No parent compound detectable in urine; numerous metabolites: main pathway is 4'-hydroxylation; also hydroxylation of the pyridyl-ring, ether cleavage, conjugation, mouse, rat, goat, hen
Toxicologically significant compounds (animals, plants and environment)	Pyriproxyfen

Acute toxicity

LD_{50} oral	>5000 mg/kg bw, mouse, rat
LD_{50} dermal	>2000 mg/kg bw, mouse, rat
LC_{50} inhalation	>1.3 mg/l, mouse, rat
Skin irritation	Not irritating, rabbit
Eye irritation	Mildly irritating, rabbit
Skin sensitization	Not a sensitizer, guinea-pig

Short-term toxicity

Target/critical effect	Mouse, rat, dog: liver/increased relative liver weight mild anaemia, altered lipid metabolism (increased serum cholesterol)
Lowest relevant oral NOAEL	13-week, rat, 24 mg/kg bw per day
Lowest relevant dermal NOAEL	21-day, rat, >1000 mg/kg bw per day
Lowest relevant inhalation NOAEL	28-day, rat, >1.3 mg/l

Genotoxicity

	Not genotoxic

Long term toxicity and carcinogenicity

Target/critical effect:	Mouse, rat, dog: liver/increased liver weight, decreased body weight, altered lipid metabolism (increased plasma cholesterol) (rat, dog)
Lowest relevant NOAEL	1-year, dog, 10 mg/kg bw per day (diet)
Carcinogenicity	Not carcinogenic, mouse, rat

Reproductive toxicity	
Reproduction target/critical effect	Reduction in number of implantations and live F_2 fetuses at F_1 developmentally toxic dose, rat
Lowest relevant reproductive NOAEL	345 mg/kg bw per day, rat
Developmental target/critical effect	Retardation of physical development in F_1, rat
Lowest relevant developmental NOAEL	100 mg/kg bw per day, rat
Neurotoxicity/Delayed neurotoxicity	
	No evidence of developmental neurobehavioural toxicity in rat. No evidence of neurotoxicty or neuropathology in medium- or long-term studies in mouse, rat, dog or during development in rat, rabbit
Other toxicological studies	
	Possible enzyme inducer, at least in dogs
Medical data	
	No data

Summary	Value	Study	Safety factor
ADI	0-0.1 mg/kg bw	1-year, dog, toxicity	100
Acute reference dose	Unnecessary		

RESIDUE AND ANALYTICAL ASPECTS

Pyriproxyfen is an insect growth regulator with insecticidal activity against public health insect pests: houseflies, mosquitoes and cockroaches. In agriculture and horticulture pyriproxyfen has registered uses for the control of scale, whitefly, bollworm, jassids, aphids and cutworms.

The Meeting received extensive information on pyriproxyfen metabolism and environmental fate, methods of residue analysis, freezer storage stability, national registered use patterns, supervised trials, farm animal feeding studies, fate of residues in processing and national MRLs.

Animal metabolism

When rats were dosed orally with [^{14}C]pyriproxyfen excretion of the ^{14}C was rapid, accounting for 88-96% in 2 days. ^{14}C levels were higher in the fat than in other tissues and slightly more persistent. The estimated biological half-life for ^{14}C depletion in fat was 36 hours. The main metabolite in the faeces was 4-(4-hydroxyphenoxy)phenyl (*RS*)-2-(2-pyridyloxy)propyl ether (4'-OH-Pyr).

When lactating goats were dosed with [^{14}C]pyriproxyfen, labelled in either the phenyl or the pyridyl ring, at the equivalent of 10 ppm in the feed for 5 consecutive days most of the dose was accounted for by residues in the excreta and the contents of the GI tract.

Pyriproxyfen (0.003-0.009 mg/kg) was a minor component of the milk residue (3-15%) with the main metabolite 4'-OH-Pyr sulfate constituting about 30-50%. Parent pyriproxyfen (0.014-0.050 mg/kg) was the main residue in fat with essentially the same levels in omental and perirenal fat. Pyriproxyfen was the main residue in muscle but levels were very low. It was a very minor component of the residues in the kidneys and liver. The main identified residue in the liver was 4'-OH-Pyr sulfate, while in the kidneys the main identified residues were 4'-OH-Pyr sulfate and 4-phenoxyphenyl sulfate (POP sulfate).

Approximately 90% of the dose appeared in the excreta of laying hens dosed with [^{14}C]pyriproxyfen labelled in either the phenyl or pyridyl ring for 8 consecutive days at the equivalent of 10 ppm in the feed. The main identified residues in the excreta were 4'-OH-Pyr and (*RS*)-2-(2-pyridyloxy)propionic acid (PYPAC). The residues were very low in the egg whites and reached a plateau in the yolks in about 6 days in one experiment and had almost reached a plateau in the other. Parent pyriproxyfen (up to 0.17 mg/kg) was the main residue in egg yolk. The residues in muscle were below in other tissues and pyriproxyfen was the main component of the residue. The residues in fat were much higher than in muscle, suggesting a fat-soluble compound, and pyriproxyfen was the main residue. Levels of pyriproxyfen in abdominal fat (0.79 and 0.92 mg/kg) were much higher than in the skin + fat (0.17 and 0.13 mg/kg). Pyriproxyfen was a minor component of the liver residue with 4'-OH-Pyr sulfate the main identified metabolite.

The Meeting concluded that the animal metabolism studies were marginally acceptable where data on freezer storage stability were available, but not for residues in milk and eggs. Summary information on the storage stability of pyriproxyfen and its metabolites in goat milk and egg yolk were provided at a late stage of the Meeting, which suggested that the residues were stable during freezer storage. The full report should be evaluated the next time pyriproxyfen is reviewed.

Plant metabolism

Pyriproxyfen accounted for most of the residue in apples when trees were treated with labelled pyriproxyfen soon after petal fall and twice more at 60 and 40 days before harvest. A surface wash accounted for only 1.5-2.6% of the total apple residue. Pyriproxyfen was not detectable in apple juice, where the main identified residue was (*RS*)-2-(2-pyridyloxy)propyl alcohol (PYPA). Pyriproxyfen was the main component of the residue in apple pomace.

When tomato plants were treated 3 times with ^{14}C-labelled pyriproxyfen 35, 21 and 7 days before harvest, a surface wash of the harvested fruit with acetonitrile accounted for 1.8-3.3% of the residues in the tomatoes. Pyriproxyfen was not detectable in the tomato juice, where the identified metabolites were PYPA, PYPAC and 2-hydroxypyridine (2-OH-PY) in free and conjugated form. Parent pyriproxyfen accounted for most of the residue in whole tomatoes and tomato pomace.

Pyriproxyfen was the main residue component in gin trash from cotton plants treated twice, 43 and 28 days before harvest, with ^{14}C-labelled pyriproxyfen. Levels of ^{14}C were much lower in the cotton seed than in the gin trash suggesting little, if any, translocation of the residue from leaf to seed. The main identified residue in cotton seed was free and conjugated PYPAC with pyriproxyfen constituting only 3.9% and 0.6% of the residue. Approximately half of the residue in cotton seed was unextractable and was associated with the protein, carbohydrate and lignin fractions.

Metabolic pathways in plants and animals are very similar.

Environmental fate in soil

Labelled pyriproxyfen disappeared rapidly in the first few days during aerobic degradation in soil but then more slowly, with an estimated half-life of 28 days from days 7 to 30 of the study. Half-lives for mineralization were 68 and 139 days for the pyridyl label and phenyl label respectively. The main identified residue was 4'-OH-Pyr, but it did not exceed 5% of the dose.

In a second study of aerobic soil degradation the half-lives for pyriproxyfen were 8.2 days for days 1-14 and 20 days for days 14-91, while mineralization half-lives were 82 and 112 days for the pyridyl and phenyl label respectively. PYPAC was the main identified product, reaching 15% of the dose with levels exceeding those of pyriproxyfen after day 28. In a further aerobic study for 6 months the results were generally consistent with the previous ones but mineralization was found to be very slow with estimated half-lives of 330 and 850 days.

The leaching of [^{14}C]pyriproxyfen was determined with columns of silt and sandy loam soils. Most of the ^{14}C (89% and 84%) remained in the treated soil at the top of the column. Pyriproxyfen is unlikely to be leached, and degradation products become substantially bound in the soil organic matter.

The leaching of residues aged by aerobic soil incubation for 9 days was also determined. Most of the residue (86-88.5%) remained in the applied soil at the top of the leaching column. PYPAC was mobile and constituted 6.5 of the 7.6% of the applied dose which appeared in the leachate.

After a series of adsorption-desorption studies, pyriproxyfen was rated as essentially immobile and unlikely to be leached from most agricultural soils. 4'-OH-Pyr was rated as having slight to low mobility in most agricultural soils or a slight chance of leaching. On the basis of its adsorption values, PYPAC was rated as having high or very high mobility with a high potential to be leached into ground water. Whether the potential to be leached is realized will depend on the persistence of PYPAC in the soil and the prevailing field conditions.

Pyriproxyfen disappeared more quickly from irradiated soil than from dark controls and produced polar and unextractable residues. However, the rate of photolysis was not so much faster than that of soil degradation as to suggest that photolysis would be a main mechanism of environmental degradation.

In a confined rotational crop study, lettuce, radishes and wheat seed were sown in a soil treated 30 days previously with [^{14}C]pyriproxyfen at 0.20 kg ai/ha. Levels of ^{14}C were negligible in lettuce leaves, radish roots and leaves and wheat forage from crops grown to maturity. The ^{14}C in wheat grain, straw and chaff was unextractable and found to be biochemically incorporated into proteins and carbohydrates. The residues of pyriproxyfen and its immediate metabolites or degradation products would not be expected above negligible levels in rotational crops.

In two field dissipation studies pyriproxyfen residues did not migrate down the soil profile and the disappearance half-lives in the top soil segment were 3.5 and 16 days. PYPAC was detected in only one sample, in the top segment of the soil. 4'-OH-Pyr was detected sporadically at concentrations close to the LOD, but the incidence could not be interpreted as evidence of systematic persistence or mobility down the soil profile.

Environmental fate in water-sediment systems

Pyriproxyfen disappeared from aerobic lake water-sediment systems with half-lives of 16 and 21 days. Pyriproxyfen was the main residue in the sediment during the 1-month studies, and 4'-OH-Pyr accounted for 7.5% and 9.5% of the dose after 7 days. PYPAC was the main residue in the water phase after 12 days and accounted for 34% of the dose on day 21.

Pyriproxyfen was the main residue throughout 1-year studies of anaerobic lake water-sediment systems and most of the residue was in the sediment. PYPAC accounted for 16% of the dose after 1 year and, because of its water solubility, it was mainly in the aqueous phase. Mineralization was negligible. Pyriproxyfen appeared to be degraded slowly for the first 6 months and subsequently more quickly.

In a photolysis study, pyriproxyfen was exposed to sunlight in sterilized distilled water and sterilized lake water. The estimated photolytic half-lives were 17.5 and 21 days respectively. A theoretical half-life of 16 days was calculated for 40° N latitude. The main photoproducts were PYPA and CO_2 accounting for 16-30% and 11-29% of the initial ^{14}C respectively.

In a laboratory photolysis study pyriproxyfen in water was subjected to light from a xenon lamp with a filter to restrict light below 290 nm for 14 days. Estimated half-lives for photolytic disappearance were 6.4 and 3.7 days. The main photoproduct was PYPA. Negligible amounts of CO_2 were produced.

Analytical methods

Methods of analysis for pyriproxyfen and its metabolites in crops, processed commodities, animal commodities, soil and water were reported.

In a typical method pyriproxyfen residues are extracted with acetone, the extract is diluted with aqueous sodium chloride, and the residues are partitioned into dichloromethane. Column chromatography is used for clean-up and the residues are determined by GLC with an NPD. The LOD is usually about 0.02 mg/kg.

PYPAC remains in the aqueous phase during the extraction with dichloromethane. After acidification it is extracted into an organic phase such as ethyl acetate. PYPAC is methylated, cleaned up on a silica gel column and determined by GLC with an NPD. The LOD is about 0.02 mg/kg. Care must be exercised not to lose methyl PYPAC during the evaporation of its solutions because it is volatile.

An acid hydrolysis step is introduced into methods for POP (4-phenoxyphenol) and 4'-OH-Pyr in animal commodities to release conjugates. After clean-up, these metabolites are

determined by HPLC with UV detection. 2,5-OH-Py (2,5-dihydroxypyridine) may be determined by HPLC with fluorescence detection.

Analytical methods for soils begin with various extractions and then follow the methods for crop residues. Typical LODs for pyriproxyfen and its degradation products in soils are 0.02 mg/kg. The validated LOD for a straightforward GLC method for pyriproxyfen in aquarium water was 1 µg/l.

Adequate recoveries of pyriproxyfen were achieved from apples and cotton seed fortified at 0.05 and 0.5 mg/kg with an FDA multi-residue method. PYPAC was not recovered from the Florisil column in this method.

Stability of pesticide residues in stored analytical samples

Pyriproxyfen and its metabolites were generally stable in crop and soil samples during freezer storage (-18°C to -20°C) for the periods tested.

Pyriproxyfen and some metabolites were of doubtful stability in animal commodities when stored for long periods.

Pyriproxyfen was stable in tomato homogenate for 12 months, cotton seed for 13 months, gin trash for 8 months, and soils for 7 months.

PYPAC was stable in cotton seed for 13 months and soils for 7 months. 4'-OH-Pyr was stable in fat for 14 weeks, muscle tissue for 10 weeks and one soil for 5 months, but decreased by 70% in another soil in 107 days. 4'-OH-Pyr sulfate was stable in cow liver for 8 weeks, but POP sulfate in cow liver decreased by about 30% in 72 days and 2,5-OH-Py in kidneys decreased by 85% in 70 days.

Definition of the residue

The main residue in the metabolism studies on plant commodities was pyriproxyfen itself. In cotton seed the levels of free + conjugated PYPAC and PYPA exceeded that of pyriproxyfen, which was very low, probably because the metabolites were translocated more readily. PYPAC in cotton seed in the metabolism study was about 60% free and 40% conjugated, but in the trials on cotton free PYPAC was generally undetected and lower than pyriproxyfen in the seed.

The residue can be defined as pyriproxyfen for enforcement in crops.

In animal commodities the composition of the residue varies in different tissues. Pyriproxyfen itself is fat-soluble (log P_{OW} 5.37) so it predominates in fat. In muscle all the residues are very low, but pyriproxyfen is again the main component. In milk and liver 4'-OH-Pyr with its sulfate conjugate are the main residues, while in kidneys POP is the main residue with 4'-OH-Pyr also a significant component. Pyriproxyfen predominates in eggs.

The feeding study on dairy cows suggests that the residues in milk and tissues will generally be undetectable and very low whatever the residue definition, except pyriproxyfen itself in fat and the fat of milk at the higher dietary burdens. The Meeting agreed it would be

unpractical to define the residue to include metabolites and their conjugates in liver and kidneys for undetectable residues; it would be a pointless additional analytical expense.

Pyriproxyfen is also a suitable definition of the residue for dietary intake estimates.

Proposed definition of the residue (for compliance with MRLs and for the estimation of dietary intake): pyriproxyfen.

The residue is fat-soluble.

Residues resulting from supervised trials

Citrus fruits. Pyriproxyfen is registered for use on citrus fruit in Israel at 0.01 kg ai/hl with the final application at the end of May for varieties picked until the end of December and the end of June for those picked after the end of December. Five trials on grapefruit in substantial accord with Israeli GAP (sprayed in early June instead of the end of May) gave pyriproxyfen residues in the whole fruit of 0.03 (3), 0.04 and 0.08 mg/kg. The residues in the pulp were below the LOD (0.01 mg/kg).

South African GAP permits 3 applications of pyriproxyfen at a spray concentration of 0.0030 kg ai/hl with harvest 90 days after the final application. One trial on mandarins and 3 on oranges substantially complying with GAP (2 applications instead of 3) produced residues of 0.02 mg/kg in the mandarins and 0.02, 0.05 and 0.06 mg/kg in the oranges.

In Spain pyriproxyfen may be applied twice to citrus fruit at 0.0025-0.0075 kg ai/hl with harvest 30 days after the final application. Four trials on mandarins with 1 application of 0.005 and 0.007 kg ai/hl and harvest after 31 and 45 days (the residue at 45 days exceeded the residue at 30 days) were acceptably close to GAP and produced residues of 0.069, 0.10, 0.20 and 0.33 mg/kg. Recoveries in trial NNR-21-0018 were low and the results should be adjusted for the recovery (62.5%). The values 0.20 and 0.33, on adjustment, become 0.32 and 0.53 mg/kg. The residues in oranges from 4 trials in Spain and 1 in Italy substantially in line with Spanish GAP produced residues of 0.06, 0.08, 0.12, 0.25 and 0.25 mg/kg.

In summary, pyriproxyfen residues in the 18 trials according to GAP were Italy oranges 0.06 mg/kg, Israel grapefruit 0.03 3, 0.04, 0.08 mg/kg, South Africa mandarins 0.02 mg/kg, oranges 0.02, 0.05 and 0.06 mg/kg, and Spain mandarins 0.069, 0.10, 0.32, 0.53; oranges 0.08, 0.12, 0.25, 0.25 mg/kg.

The Meeting agreed that the residues arising from the Spanish GAP with the 30 days PHI seemed to be a different population from the residues from South African and Israeli GAP and that the higher population would be used for the estimation of an STMR and maximum residue level. The residues in rank order (median underlined) from the trials according to Spanish GAP were 0.06, 0.069, 0.08, 0.1, 0.12, 0.25, 0.25, 0.32 and 0.53 mg/kg.

Because data were available for grapefruit, mandarins and oranges the Meeting agreed that an MRL for citrus fruits was appropriate. The Meeting estimated a maximum residue level for pyriproxyfen on citrus fruits of 1 mg/kg.

Pyriproxyfen residues were not detected (<0.01 mg/kg) in the edible pulp in 24 samples analysed during the citrus trials, but many of the samples did not reflect GAP

conditions so the results could not be used directly, and the residues in the whole fruit only just exceeded the LOD. The mean ratio of the residue in the pulp to that in the whole fruit for the 3 samples with the highest residues in the whole fruit was 0.11, which is artificially high because it is largely an artefact of the LOD. The Meeting applied this factor to the median residue from the 9 relevant trials (0.12 mg/kg) to estimate an STMR of 0.013 mg/kg for pyriproxyfen in citrus fruits.

Cotton seed. Pyriproxyfen may be applied to cotton at 0.059-0.075 kg ai/ha with the crop harvested 28 days after the single application. In a series of trials in the USA in 1994 and 1995 pyriproxyfen was applied 2 or 3 times to cotton with the final application in the range 0.072-0.10 kg ai/ha, which was considered to comply with GAP for residue purposes. The pyriproxyfen residues in cotton seed in rank order (median underlined) in the 15 trials were <0.01 (7), 0.01, 0.02, 0.03 (5) and 0.04 mg/kg.

The Meeting estimated a maximum residue level of 0.05 mg/kg and an STMR of 0.01 mg/kg for pyriproxyfen in cotton seed.

Cotton gin trash. In 6 of the US cotton trials in 1995 seed cotton (20 kg) was ginned to produce cotton seed and gin trash and pyriproxyfen residues were measured on the gin trash. The residues, expressed on a dry weight basis, in rank order (median underlined) were 0.50, 0.58, 0.84, 0.97, 1.7 and 2.7 mg/kg.

The Meeting estimated a maximum residue level and an STMR for pyriproxyfen in cotton gin trash of 5 and 0.91 mg/kg respectively.

Feeding trials

Pyriproxyfen and metabolites identified in the metabolism study were determined in the milk and tissues from dairy cows dosed for 28 days with pyriproxyfen at 0.13, 0.38 and 1.17 mg/kg bw/day, equivalent to 3, 9 and 30 ppm dry weight in the diet. In the 30 ppm group pyriproxyfen residues were not detected (<0.01 mg/kg) in whole milk, muscle, liver or kidney, but were present in cream from day 24 milk (0.012-0.015 mg/kg) and in body fat (0.046-0.072 mg/kg). In the 9 ppm feeding group, pyriproxyfen residues were not detected in milk and kidney, but were present in body fat at 0.011-0.025 mg/kg. In the 3 ppm feeding group, pyriproxyfen residues were not detected (<0.01 mg/kg) in body fat, whole milk or the cream of day 24 milk.

The residues in the body fat in the 30 ppm group (mean 0.058 mg/kg) and the 9 ppm group (mean 0.018 mg/kg) were roughly proportional to the doses.

Residues in animal commodities

The dietary burden for estimating maximum residue levels for animal commodities for beef and dairy cattle is 1.0 ppm pyriproxyfen, calculated from the maximum residue levels estimated for cotton gin trash and cotton seed. This level is sufficiently close to be evaluated against the 3 ppm feeding level which did not produce pyriproxyfen residues above the LOD (0.01 mg/kg) in the animal commodities.

The dietary burden for estimating STMRs for products of beef and dairy cattle is 0.18 ppm pyriproxyfen, calculated from the STMRs estimated for cotton gin trash and cotton seed.

The Meeting estimated maximum residue levels of 0.01* mg/kg for cattle meat (fat), cattle edible offal and cattle milk. The Meeting noted that residues resulting from feeding dairy cows at 10 ppm were quite similar to those found in the 10 ppm goat metabolism study and agreed that the estimated maximum residue levels could be extended to milks and to goat meat (fat) and goat edible offal. However, the estimated maximum residue level for milks cannot be recommended for use as an MRL because the stability of pyriproxyfen and its metabolites in goat milk is yet to be confirmed.

The residues were below the LOD in the muscle, liver and kidneys at feeding levels of 3, 9 and 30 ppm. Residues of pyriproxyfen were detected in the fat at the 9 and 30 ppm feeding levels and in the fat of milk at the 30 ppm feeding level. The Meeting noted that the dietary burden of 0.18 ppm was much lower than the lowest feeding level and as an approximation assumed proportionality between likely tissue levels and dietary intake.

STMR (animal commodity) = LOD × (STMR dietary burden) ÷ (feeding level)

STMR for meat = 0.01 × 0.18 ÷ 30 = 0.00006 mg/kg (no detections at 30 ppm feeding level)

The same calculation applies for liver, kidneys and milk. The Meeting agreed that the calculated STMRs were low enough to be treated as effectively zero. The Meeting estimated STMR levels of 0 for cattle meat, goat meat, cattle edible offal, goat edible offal and milks, but could not recommend the use of the STMR for milks until the maximum residue level estimated for milks can be recommended for use as an MRL.

Processing

In a cotton seed processing trial pyriproxyfen residues of 0.1 mg/kg in cotton seed produced residues of 0.02 mg/kg in both crude and refined oil and no detectable residues in the meal (<0.01 mg/kg). The estimated processing factors for crude oil and refined oil are therefore 0.2 and the processing factor for cotton seed meal is 0 (<0.1).

The Meeting applied the processing factors to the maximum residue level and STMR for cotton seed to produce estimated maximum residue levels of 0.01 mg/kg and STMRs of 0.002 mg/kg for crude and edible cotton seed oil, and an estimated STMR for cotton seed meal of 0.001 mg/kg. Similarly, the processing factor 0.2 applied to the maximum trials residue value for cotton seed (0.04 mg/kg) produced maximum trials residue values of 0.008 mg/kg for crude and edible cotton seed oils.

FURTHER WORK OR INFORMATION

Desirable

1. Information on the fate of pyriproxyfen during the processing of oranges. At a late stage of the Meeting information on an orange processing study was provided. It should be evaluated the next time pyriproxyfen is reviewed.

2. Information on the freezer storage stability of pyriproxyfen and the main metabolites in milk and eggs is necessary to validate the data from the metabolism studies. At a late stage of the Meeting a summary report on the freezer storage stability of residues in goat milk and egg yolk was provided. The full report should be evaluated the next time pyriproxyfen is reviewed.

DIETARY RISK ASSESSMENT

Chronic intake

Pyriproxyfen is a new compound and maximum residue and STMR levels were estimated for citrus fruits, cotton seed, animal commodities and some processed commodities. The dietary intake of pyriproxyfen is presented in Annex III.

International Estimated Daily Intakes for the 5 GEMS/Food regional diets, based on estimated STMRs, were effectively 0% of the ADI. The Meeting concluded that the intake of residues of pyriproxyfen resulting from its uses that have been considered by the JMPR is unlikely to present a public health concern.

Acute intake

The Meeting concluded that an acute RfD for pyriproxyfen is unnecessary. This conclusion was based on a determination that the pesticide is unlikely to present an acute toxicological hazard and residues are therefore unlikely to present an acute risk to consumers.

4. 30 TEBUFENOZIDE (196)

RESIDUE AND ANALYTICAL ASPECTS

The insecticide tebufenozide was first evaluated by the 1996 JMPR when an ADI was allocated and MRLs for pome fruits, grapes, walnut and husked rice were recommended. German data on supervised residue trials on apples and grapes were provided to the 1996 Meeting, but could not be evaluated against German GAP because it was only pending. The present Meeting received information on currently registered GAP in Germany for re-evaluation of tebufenozide residues in grapes and pome fruit.

