Pesticide residues in food – 2005

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T, toxicological evaluation; R, residue and analytical aspects; D, dietary risk assessment
* New compound
** Evaluated within the periodic review programme of the Code Committee on Pesticide Residues

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Geneva, 20–29 September 2005

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ABBREVIATIONS

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

ADI	acceptable daily intake
ai	active ingredient
ARfD	acute reference dose
AUC	area under the curve for concentration–time
bw	body weight
CCFAC	Codex Committee on Food Additives and Contaminants
CCN	Codex classification number (for compounds or commodities)
CCPR	Codex Committee on Pesticide Residues
EC_{50}	the concentration of agonist that elicits a response that is 50% of the possible maximum
ECD	electron capture detection
DHEQ	dihydroethoxyquin
DHMEQ	dehydromethylethoxyquin
DMEQ	demethylethoxyquin
F_1	first filial generation
F_2	second filial generation
FAO	Food and Agricultural Organization of the United Nations
GAP	good agricultural practice
GC	gas chromatography
GLC	gas–liquid chromatography
GPC	gel-permeation chromatography
GEMS/Food	Global Environment Monitoring System–Food Contamination Monitoring and Assessment Programme
HPLC	high-performance liquid chromatography
HR	highest residue in the edible portion of a commodity found in trials used to estimate a maximum residue level in the commodity
HR-P	highest residue in a processed commodity calculated by multiplying the HR of the raw commodity by the corresponding processing factor
IC_{50}	concentration required to inhibit activity by 50%
IEDI	international estimated daily intake
IESTI	international estimate of short-term dietary intake
ISO	International Organization for Standardization
IUPAC	International Union of Pure and Applied Chemistry
JECFA	Joint Expert Committee on Food Additives
JMPR	Joint Meeting on Pesticide Residues
JMPS	Joint FAO/WHO Meeting on Pesticide Specifications
LC	liquid chromatography
LC_{50}	median lethal concentration
LD_{50}	median lethal dose
LOAEL	lowest-observed-adverse-effect level
LOAEC	lowest-observed-adverse-effect concentration
LOD	limit of detection
LOQ	limit of quantification
MEQ	methylethoxyquin
MRL	maximum residue level

MS	mass spectrometry
MS/MS	tandem mass spectrometry
NOAEL	no-observed-adverse-effect level
OECD	Organization for Economic Co-operation and Development
PHI	pre-harvest interval
P_{ow}	octanol-water partion coefficient
ppm	parts per million
STMR	supervised trials median residue
STMR-P	supervised trials median residue in a processed commodity calculated by multiplying the STMR of the raw coomodity by the corresponding processing factor.
RAC	raw agricultural commodity
TRR	total radiolabelled residue
TMDI	theoretical maximum daily intake
WHO	World Health Organization

Use of JMPR reports and evaluations by registration authorities

Most of the summaries and evaluations contained in this report are based on unpublished proprietary data submitted for use by JMPR in making its assessments. 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 of the data submitted for the 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 2005 JOINT FAO/WHO MEETING OF EXPERTS

1. INTRODUCTION

A Joint FAO/WHO Meeting on Pesticide Residues (JMPR) was held at World Health Organization (WHO) headquarters, Geneva, Switzerland, from 20 to 29 September 2005. The Meeting brought together the FAO Panel of Experts on Pesticide Residues in Food and the Environment and the WHO Core Assessment Group.

The Meeting was opened by Mr Denis Aitken, Acting Director-General, Sustainable Development and Healthy Environment Cluster, WHO. On behalf of the Directors-General of the Food and Agriculture Organization of the United Nations (FAO) and WHO, Mr Aitken welcomed the participants and thanked them for providing their valuable time and expertise.

Mr Aitken noted that the JMPR plays an important role in the improvement of food safety on a global basis, by laying the scientific foundation for the development of international and national food standards. Mr Aitken said that the work of the Meeting was seen as an integral part in the safe use of pesticides to ensure food security and for overall sustainable development, and was also important in this context for the United Nations Millennium Development Goals. The methodological work of the Meeting in scientific risk assessment was important also for other areas within WHO and FAO, and the organizations now put great effort into translating the outcome of risk assessments made by expert bodies into recommendations to experts in other areas and to enforcement bodies. One example of the important methodological work of the Meeting was the recent publication of a guidance document on the setting of acute reference doses (ARfDs)[1], which was expected to facilitate international harmonization in this area.

Mr Aitken discussed the challenges faced by the JMPR in times of increased need for independent international scientific advice but limited resources, and the need to clearly prioritize and be as efficient as possible. Progress had been achieved in recent years, including the ongoing activities regarding work sharing (the use of existing national or regional evaluations as a basis for the evaluation made by JMPR); the improvements within the Codex Committee on Pesticide Residues regarding the revision of criteria for prioritization of requests for compounds for evaluation by JMPR, and the acceptance of the recommended JMPR maximum residue levels (MRLs) as temporary Codex MRLs.

Mr Aitken acknowledged the important contribution of the 38 participants from 19 different countries, and thanked the appropriate national authorities, institutes and organizations that had given participants the opportunity to work within this international programme and had provided, at least partially, infrastructure and salary during the preparation for the Meeting. He emphasized that without these contributions the programme could not work.

The speaker summarized the challenging tasks before the 2005 JMPR: the evaluation of 21 different pesticides (five of which were new compounds) as well as the consideration of several important general issues relating to the advancement and further improvement of current risk assessment procedures.

Mr Aitken reminded the participants that they had been invited in their personal capacities as international experts, and not as representatives of governments, institutes, or any other organization,

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[1] Solecki R, Davies L, Dellarco V, Dewhurst I, Raaij M, Tritscher A. Guidance on setting of acute reference dose (ARfD) for pesticides. *Food Chem. Toxicol*. 2005;43:1569–1593.

and he stressed that the discussions held during the meeting were confidential until publication was authorized.

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 Meetings (see Annex 5) contain information on acceptable daily intakes (ADIs), ARfDs, MRLs, and the general principles that have been used for evaluating pesticides. 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 levels of residues that might occur as a result of use of the pesticides according to good agricultural practice. The estimation of MRLs and supervised trials median residues (STMR) values for commodities of animal origin was elaborated. The WHO Core Assessment Group was responsible for reviewing toxicological and related data in order to establish ADIs, and ARfDs, where necessary and possible.

The Meeting evaluated 21 pesticides, including five new compounds and five compounds that were re-evaluated within the periodic review programme of the Codex Committee on Pesticide Residues (CCPR) for toxicity or residues, or both. The original schedule of compounds to be evaluated was amended for ethoxyquin, endosulfan and pyrethrins. For ethoxyquin, only its toxicology was evaluated as no residue data was received. The evaluation of endosulfan was postponed to 2006 as the residue data was received late and the Meeting agreed to conduct a residue evaluation on pyrethrins as sufficient data had been received.

The Meeting allocated ADIs and ARfDs, estimated MRLs and recommended them for use by the CCPR, and estimated STMR and highest residue (HR) levels as a basis for estimating dietary intakes.

The Meeting also estimating the dietary intakes (both short-term and long-term) of the pesticides reviewed and, based on this, performed a dietary risk assessment in relation to their ADIs or ARfDs. Cases in which ADIs or ARfDs may be exceeded were clearly indicated in order to facilitate the decision-making process by the CCPR. The rationale for methodologies for long-term and short-term dietary risk assessment are described in detail in the reports of the 1997 JMPR (Annex 5, reference *80*, section 2.3) and 1999 JMPR (Annex 5, reference *86*, section 2.2). Additional considerations are described in the report of the 2000 JMPR (Annex 5, reference *89*, sections 2.1–2.3).

ACKNOWLEDGMENTS

The Meeting learned with deep regret of the recent death of Professor Albert Besemer. Professor Besemer, a pesticide scientist of international reputation, made very valuable contributions to the work of the JMPR during more than 20 years. He is especially remembered for his preparation of the Codex Classification of Foods and Animal Feeds, used in many countries for regulation of pesticide residues, and also used continually by the JMPR.

The Meeting expressed its recognition to Dr Amelia Tejada, FAO Joint Secretary, at the end of her 6-year assignment in FAO. It was noted that during Dr Tejada's term of office the *FAO Manual* had been published and that several other initiatives had been started that aimed to address the increasing workload of the JMPR. Her warm, friendly and helpful attitude will be missed by all.

2. GENERAL CONSIDERATIONS

2.1 WORK SHARING

General considerations regarding work sharing

The Meeting discussed the advantages and limitations of work sharing in the context of the FAO/WHO/Organization for Economic Co-operation and Development (OECD) pilot project on work sharing conducted in 2004 with the pilot study on trifloxystrobin and the work-sharing project for 2006 on quinoxyfen, as proposed by the CCPR. The purpose of this project was to test whether national and regional evaluations of toxicology and pesticide residues could be used as a basis for the JMPR evaluations.

Overall, work sharing, as understood by the JMPR, should represent an independent expert peer review of critical data and existing evaluations; where possible, appropriate text from existing national/regional evaluations should be used by the JMPR experts. The Meeting noted that work sharing can be useful and save time. However, there are clear limitations to work sharing, as noted in the 2004 JMPR report. The Meeting emphasized that it is critical that JMPR continues to perform an independent evaluation and expert review of the evaluation that ensures consistency, and results in an international consensus evaluation. In this context, the JMPR monographs can be described in three parts: (1) the description of actual studies; (2) the interpretation and evaluation of the studies; and (3) the final evaluation/appraisal of the compound. Part 1 is most accessible to work sharing, provided that there is sufficient harmonization between monograph formats used by different authorities. By using study descriptions and data tables from existing evaluations, the JMPR expert may be able to save time in the preparation of the JMPR monograph. Part 2 could be taken directly or modified or rewritten from existing national/regional evaluations after a review by the JMPR experts. Part 3 should represent an independent JMPR evaluation and review.

Considerations regarding toxicological evaluations

Regarding the need to develop a JMPR toxicological monograph for compounds for which agreement exists in the evaluations made by several authorities, the Meeting pointed out that JMPR toxicological monographs are rather unique in their complete, detailed, and transparent evaluations, and are more readily accessible than other monographs. This had also been stated at the recent OECD workshop on work sharing.

For the proposed work-sharing project for 2006, a different approach from that used in the 2004 pilot project was proposed for the toxicological evaluation. Instead of using one national/regional evaluation as a “template” for the JMPR toxicological monograph and comparing this with other evaluations, the Meeting recommended that the Temporary Adviser should judge which relevant parts of different national/regional evaluations should be used in preparing the JMPR toxicological monograph.