Pome fruit. The residues in the German trials on apples evaluated according to the new German GAP were 0.02, 0.11, 0.11, 0.15, 0.16, 0.23, 0.24 and 0.35 mg/kg. The German GAP has a PHI of 14 days and would be expected to produce higher residues than the Belgian GAP (PHI 28 days) which was used by the 1996 JMPR for the evaluation of the German trials (giving residues of <0.02, 0.08, 0.09, 0.11, 0.16, 0.16, 0.2 and 0.23 mg/kg). The Meeting agreed to replace the 28-day residues of the 1996 evaluation by the corresponding residues at 14 days, giving residues in pome fruit in rank order of 0.01, 0.02, 0.02, 0.05, 0.07, 0.077, 0.08, 0.09, 0.1, 0.1, 0.11, 0.11, 0.11, 0.12, 0.14, 0.14, 0.15, 0.16, 0.16, 0.18, 0.19, 0.23, 0.23, 0.24, 0.26, 0.27, 0.28, 0.32, 0.35, 0.37, 0.37, 0.43, 0.52, 0.52, 0.55, 0.75, 0.84 and 1.1 mg/kg.

The Meeting agreed to recommend retention of the current CXL of 1 mg/kg for pome fruits and estimated an STMR of 0.17 mg/kg (previous STMR 0.16 mg/kg).

Processing factors of 2.5, 0.25 and 0.125 for apple pomace (wet), purée and juice respectively were reported by the 1996 JMPR. On the basis of the new STMR for pome fruits the Meeting estimated STMRs of 0.425 mg/kg for wet apple pomace, 0.0425 mg/kg for apple purée and 0.021 mg/kg for apple juice.

Grapes. The German residue data from 1996 evaluated according to current German GAP in rank order were 0.21, 0.22, 0.24, 0.26, 0.27, 0.28, 0.4, 0.42 and 0.5 mg/kg.

The nine trials in France in 1996 complied with GAP (3 applications at 0.144 kg ai/ha, 21 days PHI) and showed the residues 0.05, 0.06, 0.07, 0.08, 0.12, 0.18, 0.26, 0.28 and 0.28 mg/kg.

The rank order of the combined German and French trials was 0.05, 0.06, 0.07, 0.08, 0.12, 0.18, 0.21, 0.22, 0.24, 0.26, 0.26, 0.27, 0.28, 0.28, 0.28, 0.4, 0.42 and 0.5 mg/kg.

On the basis of the German and French trials, the Meeting estimated a maximum residue level of 1 mg/kg for grapes to replace current draft MRL (0.5 mg/kg) and an STMR of 0.25 mg/kg.

Processing factors of 0.25 and 2.7 for wine and grape pomace (wet) respectively, were reported by the 1996 JMPR. The Meeting estimated STMRs of 0.0625 mg/kg for wine and 0.675 mg/kg for wet grape pomace from the STMR of 0.25 mg/kg for grapes.

DIETARY RISK ASSESSMENT

Chronic intake

STMRs were established for 4 commodities (1999: pome fruits, grapes; 1996: walnuts, rice).

International Estimated Daily Intakes for the 5 GEMS/Food regional diets, based on estimated STMRs, were in the range of 0–1% of the ADI. The Meeting concluded that intake of residues of tebufenozide resulting from its uses that have been considered by JMPR is unlikely to present a public health concern.

Acute intake

The international estimate of short-term intake (IESTI) for tebufenozide was calculated for the commodities for which MRLs and STMRs were established and for which consumption data (large portion consumption and unit weight) were available (*see* Section 3). The results are shown in Annex IV. The IESTI varied from 0.001 to 0.015 mg/kg bw for the general population and from 0 to 0.058 mg/kg bw for children. As no acute reference dose has been established, the acute risk assessment for tebufenozide was not finalized.

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 2.1)

(1) that the contribution of expertise and time of JMPR members be formally recognized as a contribution by national governments to the Codex/FAO/WHO system and

(2) that national governments agree, when members are appointed to the FAO Panel or WHO Core Assessment Group, to provide them with sufficient time and resources to complete their work to a standard expected of the JMPR.

5.3 The Meeting recommended (Section 2.4), in the calculation of international estimated short-term intakes (IESTIs), (1) that body weights of children (aged 6 and under) and adults provided by national governments should be used. If these were not available the default values should be taken as 15 kg and 60 kg respectively; (2) that, in view of the variations between different regions, the unit weights of food commodities used in the calculations should be those appropriate to the region whose GAP had been used to estimate the maximum residue level.

5.4 The Meeting recommended (Section 2.8) that FAO and/or WHO specifications be developed according to the "new procedure" before pesticides are evaluated for the first time or within the Periodic Review Programme of the CCPR, but recognized that it will take some time before this recommendation is fully implemented.

5.5 The Meeting recommended (Section 2.9) that statistical calculations should be used where relevant as a further tool to assist in the estimation of maximum residue levels, and further recommended that the situation should be re-examined when more practical experience had been gained in the use of statistical methods on the readily available residue populations produced by the STMR procedure.

5.6 The Meeting noted the difficulties arising from periodic reviews of compounds undergoing national re-registration, where supervised trials were often related to proposed rather than existing registered uses, and recommended (Section 2.10) that this issue be brought to the attention of the CCPR, and that the CCPR be invited to consider accepting recommendations based on proposed uses provided it is warranted that old labels will be withdrawn by a specified time.

5.7 The Meeting recommended (Section 3) that acute toxicities of the following pesticides be evaluated as soon as possible: carbofuran, carbosulfan, diazinon, ethephon, fenpropimorph, fenpyroximate, folpet, malathion, oxydemeton-methyl, phosalone and tebufenozide.

5.8 The Meeting recommended (Section 4.6) that an evaluation of the residue and analytical aspects of chlormequat should be scheduled shortly so that an acute dietary risk assessment can be conducted.

5.9 The Meeting recommended (Section 4.11) that the JMPR re-evaluate the acute toxicity of dinocap to consider the necessity for/of establishing an acute RfD relevant to children.

6. FUTURE WORK

The following items should be considered at the 2000 and 2001 Meeting.

The compounds listed include those recommended for priority attention by the 31st or earlier Sessions of the CCPR, as well as compounds scheduled for re-evaluation in the CCPR Periodic Review Programme

6.1 2000 Meeting (tentative)

Toxicological evaluations

New compounds

chlorpropham

Periodic review compounds

acephate (095)
deltamethrin (135)
dodine (084)
fenitrothion (037)
imazalil (110)
methamidophos (100)
thiodicarb (154)
vamidothion (078)

Other evaluations

carbaryl (008)
DDT (021)
fipronil

Residue evaluations

New compounds

fipronil

Periodic review compounds

captan (007)
chlorpyriphos (017)
diphenylamine (030)
parathion (058)
parathion-methyl (059)
piperonyl butoxide (062)
pyrethrins (063)

Other evaluations

aldicarb (117)
chlormequat (015)
DDT (021)
fenthion (039)
mevinphos (053)
thiabendazole (065)

6.2 2001 Meeting

Toxicological evaluations

New compounds

imidacloprid
spinosad

Periodic review compounds

lindane (048)
mercarbam (124)
methoprene (147)
prochloraz (142)
triazophos (143)

Other evaluations

diflubenzuron (130)
guazatine (114)
methomyl (094)

Residue evaluations

New compounds

chlorpropham
imidacloprid
spinosad

Periodic review compounds

carbaryl (008)
diflubenzuron(130)
dimethipin(151)
dodine (084)
ethoprophos (149)
fenitrothion
imazalil (110)
methomyl(094)/thiodicarb(154)
propargite (113)

Other Evaluations

diquat (031)
guazatine (114)
myclobutanil (181)

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CORRECTIONS TO REPORT OF 1998 JMPRCORRECTIONS TO REPORT OF 1996 JMPR

Changes are shown **bold**. Minor typographical errors are not included.

P. 22 (Section 3), Table of estimated dietary intakes for the 1998 JMPR evaluations

The dietary intakes as percentages of the ADI of the following compounds should be changed as shown.

Code	Name	ADI (mg/kg bw)	Dietary intake, % of ADI[1]	Notes
072	Carbendazim	0.03	1-**5**	IEDI[2]
020	2,4-D	0.01	**3-14**	IEDI
027	Dimethoate	0.002[5]	**20-200**	IEDI[6]
087	Dinocap	0.001	0 - **1**	IEDI
074	Disulfoton	0.0003	**150**-840	STMRs & MRLs
132	Methiocarb	0.02	**2 - 5**	TMDI

P. 45 (Section 4.3), para 1, line 2

Change "…<0.07,<0,08…"to "… **0.07, 0.08**…".

P. 46 (Section 4.3), para 4, line 1

Change "Fourteen trials…" to "…**Twenty one** trials…".

P. 54 (Section 4.4), para 5, line 1

Change "…existing and proposed MRLs are based on the sum of…" to "…existing and proposed MRLs **for plant commodities** are based on the sum of…"

P. 99 (Section 4.8), para 4, lines 1 and 2

Change "...140% to **200%** and .. range of 10 to 80 to **20 to 130**"

P. 100 (Section 4.9), para 5, line 1

The Toxicology section of the report on dinocap was omitted. It is now printed as Section 4. of the present report.

P.119 (Section 4.11), para 4, line 2.

Change " 190 to **180,** 920 to **840**, 160 to **150"**

P. 179 (Section 4.21), last 2 lines

Change "The processing factor for apple juice was 0.5 and for sauce 1." to "The processing factor for apple juice was **1** and for sauce **0.5**."

P. 218 (Annex I), Dinocap

Change ADI from 0.001 to **0.008** mg/kg bw. [The ADI of 0.008 mg/kg bw was allocated by the 1998 Joint Meeting. The new ADI is recorded correctly in Annex I to the 1998 Evaluations.]

CORRECTIONS TO REPORT OF 1998

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Commodity							Middle Eastern		Far Eastern		African		Latin American		European	
Code	Name	MRL mg/kg	STMR mg/kg	Processing Factor	Notes	Adjusted MRL/STMR mg/kg	Diet g/day	IEDI mg/day	Diet g/day	IEDI mg/day	Diet g/day	IEDI mg/day	Diet g/day	IEDI mg/day	Diet g/day	IEDI mg/day
VR 0596	Sugar beet	0.2	0.02	1		0.02	0	0.0005	0	0	0	0	0	0.0003	0	0
VO 0447	Sweet corn	0.02	0.02	1		0.02	0	0	0	0	0.004	0.0001	0	0	0.008	0.0002

ANNEX I

ADIs, ACUTE REFERENCE DOSES, RECOMMENDED MRLs AND STMRs RECORDED BY THE 1999 MEETING

The Table includes maximum Acceptable Daily Intakes (ADIs), Acute Reference Doses (acute RfDs), recommendations for Maximum Residue Limits (MRLs), and Supervised Trials Median Residue (STMR) levels. Compounds whose estimated dietary intakes might, on the basis of the available information, exceed their ADIs are marked with footnotes. A proposal to distinguish such compounds from those whose intakes are clearly below the corresponding ADIs was made at the 1997 Joint Meeting and its rationale is described in detail in the 1997 report (Section 2.3). It should be noted that this distinction applies only to new compounds and those re-evaluated within the CCPR Periodic Review Programme.

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).

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.

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.)

The Table includes the Codex reference numbers of the compounds and the Codex Classification Numbers (CCNs) of the commodities, to facilitate reference to the Codex Maximum Limits for Pesticide Residues (*Codex Alimentarius,* Vol. 2B) and other documents and working documents of the Codex documents. Commodities are listed in alphabetical order.

Apart from the abbreviations indicated above, the following qualifications are used in the Table.

* 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
Po	The recommendation accommodates post-harvest treatment of the commodity.
T	Temporary
W in place of a recommended MRL	The previous recommendation is withdrawn, or withdrawal of the recommended MRL or existing Codex or draft MRL is recommended

Pesticide	ADI, mg/kg bw	Commodity		Recommended MRL, mg/kg		STMR, mg/kg
(Codex reference no.)		CCN	Name	New	Previous	
Bentazone (172)	0.1	Acute RfD: unnecessary				
Bitertanol **	0.01	JF 0226	Apple juice			0.034
(144)		AB 0226	Apple pomace, dry			1.78
			Apple pomace, wet			0.648
			Apple sauce			0.035
		FS 0240	Apricot	W	1	
		FI 0327	Banana	0.5	0.5	0.075
		GC 0640	Barley	0.05 *		0
		AS 0640	Barley straw and fodder, dry	0.05 *		0
		AL1030	Bean forage (green)	W	10	
		FS 0013	Cherries	1	2	0.365
			Cherry jam			0.16
			Cherry juice			0.062
			Cherry preserve			0.22
		VP 0526	Common bean (pods and/or immature seeds)	W	0.5	
		VC0424	Cucumber	0.5	0.5	0.18
		MO 0105	Edible offal (Mammalian)	0.05*		0.05
		PE 0112	Eggs	0.01 *		0

Pesticide	ADI, mg/kg bw	Commodity		Recommended MRL, mg/kg		STMR, mg/kg
(Codex reference no.)		CCN	Name	New	Previous	
		MM 0095	Meat (from mammals other than marine mammals)	0.05* (fat)		0.05
		ML 0106	Milks	0.05*		0.05
		FS 0245	Nectarine	1	1	0.20
		AF 0647	Oat forage (green)	0.05 *[1]	0.1 *	0.05
		AS 0647	Oat straw and fodder, dry	0.05 *	0.1 *	0
		GC 0647	Oats	0.05 *	0.1 *	0
		FS 0247	Peach	1	1	0.20
		SO 0697	Peanut	W	0.1 *	
		AL 1270	Peanut forage (green)	W	20	
		FS 0014	Plums (including Prunes)	2	2	0.34
			Plum jam			0.21
		FP 0009	Pome fruits	2	2	0.24
		PM 0110	Poultry meat	0.01 *		0
		PO 0111	Poultry, Edible offal of	0.01 *		0
		GC 0650	Rye	0.05 *	0.1 *	0
		AF 0650	Rye forage (green)	0.05 *[1]	0.1 *	0.05
		AS 0650	Rye straw and fodder, dry	0.05 *	0.1 *	0
		VO0448	Tomato	3		0.76
		JF 0448	Tomato juice			0.1
			Tomato paste			1.6
			Tomato preserve			0.28
		GC0653	Triticale	0.05 *		0
			Triticale straw and fodder, dry	0.05 *		0
		GC0654	Wheat	0.05 *	0.1 *	0
		AS 0654	Wheat straw and fodder, dry	0.05 *	0.1 *	0
		Residue for compliance with MRLs for plant and animal commodities: bitertanol For estimation of dietary intake for plant commodities: bitertanol For estimation of dietary intake for animal commodities: sum of bitertanol, *p*-hydroxybitertanol and acid-hydrolysable conjugates of *p*-hydrroxybiternol The residue is fat-soluble Acute RfD: Unnecessary [1]Dry weight Periodic review was for residues only				
Buprofezin (173)	0.01	FC 0004	Oranges, Sweet, Sour	0.5	0.3[1]	0.011
			Orange juice			0.012
			Orange pulp, dry			0.27
		Residue (for MRLs and STMRs): buprofezin The residue is fat-soluble Acute RfD: unnecessary [1]Recommended for withdrawal by 1995 JMPR				
Carbofuran (096)	0.002	FC 206	Mandarin	0.5		0.1
		Residue (for MRLs and STMRs): sum of carbofuran and 3-hydroxycarbofuran, expressed as carbofuran. Acute RfD: may be necessary but has not yet been established.				

Pesticide	ADI, mg/kg bw	Commodity		Recommended MRL, mg/kg		STMR, mg/kg
(Codex reference no.)		CCN	Name	New	Previous	
Carbosulfan (145)	0.01	FC 206	Mandarin	0.1		0.01
		Residue (for MRLs and STMRs): carbosulfan Acute RfD: may be necessary but has not yet been established.				
Chlormequat (015)	0.05	Acute RfD: 0.05 mg/kg bw				
Chlorpyrifos ** (017)	0.01	Acute RfD: 0.1 mg/kg bw ADI unchanged Periodic review was for toxicology only				
Clethodim (187)	0.01	VD 0071	Beans (dry)	2	0.1[1]	0.81
		AL 0061	Bean fodder (hay)	10		1.8
		AL 1030	Bean forage (green)	5		1.5
		MO 1280	Cattle, kidney	W	0.2*	
		MO 1281	Cattle, liver	W	0.2*	
		MM 0812	Cattle meat	W	0.5*	
		ML 0812	Cattle milk	W	0.1*	
		PE 0840	Chicken eggs	W	0.5*	
		PM 0840	Chicken meat	W	0.5*	
		MM 0095	Meat (from mammals other than marine mammals)	0.2*		0
		ML 0106	Milks	0.05*		0
		MO 0105	Edible offal (Mammalian)	0.2*		0
		PE 0112	Eggs	0.05*		0
		OC 0697	Peanut oil, crude			0.52
		OR 0697	Peanut oil, edible			0.12
		VR 0589	Potato[2]	0.5	0.2	
		PO 0111	Poultry, Edible offal of	0.2*		0
		PM 0110	Poultry meat	0.2*		0
		SO 0702	Sunflower seed	0.5	0.2 [1]	0.06
		OC 0702	Sunflower seed oil, crude	0.1*	0.05 [1]	0.012
		JF 0448	Tomato juice			0.27
			Tomato paste			1.2
			Tomato purée			0.77
		Residue (for MRLs and STMRs): sum of clethodim and metabolites containing 5-(2-ethylthiopropyl)cyclohexene-3-one and 5-(2-ethylthiopropyl)-5-hydroxycyclohexene-3-one moieties and their sulfoxides and sulfones, expressed as clethodim Acute RfD: unnecessary [1]Withdrawal was recommended by 1997 JMPR [2]STMR could not be estimated as the previously reviewed data from France, Italy and Ukraine were not re-submitted				
Diazinon (022) [1]	0.002	JF 0226	Apple juice			0.0004
			Apple pomace, wet			0.057
			Apple sauce			0.0004
			Apple slices, canned			0.0004
		VB 0041	Cabbages, Head	0.5	2	0.01
		MM 0814	Goat meat	2 (fat) V	2 (fat) V	0.3 (fat) [2] 0.02 (whole muscle) [2]
		MO 0098	Kidney of cattle, goats, pigs and sheep	0.03 V	0.03 V	0.01[2]
		MO 0099	Liver of cattle, goats, pigs and	0.03 V	0.03 V	0.01[2]

Pesticide	ADI, mg/kg bw	Commodity		Recommended MRL, mg/kg		STMR, mg/kg
(Codex reference no.)		CCN	Name	New	Previous	
			sheep			
		MM 0097	Meat of cattle, pigs and sheep	2 (fat) V	2 (fat) V	0.3 (fat) [2] 0.02 (whole muscle) [2]
		ML 0106	Milks	0.02 F V	0.02 F V	0.02[2]
		FP 0009	Pome fruits	0.3	2	0.04
		Residue (for MRLs and STMRs): diazinon The residue is fat-soluble Acute RfD: may be necessary but has not yet been established [1] Estimated dietary intake might, on the basis of the available information, exceed the ADI. [2] STMR estimated by the 1996 JMPR.				
Dimethipin ** (151)	0.02	Acute RfD: 0.02 mg/kg bw ADI unchanged Periodic review was for toxicology only.				
Dinocap (087)	0.008	VO 0448	Tomato	0.3		0.045
		Residue (for MRLs and STMRs): dinocap Acute RfD: 0.008 mg/kg bw				
Ethephon (106)	0.05	VC4199	Cantaloupe	1	1	0.24 [1]
		DF 0269	Dried grapes (Currants, Raisins and Sultanas)	5		0.84
		FB 0269	Grapes	1	1	0.31
		VO 0051	Peppers	5	30	0.98
		FI 0353	Pineapple	2	1	0.13
			Pineapples, canned			0.036
			Pineapple juice			0.051
		VO 0448	Tomato	2	2	0.41
		JF 0448	Tomato juice			0.14
			Tomato paste			0.31
			Wine			0.31
		Residue (for MRLs and STMRs): ethephon [1] STMR expressed on whole fruit, not edible portion Acute RfD: may be necessary but has not yet been established.				
Ethoprophos ** (149)	0.0004	Acute RfD: 0.05 mg/kg bw Previous ADI: 0.0003 mg/kg bw Periodic review was for toxicology only.				
Ethoxyquin ** (035)	0.005	FP 0230	Pear	W	3 Po	
		Residue (for compliance with MRLs and STMRs): ethoxyquin. The residue for the estimation of dietary intake cannot be defined until the toxicities of the plant metabolites are known Acute RfD: unnecessary Periodic review was for residues only.				
Fenamiphos ** (085)	0.0008	FP 0226	Apple	0.05*		0.01
		JF 0226	Apple juice			0.0078
		FI 0327	Banana[1]	0.05*	0.1	0.02
		VB 0400	Broccoli	W	0.05*	

Pesticide	ADI, mg/kg bw	Commodity		Recommended MRL, mg/kg		STMR, mg/kg
(Codex reference no.)		CCN	Name	New	Previous	
		VB 0402	Brussels sprouts	0.05	0.05*	0.01
		VB 0041	Cabbages, Head[1,2]	0.05	0.05*	0.01
		VR 0577	Carrot[1,2]	0.2	0.2	0.02
		VB 0404	Cauliflower	W	0.05*	
		SB 0716	Coffee beans	W	0.1	
		SM 0716	Coffee beans, roasted	W	0.1	
		SO 0691	Cotton seed	0.05*	0.05*	0
		OC 0691	Cotton seed oil, crude	0.05*		0.01
		MO 0105	Edible offal (Mammalian)	0.01*		0
		PE 0112	Eggs	0.01*		0
		FB 0269	Grapes[1,2]	0.1	0.1	0.02
		JF 0269	Grape juice			0.009
		FI 0341	Kiwifruit	W	0.05*	
		MM 0095	Meat (Mammalian)	0.01*		0
		VC 0046	Melons, except Watermelon[1,2]	0.05*	0.05*	0.02
		ML 0106	Milks	0.005*		0
		FC 0004	Oranges, Sweet, Sour	W	0.5	
		SO 0697	Peanut	0.05*	0.05*	0
		OC 0697	Peanut oil, crude	0.05*		0
		VO 0051	Peppers[1,2]	0.5		0.055
		FI 0353	Pineapple[1,2]	0.05*	0.05*	0.01
			Pineapple juice, canned			0.012
			Pineapple juice, raw			0.006
		VR 0589	Potato	W	0.2	
		PO 0111	Poultry, Edible offal of	0.01*		0
		PM 0110	Poultry meat	0.01*		0
		VD 0541	Soya bean (dry)	W	0.05*	
		VR 0596	Sugar beet	W	0.05*	
		VR 0508	Sweet potato	W	0.1	
		VO 0448	Tomato[1,2]	0.5	0.2	0.05
		JF 0448	Tomato juice			0.05
		VC 0432	Watermelon[1,2]	0.05*		0.02
		Residue (for MRLs and STMRs): sum of fenamiphos, its sulfoxide and sulfone, expressed as fenamiphos Acute RfD: 0.0008 mg/kg bw (1997) Periodic review was for residues only [1]The information provided to the JMPR precludes an estimate that the acute dietary intake for children would be below the acute reference dose [2]The information provided to the JMPR precludes an estimate that the acute dietary intake for the general population would be below the acute reference dose				
Fenpropimorph (188)	0.003	FI 0327	Banana	2		0.11
		PE 0112	Eggs	0.01*		0
		MO 0098	Kidney of cattle, goats, pigs and sheep	0.05		0.026
		MO 0099	Liver of cattle, goats, pigs and sheep	0.3		0.22

Pesticide	ADI, mg/kg bw	Commodity		Recommended MRL, mg/kg		STMR, mg/kg
(Codex reference no.)		CCN	Name	New	Previous	
		MF 0100	Mammalian fats (except milk fats)	0.01		0.006
		MM 0095	Meat (from mammals other than marine mammals)	0.02		0.009
		ML 0106	Milks	0.01		0.004
		PF 0111	Poultry fats	0.01*		0
		PM 0111	Poultry meat	0.01*		0
		PO 0111	Poultry, Edible offal of	0.01*		0
		Residue for compliance with MRLs and estimation of dietary intake for plant commodities: fenpropimorph For compliance with MRLs and estimation of dietary intake for animal commodities: 2-methyl-2-{4-[2-methyl-3-(*cis*-2,6-dimethylmorpholin-4-yl)propyl]phenyl}propionic acid expressed as fenpropimorph. Acute RfD: may be necessary but has not yet been established.				
Fenpyroximate (193)	0.01	FP 0226	Apple	0.3		0.09
		JF 0226	Apple juice			0.04
			Apple purée			0.05
			Beer			0.004
		MO 1280	Cattle, kidney	0.01*		0
		MO 1281	Cattle, liver	0.01*		0
		ML 0812	Cattle milk	0.005* F		0.002
		MM 0812	Cattle meat	0.02 (fat)		0.01
		FB 0269	Grapes	1		0.07
		DH 1100	Hops	10		4.4
		FC 0004	Oranges, Sweet, Sour	0.2		0.01
			Wine			0.005
		Residue (for MRLs and STMRs): fenpyroximate The residue is fat-soluble. Acute RfD: may be necessary but has not yet been established.				
Folpet (041)	0.1	FP 0226	Apple	10	10 [1]	3.1
		JF 0226	Apple juice			0.11
			Apple pomace, wet			8.1
		VC 0424	Cucumber	1	0.5 [2]	0.36
		DF 0269	Dried grapes (Currants, Raisins and Sultanas)	40	40 [1]	8.0
		FB 0269	Grapes	10	10 [1]	2.5
		JF 0269	Grape juice			0.0075
		VL 0482	Lettuce, Head	50		14
		VC 0046	Melons, except Watermelon	3	3 [2]	0.41
		VA 0385	Onion, Bulb	1		0.07
		VR 0589	Potato	0.1	0.02*[2]	0.01
		FB 0275	Strawberry	5	5 [1]	1.6
		VO 0448	Tomato	3	3 [1]	0.90
			Tomato purée			0.025
			Tomato paste			0.025
			Wine			0
		Residue (for MRLs and STMRs): folpet [1]The 1998 JMPR recommended withdrawal of current MRLs because critical supporting studies on the environmental fate of folpet were not provided. [2]Recommended for withdrawal by 1998 JMPR Acute RfD: may be necessary but has not yet been established				
Glufosinate-	0.02[1]	MO 0105	Edible offal (Mammalian)	0.1*		0