In the preparation of the present Meeting, the United States Environmental Protection Agency (EPA) made available to the toxicology experts tables of four of the five scheduled new compounds (fenhexamid, novaluron, dimethenamide-P, indoxacarb), summarizing the toxicological end-points/studies and uncertainty factors used in the evaluations made by several national/regional authorities. The WHO Core Assessment Group generally agreed that such comparison tables are a useful resource in both the preparation of the working papers for the Meeting and in discussions during the meeting, mainly for identifying differences in the selection of end-points. It was also agreed that such a comparison table would be useful in the preparation of working papers for the 2006 JMPR. The Meeting recommended, however, that less detail was needed and that a summary of

end-points, critical studies, no-observed-adverse-effect levels (NOAELs) and lowest-observed-adverse-effect levels (LOAELs), and uncertainty factors would be sufficient. Also, it was recommended that national/regional assessments should be clearly identified as being in a draft or final form.

Criteria for a work-sharing project for residue evaluations

Experience gained during the evaluation of trifloxystrobin by the 2004 JMPR indicated the need to select criteria for the acceptance of a compound to be evaluated via work sharing, in order to increase efficiency and thus reduce the workload of the JMPR and support the acceleration of the process by which MRLs are accepted.

The following criteria for the selection of a compound to be evaluated using the work-sharing process relevant to residue evaluations were recommended:

- The compound must be validated at national, regional and international levels, covering all aspects of the residue evaluation (including data from supervised trials).
- Summaries of data validated at national, regional and international levels, covering all aspects of the residue evaluation (including data from supervised trials) must be available.
- The data should be available in a standard format, harmonized at the international level (OECD, FAO). This would allow exchange of a valid database, thus saving time and potentially reducing the workload.
- In the national/regional documents, factual information should be separated from interpretations.
- The definition of the residue should preferably be identical in the different national and regional evaluations.

Conclusions

The main criterion for the selection of a new pesticide to be evaluated via work sharing (toxicological and residue evaluations) is that it has been reviewed by at least three national/regional agencies. In the event that the findings are similar, relevant parts of national/regional reviews should be used in the preparation of JMPR documents. An independent appraisal should be prepared and approved by JMPR that represents international consensus.

2.2 DEVELOPMENT OF OECD TEST GUIDELINES AND GUIDANCE DOCUMENTS FOR PESTICIDE RESIDUE CHEMISTRY

The Meeting was informed that OECD has developed five test guidelines and two guidance documents on residue chemistry based on guidelines currently used in Australia, Canada, Japan, European Union (EU), FAO, and the United States of America (USA). The documents primarily provide guidance for the generation of data but are also useful for assessing these data. Guidelines, once accepted, are mandatory among the OECD Member States, while guidance documents are not. The documents are currently out for comments by OECD Member States and other stakeholders. An OECD ad hoc Expert Group was responsible for drafting the guidelines and guidance documents. The following countries and organizations are represented in the Expert Group: Australia, Canada, Germany, Italy, Japan, Netherlands, the United Kingdom (UK), USA, the European Commission, FAO and CropLife International/BIAC (industry). The Expert Group is chaired by the USA.

Up to this point, OECD Harmonized Residue Guidelines were developed for: 1) Metabolism in Crops; 2) Metabolism in Livestock; 3) Residues in Livestock; 4) Metabolism in Rotational Crops; and 5) Residues in Rotational Crops (Limited Field Studies). The two guidance documents developed are: (1) Overview for Residue Chemistry Studies (including Livestock Feedstuff tables, tables of Raw Agricultural Commodities, and Glossary of Terms); and (2) Definition of the Residue. In the near future, three additional guidelines will be drafted, on (1) storage stability; (2) Processing studies – nature of the residue; (3) Processing studies – Magnitude of the residue. A guidance document will be developed on analytical methods. In the final phase of the project, a guideline on crop field trials will be drafted. In parallel, templates for summarizing data contained in a study report are being developed.

The Meeting agreed that harmonization of guidelines for determination of pesticide residues provides a foundation for work sharing of residue chemistry reviews among countries and that harmonization will also lead to mutual acceptance of regulatory results thus minimizing trade barriers. Therefore the Meeting welcomed the development of the above guidelines and guidance documents and looks forward to further developments.

2.3 STATISTICAL APPROACH TO MRL ESTIMATION

The Meeting considered a statistically-based procedure used routinely in the North American Free Trade Agreement (NAFTA) countries for the estimation of maximum residue limits (tolerances). The supervised field trial residue data resulting from the use of a specific pesticide on a specific commodity (or commodity group) are entered in any order into a spreadsheet which then tests the data set for fit to a log normal distribution. If the data pass the log normality test, as evidenced both by a mathematical calculation and a probability plot, the 99^{th} percentile value and the 95% upper confidence limit of the 95^{th} percentile value are calculated (LN99, LN95).

For a log normal distribution where the number of residue data points are small ($n < 15$), an alternate calculation of 3.9 times the upper confidence interval of the median is made (UPLMed95). For the situation of the mean equal to the standard deviation, this represents the 95^{th} percentile.

Finally, if the data set does not appear to be log normal, the mean plus three standard deviations is determined (California method), which represents at least 89% of data for a distribution-free situation.

A visual plot of the log normal test and the various possible values are provided. The scientist is thus presented with a series of suggested values from which he/she may select or reject, based on expert judgment. The decision-tree sequence is illustrated in Figure 1. Note that the MLE (maximum likelihood estimate), for values below the limit of quantification (LOQ) and the rounding function are options that may be toggled on or off.

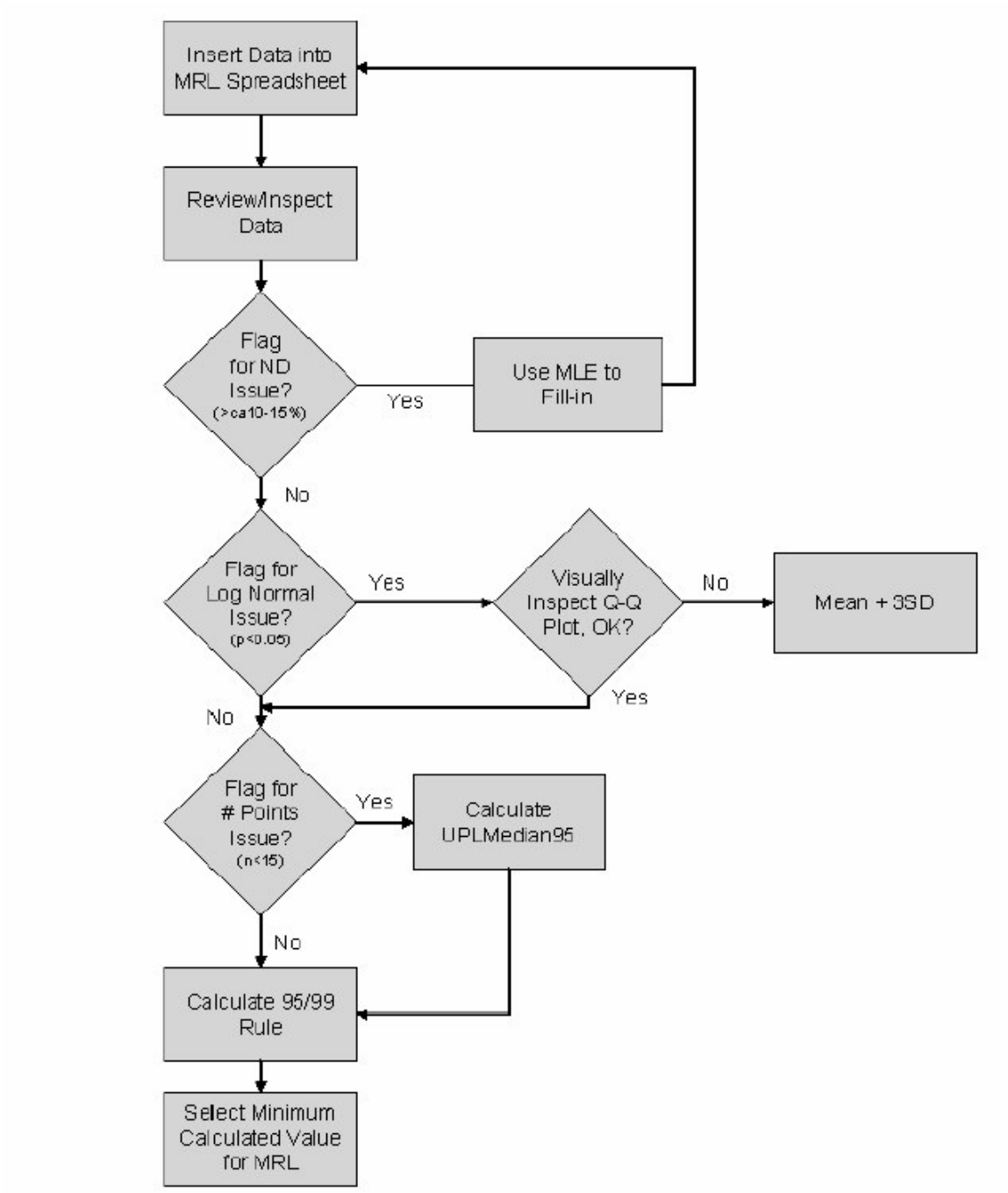


Figure 1: Options for estimation of MRL from field trial data sets

The Meeting used the spreadsheet to obtain maximum residue level estimates for several of the compounds considered. The findings were compared with the estimates made independently by the evaluators. The comparison is summarized in Table 1. Generally, the recommendations of the spreadsheet compare favourably with those determined by the evaluator.

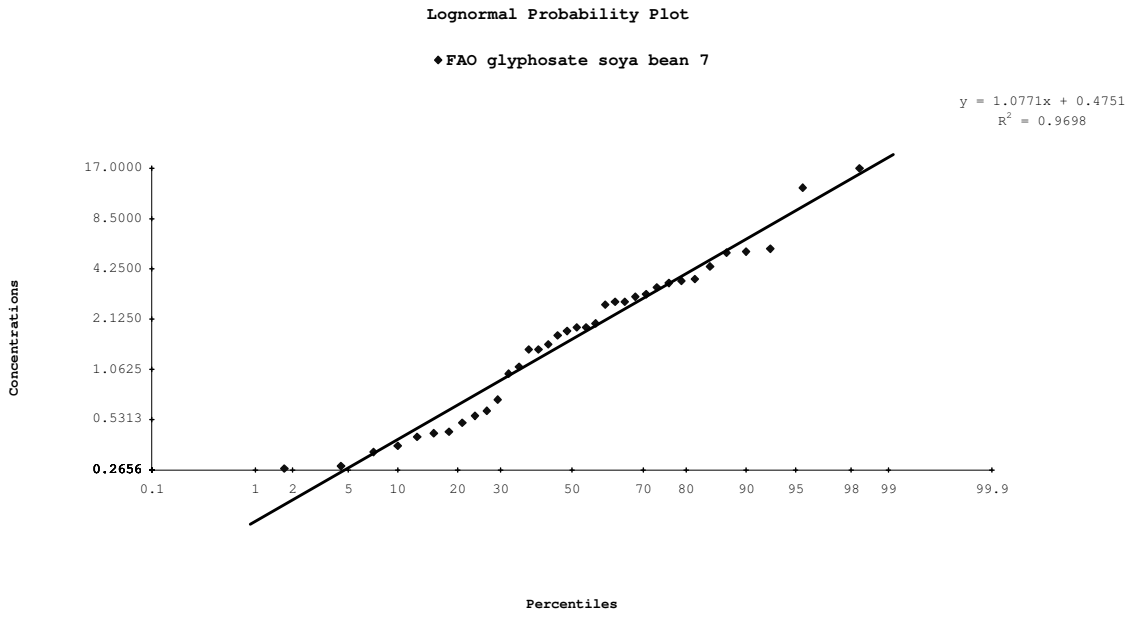
Table 1: Comparison of some MRLs as determined by JMPR and by spreadsheet