Pesticide	ADI, mg/kg bw	Commodity		Recommended MRL, mg/kg		STMR, mg/kg
(Codex reference no.)		CCN	Name	New	Previous	
ammonium (175)						
		PE 0112	Eggs	0.05*		0.05 [2]
		AS 0645	Maize fodder	10		0.72
		AF 0645	Maize forage	5	0.2	0.54
		MM 0095	Meat (from mammals other than marine mammals)	0.05*		0
		ML 0106	Milks	0.02*		0
		PM 0110	Poultry meat	0.05*		0.05 [2]
		PO 0111	Poultry, Edible offal of	0.1*		0.1 [2]
		VD 0541	Soya bean (dry)	2	0.1	0.87
		Residue (for MRLs and STMRs): sum of glufosinate-ammonium, 3-[hydroxy(methyl)phosphinoyl]propionic acid and *N*-acetyl-glufosinate, expressed as glufosinate (free acid). [1]Group ADI for glufosinate-ammonium, 3-[hydroxy(methyl)phosphinoyl]propionic acid and *N*-acetyl-glufosinate, alone or in combination. [2]LOD is assigned as STMR level Previous ADI: 0.02 mg/kg bw (1991) Acute RfD: not necessary				
Malathion ** (049)	0.3	AL 1021	Alfalfa forage (green)	500		157
		AL 1020	Alfalfa fodder	200		17
		FP 0226	Apple	W	2	
		VS 0621	Asparagus	1		0.305
		VP 0071	Beans (dry)	2	8 Po	0.36
		VP 0061	Beans, except Broad bean and Soya bean	1		0.31
		FB 0264	Blackberries	W	8	
		FB 0020	Blueberries	10	0.5	2.27
		VB 0400	Broccoli	W	5	
		VB 0041	Cabbages, Head	W	8	
		VB 0404	Cauliflower	W	0.5	
		VS 0624	Celery	W	1	
		GC 0080	Cereal grains	W	8 Po	
		VL 0464	Chard	W	0.5	
		FS 0013	Cherries	W	6	
		AL 1023	Clover	500		168
		AL 1031	Clover hay or fodder	150		33.5
		FC 0001	Citrus fruits	W	4	
		VP 0526	Common bean (pods and/or immature seeds)	W	2	
		SO 0691	Cotton seed	20		4.8
			Cotton seed meal			0.34
			Cotton seed oil, blanched and deodorized			0.038
		OC 0691	Cotton seed oil, crude	13		3.21
		OR 0691	Cotton seed oil, edible	13		3.12
		VC 0424	Cucumber	0.2		0.02
		DF 0167	Dried fruits	W	8	
		VO 0440	Egg plant	W	0.5	
		VL 0476	Endive	W	8	
		FB 0269	Grapes	W	8	
			Grass forage	200	-	49.5
			Grass hay	300	-	44
		VL 0480	Kale	W	3	
		VB 0405	Kohlrabi	W	0.5	
		VD 0533	Lentil (dry)	W	8	
		VL 0482	Lettuce, Head	W	8	

Pesticide	ADI, mg/kg bw	Commodity		Recommended MRL, mg/kg		STMR, mg/kg
(Codex reference no.)		CCN	Name	New	Previous	
		GC0645	Maize	0.05		0.01
		AS 0645	Maize fodder	50		6.65
		AF 0645	Maize forage	10		0.20
		VL 0485	Mustard greens	2		0.07
			Nuts (whole in shell)	W	8	
		VA 0385	Onion, Bulb	1		0.23
		VA 0389	Onion, Spring	5		0.52
		FS 0247	Peach	W	6	
		FP 0230	Pear	W	0.5	
		VP 0063	Peas (pods and succulent = Immature seeds)	W	0.5	
		VO 0051	Peppers	0.1	0.5	0.01
		FS 0014	Plums (including Prunes)	W	6	
		FB 0272	Raspberries, Red, Black	W	8	
		VR 0075	Root and tuber vegetables [1]	W	0.5	
		CM 0650	Rye bran, unprocessed	W	20 PoP	
		CF 1250	Rye flour	W	2 PoP	
		CF 1251	Rye wholemeal	W	2 PoP	
		VL 0502	Spinach	3	8	0.35
		FB 0275	Strawberry	1	1	0.25
		VO 0447	Sweet corn (corn-on the-cob)	0.02		0.01
		GC 0651	Sorghum	3		0.235
		VO 0448	Tomato	0.5	3	0.21
		VJ 0448	Tomato juice	0.01		0.00
			Tomato ketchup			0.09
			Tomato pomace, wet			0.20
			Tomato pomace, dry			1.6
			Tomato purée			0.07
		VR 0506	Turnip, Garden	0.2	3	0.05
		VL 0506	Turnip greens	5		1.20
		GC 0654	Wheat	0.5		0.04
			Wheat forage	20		4.14
		AS 0654	Wheat straw and fodder, dry	50		6.85
		Residue (for MRLs and STMRs): malathion [1] Except Turnip, Garden Periodic review was for residues only. Acute RfD: may be necessary but has not yet been established.				
Methiocarb** (132)	0.02	VS 0620	Artichoke, Globe	W	0.05 *	
		VB0400	Broccoli	W	0.2	
		VB0402	Brussels sprouts	W	0.2	
		VB0041	Cabbages, Head	W	0.2	
		VB0404	Cauliflower	W	0.2	
		GC0080	Cereal grains	W	0.05 *	
		FC 0001	Citrus fruits	W	0.05 *	
		PE 0840	Eggs	W	0.05 *	
		TN 0666	Hazelnuts	W	0.05 *	

Pesticide	ADI, mg/kg bw	Commodity		Recommended MRL, mg/kg		STMR, mg/kg
(Codex reference no.)		CCN	Name	New	Previous	
		VL 0482	Lettuce, Head	W	0.2	
		VL 0483	Lettuce, Leaf	W	0.2	
		MM0095	Meat (from mammals other than marine mammals)	W	0.05 *	
		ML0106	Milks	W	0.05 *	
		PM 0110	Poultry meat	W	0.05 *	
		SO 0495	Rape seed	W	0.05 *	
		VR 0596	Sugar beet	W	0.05 *	
		VO 0447	Sweet corn (corn-on-the-cob)	W	0.05 *	
		FB 0275	Strawberry	1		0.44
		Residue (for MRLs and STMRs): sum of methiocarb, methiocarb sulfoxide and methiocarb sulfone, expressed as methiocarb. Acute RfD: 0.02 mg/kg bw Periodic review was for residues only.				
Oxydemeton-methyl (166)	0.0003	ADI is for demeton-S-methyl and related compounds, alone or in combination Acute RfD: may be necessary but has not yet been established.				
Permethrin ** (120)	0.05[1]	Acute RfD: not necessary [1]For technical-grade permethrin with *cis*-: *trans*- ratios of 25:75 to 40:60. ADI unchanged Periodic review was for toxicology only.				
2-Phenylphenol ** (056)	0.4	FP 0226	Apple	W	25 Po	
		FC 0001	Citrus fruits	10	10 Po	0.20
		AB 0001	Citrus pulp, dried	60		
		JF 0004	Orange juice	0.5		0.12
			Orange oil			340
		FP 0230	Pear	W	25 Po	
		Residue (for MRLs and STMRs): Plant commodities: sum of 2-phenylphenol and sodium 2-phenylphenate, free and conjugated, expressed as 2-phenylphenol Previous ADI: 0.02 mg/kg bw (1990) Acute RfD: un necessary				
Phosalone (060)	0.02	TN 0660	Almonds	0.1	-	0.05
			Apple compote		-	0.1
		TN 0666	Hazelnuts	0.05*	-	0.05
		FP 0009	Pome fruits	2	5[1]	0.8
		FS 0012	Stone fruits	2	-	0.45
		TN 0678	Walnuts	0.05*	-	0.05
		Residue (for MRLs and STMRs): phosalone The residue is fat-soluble. Acute RfD: may be necessary but has not yet been established [1]Recommended for withdrawal by the 1994 JMPR				
Propargite **[1] (113)	0.01	Acute RfD: Unnecessary Previous ADI: 0.15 mg/kg bw Periodic review was for toxicology only. [1]The information provided to the JMPR precludes an estimate that the dietary intake would be below the ADI.				
Propylenethiourea	0.0003	Acute RfD: 0.003 mg/kg bw Previous temporary ADI: 0.0002 mg/kg bw				

Pesticide	ADI, mg/kg bw	Commodity		Recommended MRL, mg/kg		STMR, mg/kg
(Codex reference no.)		CCN	Name	New	Previous	
Pyrethrins ** (063)	0.04	Acute RfD: 0.2 mg/kg bw ADI unchanged Periodic review was for toxicology only.				
Pyriproxifen * (200)	0.1	MM0812	Cattle meat	0.01* (fat)		0
		MO0812	Cattle, Edible offal of	0.01*		0
		FC 0001	Citrus fruits	1		0.013
			Cotton gin trash	5		0.91
		SO 0691	Cotton seed	0.05		0.01
			Cotton seed meal			0.001
		OC 0691	Cotton seed oil, crude	0.01		0.002
		OR 0691	Cotton seed oil, edible	0.01		0.002
		MM0814	Goat meat	0.01* (fat)		0
		MO 0814	Goat, Edible offal of	0.01*		0
		Residue (for MRLs and STMRs): pyriproxifen The residue is fat-soluble. Acute RfD: not necessary New compound				
Tebufenozide (196)	0.02		Apple juice			0.021
			Apple pomace, wet			0.425
			Apple purée			0.043
		FB 0269	Grapes	1	0.5	0.25
			Grape pomace, wet			0.675
		FP 0009	Pome fruits	1	1	0.17
			Wine			0.063
		Residue (for MRLs and STMRs): tebufenozide The residue is fat-soluble. Acute RfD: may be necessary but has not yet been established.				

ANNEX II

INDEX OF REPORTS AND EVALUATIONS

Numbers in parentheses are Codex Classification Numbers.

[1] T = Evaluation of toxicology
R = Evaluation of residue and analytical aspects
E = Evaluation of effects on the environment

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), 1998 (R)
BENTAZONE (172)	1991 (T,R), 1992 (corr. to 1991 rpt, Annex I), 1994 (R), 1995 (R); 1998 (T,R), 1999 (corr. to 1998 rpt)
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), 1998 (T), 1999 (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.), 1999 (R)
sec-BUTYLAMINE (089)	1975 (T,R), 1977 (R), 1978 (T,R), 1979 (R), 1980 (R), 1981 (T), 1984 (T,R: withdrawal of TADI, but no evaluation)
CADUSAFOS (174)	1991 (T,R), 1992 (R), 1992 (R)
CAMPHECHLOR (071)	1968 (T,R), 1973 (T,R)

CAPTAFOL (006)	1969 (T,R), 1973 (T,R), 1974 (R), 1976 (R), 1977 (T,R), 1982 (T), 1985 (T,R), 1986 (corr. to 1985 rpt), 1990 (R); 1999 (Acute Rf D)
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); 1998 (T,R)
CARBOFURAN (096)	1976 (T,R), 1979 (T,R), 1980 (T), 1982 (T), 1991 (R), 1993 (R), 1996 (T), 1997 (R), 1999 (corr. to 1997 rpt)
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)
CARBOPHENO-THION (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), 1999 (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), 1999 (Acute Rf D)
CHLOROBENZILATE (016)	1965 (T), 1968 (T,R), 1972 (R), 1975 (R), 1977 (R), 1980 (T)
CHLOROPICRIN	1965 (T,R)
CHLOROPRO-PYLATE	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), 1999 (T)
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), 1999 (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 & corr. to 1986 rpt), 1989 (R), 1990 (R), 1992 (R)
CYHALOTHRIN (146)	1984 (T,R), 1986 (R), 1988 (R)

CYHEXATIN (TRICYCLO HEXYLTIN HYDROXIDE (067)	1970 (T,R), 1973 (T,R), 1974 (R), 1975(R), 1977 (T), 1978 (T,R), 1980 (T), 1981 (T), 1982 (R), 1983 (R), 1985 (R), 1988 (T), 1989 (T), 1991 (T,R), 1992 (R), 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); 1998 (R)
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); 1998 (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),1999 (R)
1,2-DIBROMO ETHANE (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-DICHLORO ETHANE (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); 1998 (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), 1999 (T)
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); 1998 (R)
DIMETHRIN	1965 (T)
DINOCAP (087)	1969 (T,R), 1974 (T,R), 1989 (T,R), 1992 (R); 1998 (R), 199 (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); 1998 (T)
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); 1998 (R)
DITHIANON (180)	1992 (T,R), 1995 (R), 1996 (corr. to 1995 rpt.)
DITHIOCARB AMATES (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); 1998 (T)
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), 1999 (R)
ETHOXYQUIN (035)	1969 (T,R), 1998 (T),
ETHYLENE DIBROMIDE	see 1,2-dibromoethane
ETHYLENE DICHLORIDE	see 1,2-dichloroethane
ETHYLENE OXIDE	1965 (T,R), 1968 (T,R), 1971 (R)
ETHYLENETHIO UREA (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[2]), 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), 1999 (R)
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)

[2]R evaluation omitted. Published 1986.

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)
FENPROPATHRIN (185)	1993 (T,R)
FENPROPIMORPH (188)	1994 (T), 1995 (R), 1999 (R)
FENPYROXIMATE (193)	1995 (T,R), 1996 (corr. to 1995 rpt.), 1999 (R)
FENSULFOTHION (038)	1972 (T,R), 1982 (T), 1983 (R)
FENTHION (039)	1971 (T,R), 1975 (T,R), 1977 (R), 1978 (T,R), 1979 (T), 1980 (T), 1983 (R), 1989 (R), 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); 1998 (R), 1999 (R)
FORMOTHION (042)	1969 (T,R), 1972 (R), 1973 (T,R), 1978 (R); 1998 (R)

GLUFOSINATE-AMMONIUM (175)	1991 (T,R), 1992 (corr. to 1991 rpt, Annex I), 1994 (R); 1998 (R), 1999 (T,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)
HEXACHLORO BENZENE (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); 1998 (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)
KRESOXIM-METHYL (199)	1998 (T,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), 1999 (R)
MALEIC HYDRAZIDE (102)	1976 (T,R), 1977 (T,R), 1980 (T), 1984 (T,R), 1996 (T); 1998 (R)
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[3]), 1984 (R), 1985 (T), 1989 (R), 1990 (T,R), 1994 (R), 1996 (R), 1997 (R)
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); 1998 (T), 1999 (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)

[3]R evaluation omitted. Published 1989.

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); 1998 (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); 1998 (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); 1998 (R), 1999 (corr. to 1992 rpt)
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), 1999 (T)
2-PHENYLPHENOL (056)	1969 (T,R), 1975 (R), 1983 (T), 1985 (T,R), 1989 (T), 1990 (T,R), 1999 (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), 1999 (R)
PHOSMET (103)	1976 (R), 1977 (corr. to 1976 evaluation), 1978 (T,R), 1979 (T,R), 1981 (R), 1984 (R), 1985 (R), 1986 (R), 1987 (R and corr. to 1986 evaluation), 1988 (R), 1994 (T), 1997 (R); 1998 (T)
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); 1998 (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), 1999 (T)
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)

PROPYLENETHIO UREA (PTU, 150)	1993 (T,R), 1994 (R), 1999 (T)
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), 1999 (T)
PYRIPROXYFEN	1999 (R,T)
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); 1998 (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), 1999 (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); 1998 (T,R)
THIRAM (105)	see dithiocarbamates, 1965 (T), 1967 (T,R), 1970 (T,R), 1974 (T), 1977 (T), 1983 (R), 1984 (R), 1985 (T,R), 1987 (T), 1988 (R), 1989 (R), 1992 (T), 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)
TRIAZOLYL ALANINE	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

DIETARY INTAKES OF PESTICIDES IN RELATION TO ADIs

The following Tables give details of the estimated daily intakes of the pesticides evaluated by the Meeting for the five GEMS/Food regional diets, and show the ratios of the estimated intakes to the corresponding ADIs.

(*) at or about the LOD.

The ranges of the intake/ADI ratios for all the compounds evaluated are tabulated in Section 3, page 27.

BITERTANOL (144) **INTERNATIONAL ESTIMATED DAILY INTAKE (IEDI)**

ADI =0.01 mg/kg bodyweight or 0.600 mg/person

Commodity		MRL mg/kg	STMR mg/kg	Processing Factor	Notes	Adjusted STMR mg/kg	Middle Eastern		Far Eastern		African		Latin American		European	
Code	Name						Diet g/day	IEDI mg/day	Diet g/day	IEDI mg/day	Diet g/day	IEDI mg/day	Diet g/day	IEDI mg/day	Diet g/day	IEDI mg/day
FI 0327	Banana	0.5	0.075				8.3	0.0006	26.2	0.0020	21.0	0.0016	102.3	0.0077	22.8	0.0017
GC 0640	Barley	0.05	0		(*)		1.0	0.0000	3.5	0.0000	1.8	0.0000	6.5	0.0000	19.8	0.0000
FS 0013	Cherries	1	0.365				0.0	0.0000	0.0	0.0000	0.0	0.0000	0.0	0.0000	3.0	0.0011
VC 0424	Cucumber	0.5	0.18				4.8	0.0009	4.5	0.0008	0.0	0.0000	8.3	0.0015	9.0	0.0016
MO 0105	Edible offal (mammalian)	0.05	0.05		(*)		4.2	0.0002	1.4	0.0001	2.4	0.0001	6.1	0.0003	12.4	0.0006
PE 0112	Eggs	0.01	0		(*)		14.6	0.0000	13.1	0.0000	3.7	0.0000	11.9	0.0000	37.6	0.0000
MM 0095	Meat, mammalian except marine	0.05	0.05		fat (*)		37.0	0.0019	32.8	0.0016	23.8	0.0012	47.0	0.0024	155.5	0.0078
ML 0106	Milks	0.05	0.05		(*)		116.8	0.0058	32.0	0.0016	41.8	0.0021	160.0	0.0080	294.0	0.0147
FS 0245	Nectarine	1	0.23				1.3	0.0003	0.3	0.0001	0.0	0.0000	0.4	0.0001	6.3	0.0013
GC 0647	Oats	0.05	0		(*)		0.0	0.0000	0.0	0.0000	0.2	0.0000	0.8	0.0000	2.0	0.0000
FS 0247	Peach	1	0.20				1.3	0.0003	0.3	0.0001	0.0	0.0000	0.4	0.0001	6.2	0.0013

FS 0014	Plums (including Prunes)	2	0.34				1.8	0.0006	0.5	0.0002	0.0	0.0000	0.0	0.0000	4.3	0.0015
FP 0009	Pome fruits	2	0.24				10.8	0.0026	7.5	0.0018	0.3	0.0001	6.5	0.0016	51.3	0.0123
JF 0226	Apple juice		0.24	0.14		0.0336	1.9	0.0001	1.2	0.0000	0.1	0.0000	1.4	0.0000	10.0	0.0003
PM 0110	Poultry meat	0.01	0		(*)		31.0	0.0000	13.2	0.0000	5.5	0.0000	25.3	0.0000	53.0	0.0000
PO 0111	Poultry, edible offal of	0.01	0		(*)		0.1	0.0000	0.1	0.0000	0.1	0.0000	0.4	0.0000	0.4	0.0000
GC 0650	Rye	0.05	0		(*)		0.0	0.0000	1.0	0.0000	0.0	0.0000	0.0	0.0000	1.5	0.0000
VO 0448	Tomato	3	0.76				44.1	0.0335	5.7	0.0043	14.6	0.0111	25.5	0.0194	38.2	0.0290
VJ 0448	Tomato juice			0.13		0.10	0.3	0.0000	0.0	0.0000	0.0	0.0000	0.0	0.0000	2.0	0.0002
	Tomato paste			2.1		1.60	5.8	0.0092	0.2	0.0003	0.3	0.0004	0.0	0.0000	4.0	0.0064
GC 0653	Triticale	0.05	0	1	(*)	0	0.0	0.0000	1.0	0.0000	0.0	0.0000	0.0	0.0000	0.0	0.0000
GC 0654	Wheat	0.05	0	1	(*)	0	327.3	0.0000	114.8	0.0000	28.3	0.0000	116.8	0.0000	178.0	0.0000
						TOTAL =		0.056		0.013		0.017		0.041		0.08
						% ADI =		9%		2%		3%		7%		13%
					RO			9%		2%		3%		7%		10%

BUPROFEZIN (173) **DIETARY INTAKE ESTIMATE (DIE)**

ADI = 0.01 mg/kg bodyweight or 0.600 mg/person

Commodity		MRL mg/kg	STMR mg/kg	Processing Factor	Notes	Adjusted STMR Mg/kg	Middle Eastern		Far Eastern		African		Latin American		European	
							Diet	IEDI	Diet	IEDI	Diet	IEDI	Diet	IEDI	Diet	IEDI
Code	Name						g/day	mg/day	g/day	mg/day	g/day	mg/day	g/day	mg/day	g/day	mg/day
VC 0424	Cucumber	1					4.8	0.0048	4.5	0.0045	0.0	0.0000	8.3	0.0083	9.0	0.0090
FC 0004	Oranges, Sweet, Sour	0.5	0.011				31.5	0.0003	4.0	0.0000	4.8	0.0001	31.0	0.0003	29.8	0.0003
JF 0004	Orange juice			1.1		0.0121	7.3	0.0001	0.0	0.0000	0.0	0.0000	0.3	0.0000	4.5	0.0001
VO 0448	Tomato	1					81.5	0.0815	7.0	0.0070	16.5	0.0165	25.5	0.0255	66.0	0.0660
						TOTAL =		0.087		0.012		0.017		0.034		0.075
						% ADI =		14%		2%		3%		6%		13%
						ROUNDED % ADI =		10%		2%		3%		6%		10%

CARBOFURAN (96) **INTERNATIONAL ESTIMATED DAILY INTAKE (IEDI)**

ADI = 0.002 mg/kg bodyweight or 0.120 mg/person

Commodity		MRL mg/kg	STMR mg/kg	Processing Factor	Notes	Adjusted STMR mg/kg	Middle Eastern		Far Eastern		African		Latin American		European	
							Diet	IEDI	Diet	IEDI	Diet	IEDI	Diet	IEDI	Diet	IEDI
Code	Name						g/day	mg/day	g/day	mg/day	g/day	mg/day	g/day	mg/day	g/day	mg/day
FI 0327	Banana	0.1	0.1		(*)		8.3	0.0008	26.2	0.0026	21.0	0.0021	102.3	0.0102	22.8	0.0023
VC 4199	Cantaloupe	0.2	0.02				16.0	0.0003	2.0	0.0000	0.0	0.0000	2.8	0.0001	18.3	0.0004
MF 0812	Cattle fat	0.05	0.05		(*)		0.3	0.0000	0.3	0.0000	0.3	0.0000	1.5	0.0001	0.0	0.0000
SB 0716	Coffee beans	1	0.05				5.3	0.0003	0.4	0.0000	0.0	0.0000	3.6	0.0002	7.9	0.0004
SM 0716	Coffee, roast		0.005			0	0.5	0.0000	0.2	0.0000	0.0	0.0000	0.8	0.0000	5.8	0.0000
VC 0424	Cucumber	0.3	0.05				4.8	0.0002	4.5	0.0002	0.0	0.0000	8.3	0.0004	9.0	0.0005
MO 0096	Edible offal of cattle, goats, horses, pigs, sheep	0.05	0.05		(*)		4.1	0.0002	1.3	0.0001	2.7	0.0001	6.0	0.0003	12.3	0.0006
MF 0814	Goat fat	0.05	0.05		(*)		0.1	0.0000	0.1	0.0000	0.1	0.0000	0.1	0.0000	0.1	0.0000
MF 0816	Horse fat	0.05	0.05		(*)		0.1	0.0000	0.1	0.0000	0.1	0.0000	0.1	0.0000	0.1	0.0000
MM 0096	Meat of cattle, goats, horses, pigs, sheep	0.05	0.05		(*)		34.0	0.0017	32.0	0.0016	17.5	0.0009	44.3	0.0022	150.3	0.0075
ML 0106	Milks	0.05	0.05		(*)		116.8	0.0058	32.0	0.0016	41.8	0.0021	160.0	0.0080	294.0	0.0147
FC 0004	Oranges, sweet, sour	0.5	0.1		(*)		31.5	0.0032	4.0	0.0004	4.8	0.0005	31.0	0.0031	29.8	0.0030
JF 0004	Orange juice			0.01		0.001	7.3	0.0000	0.0	0.0000	0.0	0.0000	0.3	0.0000	4.5	0.0000
FC 0003	Mandarin	0.5	0.1		(*)		8.6	0.0009	0.2	0.0000	0.0	0.0000	6.3	0.0006	6.0	0.0006
MF 0818	Pig fat	0.05	0.05		(*)		0.1	0.0000	0.1	0.0000	0.1	0.0000	0.1	0.0000	0.1	0.0000
VR 0589	Potato	0.1	0.03				59.0	0.0018	19.2	0.0006	20.6	0.0006	40.8	0.0012	240.8	0.0072
MF 0822	Sheep fat	0.05	0.05		(*)		0.1	0.0000	0.1	0.0000	0.1	0.0000	0.1	0.0000	0.1	0.0000
GC 0651	Sorghum	0.1	0.01				2.0	0.0000	9.7	0.0001	26.6	0.0003	0.0	0.0000	0.0	0.0000
VC 0431	Squash, summer	0.3	0.03				10.5	0.0003	2.2	0.0001	0.0	0.0000	14.0	0.0004	3.5	0.0001
GS 0659	Sugar cane	0.1	0.1		(*)		18.5	0.0019	7.3	0.0007	15.9	0.0016	3.5	0.0004	0.0	0.0000
SO 0702	Sunflower seed	0.1	0.1				1.0	0.0001	0.0	0.0000	0.6	0.0001	0.0	0.0000	0.0	0.0000
VO 1275	Sweet corn (kernels)	0.1	0.03				0.0	0.0000	0.0	0.0000	3.3	0.0001	0.0	0.0000	6.2	0.0002