Commodity	No.	High Residue (mg/kg)	Median Residue (mg/kg)	MRL JMPR (mg/kg)	Spreadsheet MRL		
					Source	Estimate (mg/kg)	MRL (JMPR Rounded) (mg/kg)
CYHEXATIN							
Orange	20	0.10	0.05	0.2	99LN	0.22	0.3
Apple	48	0.16	0.03	0.2	µ+3s	0.16	0.2
Grapes	36	0.19	0.08	0.3	µ+3s	0.22	0.3
FENHEXAMID							
Cherries	20	4.7	1.35	7	LN99	5.38	7
Peaches	12	5.9	3.85	10	µ+3s	8.79	10
Plums	27	0.79	0.31	1	µ+3s	0.91	1
Grapes	11	11	4.3	15	µ+3s	13.42	15
Strawberry	6	5.9	3.3	10	µ+3s[1]	10.29	15
Bushberry	16	2.9	1.65	5	LN99	3.68	5
Caneberry	13	11	2.0	15	UPLMed95	14.21	15
Kiwi	9	11	6.3	15	LN99	14.88	15
Cucumber	16	0.65	0.185	1	µ+3s	0.60	0.7
Tomato	17	0.93	0.40	2	LN95	1.17	2
Pepper	18	1.5	0.71	2	LN99	1.60	2
Lettuce	8	19	11.5	30	µ+3s[2]	29.78	30
Almonds	5	0.02	0.02	0.02*	µ+3s	0.02	0.02
GLYPHOSATE							
Beans, dry	19	1.8	0.17	2	LN99	2.19	3
Peas, dry	11	2.1	0.50	5	UPLMed95	3.81	5
Soya beans	36	17	1.85	20	LN95	16.11	20
Maize	21	3.0	0.05	5	µ+3s	2.16	3
Cereal grains (ex maize and rice)	84	20	3.85	30	LN95	30.92	40
Cotton seed	23	28	5.00	40	µ+3s[3]	33.97	40
Rape	35	12	0.96	20	LN95	17.46	20
Sunflower	8	5.6	0.40	7	µ+3s[4]	9.11	10
Alfalfa hay (fodder)	23	341	189	500	LN99	568.15/.89	700
Grass hay	13	259	187	500	µ+3s	409/0.88	500
Bean fodder	10	93	22.5	200	UPLMed95	179.46/0.90	200
Pea fodder	10	320	102	500	LN99	710.27 /0.88	800
Barley straw	27	160	47	400	LN95	356.81/0.88	400
Maize fodder	20	92	20.5	150	UPLMed95	126.85/0.83	160
Oat straw	11	27	64	100	LN99	145.81/0.90	160
Sorghum fodder	10	33	18.5	50	µ+3s[5]	51.35/0.89	60
Wheat straw	29	198	47	300	LN95	327.72/0.88	400
INDOXACARB							
Apple	14	0.30	0.21	0.5	LN99	0.42	0.5
Pear	6	0.11	0.06	0.2	LN99	0.13	0.2
Peach	9	0.18	0.11	0.3	LN99	0.28	0.3

Commodity	No.	High Residue (mg/kg)	Median Residue (mg/kg)	MRL JMPR (mg/kg)	Spreadsheet MRL		
					Source	Estimate (mg/kg)	MRL (JMPR Rounded) (mg/kg)
Grapes	16	1.5	0.30	2	LN99	2.5	3
Cabbage	8	2.7	0.44	3	UPLMed95	3.95	5
Broccoli	8	0.14	0.06	0.2	LN99	0.24	0.3
Cauliflower	19	0.14	0.02	0.2	μ+3s	0.13	0.2
Cucumber	13	0.10	0.02	0.2	μ+3s	0.10	0.1
Melons	18	0.09	0.03	0.1	μ+3s	0.08	0.1
Tomato	8	0.30	0.11	0.5	LN99	0.57	0.7
Pepper	30	0.21	0.04	0.3	μ+3s	0.19	0.2
Sweet corn	12	0.01	0.01	0.02*	μ+3s	0.01	0.02
Head lettuce	9	4.3	2.8	7	μ+3s	6.27	7
Leaf lettuce	9	8.4	6.6	15	LN99	14.27	15
Pulses	7	0.13	0.02	0.2	μ+3s	0.16	0.2
Soy bean	20	0.45	0.03	0.5	μ+3s	0.50	0.5
Potato	17	0.0085	0.003	0.02	μ+3s	0.01	0.01
Peanuts	13	0.003	0.003	0.02*	μ+3s	0.003	0.003
Cotton seed	7	0.92	0.36	1	LN99	2.25	3
Peanut hay	12	45	16	50	LN99	90.74	100
Alfalfa hay	43	43	17	60	LN95	42.81	50
Maize fodder	5	15	7.8	25	LN99	23.23	25
Cotton gin trash	7	11	8.0	20	LN99	16.19	20
METHOPRENE							
Cereal grains	12	8.1	4.85	10	LN99	13.83	15
NOVALURON							
Pome fruit	37	1.8	0.65	3	LN95	1.76	2
Soya	11	0.01	0.01	0.01*	μ+3s	0.01	0.01
Cotton seed	16	0.40	0.07	0.7	μ+3s	0.48	0.5
TERBUFOS							
Banana	21	0.03	0.01	0.05	μ+3s	0.03	0.03
Sugar beet tops	26	0.82 (3.56 dry)	0.05	5 (dry)	μ+3s	0.54 (2.35 dry)	3

[1] Rejected spreadsheet finding of a log normal situation (29 mg/kg).
[2] Rejected spreadsheet finding of a log normal situation (72 mg/kg).
[3] Rejected spreadsheet finding of a log normal situation (96 mg/kg).
[4] Rejected spreadsheet finding of a log normal situation (3.59 mg/kg).
[5] Rejected spreadsheet finding of a log normal situation (97 mg/kg).

Estimation of the maximum residue level for glyphosate on soya beans is an example of how the spreadsheet may assist the evaluator. The data set contains 36 residue values ranging from 0.27 to 17 mg/kg with a median value of 1.85 mg/kg and an average of 2.76 mg/kg. The evaluator would most likely consider 20 or 30 mg/kg, based on the JMPR rounding system. The spreadsheet calculations (Figure 2) indicate that the data appear to be log normally distributed, as indicated from both the Shapiro-Francia Normality Test and a visual inspection of the probability plot. The 99th percentile value is 19.27 mg/kg and the 95% upper confidence limit of the 95th percentile is 16.11mg/kg. Under JMPR rounding procedures of these estimates, the appropriate estimate would be 20 mg/kg. The spreadsheet proves useful in helping the evaluator decide between the 20 mg/kg and 30 mg/kg values and provides a good statistical rationale for the choice.



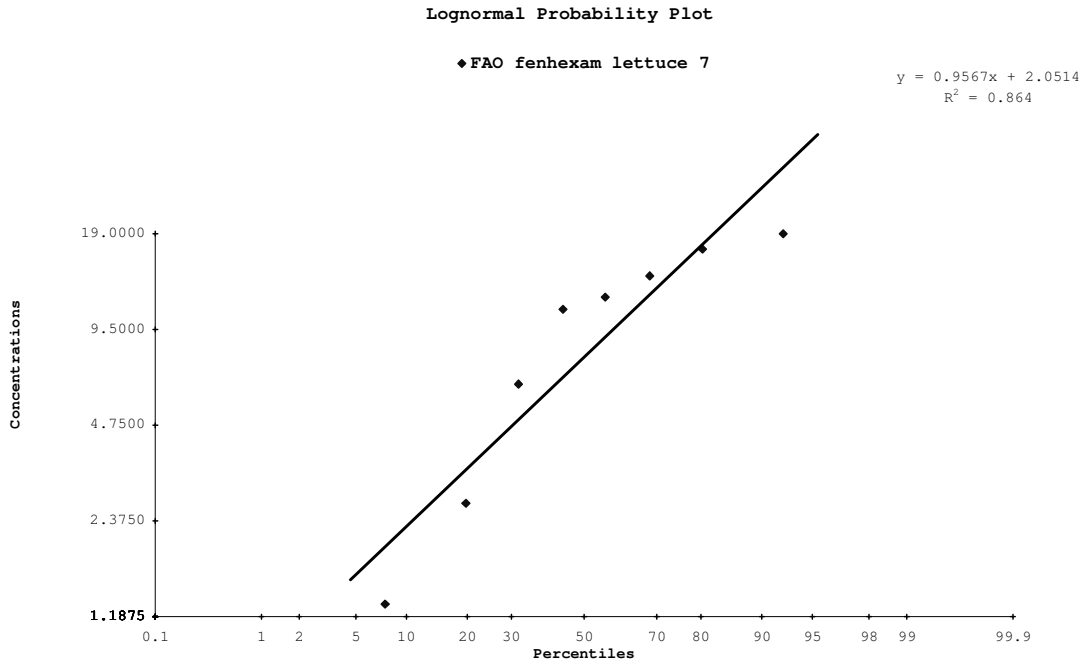
	Regulator:	FAO	
		glyphosate	
	Crop:	soya bean	
	PHI:	7	
	App. Rate:		
	Submitter:		
	n:	36	
	min:	0.27	
	max:	17.00	
	median;	1.85	
	average:	2.76	
	95th Percentile	**99th Percentile**	**99.9th Percentile**
EU Method I Normal	8.38 (10.13)	10.71 (12.95)	13.32 (--)
EU Method I Log Normal	9.31 **(16.11)**	**19.27** (38.87)	43.57 (--)
EU Method II Distribution-Free		6.90	
California Method μ + 3σ		**13.01**	
UPLMedian95th		**10.07**	
Approximate Shapiro-Francia Normality Test	0.9698 p-value > 0.05 : Do not reject lognormality assumption		

(Values in parentheses are confidence limits on the 95th or 99th percentiles)

Figure 2: Log normality test and possible MRLs for glyphosate on soya bean.