					TOTAL =	0.017		0.008		0.008		0.027		0.037
					% ADI =	15%		7%		7%		23%		31%
					ROUNDED % ADI =	10%		7%		7%		20%		30%

CARBOSULFAN (145) **INTERNATIONAL ESTIMATED DAILY INTAKE (IEDI)**

ADI = 0.01 mg/kg bodyweight or 0.600 mg/person

Commodity		MRL mg/kg	STMR mg/kg	Processing Factor	Notes	Adjusted STMR mg/kg	Middle Eastern		Far Eastern		African		Latin American		European	
							Diet	IEDI	Diet	IEDI	Diet	IEDI	Diet	IEDI	Diet	IEDI
Code	Name						g/day	mg/day	g/day	mg/day	g/day	mg/day	g/day	mg/day	g/day	mg/day
FC 0004	Oranges, Sweet, Sour	0.1	0.01				31.5	0.0003	4.0	0.0000	4.8	0.0000	31.0	0.0003	29.8	0.0003
JF 0004	Orange juice			0		0	7.3	0.0000	0.0	0.0000	0.0	0.0000	0.3	0.0000	4.5	0.0000
FC 0003	Mandarin	0.1	0.01				8.6	0.0001	0.2	0.0000	0.0	0.0000	6.3	0.0001	6.0	0.0001
						TOTAL =		0.0004		0.0000		0.0000		0.0004		0.0004
						% ADI =		0%		0%		0%		0%		0%

CHLORPYRIFOS (17) **(THEORETICAL MAXIMUM DAILY INTAKE (TMDI)**

ADI = 0.01 mg/kg bodyweight or 0.600 mg/person

Commodity		MRL mg/kg	**Notes**	Middle Eastern		Far Eastern		African		Latin American		European	
				Diet	TMDI	Diet	TMDI	Diet	TMDI	Diet	TMDI	Diet	TMDI
Code	Name			g/day	mg/day	g/day	mg/day	g/day	mg/day	g/day	mg/day	g/day	mg/day
FP 0226	Apple	1		7.5	0.0075	4.7	0.0047	0.3	0.0003	5.5	0.0055	40.0	0.0400
VB 0041	Cabbages, Head	0.05	(*)	5.0	0.0003	9.7	0.0005	0.0	0.0000	10.5	0.0005	26.8	0.0013
VR 0577	Carrot	0.5		2.8	0.0014	2.5	0.0013	0.0	0.0000	6.3	0.0031	22.0	0.0110

MM0812	Cattle meat	2	(fat) V	3.7	0.0074	0.7	0.0014	2.1	0.0042	6.0	0.0120	12.7	0.0254
VB 0404	Cauliflower	0.05	(*)	1.3	0.0001	1.5	0.0001	0.0	0.0000	0.3	0.0000	13.0	0.0007
VS 0624	Celery	0.05	(*)	0.5	0.0000	0.0	0.0000	0.0	0.0000	0.3	0.0000	2.0	0.0001
PM 0840	Chicken meat	0.1	(fat)	3.0	0.0003	1.2	0.0001	0.6	0.0001	2.5	0.0003	4.4	0.0004
VL 0467	Chinese cabbage, type "Pe-tsai"	1		0.1	0.0001	0.1	0.0001	0.1	0.0001	0.1	0.0001	0.1	0.0001
FC 0001	Citrus fruits	0.3		54.3	0.0163	6.3	0.0019	5.1	0.0015	54.8	0.0164	49.0	0.0147
VP 0526	Common bean (pods and/or immature seeds)	0.2		3.5	0.0007	0.8	0.0002	0.0	0.0000	4.0	0.0008	12.0	0.0024
SO 0691	Cotton seed	0.05	(*)	0.0	0.0000	0.0	0.0000	0.0	0.0000	0.0	0.0000	0.0	0.0000
OC 0691	Cotton seed oil, crude	0.05	(*)	3.8	0.0002	0.5	0.0000	0.5	0.0000	0.5	0.0000	0.0	0.0000
DF 0269	Dried grapes	2		0.3	0.0005	0.0	0.0000	0.0	0.0000	0.3	0.0005	2.3	0.0045
VO 0440	Egg plant	0.2		6.3	0.0013	3.0	0.0006	0.7	0.0001	6.0	0.0012	2.3	0.0005
PE 0112	Eggs	0.05	(*)	14.6	0.0007	13.1	0.0007	3.7	0.0002	11.9	0.0006	37.6	0.0019
FB 0269	Grapes	1		15.5	0.0155	1.0	0.0010	0.0	0.0000	1.0	0.0010	11.5	0.0115
VL 0480	Kale	1		0.5	0.0005	0.0	0.0000	0.0	0.0000	0.3	0.0003	2.0	0.0020
FI 0341	Kiwifruit	2		0.0	0.0000	0.0	0.0000	1.9	0.0039	0.1	0.0002	1.5	0.0030
VL 0482	Lettuce, Head	0.1		2.3	0.0002	0.0	0.0000	0.0	0.0000	5.8	0.0006	22.5	0.0023
ML 0106	Milks	0.01	(*) F V	116.8	0.0012	32.0	0.0003	41.8	0.0004	160.0	0.0016	294.0	0.0029
VO 0450	Mushrooms	0.05	(*)	0.3	0.0000	0.5	0.0000	0.0	0.0000	0.0	0.0000	4.0	0.0002
VA 0385	Onion, bulb	0.05	(*)	23.0	0.0012	11.5	0.0006	7.3	0.0004	13.8	0.0007	27.8	0.0014
FP 0230	Pear	0.5		3.3	0.0016	2.8	0.0014	0.0	0.0000	1.0	0.0005	11.3	0.0056
VO 0051	Peppers	0.5		3.4	0.0017	2.1	0.0011	5.4	0.0027	2.4	0.0012	10.4	0.0052
VR 0589	Potato	0.05	(*)	59.0	0.0030	19.2	0.0010	20.6	0.0010	40.8	0.0020	240.8	0.0120
FB 0272	Raspberries, Red, Black	0.2		0.0	0.0000	0.0	0.0000	0.0	0.0000	0.0	0.0000	0.5	0.0001
GC 0649	Rice	0.1		48.8	0.0049	279.3	0.0279	103.4	0.0103	86.5	0.0087	11.8	0.0012
MM 0822	Sheep meat	0.2	(fat) V	2.7	0.0005	0.1	0.0000	0.4	0.0001	0.1	0.0000	2.1	0.0004
VR 0596	Sugar beet	0.05	(*)	0.5	0.0000	0.0	0.0000	0.0	0.0000	0.3	0.0000	2.0	0.0001
VO 0448	Tomato	0.5		81.5	0.0408	7.0	0.0035	16.5	0.0083	25.5	0.0128	66.0	0.0330
PM 0848	Turkey meat	0.2	(fat) V	0.0	0.0000	0.0	0.0000	0.0	0.0000	0.0	0.0000	0.7	0.0001
		TOTAL =			0.108		0.048		0.034		0.071		0.184
		% ADI =			18%		8%		6%		12%		31%
		ROUNDED % ADI =			20%		8%		6%		10%		30%

CLETHODIM (187) **DIETARY INTAKE ESTIMATE (DIE)**

ADI = 0.01 mg/kg bodyweight or 0.600 mg/person

Commodity		MRL mg/kg	STMR mg/kg	Processing Factor	Notes	Adjusted STMR mg/kg	Middle Eastern		Far Eastern		African		Latin American		European	
							Diet	IEDI	Diet	IEDI	Diet	IEDI	Diet	IEDI	Diet	IEDI
Code	Name						g/day	mg/day	g/day	mg/day	g/day	mg/day	g/day	mg/day	g/day	mg/day
VD 0071	Beans, dry	2	0.81				6.8	0.0055	6.8	0.0055	0.0	0.0000	13.5	0.0109	4.3	0.0035
VP 0061	Beans, except broad and soya	0.5	0.05				0.1	0.0000	0.1	0.0000	0.1	0.0000	0.1	0.0000	0.1	0.0000
SO 0702	Cotton seed oil, edible		0.5	0.1		0.05	1.0	0.0001	0.0	0.0000	0.6	0.0000	0.0	0.0000	0.0	0.0000
MO 0105	Edible offal, mammalian	0.2	0		(*)		4.2	0.0000	1.4	0.0000	2.4	0.0000	6.1	0.0000	12.4	0.0000
PE 0112	Eggs	0.05	0		(*)		14.6	0.0000	13.1	0.0000	3.7	0.0000	11.9	0.0000	37.6	0.0000
VD 0561	Field pea (dry)	2	0.08				0.5	0.0000	1.7	0.0001	0.0	0.0000	1.3	0.0001	1.8	0.0001
VA 0381	Garlic	0.5	0.1		(*)		2.0	0.0002	2.2	0.0002	0.0	0.0000	0.5	0.0001	3.0	0.0003
VA 0385	Onion, bulb	0.5	0.1		(*)		23.0	0.0023	11.5	0.0012	7.3	0.0007	13.8	0.0014	27.8	0.0028
MM 0095	Meat, mammalian except marine	0.05	0		(*)		37.0	0.0000	32.8	0.0000	23.8	0.0000	47.0	0.0000	155.5	0.0000
ML 0106	Milks	0.05	0		(*)		116.8	0.0000	32.0	0.0000	41.8	0.0000	160.0	0.0000	294.0	0.0000
SO 0697	Peanut	5	1.3				0.3	0.0003	0.2	0.0002	2.3	0.0030	0.3	0.0004	3.0	0.0039
OR 0697	Peanut oil, edible			0.09		0.12	0.0	0.0000	1.8	0.0002	3.5	0.0004	0.5	0.0001	1.8	0.0002
VR 0589	Potato	0.5					59.0	0.0295	19.2	0.0096	20.6	0.0103	40.8	0.0204	240.8	0.1204
PO 0111	Poultry offal	0.2	0		(*)		0.1	0.0000	0.1	0.0000	0.1	0.0000	0.4	0.0000	0.4	0.0000
PM 0110	Poultry meat	0.2	0		(*)		31.0	0.0000	13.2	0.0000	5.5	0.0000	25.3	0.0000	53.0	0.0000
OR 0495	Rape seed oil, edible	0.5	0.5		(*)		4.5	0.0023	2.7	0.0014	0.0	0.0000	0.3	0.0001	7.3	0.0037
OR 0541	Soya bean oil, edible	0.5	0.5	0.002	(*)	0.001	1.3	0.0000	1.7	0.0000	3.0	0.0000	14.5	0.0000	4.3	0.0000
VR 0596	Sugar beet	0.1	0.1				0.5	0.0001	0.0	0.0000	0.0	0.0000	0.3	0.0000	2.0	0.0002
SO 0702	Sunflower seed	0.5	0.06				1.0	0.0001	0.0	0.0000	0.6	0.0000	0.0	0.0000	0.0	0.0000
OC 0702	Sunflower seed oil, crude	0.1	0.012		(*)		9.3	0.0001	0.5	0.0000	0.3	0.0000	0.8	0.0000	8.5	0.0001
VO 0448	Tomato	1	0.35				44.1	0.0154	5.7	0.0020	14.6	0.0051	25.5	0.0089	38.2	0.0134
VJ 0448	Tomato juice		0.35	0.77		0.27	0.3	0.0001	0.0	0.0000	0.0	0.0000	0.0	0.0000	2.0	0.0005

	Tomato paste		0.35	3.43		1.20	5.8	0.0069	0.2	0.0002	0.3	0.0003	0.0	0.0000	4.0	0.0048
	Tomato puree		0.35	2.2		0.77	0.3	0.0002	0.0	0.0000	0.0	0.0000	0.0	0.0000	2.0	0.0015
						TOTAL =		0.0630		0.0206		0.0198		0.0424		0.1554
						% ADI =		11%		3%		3%		7%		26%
						ROUNDED % ADI =		10%		3%		3%		7%		30%

DIAZINON (22) **DIETARY INTAKE ESTIMATE (DIE)**

ADI = 0.002 mg/kg bodyweight or 0.120 mg/person

Commodity		MRL mg/kg	STMR mg/kg	Processing Factor	Notes	Adjusted STMR mg/kg	Middle Eastern		Far Eastern		African		Latin American		European	
							Diet	IEDI	Diet	IEDI	Diet	IEDI	Diet	IEDI	Diet	IEDI
Code	Name						g/day	mg/day	g/day	mg/day	g/day	mg/day	g/day	mg/day	g/day	mg/day
TN 0660	Almonds	0.05					0.5	0.0000	0.0	0.0000	0.0	0.0000	0.1	0.0000	1.8	0.0001
GC 0640	Barley	0.1					1.0	0.0001	3.5	0.0004	1.8	0.0002	6.5	0.0007	19.8	0.0020
FB 0264	Blackberries	0.1					0.0	0.0000	0.0	0.0000	0.0	0.0000	0.0	0.0000	0.0	0.0000
FB 4079	Boysenberry	0.1					0.0	0.0000	0.0	0.0000	0.0	0.0000	0.0	0.0000	0.0	0.0000
VB 0400	Broccoli	0.5					0.5	0.0003	1.0	0.0005	0.0	0.0000	1.1	0.0005	2.7	0.0013
VB 0041	Cabbages, Head	0.5	0.01				4.5	0.0000	8.7	0.0001	0.0	0.0000	9.5	0.0001	24.1	0.0002
VC 4199	Cantaloupe	0.2					16.0	0.0032	2.0	0.0004	0.0	0.0000	2.8	0.0006	18.3	0.0037
VR 0577	Carrot	0.5					2.8	0.0014	2.5	0.0013	0.0	0.0000	6.3	0.0031	22.0	0.0110
FS 0013	Cherries	1					0.0	0.0000	0.0	0.0000	0.0	0.0000	0.0	0.0000	3.0	0.0030
VL 0467	Chinese cabbage, type "Pe-tsai"	0.05					0.1	0.0000	0.1	0.0000	0.1	0.0000	0.1	0.0000	0.1	0.0000
FC 0001	Citrus fruits	0.7					54.3	0.0380	6.3	0.0044	5.1	0.0036	54.8	0.0383	49.0	0.0343
VP 0526	Common bean (pods and/or immature seeds)	0.2					3.5	0.0007	0.8	0.0002	0.0	0.0000	4.0	0.0008	12.0	0.0024
SO 0691	Cotton seed	0.1					0.0	0.0000	0.0	0.0000	0.0	0.0000	0.0	0.0000	0.0	0.0000
VC 0424	Cucumber	0.1					4.8	0.0005	4.5	0.0005	0.0	0.0000	8.3	0.0008	9.0	0.0009
FB 0021	Currants, Black, Red, White	0.2					0.0	0.0000	0.0	0.0000	0.0	0.0000	0.0	0.0000	0.3	0.0001
VP 0529	Garden pea, shelled	0.2					5.5	0.0011	0.7	0.0001	0.0	0.0000	0.3	0.0001	14.0	0.0028

TN 0666	Hazelnuts	0.1					0.0	0.0000	0.0	0.0000	0.0	0.0000	0.1	0.0000	0.3	0.0000
VL 0480	Kale	0.05					0.5	0.0000	0.0	0.0000	0.0	0.0000	0.3	0.0000	2.0	0.0001
FI 0341	Kiwifruit	0.2					0.0	0.0000	0.0	0.0000	1.9	0.0004	0.1	0.0000	1.5	0.0003
VB 0405	Kohlrabi	0.2					0.1	0.0000	0.1	0.0000	0.1	0.0000	0.1	0.0000	0.1	0.0000
VL 0053	Leafy vegetables	0.7					3.3	0.0023	1.0	0.0007	0.0	0.0000	7.1	0.0049	27.2	0.0190
VL 0482	Lettuce, Head	0.5					2.3	0.0011	0.0	0.0000	0.0	0.0000	5.8	0.0029	22.5	0.0113
VL 0483	Lettuce, Leaf	0.5					2.3	0.0011	0.0	0.0000	0.0	0.0000	5.8	0.0029	22.5	0.0113
GC 0645	Maize	0.02			(*)		48.3	0.0010	31.2	0.0006	106.2	0.0021	41.8	0.0008	8.8	0.0002
MO 0099	Liver of cattle, goats, pigs and sheep	0.03	0.01		V		2.7	0.0000	0.9	0.0000	1.8	0.0000	4.0	0.0000	8.2	0.0001
MO 0098	Kidney of cattle, goats, pigs and sheep	0.03	0.01		V		1.4	0.0000	0.4	0.0000	0.9	0.0000	2.0	0.0000	4.1	0.0000
MM 0097	Meat of cattle, pigs and sheep	2	0.3		(fat) V		6.4	0.0019	6.3	0.0019	3.0	0.0009	8.7	0.0026	29.8	0.0089
MM 0814	Meat of goat	2	0.3		(fat) V		0.4	0.0001	0.1	0.0000	0.5	0.0001	0.2	0.0000	0.1	0.0000
ML 0106	Milks	0.02	0.02		F V		116.8	0.0023	32.0	0.0006	41.8	0.0008	160.0	0.0032	294.0	0.0059
OC 0305	Olive oil, virgin	2	2				1.5	0.0030	0.0	0.0000	0.0	0.0000	0.0	0.0000	7.8	0.0155
FT 0305	Olives	2	2				1.3	0.0025	0.0	0.0000	0.0	0.0000	0.3	0.0005	2.8	0.0055
VA 0385	Onion, bulb	0.05	0.05				23.0	0.0012	11.5	0.0006	7.3	0.0004	13.8	0.0007	27.8	0.0014
FS 0247	Peach	0.2	0.2				2.5	0.0005	0.5	0.0001	0.0	0.0000	0.8	0.0002	12.5	0.0025
SO 0697	Peanut	0.1	0.1				0.3	0.0000	0.2	0.0000	2.3	0.0002	0.3	0.0000	3.0	0.0003
TN 0672	Pecan	0.1	0.1				0.0	0.0000	0.0	0.0000	0.0	0.0000	0.0	0.0000	0.3	0.0000
VO 0445	Peppers, Sweet	0.05	0.05				3.3	0.0002	2.0	0.0001	5.3	0.0003	2.3	0.0001	10.3	0.0005
FI 0353	Pineapple	0.1	0.1				0.0	0.0000	0.8	0.0001	10.2	0.0010	3.1	0.0003	15.8	0.0016
FS 0014	Plums (including Prunes)	1	1				1.8	0.0018	0.5	0.0005	0.0	0.0000	0.0	0.0000	3.8	0.0038
FP 0009	Pome fruits	0.3	0.04				8.8	0.0004	6.3	0.0003	0.2	0.0000	5.1	0.0002	41.3	0.0017
JF 0226	Apple juice			0.001		0.00004	1.9	0.0000	1.2	0.0000	0.1	0.0000	1.4	0.0000	10.0	0.0000
VR 0589	Potato	0.01	0.01		(*)		59.0	0.0006	19.2	0.0002	20.6	0.0002	40.8	0.0004	240.8	0.0024
DF 0014	Prunes	2					0.0	0.0000	0.0	0.0000	0.0	0.0000	0.0	0.0000	0.5	0.0010
VR 0494	Radish	0.1					0.5	0.0001	0.0	0.0000	0.0	0.0000	0.3	0.0000	2.0	0.0002
FB 0272	Raspberries, Red, Black	0.2					0.0	0.0000	0.0	0.0000	0.0	0.0000	0.0	0.0000	0.5	0.0001
CM 1205	Rice, polished	0.1					48.8	0.0049	277.5	0.0278	68.8	0.0069	65.5	0.0066	9.3	0.0009
SO 0699	Safflower seed	0.1					0.0	0.0000	0.0	0.0000	0.2	0.0000	0.0	0.0000	0.0	0.0000
VL 0502	Spinach	0.5					0.5	0.0003	0.0	0.0000	0.0	0.0000	0.3	0.0001	2.0	0.0010
VA 0389	Spring onion	1					0.0	0.0000	2.0	0.0020	1.5	0.0015	4.0	0.0040	1.0	0.0010
VC 0431	Squash, Summer	0.05					10.5	0.0005	2.2	0.0001	0.0	0.0000	14.0	0.0007	3.5	0.0002

FB 0275	Strawberry	0.1					0.0	0.0000	0.0	0.0000	0.0	0.0000	0.0	0.0000	5.3	0.0005
VR 0596	Sugar beet	0.1					0.5	0.0001	0.0	0.0000	0.0	0.0000	0.3	0.0000	2.0	0.0002
SO 0702	Sunflower seed	0.1					1.0	0.0001	0.0	0.0000	0.6	0.0001	0.0	0.0000	0.0	0.0000
VO 0447	Sweet corn (corn-on-the-cob)	0.02					0.0	0.0000	0.0	0.0000	4.4	0.0001	0.0	0.0000	8.3	0.0002
VO 0448	Tomato	0.5					81.5	0.0408	7.0	0.0035	16.5	0.0083	25.5	0.0128	66.0	0.0330
TN 0678	Walnuts	0.01			(*)		0.0	0.0000	0.0	0.0000	0.0	0.0000	0.0	0.0000	0.5	0.0000
GC 0654	Wheat	0.1					327.3	0.0327	114.8	0.0115	28.3	0.0028	116.8	0.0117	178.0	0.0178
					TOTAL =			0.1463		0.0587		0.0299		0.1012		0.2189
					% ADI =			122%		49%		25%		84%		182%
					ROUNDED % ADI =			120%		50%		20%		80%		180%

DIMETHIPIN (151) **THEORETICAL MAXIMUM DAILY INTAKE (TMDI)**

ADI = 0.02 mg/kg bodyweight or 1.200 mg/person

Commodity		MRL mg/kg	Notes	Middle Eastern		Far Eastern		African		Latin American		European	
				Diet	TMDI	Diet	TMDI	Diet	TMDI	Diet	TMDI	Diet	TMDI
Code	Name			g/day	mg/day	g/day	mg/day	g/day	mg/day	g/day	mg/day	g/day	mg/day
OR 0691	Cotton seed oil, edible	0.02	(*)	3.8	0.0001	0.5	0.0000	0.5	0.0000	0.5	0.0000	0.0	0.0000
MO 0105	Edible offal (mammalian)	0.02	(*)	4.2	0.0001	1.4	0.0000	2.4	0.0000	6.1	0.0001	12.4	0.0002
PE 0112	Eggs	0.02	(*)	14.6	0.0003	13.1	0.0003	3.7	0.0001	11.9	0.0002	37.6	0.0008
MM 0095	Meat	0.02	(*)	37.0	0.0007	32.8	0.0007	23.8	0.0005	47.0	0.0009	155.5	0.0031
ML 0106	Milks	0.02	(*)	116.8	0.0023	32.0	0.0006	41.8	0.0008	160.0	0.0032	294.0	0.0059
VR 0589	Potato	0.05	(*)	59.0	0.0030	19.2	0.0010	20.6	0.0010	40.8	0.0020	240.8	0.0120
PM 0110	Poultry meat	0.02	(*)	31.0	0.0006	13.2	0.0003	5.5	0.0001	25.3	0.0005	53.0	0.0011
PO 0111	Poultry, Edible offal of	0.02	(*)	0.1	0.0000	0.1	0.0000	0.1	0.0000	0.4	0.0000	0.4	0.0000
SO 0495	Rape seed	0.1		0.0	0.0000	0.0	0.0000	0.0	0.0000	0.0	0.0000	0.0	0.0000
SO 0702	Sunflower seed	0.5		1.0	0.0005	0.0	0.0000	0.6	0.0003	0.0	0.0000	0.0	0.0000
OR 0702	Sunflower seed oil, edible	0.02	(*)	9.3	0.0002	0.5	0.0000	0.3	0.0000	0.8	0.0000	8.5	0.0002
				TOTAL =	0.009		0.003		0.003		0.007		0.024
				% ADI =	1%		0%		0%		1%		2%