However, it is also evident from the worked examples that the evaluator must not simply default to the output of the spreadsheet but must always use scientific judgment. Particular caution is required with small data sets. Consider the supervised field trial results for fenhexamid on lettuce. There are only 8 sample points, with a median of 11.5 mg/kg, an average of 10.4 mg/kg, and a maximum of 19 mg/kg. The Meeting agreed that 30 mg/kg was a reasonable estimate of the maximum residue level. The spreadsheet determined that the distribution was log normal, with a 99th percentile value of 72.17, or a maximum residue level estimate of 75 mg/kg. This value is

unreasonably high when compared with the maximum value, in fact, more than three times the maximum. Also, the finding of log normality seems not so evident upon inspection of the probability plot (Figure 3). If log normality is rejected, the nonparametric estimate is 29.78 mg/kg, in agreement with the 30 mg/kg Meeting estimate.



	Regulator:	FAO	
		fenhexam	
	Crop:	lettuce	
	PHI:	7	
	App. Rate:		
	Submitter:		
	n:	8	
	min:	1.30	
	max:	19.00	
	median;	11.50	
	average:	10.43	
	95th Percentile	**99th Percentile**	**99.9th Percentile**
EU Method I Normal	21.04 (30.99)	25.43 (38.52)	30.36 (--)
EU Method I Log Normal	37.59 **(164.62)**	**72.17** (503.36)	150.02 (--)
EU Method II Distribution-Free		32.50	
California Method μ + 3σ		**29.78**	
UPLMedian95th		**104.40**	
Approximate Shapiro-Francia Normality Test		0.8640 p-value > 0.05 : Do not reject lognormality assumption	

(Values in parentheses are confidence limits on the 95th or 99th percentiles)

Figure 3: Log normality test and possible MRLs for fenhexamid on lettuce.

The Meeting agreed that the statistical spreadsheet is a useful tool that can assist the evaluator in deriving an appropriate maximum residue level estimate from the supervised field trial

data. It was also recognized that the evaluator should not rely upon the spreadsheet to provide the proper value, but he/she must exercise good scientific judgment in selecting among the optional outputs or in proposing a value not provided by the spreadsheet. The greatest attribute of the new procedure is in providing a statistical analysis of the data and thereby a more defensible basis for the estimate. The Meeting noted that further development of the procedure may be necessary for small data sets.

The Meeting also considered that the widespread use of a standardized estimation procedure has the potential to advance consistency in the estimation of MRLs at the national and international levels.

The Meeting concluded that (1) evaluators may use the spreadsheet in the evaluation of verified field trial residue data as an aid in the estimation of the maximum residue level; and that (2) the procedure will be included in the next update of the *FAO Manual*.

2.4 CROP CLASSIFICATION AND HARMONIZATION

The Meeting noted the two well established crop classification systems: the Codex Crop Classification and the United States Crop Grouping Scheme. Both systems originated from the same source, the work of Dr R. Duggan, USDA, and were developed in synchronic timelines. They are fairly similar (approximately 70–80%) on the commodities identified.

Besides the similarities, some major differences also exist between the two systems and these are noted in the following table:

Content	Codex System	US System
Crop Group scheme	40 crop groups (plant origin)	20 crop groups (to be increased)
Commodity scheme	1096 commodities	508 commodities (commodities in Crop Definitions are not included)
Numbering system	Class-Type-Groups	Groups
Subgroups and Definitions	Limited	Yes (to facilitate registration in more related crops)
Representative crops	None	Yes (based on economic value & residues; help standardize residue data requirement)
Number of trials required	Not relevant	Yes (based on acreages, economic importance, and diet of children)
Trial distribution required	Not relevant	Yes (based on % of production in Zones)

Given the above differences, it was recognized that the two classification systems were originally developed with different focuses. The Codex system was for MRL settings from agricultural and trade perspectives while the US system was for residue extrapolations from the point of view of residue exposure and pesticide use patterns.

Currently both systems are undergoing revisions led by the CCPR Delegation of the Netherlands for Codex, and IR-4 and US EPA for the USA. The US revision is a joint effort of the International Crop Grouping Consulting Committee, which is formed by representatives from Asia, Australia, EU, Middle East, and NAFTA countries, including representatives of the Netherlands, the Codex revision leading group.

The Meeting supports the collaboration initiatives being made by the two workgroups to bring the strengths of the two systems together in a harmonized classification system. It was recognized that such a system would facilitate the work of JMPR and CCPR, and would benefit participating countries in residue research, risk assessment, and MRL setting.

2.5 INTERNATIONAL SPECIALITY CROP FOUNDATION INITIATIVE FOR MINOR USE

Obstacles to the registration of pesticides for minor uses and specialty crops are observed in many countries, as the development of pesticide uses for these purposes is not economically attractive to manufacturers. Specialty crops are traded regionally and internationally and are often of high economic value; however, the establishment of MRLs for these crops remains scarce due to the lack of available residue data and/or registered uses.

The Meeting noted the activities of the USDA/IR 4-Project within NAFTA and its recent collaborations with EU member states and Asian countries. IR-4 is a special minor use programme funded by the US-government and the private sector. This programme has developed residue data to support registration of agrichemicals on specialty crops for over 40 years with over 8,300 food use clearances and 10,600 ornamental use clearances. Since 2001, IR-4's tolerance petitions comprised 50% of the total numbers approved by the US EPA (IR-4 website: http://ir4.rutgers.edu).