DINOCAP (87) **INTERNATIONAL ESTIMATED DAILY INTAKE (IEDI)**

ADI = 0.008 mg/kg bodyweight or 0.480 mg/person

Commodity		MRL mg/kg	STMR mg/kg	Processing Factor	Notes	Adjusted STMR mg/kg	Middle Eastern		Far Eastern		African		Latin American		European	
							Diet	IEDI	Diet	IEDI	Diet	IEDI	Diet	IEDI	Diet	IEDI
Code	Name						g/day	mg/day	g/day	mg/day	g/day	mg/day	g/day	mg/day	g/day	mg/day
FP 0226	Apple	0.2	0.05				7.5	0.0004	4.7	0.0002	0.3	0.0000	5.5	0.0003	40.0	0.0020
FB 0269	Grape	1	0.11				15.8	0.0017	1.0	0.0001	0.0	0.0000	1.3	0.0001	13.8	0.0015
FB 0275	Strawberry	0.5	0.06				0.0	0.0000	0.0	0.0000	0.0	0.0000	0.0	0.0000	5.3	0.0003
FS 0247	Peach	0.1	0.05				2.5	0.0001	0.5	0.0000	0.0	0.0000	0.8	0.0000	12.5	0.0006
VO 0051	Pepper	0.2	0.06				3.4	0.0002	2.1	0.0001	5.4	0.0003	2.4	0.0001	10.4	0.0006
VC 0045	Cucurbits, fruiting vegetables	0.05	0.05		(*)		80.5	0.0040	18.2	0.0009	0.0	0.0000	30.5	0.0015	38.5	0.0019
VO 0448	Tomato	0.3	0.045				81.5	0.0037	7.0	0.0003	16.5	0.0007	25.5	0.0011	66.0	0.0030
					TOTAL =			0.0101		0.0017		0.0011		0.0033		0.0100
					ROUNDED % ADI =			2%		0%		0%		1%		2%

ETHEPHON (106) **DIETARY INTAKE ESTIMATE (DIE)**

ADI = 0.05 mg/kg bodyweight or 3.000 mg/person

Commodity		MRL mg/kg	STMR mg/kg	Processing Factor	Notes	Adjusted STMR mg/kg	Middle Eastern		Far Eastern		African		Latin American		European	
							Diet	IEDI	Diet	IEDI	Diet	IEDI	Diet	IEDI	Diet	IEDI
Code	Name						g/day	mg/day	g/day	mg/day	g/day	mg/day	g/day	mg/day	g/day	mg/day
FP 0226	Apple	5					7.5	0.0375	4.7	0.0233	0.3	0.0013	5.5	0.0275	40.0	0.2000
GC 0640	Barley	1					1.0	0.0010	3.5	0.0035	1.8	0.0018	6.5	0.0065	19.8	0.0198
FB 0020	Blueberries	20					0.0	0.0000	0.0	0.0000	0.0	0.0000	0.0	0.0000	0.5	0.0100

VC 4199	Cantaloupe	1	0.24				16.0	0.0038	2.0	0.0005	0.0	0.0000	2.8	0.0007	18.3	0.0044
FS 0013	Cherries	10					0.0	0.0000	0.0	0.0000	0.0	0.0000	0.0	0.0000	3.0	0.0300
PE 0840	Chicken eggs	0.2	0.2		(*)		14.5	0.0029	13.0	0.0026	3.6	0.0007	11.8	0.0024	37.5	0.0075
SO 0691	Cotton seed	2					0.0	0.0000	0.0	0.0000	0.0	0.0000	0.0	0.0000	0.0	0.0000
DF 0297	Fig, dried	10					0.5	0.0050	0.0	0.0000	0.0	0.0000	0.0	0.0000	0.0	0.0000
FB 0269	Grapes	1	0.31				15.5	0.0048	1.0	0.0003	0.0	0.0000	1.0	0.0003	11.5	0.0036
DF 0269	Dried grapes	5	0.84				0.3	0.0002	0.0	0.0000	0.0	0.0000	0.3	0.0002	2.3	0.0019
TN 0666	Hazelnuts	0.2					0.0	0.0000	0.0	0.0000	0.0	0.0000	0.1	0.0000	0.3	0.0001
MM 0096	Meat of cattle, goats, horses, pigs, sheep	0.1			(*)		34.0	0.0034	32.0	0.0032	17.5	0.0018	44.3	0.0044	150.3	0.0150
ML 0107	Milk of cattle, goats, sheep	0.05			(*)		114.5	0.0057	32.0	0.0016	41.3	0.0021	160.0	0.0080	294.0	0.0147
MO 0096	Offal of cattle, goats, horses, pigs, sheep	0.2			(*)		4.1	0.0008	1.3	0.0003	2.7	0.0005	6.0	0.0012	12.3	0.0025
VO 0051	Peppers	5	0.98				3.4	0.0033	2.1	0.0021	5.4	0.0053	2.4	0.0024	10.4	0.0102
PM 0110	Poultry meat	0.1			(*)		31.0	0.0031	13.2	0.0013	5.5	0.0006	25.3	0.0025	53.0	0.0053
PO 0111	Poultry, edible offal of	0.2			(*)		0.1	0.0000	0.1	0.0000	0.1	0.0000	0.4	0.0001	0.4	0.0001
FI 0353	Pineapple	2	0.13				0.0	0.0000	0.8	0.0001	10.2	0.0013	3.1	0.0004	15.8	0.0020
GC 0650	Rye	1					0.0	0.0000	1.0	0.0010	0.0	0.0000	0.0	0.0000	1.5	0.0015
VO 0448	Tomato	2	0.41				44.1	0.0181	5.7	0.0023	14.6	0.0060	25.5	0.0105	38.2	0.0157
VJ 0448	Tomato juice			0.34		0.14	0.3	0.0000	0.0	0.0000	0.0	0.0000	0.0	0.0000	2.0	0.0003
	Tomato paste			0.75		0.31	5.8	0.0018	0.2	0.0001	0.3	0.0001	0.0	0.0000	4.0	0.0012
GC 0654	Wheat	1					327.3	0.3273	114.8	0.1148	28.3	0.0283	116.8	0.1168	178.0	0.1780
TN 0678	Walnuts	0.5					0.0	0.0000	0.0	0.0000	0.0	0.0000	0.0	0.0000	0.5	0.0003
						TOTAL =		0.4508		0.1610		0.0496		0.1892		0.5605
						% ADI =		15%		5%		2%		6%		19%
						ROUNDED % ADI =		20%		5%		2%		6%		20%

ETHOPROPHOS (149) **THEORETICAL MAXIMUM DAILY INTAKE (TMDI)**

ADI = 0.0004 mg/kg bodyweight or 0.024 mg/person

Commodity		MRL mg/kg	Note	Middle Eastern		Far Eastern		African		Latin American		European	
				et	TMDI	Diet	TMDI	Diet	TMDI	Diet	TMDI	Diet	TMDI
Code	Name			g/day	mg/day	g/day	mg/day	g/day	mg/day	g/day	mg/day	g/day	mg/day
FI 0327	Banana	0.02	(*)	83	0.0002	26.2	0.0005	21.0	0.0004	102.3	0.0020	22.8	0.0005
VR 0574	Beetroot	0.02	(*)	0.5	0.0000	0.0	0.0000	0.0	0.0000	0.3	0.0000	2.0	0.0000
VB 0041	Cabbages, Head	0.02	(*)	5.0	0.0001	9.7	0.0002	0.0	0.0000	10.5	0.0002	26.8	0.0005
VC 0424	Cucumber	0.02	(*)	2.4	0.0000	2.3	0.0000	0.0	0.0000	4.1	0.0001	4.5	0.0001
VC 0425	Gherkin	0.02	(*)	2.4	0.0000	2.3	0.0000	0.0	0.0000	4.1	0.0001	4.5	0.0001
FB 0269	Grapes	0.02	(*)	15.8	0.0003	1.0	0.0000	0.0	0.0000	1.3	0.0000	13.8	0.0003
VL 0482	Lettuce, Head	0.02	(*)	2.3	0.0000	0.0	0.0000	0.0	0.0000	5.8	0.0001	22.5	0.0005
GC 0645	Maize	0.02	(*)	48.3	0.0010	31.2	0.0006	106.2	0.0021	41.8	0.0008	8.8	0.0002
VC 0046	Melons, except Watermelon	0.02	(*)	16.0	0.0003	2.0	0.0000	0.0	0.0000	2.8	0.0001	18.3	0.0004
VA 0385	Onion, bulb	0.02	(*)	23.0	0.0005	11.5	0.0002	7.3	0.0001	13.8	0.0003	27.8	0.0006
SO 0697	Peanut	0.02	(*)	0.3	0.0000	0.2	0.0000	2.3	0.0000	0.3	0.0000	3.0	0.0001
VP 0063	Peas	0.02	(*)	5.5	0.0001	0.7	0.0000	0.0	0.0000	0.3	0.0000	14.0	0.0003
VO 0051	Peppers	0.02	(*)	3.4	0.0001	2.1	0.0000	5.4	0.0001	2.4	0.0000	10.4	0.0002
FI 0353	Pineapple	0.02	(*)	0.0	0.0000	0.8	0.0000	10.2	0.0002	3.1	0.0001	15.8	0.0003
VR 0589	Potato	0.02	(*)	59.0	0.0012	19.2	0.0004	20.6	0.0004	40.8	0.0008	240.8	0.0048
VD 0541	Soya bean (dry)	0.02	(*)	4.5	0.0001	2.0	0.0000	0.5	0.0000	0.0	0.0000	0.0	0.0000
FB 0275	Strawberry	0.02	(*)	0.0	0.0000	0.0	0.0000	0.0	0.0000	0.0	0.0000	5.3	0.0001
GS 0659	Sugar cane	0.02	(*)	18.5	0.0004	7.3	0.0001	15.9	0.0003	3.5	0.0001	0.0	0.0000
VR 0508	Sweet potato	0.02	(*)	1.5	0.0000	81.3	0.0016	14.3	0.0003	13.8	0.0003	1.3	0.0000
VO 0448	Tomato	0.02	(*)	81.5	0.0016	7.0	0.0001	16.5	0.0003	25.5	0.0005	66.0	0.0013
VR 0506	Turnip, Garden	0.02	(*)	0.5	0.0000	0.0	0.0000	0.0	0.0000	0.3	0.0000	2.0	0.0000
				TOTAL =	0.0060		0.0041		0.0044		0.0055		0.0102
				% ADI =	20%		20%		20%		20%		40%

ETHOXYQUIN (35) **THEORETICAL MAXIMUM DAILY INTAKE (TMDI)**

ADI = 0.005 mg/kg bodyweight or 0.300 mg/person

Commodity		MRL mg/kg	Notes	Middle Eastern		Far Eastern		African		Latin American		European	
Code	Name			Diet g/day	TMDI mg/day	Diet g/day	TMDI mg/day	Diet g/day	TMDI mg/day	Diet g/day	TMDI mg/day	Diet g/day	TMDI mg/day
FP 0226	Apple	3		7.5	0.0225	4.7	0.0140	0.3	0.0008	5.5	0.0165	40.0	0.1200
				TOTAL =	0.0225		0.0140		0.0008		0.0165		0.1200
				% ADI =	8%		5%		0%		6%		40%
			Rounded % ADI =		8%		5%		0%		6%		40%

FENAMIPHOS (85) **INTERNATIONAL ESTIMATED DIETARY INTAKE (IEDI)**

ADI = 0.0008 mg/kg bodyweight or 0.048 mg/person

Commodity		MRL mg/kg	STMR mg/kg	Processing Factor	Notes	Adjusted STMR mg/kg	Middle Eastern		Far Eastern		African		Latin American		European	
Code	Name						Diet g/day	IEDI mg/day	Diet g/day	IEDI mg/day	Diet g/day	IEDI mg/day	Diet g/day	IEDI mg/day	Diet g/day	IEDI mg/day
FP 0226	Apple	0.05	0.01				7.5	0.0001	4.7	0.0000	0.3	0.0000	5.5	0.0001	40.0	0.0004
JF 0226	Apple juice		0.01	0.78		0.008	0.1	0.0000	0.1	0.0000	0.1	0.0000	0.1	0.0000	0.1	0.0000
FI 0327	Banana	0.05	0.02		(*)		8.3	0.0002	26.2	0.0005	21.0	0.0004	102.3	0.0020	22.8	0.0005
VB 0402	Brussels sprouts	0.05	0.01				0.5	0.0000	1.0	0.0000	0.0	0.0000	1.1	0.0000	2.7	0.0000
VB 0041	Cabbages, Head	0.05	0.01				4.5	0.0000	8.7	0.0001	0.0	0.0000	9.5	0.0001	24.1	0.0002
VR 0577	Carrot	0.2	0.02				2.8	0.0001	2.5	0.0001	0.0	0.0000	6.3	0.0001	22.0	0.0004
OC 0691	Cotton seed oil, crude	0.05	0.01				3.8	0.0000	0.5	0.0000	0.5	0.0000	0.5	0.0000	0.0	0.0000
MO 0105	Edible offal (mammalian)	0.01	0		(*)		4.2	0.0000	1.4	0.0000	2.4	0.0000	6.1	0.0000	12.4	0.0000
PE 0112	Eggs	0.01	0		(*)		14.6	0.0000	13.1	0.0000	3.7	0.0000	11.9	0.0000	37.6	0.0000
FB 0269	Grapes	0.1	0.02				15.8	0.0003	1.0	0.0000	0.0	0.0000	1.3	0.0000	13.8	0.0003
MM 0095	Meat (mammalian)	0.01	0		(*)		37.0	0.0000	32.8	0.0000	23.8	0.0000	47.0	0.0000	155.5	0.0000
VC 0046	Melons, except Watermelon	0.05	0.02		(*)		16.0	0.0003	2.0	0.0000	0.0	0.0000	2.8	0.0001	18.3	0.0004

ML 0106	Milks	0.005	0		(*)		116.8	0.0000	32.0	0.0000	41.8	0.0000	160.0	0.0000	294.0	0.0000
SO 0697	Peanut	0.05	0		(*)		0.3	0.0000	0.2	0.0000	2.3	0.0000	0.3	0.0000	3.0	0.0000
OC 0697	Peanut oil, crude	0.05	0		(*)		0.0	0.0000	1.8	0.0000	3.5	0.0000	0.5	0.0000	1.8	0.0000
VO 0051	Peppers	0.5	0.055				3.4	0.0002	2.1	0.0001	5.4	0.0003	2.4	0.0001	10.4	0.0006
FI 0353	Pineapple	0.05	0.01		(*)		0.0	0.0000	0.8	0.0000	10.2	0.0001	3.1	0.0000	15.8	0.0002
PO 0111	Poultry, edible offal of	0.01	0		(*)		0.1	0.0000	0.1	0.0000	0.1	0.0000	0.4	0.0000	0.4	0.0000
PM 0110	Poultry meat	0.01	0		(*)		31.0	0.0000	13.2	0.0000	5.5	0.0000	25.3	0.0000	53.0	0.0000
VO 0448	Tomato	0.5	0.05				81.2	0.0041	7.0	0.0004	16.5	0.0008	25.5	0.0013	63.9	0.0032
VJ 0448	Tomato juice			0.6		0.03	0.3	0.0000	0.0	0.0000	0.0	0.0000	0.0	0.0000	2.0	0.0001
VC 0432	Watermelon	0.05	0.02		(*)		49.3	0.0010	9.5	0.0002	0.0	0.0000	5.5	0.0001	7.8	0.0002
						TOTAL =		0.0063		0.0014		0.0017		0.0040		0.0065
						% ADI =		13%		3%		3%		8%		14%
						ROUNDED % ADI =		10%		3%		3%		8%		10%

FENPROPIMORPH (188) **DIETARY INTAKE ESTIMATE (DIE)**

ADI = 0.003 mg/kg bodyweight or 0.180 mg/person

Commodity		MRL mg/kg	STMR mg/kg	Processing Factor	Notes	Adjusted STMR mg/kg	Middle Eastern		Far Eastern		African		Latin American		European	
							Diet g/day	IEDI mg/day	Diet g/day	IEDI mg/day	Diet g/day	IEDI mg/day	Diet g/day	IEDI mg/day	Diet g/day	IEDI mg/day
Code	Name															
FI 0327	Banana	2	0.11				8.3	0.0009	26.2	0.0029	21.0	0.0023	102.3	0.0112	22.8	0.0025
GC 0640	Barley	0.5					1.0	0.0005	3.5	0.0018	1.8	0.0009	6.5	0.0033	19.8	0.0099
PE 0112	Eggs	0.01	0		(*)		14.6	0.0000	13.1	0.0000	3.7	0.0000	11.9	0.0000	37.6	0.0000
MO 0098	Kidney of cattle, goats, pigs and sheep	0.05	0.026				1.4	0.0000	0.4	0.0000	0.8	0.0000	2.0	0.0001	4.1	0.0001
MO 0099	Liver of cattle, goats, pigs and sheep	0.3	0.22				2.8	0.0006	1.0	0.0002	1.6	0.0004	4.1	0.0009	8.3	0.0018
MF 0100	Mammalian fats (except milk fats)	0.01	0.006				0.7	0.0000	1.7	0.0000	0.7	0.0000	4.4	0.0000	7.7	0.0000

MM 0095	Meat, mammalian except marine	0.02	0.009				37.0	0.0003	32.8	0.0003	23.8	0.0002	47.0	0.0004	155.5	0.0014
ML 0106	Milks	0.01	0.004				116.8	0.0005	32.0	0.0001	41.8	0.0002	160.0	0.0006	294.0	0.0012
GC 0647	Oat	0.5					0.0	0.0000	0.0	0.0000	0.2	0.0001	0.8	0.0004	2.0	0.0010
GC 0650	Rye	0.5					0.0	0.0000	1.0	0.0005	0.0	0.0000	0.0	0.0000	1.5	0.0008
VR 0596	Sugar beet	0.05			(*)		0.5	0.0000	0.0	0.0000	0.0	0.0000	0.3	0.0000	2.0	0.0001
GC 0654	Wheat	0.5					327.3	0.1636	114.8	0.0574	28.3	0.0142	116.8	0.0584	178.0	0.0890
						TOTAL =		0.1665		0.0632		0.0182		0.0753		0.1078
						% ADI =		93%		35%		10%		42%		60%
						ROUNDED % ADI=		90%		40%		10%		40%		60%

FENPYROXIMATE (193) INTERNATIONAL ESTIMATED DAILY INTAKE (IEDI)

ADI =0.01 mg/kg bodyweight or 0.600 mg/person

Commodity		MRL mg/kg	STMR mg/kg	Processing Factor	Notes	Adjusted STMR mg/kg	Middle Eastern		Far Eastern		African		Latin American		European	
							Diet	IEDI	Diet	IEDI	Diet	IEDI	Diet	IEDI	Diet	IEDI
Code	Name						g/day	mg/day	g/day	mg/day	g/day	mg/day	g/day	mg/day	g/day	mg/day
FP 0226	Apple	0.3	0.09				5.6	0.0005	3.5	0.0003	0.2	0.0000	4.1	0.0004	30.0	0.0027
JF 0226	Apple juice		0.09	0.44		0.04	1.9	0.0001	1.2	0.0000	0.1	0.0000	1.4	0.0001	10.0	0.0004
FC 0004	Oranges	0.2	0.01				31.5	0.0003	4.0	0.0000	4.8	0.0000	31.0	0.0003	29.8	0.0003
FB 0269	Grapes	1	0.07				15.8	0.0011	1.0	0.0001	0.0	0.0000	1.3	0.0001	13.8	0.0010
DH 1100	Hops	10	4.4				0.1	0.0004	0.1	0.0004	0.1	0.0004	0.1	0.0004	0.1	0.0004
ML 0812	Cattle milk	0.005	0.002		(*) F		79.5	0.0002	23.2	0.0000	35.8	0.0001	159.3	0.0003	287.0	0.0006
MM 0812	Cattle meat	0.02	0.01		(fat)		18.5	0.0002	3.5	0.0000	10.4	0.0001	30.0	0.0003	63.3	0.0006
MO 1280	Cattle kidney	0.01	0		(*)		0.1	0.0000	0.0	0.0000	0.1	0.0000	0.2	0.0000	0.2	0.0000
MO 1281	Cattle liver	0.01	0		(*)		0.2	0.0000	0.0	0.0000	0.1	0.0000	0.3	0.0000	0.4	0.0000
						TOTAL =		0.0028		0.0010		0.0007		0.0019		0.0060
						% ADI =		0%		0%		0%		0%		1%

FOLPET (41) **INTERNATIONAL ESTIMATED DAILY INTAKE (IEDI)**

ADI = 0.1 mg/kg bodyweight or 6.000 mg/person

Commodity		MRL mg/kg	STMR mg/kg	Processing Factor	Notes	Adjusted STMR mg/kg	Middle Eastern		Far Eastern		African		Latin American		European	
							Diet	IEDI	Diet	IEDI	Diet	IEDI	Diet	IEDI	Diet	IEDI
Code	Name						g/day	mg/day	g/day	mg/day	g/day	mg/day	g/day	mg/day	g/day	mg/day
FP 0226	Apple	10	3.1				5.6	0.0174	3.5	0.0109	0.2	0.0006	3.1	0.0096	30.0	0.0930
JF 0226	Apple juice			0.035		0.11	1.9	0.0002	1.2	0.0001	0.1	0.0000	1.4	0.0002	10.0	0.0011
VC 0424	Cucumber	1	0.36				4.8	0.0017	4.5	0.0016	0.0	0.0000	8.3	0.0030	9.0	0.0032
FB 0269	Grapes	10	2.5				15.5	0.0388	1.0	0.0025	0.0	0.0000	1.0	0.0025	11.5	0.0288
DF 0269	Grapes, dried (incl. currants, raisins & sultanas)	40	8				0.3	0.0020	0.0	0.0000	0.0	0.0000	0.3	0.0020	2.3	0.0180
VL 0482	Lettuce, Head	50	14				2.3	0.0315	0.0	0.0000	0.0	0.0000	5.8	0.0805	22.5	0.3150
VC 0046	Melons, except watermelon	3	0.405				16.0	0.0065	2.0	0.0008	0.0	0.0000	2.8	0.0011	18.3	0.0074
VA 0385	Onion, Bulb	1	0.07				23.0	0.0016	11.5	0.0008	7.3	0.0005	13.8	0.0010	27.8	0.0019
VR 0589	Potato	0.1	0.01				59.0	0.0006	19.2	0.0002	20.6	0.0002	40.8	0.0004	240.8	0.0024
FB 0275	Strawberry	5	1.6				0.0	0.0000	0.0	0.0000	0.0	0.0000	0.0	0.0000	5.3	0.0084
VO 0448	Tomato	3	0.9				44.1	0.0397	5.7	0.0051	14.6	0.0131	25.5	0.0230	38.2	0.0344
	Tomato paste			0.028		0.0252	5.8	0.0001	0.2	0.0000	0.3	0.0000	0.0	0.0000	4.0	0.0001
	Tomato puree			0.028		0.0252	0.3	0.0000	0.0	0.0000	0.0	0.0000	0.0	0.0000	2.0	0.0001
						TOTAL =		0.1400		0.0220		0.0145		0.1232		0.5138
						% ADI =		2%		0%		0%		2%		9%

GLUFOSINATE-AMMONIUM (175) **DIETARY INTAKE ESTIMATE (DIE)**

ADI = 0.02 mg/kg bodyweight or 1.200 mg/person

Commodity		MRL mg/kg	STMR mg/kg	Processing Factor	Notes	Adjusted STMR mg/kg	Middle Eastern		Far Eastern		African		Latin American		European	
							Diet g/day	IEDI mg/day	Diet g/day	IEDI mg/day	Diet g/day	IEDI mg/day	Diet g/day	IEDI mg/day	Diet g/day	IEDI mg/day
Code	Name															
VS 0621	Asparagus	0.05			(*)		0.0	0.0000	0.0	0.0000	0.0	0.0000	0.0	0.0000	1.5	0.0001
FI 0030	Assorted tropical & subtropical fruits - inedible peel (except Banana))	0.05	0.05		(*)		2.3	0.0001	34.1	0.0017	11.0	0.0006	45.6	0.0023	10.3	0.0005
FI 0327	Banana	0.2					8.3	0.0017	26.2	0.0052	21.0	0.0042	102.3	0.0205	22.8	0.0046
FB 0018	Berries and other small fruits	0.1					0.0	0.0000	16.0	0.0016	1.0	0.0001	0.0	0.0000	1.5	0.0002
VD 0523	Broad bean (dry)	2					4.5	0.0090	2.0	0.0040	0.0	0.0000	0.5	0.0010	0.8	0.0015
VR 0577	Carrot	0.05			(*)		2.8	0.0001	2.5	0.0001	0.0	0.0000	6.3	0.0003	22.0	0.0011
FC 0001	Citrus fruits	0.1					54.3	0.0054	6.3	0.0006	5.1	0.0005	54.8	0.0055	49.0	0.0049
VD 0526	Common bean (dry)	2					0.1	0.0002	0.1	0.0002	0.1	0.0002	0.1	0.0002	0.1	0.0002
VP 0526	Common bean (pods and/ or immature seeds)	0.05			(*)		3.5	0.0002	0.8	0.0000	0.0	0.0000	4.0	0.0002	12.0	0.0006
VL 0470	Corn salad	0.05			(*)		0.1	0.0000	0.1	0.0000	0.1	0.0000	0.1	0.0000	0.1	0.0000
FB 0021	Currant, Black, Red, White	0.5					0.0	0.0000	0.0	0.0000	0.0	0.0000	0.0	0.0000	0.3	0.0002
MO 0105	Edible offal, mammalian	0.1	0.00		(*)		4.2	0.0000	1.4	0.0000	2.4	0.0000	6.1	0.0000	12.4	0.0000
PE 0112	Eggs	0.05	0.05		(*)		14.6	0.0000	13.1	0.0000	3.7	0.0000	11.9	0.0000	37.6	0.0000
GC 0645	Maize	0.1					48.3	0.0048	31.2	0.0031	106.2	0.0106	41.8	0.0042	8.8	0.0009
MM 0095	Meat (from mammals other than marine mammals)	0.05	0.00		(*)		37.0	0.0000	32.8	0.0000	23.8	0.0000	47.0	0.0000	155.5	0.0000
ML 0106	Milks	0.02	0.00		(*)		116.8	0.0000	32.0	0.0000	41.8	0.0000	160.0	0.0000	294.0	0.0000
PM 0110	Poultry meat	0.05	0.05		(*)		31.0	0.0000	13.2	0.0000	5.5	0.0000	25.3	0.0000	53.0	0.0000
PO 0111	Poultry, Edible offal of	0.1	0.1		(*)		0.1	0.0000	0.1	0.0000	0.1	0.0000	0.4	0.0000	0.4	0.0000
VA 0385	Onion, bulb	0.05					23.0	0.0012	11.5	0.0006	7.3	0.0004	13.8	0.0007	27.8	0.0014
VD 0072	Peas (dry)	3					0.5	0.0015	1.7	0.0050	0.0	0.0000	1.3	0.0038	1.8	0.0053
FP 0009	Pome fruits	0.05			(*)		10.8	0.0005	7.5	0.0004	0.3	0.0000	6.5	0.0003	51.3	0.0026
VR 0589	Potato	0.5					59.0	0.0295	19.2	0.0096	20.6	0.0103	40.8	0.0204	240.8	0.1204

SO 0495	Rape seed	5					0.0	0.0000	0.0	0.0000	0.0	0.0000	0.0	0.0000	0.0	0.0000
VR 0596	Sugar beet	0.05			(*)		0.5	0.0000	0.0	0.0000	0.0	0.0000	0.3	0.0000	2.0	0.0001
VD 0541	Soya bean (dry)	2	0.87				4.5	0.0039	2.0	0.0017	0.5	0.0004	0.0	0.0000	0.0	0.0000
FS 0012	Stone fruits	0.05			(*)		7.3	0.0004	1.0	0.0001	0.0	0.0000	0.8	0.0000	22.8	0.0011
SO 0702	Sunflower seed	5					1.0	0.0050	0.0	0.0000	0.6	0.0029	0.0	0.0000	0.0	0.0000
OC 0702	Sunflower seed oil, crude	0.05			(*)		9.3	0.0005	0.5	0.0000	0.3	0.0000	0.8	0.0000	8.5	0.0004
TN 0085	Tree nuts	0.1	0.05				1.0	0.0001	13.5	0.0007	3.4	0.0002	17.5	0.0009	3.8	0.0002
					TOTAL =			0.0640		0.0347		0.0304		0.0602		0.1461
					% ADI =			5%		3%		3%		5%		12%
					ROUNDED % ADI =			5%		3%		3%		5%		10%

MALATHION (49) INTERNATIONAL ESTIMATED DAILY INTAKE (IEDI)

ADI = 0.3 mg/kg bodyweight or 18.000 mg/person

Commodity		MRL mg/kg	STMR mg/kg	Processing Factor	Notes	Adjusted STMR mg/kg	Middle Eastern		Far Eastern		African		Latin American		European	
Code	Name						Diet g/day	IEDI mg/day	Diet g/da y	IEDI mg/day	Diet g/day	IEDI mg/day	Diet g/day	IEDI mg/day	Diet g/day	IEDI mg/day
VS 0621	Asparagus	1	0.305	1		0.305	0.0	0.0000	0.0	0.0000	0.0	0.0000	0.0	0.0000	1.5	0.0005
VD 0071	Beans (dry)	2	0.36	1		0.36	6.8	0.0024	6.8	0.0024	0.0	0.0000	13.5	0.0049	4.3	0.0015
VP 0061	Beans, except broad and soya beans	1	0.31	1		0.31	0.1	0.0000	0.1	0.0000	0.1	0.0000	0.1	0.0000	0.1	0.0000
FB 0020	Blueberries	10	2.27	1		2.27	0.0	0.0000	0.0	0.0000	0.0	0.0000	0.0	0.0000	0.5	0.0011
OR 0691	Cotton seed oil, refined	13	3.06	1		3.06	3.8	0.0115	0.5	0.0015	0.5	0.0015	0.5	0.0015	0.0	0.0000
VC 0424	Cucumber	0.2	0.02	1		0.02	4.8	0.0001	4.5	0.0001	0.0	0.0000	8.3	0.0002	9.0	0.0002
GC 0645	Maize	0.05	0.01	1		0.01	48.3	0.0005	31.2	0.0003	106.2	0.0011	41.8	0.0004	8.8	0.0001
VL 0485	Mustard green	2	0.07	1		0.07	0.1	0.0000	0.1	0.0000	0.1	0.0000	0.1	0.0000	0.1	0.0000
VA 0385	Onion, bulb	1	0.23	1		0.23	23.0	0.0053	11.5	0.0026	7.3	0.0017	13.8	0.0032	27.8	0.0064
VA 0388	Onion, green	5	0.52	1		0.52	0.0	0.0000	2.0	0.0010	1.5	0.0008	4.0	0.0021	1.0	0.0005

VO 0051	Peppers	0.1	0.01	1		0.01	3.4	0.0000	2.1	0.0000	5.4	0.0001	2.4	0.0000	10.4	0.0001
VL 0502	Spinach	3	0.35	1		0.35	0.5	0.0002	0.0	0.0000	0.0	0.0000	0.3	0.0001	2.0	0.0007
FB 0275	Strawberry	1	0.25	1		0.25	0.0	0.0000	0.0	0.0000	0.0	0.0000	0.0	0.0000	5.3	0.0013
VO 0447	Sweet corn	0.02	0.01	1		0.01	0.0	0.0000	0.0	0.0000	4.4	0.0000	0.0	0.0000	8.3	0.0001
GC 0651	Sorghum	3	0.235	1		0.235	2.0	0.0005	9.7	0.0023	26.6	0.0062	0.0	0.0000	0.0	0.0000
VO 0448	Tomato	0.5	0.21	1		0.21	44.1	0.0093	5.7	0.0012	14.6	0.0031	25.5	0.0054	38.2	0.0080
VJ 0448	Tomato, juice	0.01	0	1		0	0.3	0.0000	0.0	0.0000	0.0	0.0000	0.0	0.0000	2.0	0.0000
	Tomato, puree		0.21	0.334		0.0701	0.3	0.0000	0.0	0.0000	0.0	0.0000	0.0	0.0000	2.0	0.0001
VR 0506	Turnip, Garden	0.2	0.05	1		0.05	0.5	0.0000	0.0	0.0000	0.0	0.0000	0.3	0.0000	2.0	0.0001
GC 0654	Wheat	0.5	0.04	1		0.04	327.3	0.0131	114.8	0.0046	28.3	0.0011	116.8	0.0047	178.0	0.0071
							TOTAL =	0.0429		0.0162		0.0156		0.0224		0.0279
							% ADI =	0%		0%		0%		0%		0%

PERMETHRIN (120) THEORETICAL MAXIMUM DAILY INTAKE (TMDI)

ADI = 0.05 mg/kg bodyweight or 3.000 mg/person

Commodity		MRL mg/kg	Notes	Middle Eastern		Far Eastern		African		Latin American		European	
				Diet	TMDI	Diet	TMDI	Diet	TMDI	Diet	TMDI	Diet	TMDI
Code	Name			g/day	mg/day	g/day	mg/day	g/day	mg/day	g/day	mg/day	g/day	mg/day
TN 0660	Almonds	0.1		0.5	0.0001	0.0	0.0000	0.0	0.0000	0.1	0.0000	1.8	0.0002
VS 0621	Asparagus	1		0.0	0.0000	0.0	0.0000	0.0	0.0000	0.0	0.0000	1.5	0.0015
VD 0071	Beans (dry)	0.1		6.8	0.0007	6.8	0.0007	0.0	0.0000	13.5	0.0014	4.3	0.0004
FB 0264	Blackberries	1		0.0	0.0000	0.0	0.0000	0.0	0.0000	0.0	0.0000	0.0	0.0000
VB 0400	Broccoli	2		0.5	0.0010	1.0	0.0019	0.0	0.0000	1.1	0.0021	2.7	0.0054
VB 0402	Brussels sprouts	1		0.5	0.0005	1.0	0.0010	0.0	0.0000	1.1	0.0011	2.7	0.0027
VB 0041	Cabbages, Head	5		4.0	0.0200	7.7	0.0387	0.0	0.0000	8.4	0.0420	21.4	0.1070
VB 0403	Cabbage, Savoy	5		0.1	0.0005	0.1	0.0005	0.1	0.0005	0.1	0.0005	0.1	0.0005
VR 0577	Carrot	0.1		2.8	0.0003	2.5	0.0003	0.0	0.0000	6.3	0.0006	22.0	0.0022

VB 0404	Cauliflower	0.5		1.3	0.0006	1.5	0.0008	0.0	0.0000	0.3	0.0001	13.0	0.0065
VS 0624	Celery	2		0.5	0.0010	0.0	0.0000	0.0	0.0000	0.3	0.0005	2.0	0.0040
GC 0080	Cereal grains	2	Po	106.6	0.2131	338.0	0.6759	290.1	0.5802	137.7	0.2754	49.3	0.0986
VL 0467	Chinese cabbage, type "Pe-tsai"	5		0.1	0.0005	0.1	0.0005	0.1	0.0005	0.1	0.0005	0.1	0.0005
FC 0001	Citrus fruits	0.5		54.3	0.0271	6.3	0.0032	5.1	0.0025	54.8	0.0274	49.0	0.0245
SB 0716	Coffee beans	0.05	(*)	5.3	0.0003	0.4	0.0000	0.0	0.0000	3.6	0.0002	7.9	0.0004
VP 0526	Common bean (pods and/or immature seeds)	1		3.5	0.0035	0.8	0.0008	0.0	0.0000	4.0	0.0040	12.0	0.0120
SO 0691	Cotton seed	0.5		0.0	0.0000	0.0	0.0000	0.0	0.0000	0.0	0.0000	0.0	0.0000
OR 0691	Cotton seed oil, edible	0.1		3.8	0.0004	0.5	0.0001	0.5	0.0001	0.5	0.0001	0.0	0.0000
VC 0424	Cucumber	0.5		2.4	0.0012	2.3	0.0011	0.0	0.0000	4.1	0.0021	4.5	0.0023
FB 0021	Currants, Black, Red, White	2		0.0	0.0000	0.0	0.0000	0.0	0.0000	0.0	0.0000	0.3	0.0006
FB 0266	Dewberries	1		0.0	0.0000	0.0	0.0000	0.0	0.0000	0.0	0.0000	0.0	0.0000
MO 0105	Edible offal (mammalian)	0.1	V	4.2	0.0004	1.4	0.0001	2.4	0.0002	6.1	0.0006	12.4	0.0012
VO 0440	Egg plant	1		6.3	0.0063	3.0	0.0030	0.7	0.0007	6.0	0.0060	2.3	0.0023
PE 0112	Eggs	0.1		14.6	0.0015	13.1	0.0013	3.7	0.0004	11.9	0.0012	37.6	0.0038
VC 0425	Gherkin	0.5		2.4	0.0012	2.3	0.0011	0.0	0.0000	4.1	0.0021	4.5	0.0023
FB 0268	Gooseberry	2		0.0	0.0000	0.0	0.0000	0.0	0.0000	0.0	0.0000	0.5	0.0010
FB 0269	Grapes	2		15.8	0.0315	1.0	0.0020	0.0	0.0000	1.3	0.0025	13.8	0.0275
DH 01100	Hops, dry	50		0.1	0.0050	0.1	0.0050	0.1	0.0050	0.1	0.0050	0.1	0.0050
VR 0583	Horseradish	0.5		0.5	0.0003	0.7	0.0003	0.0	0.0000	0.3	0.0001	0.0	0.0000
VL 0480	Kale	5		0.5	0.0025	0.0	0.0000	0.0	0.0000	0.3	0.0013	2.0	0.0100
FI 0341	Kiwifruit	2		0.0	0.0000	0.0	0.0000	1.9	0.0039	0.1	0.0002	1.5	0.0030
VB 0405	Kohlrabi	0.1		0.1	0.0000	0.1	0.0000	0.1	0.0000	0.1	0.0000	0.1	0.0000
VA 0384	Leek	0.5		0.5	0.0003	0.0	0.0000	0.0	0.0000	0.3	0.0001	2.0	0.0010
VL 0482	Lettuce, Head	2		2.3	0.0045	0.0	0.0000	0.0	0.0000	5.8	0.0115	22.5	0.0450
MM 0095	Meat	1	(fat) V	37.0	0.0370	32.8	0.0328	23.8	0.0238	47.0	0.0470	155.5	0.1555
VC 0046	Melons, except Watermelon	0.1		16.0	0.0016	2.0	0.0002	0.0	0.0000	2.8	0.0003	18.3	0.0018
ML 0106	Milks	0.1	F	116.8	0.0117	32.0	0.0032	41.8	0.0042	160.0	0.0160	294.0	0.0294
VO 0450	Mushrooms	0.1		0.3	0.0000	0.5	0.0001	0.0	0.0000	0.0	0.0000	4.0	0.0004
FT 0305	Olives	1		1.3	0.0013	0.0	0.0000	0.0	0.0000	0.3	0.0003	2.8	0.0028
SO 0697	Peanut	0.1		0.3	0.0000	0.2	0.0000	2.3	0.0002	0.3	0.0000	3.0	0.0003
VP 0064	Peas, shelled	0.1		4.0	0.0004	0.5	0.0001	0.0	0.0000	0.2	0.0000	10.1	0.0010
VO 0051	Peppers	1		3.4	0.0034	2.1	0.0021	5.4	0.0054	2.4	0.0024	10.4	0.0104
TN 0675	Pistachio nuts	0.05	(*)	0.3	0.0000	0.0	0.0000	0.0	0.0000	0.0	0.0000	0.0	0.0000

FP 0009	Pome fruits	2		10.8	0.0215	7.5	0.0150	0.3	0.0005	6.5	0.0130	51.3	0.1026
VR 0589	Potato	0.05	(*)	59.0	0.0030	19.2	0.0010	20.6	0.0010	40.8	0.0020	240.8	0.0120
PM 0110	Poultry meat	0.1		31.0	0.0031	13.2	0.0013	5.5	0.0006	25.3	0.0025	53.0	0.0053
VR 0591	Radish, Japanese	0.1		0.5	0.0001	0.7	0.0001	0.0	0.0000	0.3	0.0000	0.0	0.0000
SO 0495	Rape seed	0.05	(*)	0.0	0.0000	0.0	0.0000	0.0	0.0000	0.0	0.0000	0.0	0.0000
FB 0272	Raspberries, Red, Black	1		0.0	0.0000	0.0	0.0000	0.0	0.0000	0.0	0.0000	0.5	0.0005
OC 0541	Soya bean oil, crude	0.1		1.3	0.0001	1.7	0.0002	3.0	0.0003	14.5	0.0015	4.3	0.0004
VD 0541	Soya bean (dry)	0.05	(*)	4.5	0.0002	2.0	0.0001	0.5	0.0000	0.0	0.0000	0.0	0.0000
VL 0502	Spinach	2		0.5	0.0010	0.0	0.0000	0.0	0.0000	0.3	0.0005	2.0	0.0040
VA 0389	Spring onion	0.5		0.0	0.0000	2.0	0.0010	1.5	0.0008	4.0	0.0020	1.0	0.0005
VC 0431	Squash, Summer	0.5		10.5	0.0053	2.2	0.0011	0.0	0.0000	14.0	0.0070	3.5	0.0018
FS 0012	Stone fruits	2		7.3	0.0146	1.0	0.0020	0.0	0.0000	0.8	0.0016	22.8	0.0456
FB 0275	Strawberry	1		0.0	0.0000	0.0	0.0000	0.0	0.0000	0.0	0.0000	5.3	0.0053
VR 0596	Sugar beet	0.05	(*)	0.5	0.0000	0.0	0.0000	0.0	0.0000	0.3	0.0000	2.0	0.0001
SO 0702	Sunflower seed	1		1.0	0.0010	0.0	0.0000	0.6	0.0006	0.0	0.0000	0.0	0.0000
OR 0702	Sunflower seed oil, edible	1		9.3	0.0093	0.5	0.0005	0.3	0.0003	0.8	0.0008	8.5	0.0085
VO 0447	Sweet corn (corn-on-the-cob)	0.1		0.0	0.0000	0.0	0.0000	4.4	0.0004	0.0	0.0000	8.3	0.0008
DT 1114	Tea, Green, Black	20		2.3	0.0460	1.2	0.0240	0.5	0.0100	0.5	0.0100	2.3	0.0460
VO 0448	Tomato	1		81.5	0.0815	7.0	0.0070	16.5	0.0165	25.5	0.0255	66.0	0.0660
CM 0654	Wheat bran, unprocessed	5		0.3	0.0013	0.0	0.0000	0.0	0.0000	0.0	0.0000	0.0	0.0000
CF 1211	Wheat flour	0.5		323.0	0.1615	114.0	0.0570	28.3	0.0142	112.0	0.0560	175.8	0.0879
CF 1210	Wheat germ	2		0.1	0.0002	0.1	0.0002	0.0	0.0000	0.1	0.0002	0.1	0.0002
CF 1212	Wheat whole meal	2		1.0	0.0020	0.3	0.0007	0.0	0.0000	2.8	0.0055	1.3	0.0025
VC 0433	Winter squash	0.5		1.5	0.0008	0.3	0.0002	0.0	0.0000	2.0	0.0010	0.5	0.0003
			TOTAL =		0.7317		0.8879		0.6727		0.5835		0.9630
			% ADI =		24%		30%		22%		19%		32%
			ROUNDED % ADI =		20%		30%		20%		20%		30%

2-PHENYLPHENOL (56) **INTERNATIONAL ESTIMATED DAILY INTAKE (IEDI)**

ADI = 0.4 mg/kg bodyweight or 24.000 mg/person

Commodity		MRL mg/kg	STMR mg/kg	Processing Factor	Notes	Adjusted STMR mg/kg	Middle Eastern		Far Eastern		African		Latin American		European	
							Diet	IEDI	Diet	IEDI	Diet	IEDI	Diet	IEDI	Diet	IEDI
Code	Name						g/day	mg/day	g/day	mg/day	g/day	mg/day	g/day	mg/day	g/day	mg/day
FC 0001	Citrus fruits	10	0.2				54.3	0.0109	6.3	0.0013	5.1	0.0010	54.8	0.0110	49.0	0.0098
JF 0004	Orange juice	0.5	0.12				7.3	0.0009	0.0	0.0000	0.0	0.0000	0.3	0.0000	4.5	0.0005
						TOTAL =		0.0117		0.0013		0.0010		0.0110		0.0103
						% ADI =		0%		0%		0%		0%		0%

PHOSALONE (60) **INTERNATIONAL ESTIMATED DAILY INTAKE (IEDI)**

ADI = 0.02 mg/kg bodyweight or 1.200 mg/person\

Commodity		MRL mg/kg	STMR mg/kg	Processing Factor	Notes	Adjusted STMR mg/kg	Middle Eastern		Far Eastern		African		Latin American		European	
							Diet	IEDI	Diet	IEDI	Diet	IEDI	Diet	IEDI	Diet	IEDI
Code	Name						g/day	mg/day	g/day	mg/day	g/day	mg/day	g/day	mg/day	g/day	mg/day
TN 0660	Almonds	0.1	0.05				0.5	0.0000	0.0	0.0000	0.0	0.0000	0.1	0.0000	1.8	0.0001
TN 0666	Hazelnuts	0.05	0.05		(*)		0.0	0.0000	0.0	0.0000	0.0	0.0000	0.1	0.0000	0.3	0.0000
FP 0009	Pome fruits	2	0.8				10.8	0.0086	7.5	0.0060	0.3	0.0002	6.5	0.0052	51.3	0.0410
FS 0012	Stone fruits	2	0.45				7.3	0.0033	1.0	0.0005	0.0	0.0000	0.8	0.0004	22.8	0.0103
TN 0678	Walnuts	0.05	0.05		(*)		0.0	0.0000	0.0	0.0000	0.0	0.0000	0.0	0.0000	0.5	0.0000
						TOTAL =		0.0119		0.0065		0.0002		0.0056		0.0514
						% ADI =		1%		1%		0%		0%		4%

PROPARGITE (113) **THEORETICAL MAXIMUM DAILY INTAKE (TMDI)**

ADI = 0.01 mg/kg bodyweight or 0.600 mg/person

Commodity		MRL mg/kg	Notes	Middle Eastern		Far Eastern		African		Latin American		European	
				Diet	TMDI	Diet	TMDI	Diet	TMDI	Diet	TMDI	Diet	TMDI
Code	Name			g/day	mg/day	g/day	mg/day	g/day	mg/day	g/day	mg/day	g/day	mg/day
TN 0660	Almonds	0.1	(*)	0.5	0.0001	0.0	0.0000	0.0	0.0000	0.1	0.0000	1.8	0.0002
FP 0226	Apple	5		7.5	0.0375	4.7	0.0233	0.3	0.0013	5.5	0.0275	40.0	0.2000
FS 0240	Apricot	7		3.0	0.0210	0.0	0.0000	0.0	0.0000	0.0	0.0000	3.5	0.0245
VD 0071	Beans (dry)	0.2		6.8	0.0014	6.8	0.0014	0.0	0.0000	13.5	0.0027	4.3	0.0009
FC 0001	Citrus fruits	5		54.3	0.2713	6.3	0.0317	5.1	0.0254	54.8	0.2738	49.0	0.2450
VP 0526	Common bean (pods and/or immature seeds)	20		3.5	0.0700	0.8	0.0167	0.0	0.0000	4.0	0.0800	12.0	0.2400
SO 0691	Cotton seed	0.1	(*)	0.0	0.0000	0.0	0.0000	0.0	0.0000	0.0	0.0000	0.0	0.0000
FB 0265	Cranberry	10		0.0	0.0000	0.0	0.0000	0.0	0.0000	0.0	0.0000	0.3	0.0025
VC 0424	Cucumber	0.5		4.8	0.0024	4.5	0.0023	0.0	0.0000	8.3	0.0041	9.0	0.0045
DF 0269	Dried grapes	10		0.3	0.0025	0.0	0.0000	0.0	0.0000	0.3	0.0025	2.3	0.0225
PE 0112	Eggs	0.1		14.6	0.0015	13.1	0.0013	3.7	0.0004	11.9	0.0012	37.6	0.0038
FT 0297	Fig	2		2.3	0.0045	0.0	0.0000	0.0	0.0000	0.3	0.0005	0.5	0.0010
FB 0269	Grapes	10		15.5	0.1550	1.0	0.0100	0.0	0.0000	1.0	0.0100	11.5	0.1150
DH 1100	Hops, dry	30		0.1	0.0030	0.1	0.0030	0.1	0.0030	0.1	0.0030	0.1	0.0030
GC 0645	Maize	0.1	(*)	48.3	0.0048	31.2	0.0031	106.2	0.0106	41.8	0.0042	8.8	0.0009
MM 0095	Meat	0.1	(fat)	7.4	0.0007	6.3	0.0006	4.8	0.0005	9.4	0.0009	31.1	0.0031
ML 0106	Milks	0.1	F	116.8	0.0117	32.0	0.0032	41.8	0.0042	160.0	0.0160	294.0	0.0294
FS 0245	Nectarine	7		1.3	0.0088	0.3	0.0018	0.0	0.0000	0.4	0.0026	6.3	0.0441
FS 0247	Peach	7		1.3	0.0088	0.3	0.0018	0.0	0.0000	0.4	0.0026	6.2	0.0434
SO 0697	Peanut	0.1	(*)	0.3	0.0000	0.2	0.0000	2.3	0.0002	0.3	0.0000	3.0	0.0003
FP 0230	Pear	5		3.3	0.0163	2.8	0.0142	0.0	0.0000	1.0	0.0050	11.3	0.0563
FS 0014	Plums (including Prunes)	7		1.8	0.0123	0.5	0.0035	0.0	0.0000	0.0	0.0000	4.3	0.0301
VR 0589	Potato	0.1	(*)	59.0	0.0059	19.2	0.0019	20.6	0.0021	40.8	0.0041	240.8	0.0241
PM 0110	Poultry meat	0.1	(fat)	3.1	0.0003	1.3	0.0001	0.6	0.0001	2.5	0.0003	5.3	0.0005
GC 0651	Sorghum	5		2.0	0.0100	9.7	0.0483	26.6	0.1329	0.0	0.0000	0.0	0.0000
FB 0275	Strawberry	7		0.0	0.0000	0.0	0.0000	0.0	0.0000	0.0	0.0000	5.3	0.0368
DT 1114	Tea, Green, Black	10		2.3	0.0230	1.2	0.0120	0.5	0.0050	0.5	0.0050	2.3	0.0230

VO 0448	Tomato	2		81.5	0.1630	7.0	0.0140	16.5	0.0330	25.5	0.0510	66.0	0.1320
TN 0678	Walnuts	0.1	(*)	0.0	0.0000	0.0	0.0000	0.0	0.0000	0.0	0.0000	0.5	0.0001
			TOTAL =		0.8355		0.1941		0.2186		0.4970		1.2867
			% ADI =		139%		32%		36%		83%		214%
			ROUNDED % ADI =		140%		30%		40%		80%		210%

PYRETHRINS (63) THEORETICAL MAXIMUM DAILY INTAKE (TMDI)

ADI = 0.04 mg/kg bodyweight or 2.400 mg/person

Commodity		MRL mg/kg	Notes	Middle Eastern		Far Eastern		African		Latin American		European	
				Diet	TMDI	Diet	TMDI	Diet	TMDI	Diet	TMDI	Diet	TMDI
Code	Name			g/day	mg/day	g/day	mg/day	g/day	mg/day	g/day	mg/day	g/day	mg/day
GC 0080	Cereal grains	3		430.8	1.2924	452.3	1.3569	318.4	0.9553	252.5	0.7574	226.3	0.6789
MD 0180	Dried fish	3		0.3	0.0008	2.8	0.0085	4.4	0.0133	4.8	0.0143	0.8	0.0023
DF 0167	Dried fruits	1		1.2	0.0012	0.3	0.0003	0.4	0.0004	0.7	0.0007	2.9	0.0029
DV 0168	Dried vegetables	1		0.5	0.0005	0.2	0.0002	0.0	0.0000	0.0	0.0000	0.5	0.0005
SO 0088	Oilseed	1		23.7	0.0237	4.4	0.0044	2.4	0.0024	3.1	0.0031	15.8	0.0158
TN 0085	Tree nuts	1		1.0	0.0010	13.5	0.0135	3.4	0.0034	17.5	0.0175	3.8	0.0038
			TOTAL =		1.3196		1.3838		0.9748		0.7929		0.7041
			% ADI =		55%		58%		41%		33%		29%
			ROUNDED % ADI =		50%		60%		40%		30%		30%

PYRIPROXIFEN (200) **INTERNATIONAL ESTIMATED DAILY INTAKE (IEDI)**

ADI = 0.1 mg/kg bodyweight or 6.000 mg/person

Commodity		MRL mg/kg	STMR mg/kg	Processing Factor	Notes	Adjusted STMR mg/kg	Middle Eastern		Far Eastern		African		Latin American		European	
							Diet	IEDI	Diet	IEDI	Diet	IEDI	Diet	IEDI	Diet	IEDI
Code	Name						g/day	mg/day	g/day	mg/day	g/day	mg/day	g/day	mg/day	g/day	mg/day
MM 0812	Cattle meat	0.01	0		(*)(fat)		2.7	0.0000	0.7	0.0000	2.1	0.0000	6.0	0.0000	12.7	0.0000
MO 0812	Cattle, Edible offal of	0.01	0		(*)		2.5	0.0000	0.3	0.0000	1.8	0.0000	5.0	0.0000	6.0	0.0000
FC 0001	Citrus fruits	1	0.013				54.3	0.0007	6.3	0.0001	5.1	0.0001	54.8	0.0007	49.0	0.0006
OR 0691	Cotton seed oil, edible	0.01	0.002				3.8	0.0000	0.5	0.0000	0.5	0.0000	0.5	0.0000	0.0	0.0000
MM 0814	Goat meat	0.01	0		(*)(fat)		0.4	0.0000	0.0	0.0000	0.5	0.0000	0.2	0.0000	0.1	0.0000
MO 0814	Goat, Edible offal of	0.01	0		(*)		0.3	0.0000	0.0	0.0000	0.4	0.0000	0.0	0.0000	0.0	0.0000
						TOTAL =		0.0007		0.0001		0.0001		0.0007		0.0006
						% ADI =		0%		0%		0%		0%		0%

TEBUFENOZIDE (196) **INTERNATIONAL ESTIMATED DAILY INTAKE (IEDI)**

ADI = 0.02 mg/kg bodyweight or 1.200 mg/person

Commodity		MRL mg/kg	STMR mg/kg	Processing Factor	Notes	Adjusted STMR mg/kg	Middle Eastern		Far Eastern		African		Latin American		European	
							Diet	IEDI	Diet	IEDI	Diet	IEDI	Diet	IEDI	Diet	IEDI
Code	Name						g/day	mg/day	g/day	mg/day	g/day	mg/day	g/day	mg/day	g/day	mg/day
FB 0269	Grapes	1	0.25				15.8	0.0039	1.0	0.0003	0.0	0.0000	1.3	0.0003	13.8	0.0034
FI 0341	Kiwifruit	0.5	0.14				0.0	0.0000	0.0	0.0000	1.9	0.0003	0.1	0.0000	1.5	0.0002
FP 0009	Pome fruits	1	0.17				8.8	0.0015	6.3	0.0011	0.2	0.0000	5.1	0.0009	41.3	0.0070
JF 0226	Apple juice		0.17	0.124		0.021	1.9	0.0000	1.2	0.0000	0.1	0.0000	1.4	0.0000	10.0	0.0002
CM 0649	Rice, husked	0.1	0.03				0.0	0.0000	1.8	0.0001	34.7	0.0010	21.0	0.0006	2.5	0.0001
TN 0678	Walnut	0.05	0.003				0.0	0.0000	0.0	0.0000	0.0	0.0000	0.0	0.0000	0.5	0.0000
						TOTAL =		0.0055		0.0014		0.0013		0.0019		0.0110
						% ADI =		0%		0%		0%		0%		1%

ANNEX IV

ESTIMATES OF ACUTE DIETARY INTAKE

The following Tables give details of the estimated acute dietary intakes of the pesticides for general population and children up to six years old evaluated by the Meeting and show the ratios of the estimated intakes to the corresponding acute reference dose (RfD).

In the case of compounds for which an acute RfD might be necessary but has not yet been established IESTIs were calculated, but the acute risk assessments could not be finalized. Depending on the commodity consumption data, the IESTI for each commodity is calculated for the relevant case described below:

Case 1. Composite sampling data reflect the residue level in the food.
Case 2. Composite residue data do not reflect the residue level in individual food commodity units.
Case 2a. Unit weight is less than large portion weight.
Case 2b. Unit weight exceeds large portion weight.
Case 3. Processed commodity, where bulking or blending means that the STMR-P represents the likely highest residue

The percentages of the acute RfD are rounded to one significant figure for values up to and including 100% and to two significant figures for values above 100%.

CARBOFURAN (96) **INTERNATIONAL ESTIMATE OF SHORT TERM INTAKE (IESTI)**
ADULTS

Acute RfD: May be necessary but has not yet been established

Commodity		MRL mg/kg	STMR or STMR-P, mg/kg	Processing Factor	HR or HR-P (mg/kg)	Country	Body weight, kg	Large portion g	Unit weight g	Country	% Edible portion	Unit weight, edible portion	Variability factor	Case	IESTI, mg/kg bw	% Acute RfD
Code	Name															
FC 0003	Mandarins	0.5	0.00726		0.0363	JPN	60	466	100	FRA	72	72	7	Case 2a	0.00035	-
FC 0004	Oranges	0.5	0.00726		0.0363	USA	65	963	190	FRA	72	137	7	Case 2a	0.00063	-

CARBOFURAN (96) **INTERNATIONAL ESTIMATE OF SHORT TERM INTAKE (IESTI)**
CHILDREN UP TO 6 YEARS

Acute RfD: May be necessary but has not yet been established

Commodity		MRL mg/kg	STMR or STMR-P, mg/kg	Processing Factor	HR or HR-P mg/kg	Country	Body weight, kg	Large portion g	Unit weight g	Country	% Edible portion	Unit weight, edible portion	Variability factor	Case	IESTI, mg/kg bw	% Acute RfD
Code	Name															
FP 0003	Mandarins	0.5	0.00726		0.0363	JPN	15	333	100	FRA	72	72	7	Case 2a	0.00135	-
FC 0004	Oranges	0.5	0.00726		0.0363	UK	14.5	495	190	FRA	72	137	7	Case 2a	0.00258	-

CARBOSULFAN (145) **INTERNATIONAL ESTIMATE OF SHORT TERM INTAKE (IESTI)**
ADULTS

Acute RfD: May be necessary but has not yet been established

Commodity		MRL mg/kg	STMR or STMR-P, mg/kg	Processing Factor	HR or HR-P mg/kg	Country	Body weight, kg	Large portion g	Unit weight g	Country	% Edible portion	Unit weight, edible portion	Variability factor	Case	IESTI, mg/kg bw	% Acute RfD
Code	Name															
FC 003	Mandarins	0.1	0.0007		0.0058	JPN	60	466	100	FRA	72	72	7	Case 2a	0.00005	-
FC 0004	Oranges	0.1	0.0007		0.0058	USA	65	963	190	FRA	72	137	7	Case 2a	0.00009	-

CARBOSULFAN (145) INTERNATIONAL ESTIMATE OF SHORT TERM INTAKE (IESTI)
CHILDREN UP TO 6 YEARS

Acute RfD: May be necessary but has not yet been established

Commodity		MRL mg/kg	STMR or STMR-P, mg/kg	Processing Factor	HR or HR-P mg/kg	Country	Body weight, kg	Large portion g	Unit weight g	Country	% Edible portion	Unit weight, edible portion	Variability factor	Case	IESTI, mg/kg bw	% Acute RfD
Code	Name															
FP 0003	Mandarins	0.1	0.0007		0.0058	JPN	15	333	100	FRA	72	72	7	Case 2a	0.00021	-
FC 0004	Oranges	0.1	0.0007		0.0058	UK	14.5	495	190	FRA	72	137	7	Case 2a	0.00040	-

DIAZINON (022) INTERNATIONAL ESTIMATE OF SHORT TERM INTAKE (IESTI)
ADULTS

Acute RfD: May be necessary but has not yet been established

Commodity		MRL (mg/kg)	STMR (mg/kg)	HR or HR-P (mg/kg)	Body weight, kg	Country	Unit weight g	Country	Variability factor	Case	IESTI mg/kg bw	% Acute RfD
Code	Name											
FP 0226	Apple 1/	0.3	0.04	0.24	65	USA	127	USA	7	Case 2a	0.004	-
FP 0230	Pear 1/	0.3	0.04	0.24	65	USA	151	USA	7	Case 2a	0.004	-
VB 0041	Cabbages, head	0.5	0.01	0.35	60	JPN	717	USA	5	Case 2b	0.008	-
VO 0448	Tomatoes		0.12	0.48	65	USA	123	USA	7	Case 2a	0.007	-
MM 0814	Goat meat	2 (fat) V	0.02									-
MO 0098	Kidney of cattle, goats, pigs and sheep	0.03 V	0.01									

MO 0099	Liver of cattle, goats, pigs and sheep	0.03 V	0.01									-
MM 0097	Meat of cattle, pigs and sheep	2 (fat) V	0.02									-
ML 0106	Milks	0.02 F V	0.02									-

DIAZINON (022) **INTERNATIONAL ESTIMATE OF SHORT TERM INTAKE (IESTI)**
CHILDREN UP TO 6 YEARS

Acute RfD: May be necessary but has not yet been established

Commodity		MRL (mg/kg)	STMR (mg/kg)	HR or HR-P (mg/kg)	Body weight, kg	Country	Unit weight, g	Country	Variability factor	Case	IESTI (mg/kgbw)	% Acute RfD
Code	Name											
FP 0226	Apple 1/	0.3	0.04	0.24	15	USA	130	USA	7	Case 2a	0.016	-
FP 0230	Pear 1/	0.3	0.04	0.24	14.5	UK	151	USA	7	Case 2a	0.018	-
VB 0041	Cabbages, head	0.5	0.01	0.35	17.8	FRA	717	USA	5	Case 2b	0.016	-
VO 0448	Tomatoes	0.5	0.12	0.48	15	USA	123	USA	7	Case 2a	0.028	-
MM 0814	Goat meat	2 (fat) V	0.02									-
MO 0098	Kidney of cattle, goats, pigs and sheep	0.03 V	0.01									-
MO 0099	Liver of cattle, goats, pigs and sheep	0.03 V	0.01									-
MM 0097	Meat of cattle, pigs and sheep	2 (fat) V	0.02									-
ML 0106	Milks	0.02 F V	0.02									-

DINOCAP (87) **INTERNATIONAL ESTIMATE OF SHORT TERM INTAKE (IESTI)**
ADULTS

Acute RfD = 0.008 mg/kg bw

Commodity		MRL mg/kg	STMR (mg/kg)	HR or HR-P mg/kg	Body weight, kg	Country	Unit weight, g	Country	Variability factor	Case	IESTI mg/kg bw	%Acute RfD
Code	Name											
VO 0448	Tomato	0.3	0.045	0.18	65	USA	102	FRA	7	Case 2b	0.008	94.6

DINOCAP (87) **INTERNATIONAL ESTIMATE OF SHORT TERM INTAKE (IESTI)**
CHILDREN UP TO 6 YEARS

Acute RfD = 0.008 mg/kg bw

Commodity		MRL mg/kg	STMR mg/kg)	HR or HR-P mg/kg	Body weight, kg	Country	Unit weight, g	Country	Variability factor	Case	IESTI mg/kgbw	% Acute RfD
Code	Name											
VO 0448	Tomato	0.3	0.045	0.18	15	USA	102	USA	7	Case 2a	0.0087	94.6

ETHEPHON (106) **INTERNATIONAL ESTIMATED SHORT-TERM INTAKE (IESTI)**
ADULTS

Acute RfD: May be necessary but has not yet been established

Commodity															

Code	Name	MRL mg/kg	STMR or STMR-P, mg/kg	Process factor	HR or HR-P, mg/kg	Country	Body weight, kg	Large portion, g	Unit weight g	Country	% Edible portion	Unit weight, edible portion	Variability factor	Case	IESTI, mg/kg bw	% Acute RfD
VC 4199	Cantaloupe	1	0.24		0.63	USA	65	655	1000	USA	63	630	5	Case 2a	0.031	-
DF 0269	Dried grapes	5	0.84	2.7	2.2	FRA	62.3	135				0		Case 1	0.005	-
FB 0269	Grapes	1	0.31		0.82	AUS	70	513	125	FRA	94	118	7	Case 2a	0.011	-
VO0051	Peppers	5	0.98		2.4	FRA	62.3	207	119	USA	92	109	7	Case 2a	0.031	-
FI 0353	Pineapple	2	0.13		0.97	JPN	55	388	472	USA	52	245	5	Case 2a	0.022	-
	Pineapple juice		0.051	0.39			60							Case 3		-
	Pineapples, canned		0.036	0.28	0.27		60							Case 1		-
VO 0448	Tomato	2	0.41		1.7	USA	65	391	123	USA	100	123	7	Case 2a	0.024	-
	Tomato juice		0.14	0.34			60							Case 3		-
	Tomato paste		0.31	0.75			60							Case 3		-
	Wine		0.31	1		AUS	70	1182						Case 3	0.005	-

ETHEPHON (106) **INTERNATIONAL ESTIMATED SHORT-TERM INTAKE (IESTI)**
CHILDREN UP TO 6 YEARS

Acute RfD: May be necessary but has not yet been established

Commodity			STMR or STMR-P, mg/kg	Process Factor	HR or HR-P, mg/kg	Country	Body weight, kg	Large portion, g	Unit weight g	Country	% Edible portion	Unit weight, edible portion	Variability factor	Case	IESTI, mg/kg bw	% Acute RfD
Code	Name	MRL mg/kg														
VC4199	Cantaloupe	1	0.24		0.63	AUS	19	413	1000	USA	63	630	5	Case 2b	0.068	-
DF 0269	Dried grapes	5	0.84	2.7	2.2	USA	15	59						Case 1	0.009	-

FB 0269	Grapes	1	0.31		0.82	AUS	19	342	125	FRA	94	118	7	Case 2a	0.039	-
VO0051	Peppers	5	0.98		2.4	AUS	19	60	119	USA	92	109	7	Case 2b	0.053	-
FI 0353	Pineapple	2	0.13		0.97	JPN	15	204	472	USA	52	245	5	Case 2b	0.066	-
	Pineapple juice		0.051	0.39			15							Case 3		-
	Pineapples, canned		0.036	0.28	0.27		15							Case 1		-
VO 0448	Tomato	2	0.41		1.7	USA	15	159	123	USA	100	123	7	Case 2a	0.099	-
	Tomato juice		0.14	0.34			15							Case 3		-
	Tomato paste		0.31	0.75			15							Case 3		-
	Wine		0.31	1		AUS	19	4						Case 3	0	-

FENAMIPHOS (85) **INTERNATIONAL ESTIMATE OF SHORT TERM DIETARY INTAKE (IESTI)**
ADULTS

Acute RfD = 0.0008 mg/kg bw

Commodity		MRL mg/kg	STMR or STMR-P, mg/kg	Process factor	HR or HR-P, mg/kg	Country (LP)	Body weight, kg	Large portion, g	Unit weight, g	Country (UW)	% Edible portion	Unit weight, edible portion, g	Variability factor	Case	IESTI mg/kg bw	% Acute RfD
Code	Name															
FP 0226	Apple	*0.05	0.01		0.01	USA	65	1348.1	138	USA	92	126.96	7	Case 2a	0.00034	42.1
	Apple juice (a)		0.0078	0.78										Case 3		
FI 0327	Banana	*0.05	0.02		0.025	USA	65	556.4	150	FRA	68	102	7	Case 2a	0.00054	68.0
VB 0402	Brussels sprouts	0.05	0.01		0.01	NLD	63	393.75	7	FRA	70	4.9	0	Case 1	0.00006	7.8
VB 0041	Cabbage, head	0.05	0.01		0.05	NLD	63	303.66	908	USA	79	717.32	5	Case 2b	0.00354	442.2
VR 0577	Carrot	0.2	0.02		0.08	NLD	63	335.16	100	FRA	89	89	7	Case 2a	0.00097	120.9

OC 0691	Cotton seed oil (a)	*0.05	0.01			USA	65	9.1								
MO 0105	Edible offal (a)	*0.01	0			FRA	62.3	276.612								
PE 0112	Eggs (a)	*0.01	0			FRA	62.3	218.673								
FB 0269	Grapes	0.1	0.02		0.09	AUS	70	1007.3	5.8	USA	99	5.742	0	Case 1	0.00129	161.9
	Grape juice (a)		0.009	0.45	0.04									Case 3		
	Raisins (a)		0.03	1.57	0.14	FRA	62.3	135.191								
MM095	Meat (a)	*0.01	0			AUS	70	526.4								
VC 0046	Melons	*0.05	0.02		0.02	USA	65	655.2	700	FRA	60	420	5	Case 2b	0.00115	143.7
ML 0106	Milk (a)	*0.01	0			USA	65	2466.1								
SO 0697	Peanuts (a)	*0.05	0		0.01	FRA	62.3	161.357								
VO 0051	Peppers	0.5	0.055		0.35	FRA	62.3	207.459	119	USA	82	97.58	7	Case 2a	0.00478	597.1
FI 0353	Pineapple	*0.05	0.01		0.14	JPN	60	423.6	472	USA	52	245.44	5	Case 2b	0.00554	692.0
	Pineapple juice (a)		0.012	1.2	0.17									Case 3		
PO 0111	Poultry offal (a)	*0.01	0			USA	65	247.65								
PM 0110	Poultry meat (a)	*0.01	0			AUS	70	434.7								
VO 0048	Tomato	0.5	0.05		0.3	USA	65	390.65	105	FRA	97	101.85	7	Case 2a	0.00361	451.8
	Tomato juice (a)		0.05	0.88	0.27									Case 3		
VC 0432	Watermelon	*0.05	0.02		0.02	USA	65	1938.95	4518	USA	46	2078.28	5	Case 2b	0.00691	863.5

FENAMIPHOS (85) **INTERNATIONAL ESTIMATE OF SHORT TERM DIETARY INTAKE (IESTI)**
CHILDREN UP TO 6 YEARS

Acute RfD = 0.0008 mg/kg bw

Commodity		MRL mg/kg	STMR or STMR-P. mg/kg	Process Factor	HR or HR-P, mg/kg	Country (LP)	Body weight, kg	Large portion, g	Unit weight, g	Country (UW)	% Edible portion	Unit weight, edible portion g	Variability factor	Case	IESTI mg/kg	% Acute RfD
Code	Name															
FP 0226	Apple	*0.05	0.01		0.01	USA	15	678.75	138	USA	92	126.96	7	Case 2a	0.00101	126.5
	Apple juice		0.0078	0.78										Case 3		
FI 0327	Banana	*0.05	0.02		0.025	JPN	15	294.15	150	FRA	68	102	7	Case 2a	0.00201	250.8
VB 0402	Brussels sprouts	0.05	0.01		0.01	NLD	17	212.5	7	FRA	70	4.9	0	Case 1	0.00012	15.6
VB 0041	Cabbage, head	0.05	0.01		0.05	NLD	17	110.16	908	USA	79	717.32	5	Case 2b	0.01300	1624.5
VR 0577	Carrot	0.2	0.02		0.08	FRA	17.8	204.7	100	FRA	89	89	7	Case 2a	0.00328	409.5
OC 0691	Cotton seed oil	*0.05	0.01			USA	15	6.15								
MO 0105	Edible offal (a)	*0.01	0			FRA	17.8	202.742								
PE 0112	Eggs (a)	*0.01	0			FRA	17.8	133.5								
FB 0269	Grapes	0.1	0.02		0.09	AUS	19	342	5.8	USA	99	5.742	0	Case 1	0.00162	202.5
	Grape juice		0.009	0.45	0.04									Case 3		
	Raisins (a)		0.03	1.57	0.14	USA	15	59.25								
MM095	Meat (a)	*0.01	0			AUS	19	260.49								
VC 0046	Melons	*0.05	0.02		0.02	AUS	19	413.06	700	FRA	60	420	5	Case 2b	0.00368	459.6
ML 0106	Milk (a)	*0.01	0			USA	15	1285.65								
SO 0697	Peanuts (a)	*0.05	0		0.01	USA	15	77.7								
VO 0051	Peppers	0.5	0.055		0.35	AUS	19	60.04	119	USA?	82	97.58	7	Case 2a	0.01524	1904.5
FI 0353	Pineapple	*0.05	0.01		0.14	JPN	15	204.15	472	USA?	52	245.44	5	Case 2b	0.02200	2749.9
	Pineapple juice		0.012	1.2	0.17									Case 3		
PO 0111	Poultry offal (a)	*0.01	0			USA	15	37.05								
PM 0110	Poultry meat (a)	*0.01	0			AUS	19	223.82								
VO 0048	Tomato	0.5	0.05		0.3	USA	15	159	105	FRA	97	101.85	7	Case 2a	0.01489	1861.3
	Tomato juice		0.05	0.88	0.27									Case 3		
VC 0432	Watermelon	*0.05	0.02		0.02	AUS	19	1472.69	4518	USA	46	2078.28	5	Case 2b	0.02314	2892.7

FENPROPIMORPH (188) **INTERNATIONAL ESTIMATE OF SHORT TERM INTAKE (IESTI)**
ADULTS

Acute RfD: May be necessary but has not yet been established

Commodity		MRL mg/kg	STMR mg/kg	HR or HR-P mg/kg	Body weight, kg	Country	Unit weight, g	Country	Variability factor	Case	IESTI mg/kg bw	% Acute RfD
Code	Name											
FI 0327	Banana	2	0.11	0.43	65	USA	80	USA	7	Case 2a	0.0045	
PE 0112	Eggs	0.01*	0									
MO 0098	Kidney of cattle, goats, pigs and sheep	0.05	0.026									
MO 0099	Liver of cattle, goats, pigs and sheep	0.3	0.22									
MF 0100	Mammalian fats (except milk fats)	0.01	0.006									
MM 0095	Meat (from mammals other than marine mammals)	0.02	0.009									
ML 0106	Milks	0.01	0.004									
PF 0111	Poultry fats	0.01*	0									
PM 0111	Poultry meat	0.01*	0									
PO 0111	Poultry, Edible offal of	0.01*	0									

FENPROPIMORPH (188) **INTERNATIONAL ESTIMATE OF SHORT TERM INTAKE (IESTI)**
CHILDREN UP TO 6 YEARS

Acute RfD: May be necessary but has not yet been established

Commodity												

Code	Name											
FI 0327	Banana	2	0.11	0.43	15	JPN	0.08	USA	7	Case 2a	0.0176	
PE 0112	Eggs	0.01*	0									
MO 0098	Kidney of cattle, goats, pigs and sheep	0.05	0.026									
MO 0099	Liver of cattle, goats, pigs and sheep	0.3	0.22									
MF 0100	Mammalian fats (except milk fats)	0.01	0.006									
MM 0095	Meat (from mammals other than marine mammals)	0.02	0.009									
ML 0106	Milks	0.01	0.004									
PF 0111	Poultry fats	0.01*	0									
PM 0111	Poultry meat	0.01*	0									
PO 0111	Poultry, Edible offal of	0.01*	0									

FENPYROXIMATE (193) **INTERNATIONAL ESTIMATE OF SHORT TERM INTAKE (IESTI) ADULTS**

Acute RfD = 0.01 mg/kg bw

Commodity		MRL mg/kg	STMR or STMR-P, mg/kg	Process factor	HR or HR-P mg/kg	Country	Body weight kg	Large portion, g	Unit weight, g	Country	% Edible portion	Unit weight, edible portion	Variability factor	Case	IESTI, mg/kg bw	% Acute RfD
Code	Name															
FP 0226	Apples	0.3	0.09		0.18	USA	70	1452	138	USA	92	127	7	Case 2a	0.004	40
FC 0004	Oranges	0.2	0.01		0.09	USA	70	608	190	FRA	72	137	7	Case 2a	0.001	13
FB 0269	Grapes	1	0.07		0.57	AUS	70	1007	125	FRA	94	118	7	Case 2a	0.008	76

DH 1100	Hops	10	4.4		8.4	USA	70	6				0		Case 1	0.001	8
ML 0812	Cattle milk	0.005	0.005			NLD	63	2515				0		Case 3	0	2
MM 0821	Cattle meat	0.05	0.01			AUS	70	481				0		Case 3	0	1
JF 0226	Apple juice		0.04	0.42			60	0				0		Case 3	0	0
	Apple puree		0.05	0.54			60	0				0		Case 3	0	0
	Wine		0.005	0.07		AUS	70	1182				0		Case 3	0	1
	Beer		0.004	0.001			60	0				0		Case 3		0

FENPYROXIMATE (193) **INTERNATIONAL ESTIMATE OF SHORT TERM INTAKE (IESTI)**
CHILDREN

Acute RfD = 0.01 mg/kg bw

Commodity		**MRL mg/kg**	**STMR or STMR-P, mg/kg**	**Process factor**	**HR or HR-P mg/kg**	**Country**	**Body weight, kg**	**Large portion, g**	**Unit weight, g**	**Country**	**% Edible portion**	**Unit weight, edible portion**	**Variability factor**	**Case**	**IESTI, mg/kg bw**	**% Acute RfD**
Code	**Name**															
FP 0226	Apples	0.3	0.09		0.18	USA	15	679	138	USA	92	127	7	Case 2a	0.014	140
FC 0004	Oranges	0.2	0.01		0.09	UK	14.5	495	190	FRA	72	137	7	Case 2a	0.006	62
FB 0269	Grapes	1	0.07		0.57	JPN	15	366	125	FRA	94	118	7	Case 2a	0.032	324
DH 1100	Hops	10	4.4		8.4	JPN	15	0				0		Case 1	0	3
ML 0812	Cattlemilk	0.005	0.005			AUS	19	1450				0		Case 3	0	4
MM 0821	Cattle meat	0.05	0.01			AUS	19	238				0		Case 3	0	1
MO 1280	Cattle kidney	0.01	0													

MO 1281	Cattle liver	0.01	0													
JF 0226	Apple juice		0.04	0.42			15	0				0		Case 3	0	0
	Apple puree		0.05	0.54			15	0				0		Case 3	0	0
	Wine		0.005	0.07		AUS	19	4				0		Case 3	0	0
	Beer		0.004	0.001			15	0				0		Case 3	0	0

FOLPET (41)

INTERNATIONAL ESTIMATE OF SHORT TERM INTAKE (IESTI)
ADULTS

Acute RfD = 0.1 mg/kg bw

Commodity		**MRL mg/kg**	**STMR or STMR-P, mg/kg**	**Process factor**	**HR or HR-P mg/kg**	**Country**	**Body weight, kg**	**Large portion, g**	**Unit weight, g**	**Country**	**% Edible portion**	**Unit weight, edible portion**	**Variability factor**	**Case**	**IESTI, mg/kg bw**	**% Acute RfD**
Code	**Name**															
FP 0226	Apple	10	3.1		8.0	USA	70	1452	110	FRA	91	100	7	Case 2a	0.140	140
VC 0424	Cucumber	1	0.36		0.7	NLD	63	313	301	USA	95	286	5	Case 2a	0.016	16
DF 0269	Dried grapes	40	8.0		18.9	FRA	62.3	135				0		Case 1	0.041	41
FB 0269	Grapes	10	2.5		5.9	AUS	70	513	125	FRA	94	118	7	Case 2a	0.083	83
VL 0482	Lettuce, Head	50	14		39	USA	70	229				0	5	Case 1	0.128	128
VC 0046	Melons, except Watermelon	3	0.410		2.20	USA	70	652	552	USA	50	276	5	Case 2a	0.046	46
VA 0385	Onion, Bulb	1	0.070		0.41	FRA	62.3	306	140	FRA	90	126	7	Case 2a	0.006	6
VR 0589	Potato	0.1	0.01		0.08	NLD	63	687	200	FRA	80	160	7	Case 2a	0.002	2
FB 0275	Strawberry	5	1.60		2.20	FRA	62.3	346				0		Case 1	0.012	12
VO 0448	Tomato	3	0.90		2.40	USA	70	421	123	USA	100	123	7	Case 2a	0.033	33
	Apple juice		0.11				60	0				0		Case 3	0	0
	Grape juice		0.0075				60	0				0		Case 3	0	0
	Wine		0.00			AUS	70	1182				0		Case 3	0	0

	Tomato paste		0.025				60	0				0		Case 3	0	0
	Tomato puree		0.025				60	0				0		Case 3	0	0

FOLPET (41)

INTERNATIONAL ESTIMATE OF SHORT TERM INTAKE (IESTI)
CHILDREN UP TO 6 YEARS

Acute RfD = 0.1 mg/kg bw

Commodity		MRL mg/kg	STMR or STMR-P, mg/kg	Process factor	HR or HR-P mg/kg	Country	Body weight, kg	Large portion, g	Unit weight, g	Country	% Edible portion	Unit weight, edible portion	Variability factor	Case	IESTI, mg/kg bw	% Acute RfD
Code	**Name**															
FP 0226	Apple	10	3.1		8.0	USA	15	679	110	FRA	91	100	7	Case 2a	0.493	493
VC 0424	Cucumber	1	0.36		0.7	NLD	17	162	301	USA	95	286	5	Case 2b	0.033	33
DF 0269	Dried grapes	40	8.0		18.9	USA	15	59				0		Case 1	0.075	75
FB 0269	Grapes	10	2.5		5.9	AUS	19	342	125	FRA	94	118	7	Case 2a	0.285	285
VL 0482	Lettuce, Head	50	14		39	NLD	17	84				0	5	Case 1	0.192	192
VC 0046	Melons, except Watermelon	3	0.410		2.20	AUS	19	413	552	USA	50	276	5	Case 2a	0.163	163
VA 0385	Onion, Bulb	1	0.070		0.41	FRA	17.8	127	140	FRA	90	126	7	Case 2a	0.020	20
VR 0589	Potato	0.1	0.01		0.08	UK	14.5	279	200	FRA	80	160	7	Case 2a	0.006	6
FB 0275	Strawberry	5	1.60		2.20	AUS	19	176				0		Case 1	0.020	20
VO 0448	Tomato	3	0.90		2.40	USA	15	159	123	USA	100	123	7	Case 2a	0.140	140
	Apple juice		0.11				15	0				0		Case 3	0	0
	Grape juice		0.0075				15	0				0		Case 3	0	0
	Wine		0.00			AUS	19	4				0		Case 3	0	0
	Tomato paste		0.025				15	0				0		Case 3	0	0
	Tomato puree		0.025				15	0				0		Case 3	0	0

MALATHION (049) **INTERNATIONAL ESTIMATE OF SHORT TERM INTAKE (IESTI)**
ADULTS

Acute RfD: May be necessary but has not yet been established

Commodity		MRL mg/kg	STMR mg/kg	HR or HR-P mg/kg	Body weight, kg	Large portion, g	Country	Unit weight, g	Country	Variability factor	Case	IESTI mg/kg bw	% Acute RfD
Code	Name												
VS 0621	Asparagus	1	0.305	0.69	63	398.2	NLD	10	USA	7	Case 2a	0.003	-
FB 0264	Blueberries	10	2.27	7.5	70	158.2	AUS				Case 1	0.017	-
VD 0071	Beans, dry	2	0.215	1.2	62.3	255.4	FRA				Case 1	0.005	-
VP 0061	Beans	1	0.31	0.9	62.3	311.5	FRA				Case 1	0.005	-
SO 0691	Cotton seed	20	4.8	14	65	0	USA				Case 1	0.001	-
OR 0691	Cotton seed oil	13	3.06	9.1	65	9.1	USA				Case 3	0.001	-
VC 0424	Cucumber	0.2	0.02	0.1	63	313.1	NLD						-
GC 0645	Maize	0.05	0.01	0.02	62.3	259.8	FRA				Case 1	0	-
VL 0485	Mustard green	2	0.07	1.1	65	227.5	USA						-
VA 0385	Onion, bulb	1	0.23	1	62.3	305.9	FRA	100.1	USA	7	Case 2a	0.012	-
VO 0051	Peppers	0.1	0.01	0.08	62.3	207.5	FRA	97.6	USA	7	Case 2a	0.001	-
VL 0502	Spinach	3	0.35	2.2	63	825.3	NLD	244.8	USA	7	Case 1	0.009	-
VA 0389	Spring onion	5	0.52	5	70	60.2	AUS				Case 1	0.004	-
FB 0275	Strawberry	1	0.25	0.59	62.3	345.8	FRA				Case 1	0.003	-
VO 0447	Sweet corn	0.02	0.01	0.02	65	367.3	USA						-
VO 0448	Tomato	0.5	0.21	0.41	65	390.7	USA	123	USA	7	Case 2a	0.006	-
VJ 0448	Tomato juice	0.01	0.03	0.0123									-
	Tomato pure		0.07										-
	Tomato catsup		0.09										-
VJ 0506	Turnip, garden	0.2	0.05	0.13	65	234.7	USA						-
GC 0654	Wheat	0.5	0.702	1.9	65	382.9	USA			1		0.011	-

MALATHION (049) **INTERNATIONAL ESTIMATE OF SHORT TERM INTAKE (IESTI)**
CHILDREN UP TO 6 YEARS

Acute RfD: May be necessary but has not yet been established

Commodity		MRL mg/kg	STMR mg/kg	HR or HR-P mg/kg	Body weight, kg	Large portion, g	Country	Unit weight, g	Country	Variability factor	Case	IESTI mg/kg bw	% Acute RfD
Code	Name												
VS 0621	Asparagus	1	0.305	0.69	15	178.2	USA	10	USA	7	Case 2a	0.006	-
FB 0264	Blueberries	10	2.27	7.5	17.8	138.3	FRA				Case 1	0.058	-
VD 0071	Beans, dry	2	0.215	1.2	17.8	209.3	FRA				Case 1	0.014	-
VP 0061	Beans	1	0.31	0.9	17.8	202.7	FRA				Case 1	0.010	-
SO 0691	Cotton seed	20	4.8	14	15	0	USA				Case 1	0.001	-
OR 0691	Cotton seed oil	13	3.06	9.1	15	6.15	USA				Case 3	0.004	-
VC 0424	Cucumber	0.2	0.02	0.1	17	162.0	NLD						-
GC 0645	Maize	0.05	0.01	0.02	17.8	148.3	FRA				Case 1	0	-
VL 0485	Mustard green	2	0.07	1.1	15	52.8	USA						-
VA 0385	Onion, bulb	1	0.23	1	17.8	127.1	FRA	100.1	USA	7	Case 2a	0.040	-
VO 0051	Peppers	0.1	0.01	0.08	19	60.0	AUS	97.58	USA	7	Case 2a	0.003	-
VL 0502	Spinach	3	0.35	2.2	17	343.4	NLD	244.8	USA	7	Case 1	0.032	-
VA 0389	Spring onion	5	0.52	5	19	28.9	AUS				Case 1	0.008	-
FB 0275	Strawberry	1	0.25	0.59	19	176.3	AUS				Case 1	0.005	-
VO 0447	Sweet corn	0.02	0.01	0.02	14.5	160.8	UK						-
VO 0448	Tomato	0.5	0.21	0.41	15	159.0	USA	123	USA	7	Case 2a	0.024	-
VJ 0448	Tomato juice	0.01	0.03	0.0123									-
	Tomato pure		0.07										-
	Tomato catsup		0.09										-
VJ 0506	Turnip, garden	0.2	0.05	0.13	15	86.7	JPN						-
GC 0654	Wheat	0.5	0.702	1.9	15	151.0	USA			1		0.019	-

METHIOCARB (132) **INTERNATIONAL ESTIMATE OF SHORT TERM DIETARY INTAKE (IESTI)**
ADULTS

Acute RfD = 0.02 mg/kg bw

Commodity		MRL mg/kg	STMR or STMR-P, mg/kg	Process factor	HR or HR-P mg/kg	Country	Body weight, kg	Large portion g	Unit weight g	Country	% Edible portion	Unit weight, edible portion	Variability factor	Case	IESTI, mg/kg bw	% Acute RfD
Code	Name															
FB 0275	Strawberry	1	0.44	1	0.83	FRA	62	344						Case 1	0.005	23

METHIOCARB (132) **INTERNATIONAL ESTIMATE OF SHORT TERM DIETARY INTAKE (IESTI)**
CHILDREN UP TO 6 YEARS

Acute RfD = 0.02 mg/kg bw

Commodity		MRL mg/kg	STMR or STMR-P, mg/kg	Process factor	HR or HR-P mg/kg	Country	Body weight, kg	Large portion g	Unit weight g	Country	% Edible portion	Unit weight, edible portion	Variability factor	Case	IESTI, mg/kg bw	% Acute RfD
Code	Name															
FB 0275	Strawberry	1	0.44	1	0.83	AUS	19	176						Case 1	0.008	38

PHOSALONE (060) **INTERNATIONAL ESTIMATE OF SHORT TERM INTAKE (IESTI)**
ADULTS

Acute RfD = 0.02 mg/kg bw

Commodity		MRL mg/kg	STMR or STMR-P, mg/kg	Process factor	HR, mg/kg	Country	Body weight, kg	Large portion g	Unit weight g	Country	% Edible portion	Unit weight, edible portion	Variability	Case	IESTI, mg/kg bw	% Acute RfD
Code	Name															
FP 0009	Pome fruits	2	0.8		1.5											
FP 0226	Apples	2	0.8		1.5	USA	70	1452	138	USA	92	127	7	Case 2a	0.034	171
FP 0230	Pears	2	0.8		1.5	USA	70	746	166	USA	91	151	7	Case 2a	0.029	147
FS 0012	Stone fruits	2	0.45		1.6											
FS 0013	Cherries	2	0.45		1.6	FRA	62.3	375				0		Case 1	0.010	48
FS 0240	Apricot	2	0.45		1.6	JPN	55	305	40	FRA	93	37	7	Case 2a	0.010	49
FS 0245	Nectarine	2	0.45		1.6	USA	70	636	136	USA	92	125	7	Case 2a	0.023	117
FS 0247	Peaches	2	0.45		1.6	JPN	55	655	110	FRA	90	99	7	Case 2a	0.025	124
TN 0660	Almonds	0.1	0.05		0.074	JPN	55	77				0		Case 1	0	1
TN 0666	Hazelnuts	0.05	0.05		0.05	AUS	70	70				0		Case 1	0	0
TN 0678	Walnuts	0.05	0.05		0.05	FRA	62.3	136				0		Case 1	0	1
	Apple compote		0.1	0.14			60	0				0		Case 3	0	0

PHOSALONE (060) **INTERNATIONAL ESTIMATE OF SHORT TERM INTAKE (IESTI)**
CHILDREN UP TO 6 YEARS

Acute RfD = 0.02 mg/kg bw

Commodity		MRL mg/kg	STMR or STMR-P, mg/kg	Process factor	HR, mg/kg	Country	Body weight, kg	Large portion g	Unit weight g	Country	% Edible portion	Unit weight, edible portion	Variability factor	Case	IESTI, mg/kg bw	% Acute RfD
Code	Name															
FP 0009	Pome fruits	2			1.5			0				0				
FP 0226	Apples	2	0.8		1.5	USA	15	679	138	USA	92	127	7	Case 2a	0.118	592
FP 0230	Pears	2	0.8		1.5	UK	14.5	279	166	USA	91	151	7	Case 2a	0.116	582
FS 0012	Stone fruits	2	0.45		1.6											
FS 0013	Cherries	2	0.45		1.6	FRA	17.8	297				0		Case 1	0.027	133
FS 0240	Apricot	2	0.45		1.6	AUS	19	414	40	France	93	37	7	Case 2a	0.031	154
FS 0245	Nectarine	2	0.45		1.6	AUS	19	302	136	USA	92	125	7	Case 2a	0.078	390
FS 0247	Peaches	2	0.45		1.6	AUS	19	316	110	France	90	99	7	Case 2a	0.063	317
TN 0660	Almonds	0.1	0.05		0.074	FRA	17.8	31				0		Case 1	0	1
TN 0666	Hazelnuts	0.05	0.05		0.05	NLD	17	11				0		Case 1	0	0
TN 0678	Walnuts	0.05	0.05		0.05	USA	15	6				0		Case 1	0	0
	Apple compote		0.1	0.14			15	0				0		Case 3	0	0

TEBUFENOZIDE **INTERNATIONAL ESTIMATE OF SHORT TERM INTAKE (IESTI)**
ADULTS

Acute RfD: May be necessary but has not yet been established

Commodity		MRL mg/kg	MR mg/kg	HR mg/kg	ody weight, kg	arge portion, g	Country	Unit weight , g	Country	Variability factor	Case	IESTI mg/kg bw	% Acute RfD
Code	Name												
FP 0226	Apple 1/	1	0.17	1.1	65	1,348	USA	100	FRA	7	Case 2a	0.015	-
FP 0230	Pear 1/	1	0.17	1.1	65	693	USA	89	FRA	7	Case2a	0.012	-
FB 0269	Grapes	1	0.25	0.5	70	513	AUS	118	FRA	7	Case2a	0.007	-
	Wine		0.0625		70	1,182	AUS			1	Case3	0.001	-

TEBUFENOZIDE (196) **INTERNATIONAL ESTIMATE OF SHORT TERM INTAKE (IESTI)**
CHILDREN UP TO 6 YEARS

Acute RfD: May be necessary but has not yet been established

Commodity		MRL mg/kg	STMR mg/kg	HR mg/kg	Body weight kg	Large portion, g	Country	Unit weight, g	Country	Variability factor	Case	IESTI mg/kgbw	% Acute RfD
Code	Name												
FP 0226	Apple 1/	1	0.17	1.1	15	679	USA	100	FRA	7	Case 2a	0.058	-
FP 0230	Pear 1/	1	0.17	1.1	14.5	279	UK	89	FRA	7	Case 2a	0.049	-
FB 0269	Grapes	1	0.25	0.5	19	342	AUS	118	FRA	7	Case 2a	0.025	-
	Wine		0.0625		19	3.8	AUS			1	Case 3	0	-

ANNEX V

Draft Report of an *ad-hoc* Expert Meeting on Acute Dietary Intake of Pesticide Residues

8-9 April 1999

Introduction

At an ad-hoc meeting organised by the Dutch Government, 12 invited experts met to develop guidance for use by the Joint Meeting on Pesticide Residues (JMPR) in estimating acute dietary risk from pesticide residues at an international level i.e. the International Estimate of Short Term Intake (IESTI). Details of participants are given in Appendix 1. The recommendations made during the FAO/WHO Consultation meeting held in Geneva in 1997 (WHO, 1997) were used as the starting point for the discussions. The meeting focused on risk assessment issues and did not consider issues relating to the setting of the acute reference dose (acute RfD).

The discussions made particular reference to the FAO/WHO report 'Food Consumption and Exposure Assessment of Chemicals' (WHO, 1997) and the UK document 'The Report of the International Conference on Pesticide Residues Variability and Acute Dietary Risk Assessment' (PSD, 1999), and also to worked examples provided by the participants. WHO also provided preliminary information on 'large portion sizes' and 'unit weights' which had been provided to the WHO by six Governments in response to the request made in CL 1998/29 - PR (September 1998).

Background

The FAO/WHO 1997 Consultation developed two equations for calculating acute exposure using the IESTI:

Case 1 where the composite sampling data reflect the residue level in the food commodity:

$$\text{IESTI} = \frac{(\text{LP} * \text{MRL-P})}{\text{bw}}$$

where LP = large portion consumption data for the commodity [kg]
MRL-P = maximum residue limit incorporating processing or edible portion factor(s) [mg/kg]
bw = mean body weight for the target population subgroup [kg]

Case 2 where composite residue data does not reflect the residue level in individual food commodities

$$\text{IESTI} = \frac{[U * \text{RL-P} * v] + [\max(0, \text{LP} - U) * \text{STMR-P}}{\text{bw}}$$

where U = median weight of the commodity unit [kg]
RL-P = highest residue level reported on a composite sample incorporating processing or edible portion factor(s) [mg/kg]
v = variability factor
max = the function indicating that the maximum of either zero or the value produced by subtracting the weight of one commodity unit (U) from the large portion consumption weight (LP) is used
STMR-P = supervised trial median residue level incorporating processing and/or edible portion factors [mg/kg].

Elements of these calculations were discussed in order to clarify some of the terms to facilitate the practical use of this methodology.

Clarification of methodology

The meeting considered the factors included in the case 1 and case 2 equations.

As a guiding principle, the best use of data should be made to ensure that no portion of the world population will be exposed to unacceptable levels of pesticide residues.

Large portion size data (LP)
Data have been submitted to the WHO by the Australian, Dutch, French, Japanese, UK and USA governments. The highest consumption figure from these data was included in the database prepared by WHO. It was agreed that this was acceptable since acute exposure assessments were based on single commodity consumption rather than the sum of intakes as is the case in the assessment of chronic exposure. Because so few countries appear to have data, it was further agreed that a global database be used incorporating the highest large portion size reported from any region.

The acute consumption database (based on 97.5^{th} percentile consumption) have been produced for the general population (all ages) and for children (aged 6 and under). The information was based on eaters only i.e. the consumption figures have not been reduced by taking account of non-consumers. It was noted that consumption data provided did not always fall entirely into these groups particularly for children where age ranges varied between data sets. The meeting considered that this was not a major problem since consumption was expressed on a body weight basis. Generally, consumption by children was higher than that for adults.

It was noted that there was an urgent need to improve the coverage and quality of databases of consumption data. It was recommended that where these data were being collected that this should be done in such a way as to allow their usage in

probabilistic modelling in the future at a national level. National governments should be encouraged to develop national dietary data that will enable the calculation of national estimates of short term intake (NESTIs). WHO will develop guidance for data collection and submission in the future.

It was recommended that the JMPR use the database prepared by WHO for acute risk assessment once validation has been carried out to ensure that data are correct and have been reported in a consistent manner (i.e. whether consumption data were based on a whole weight or edible portion basis). Governments should also state the range of body weights covered in the surveys in addition to the mean/median body weight.

Maximum residue level in the edible portion (MRL-P)

The meeting recommended that the MRL-P term in the case 1 equation should be replaced by RL-P in line with the recommendations made by the UK Conference and particularly in the case where there was a large difference between the MRL-P and the RL-P due to the geometric progression used in deriving MRLs.

The residue included in the residue definition for acute risk assessment should be taken into account in the RL value.

Body weight (bw)

The meeting recommended that a body weight of 15 kg should be used for the calculation of intakes by children. This was considered appropriate because large portion sizes were based on mean body weight ranges of 14.5-19 kg. The 15kg was also in line with the values by the WHO in drinking water quality guidelines. 60 kg would be used for adults.

Unit weight data (U)

It was agreed that the median unit weight data should be used in line with the recommendations made at the Geneva Consultation. France, the UK and the USA have provided unit weight data to the WHO. It was agreed that for risk assessments at an international level, the highest reported median unit weight should be used.

As it was unclear whether these data conformed to the recommendations of the Geneva Consultation, Governments should also be asked to provide information on the way these data were collected to ensure that these were reported on a consistent basis e.g. edible portion versus whole commodity, mean versus median, etc. The meeting noted that if both the unit weight and large portion size data were reported on a whole commodity basis then corrections needed to be made at the time of calculation of acute exposure to express these as edible portion weights when the residues in the commodity were also expressed on an edible weight basis.

Variability factor (*v*)

The variability factor is one of the main elements that influence the outcome of case 2 calculations. It was noted that the UK conference indicated that there was room for refinement of *v* but that further data were required in order to calculate new generic factors for *v*. For the present, the recommendations from the Geneva Consultation (*v* = 10 for medium sized commodities and *v* = 5 for large commodities) should continue to be used. In generating data to define *v*, the recommendations from the UK conference should be used.

Use of the 97.5th percentile consumption data

The meeting noted that the differences between acute consumption at 95th, 97.5th and 99th percentile did not make a significant difference to the overall calculation of intake in the case 2 equation. The largest influence in the calculation was the contribution from the first unit consumed. It was also noted the database did not include non-consumers. Therefore the meeting concluded that use of the 97.5th percentile (eaters only) was sufficient to take account of the whole population.

Use of survey data for calculating acute intakes

The value of using reliable, selective survey data, i.e. data accompanied by treatment records, origin of samples known, treatment according to GAP, etc., at a national level was acknowledged. These should not be confused with random monitoring of commodities of unknown origin.

Contributions from metabolites

The meeting recognised that the residue definition may not always be identical for acute and chronic risk assessments. Care should also be taken to ensure that appropriate corrections were made for metabolite contribution to toxicity.

Acute RfD exceedances

Both the Geneva Consultation and the 1998 JMPR report state that exceedances of the acute RfD were not generally considered acceptable. The meeting recommended that where an exceedance of the acute RfD was seen, the JMPR should consider its toxicological significance with particular attention to the basis for the safety/uncertainty factor and the severity of the effects on which the acute RfD was based. The seriousness of the exceedances should be considered on a case by case basis in order to advise risk managers.

Probabilistic modelling

It was noted that use of probabilistic modelling at an international level was impractical as sufficient data do not exist to carry out these calculations. It was also noted that this was only 'a tool to aid decision making and risk management'. The possibility of the acute RfD being exceeded in individual cases would still exist if determined by deterministic estimate calculations, despite probabilistic modelling showing non-exceedance of the acute RfD by a high percentage of consumers.

Annex V

Other recommendations

1. The meeting recommended that beginning in 1999, RLs should be routinely estimated along with MRLs and STMRs at the time of evaluation by the JMPR.
2. When residues are at or below the limit of determination (LoD), the existing guidelines for chronic exposure assessment allows the use of zero for the STMR value when evidence suggests that levels are essentially zero. In this 'nil residue situation', the meeting considered that the assessment of acute risk was not necessary. However, when this assurance is not provided, these should be evaluated using the JMPR procedures i.e. assuming a residue level equivalent to the LoD and an acute risk assessment should be carried out.
3. The number of data points considered sufficient for the estimation of STMRs and MRLs were also acceptable for deterministic assessments of acute dietary exposure.
4. The meeting reinforced the recommendations of the UK Conference noting that where data were generated on residues in individual units, such trials should be carried out using commercial equipment and be representative of commercial practices; small plot trials would not be acceptable.

References

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