The Meeting was informed that IR-4 is willing to share its data and experiences with other countries, and is willing to support an international collaboration, proposed as the International Specialty Crop Foundation, to be housed and led by IR-4. This Foundation should be funded by various sources, i.e. governments, pesticide industry, growers associations, importers/exporters and others, and hopefully will have the participation of international organizations such as FAO and OECD.

Such an initiative would enhance the availability of residue data for minor uses and specialty crops being submitted to national registration authorities for their approval and subsequently to the JMPR. It would maximize efforts and save resources of participating countries, and would further strengthen the process of establishing international MRLs, benefiting both industrialized and developing countries.

The essential elements in this process are:

- Identifying needs and establishing a list of tasks to be included in the Foundation’s programme;
- Elaborating harmonized protocols for residue trials to produce data for the registration of pesticides on minor or specialty crops;
- Organizing training courses for representatives of developing countries intending to participate in the programme, to facilitate good agricultural practice (GAP) trials resulting in acceptable residues.

The Meeting encourages governments and international organizations, such as FAO, to support and participate in this initiative.

2.6 ESTIMATION OF LONG-TERM INTAKES OF PESTICIDES IN/ON DRIED CHILI PEPPERS AND SHORT-TERM INTAKE OF MEVINPHOS ON SPICES.

The 2004 JMPR estimated maximum residue levels for spices based on monitoring data and for dried chili peppers taking into account the MRLs on fresh peppers. The 37th Session of CCPR advanced the proposed MRLs for dried chili peppers to Step 5 (Annex 1) and requested the JMPR to perform an overall long-term intake assessment for each compound where the TMDI for dried chili peppers was > 5% of the ADI (acephate, carbaryl, dicofol, dimethoate, methamidophos, oxamyl, profenofos, and vinclozolin).

The Committee did not advance the recommended limits for mevinphos for spices to step 8 with omission of step 6 and 7 due to acute intake concern.

Estimation of long-term intake for pesticides for which MRLs were recommended for dried chili peppers

The 2004 JMPR calculated TMDIs only for dried chili peppers, without considering the other uses of a compound. The long term intakes were reported without taking into account the assumption that 10% of fresh peppers are consumed as dry chili pepper. Therefore the calculations of IEDI and TMDI were carried out by the 2005 JMPR for all uses of the compounds including dried chili peppers and spices, where relevant, based on the most recent evaluation by JMPR. In general, IEDIs were calculated for compounds evaluated from 1999 to 2004 where STMRs were available. For compounds evaluated before 1999, only the TMDI could be calculated. In all cases, the contribution to long-term intakes from the use of the compound on dried chili peppers was also calculated.

Dried chili pepper consumption was estimated to be approximately 10% of the total consumption of fresh peppers and chili peppers, i.e. VO 0051, VO 0444, and VO 0445. Given that the water content of fresh peppers is about 90% and that 10% of the consumption of sweet peppers is derived from dried chili peppers, then dried chili pepper consumption can be estimated as approximately 1% of fresh peppers, based on dry weight vs fresh weight. The residues were derived by extrapolation from the MRL or STMR (where available) for fresh peppers by applying a concentration factor of 10.

Long-term intake estimates (total IEDIs) for compounds that initially showed a TMDI > 5% for chili peppers are summarized in Table 2.

Acephate, carbaryl, methamidophos, oxamyl, and profenofos

The IEDI for each of the five GEMS/Food regional diets were in the range of 2–70% of the ADI for acephate, carbaryl, methamidophos, and oxamyl when considering all of the uses of each compound, including the proposed use on dried chili peppers. The TMDIs for all regional diets were within the ADI for profenofos. Therefore, the long-term intake of residues of these five compounds from all uses that have been considered is unlikely to present a public health concern.

Dimethoate

The IEDI for the European diet was already about 120% of the ADI for dimethoate even without the addition of dried chili peppers. Based on the STMR estimated by the JMPR, the dry chili pepper contribution, to the ADI is 3 to 14%, resulting in an intake of 130% of the ADI in the European diet.

Table 2: Intake estimates (total IEDI) for compounds with TMDI > 5% of ADI

Compound	ADI, mg/kg bw/day	Long-term intakes (% ADI, Rounded)					Contribution of dried chili peppers at proposed MRL (% ADI, rounded					Reference (JMPR Report)
		Mid-East	Far-East	Africa	Latin America	Europe	Mid-East	Far-East	Africa	Latin America	Europe	
IEDI Calculations												
Acephate	0.03	9	3	4	5	20	1	1	2	1	3	2003
Carbaryl	0.008	60	20	10	20	70	1	1	2	1	4	2002
Dimethoate	0.002	60	30	30	50	130	5	3	7	3	14	2003
Methamidophos	0.004	10	2	3	6	20	0	0	1	0	1	2003
Oxamyl	0.009	10	2	3	6	10	0	0	1	0	1	2002
TMDI Calculations												
Dicofol	0.002	520	120	100	400	690	3	2	5	2	9	1994
Profenofos	0.01	30	5	10	10	40	3	2	5	2	9	1995
Vinclozolin	0.01	60	10	20	30	120	2	1	3	1	5	1992

Dicofol

TMDI calculations (last evaluated in 1994) showed that even without dried chili peppers, intakes for all the five regional diets greatly exceeded the ADI (100–690% of ADI). In fact, the contribution of dried chili peppers was only from 2% to 9% of the ADI for the five regional diets.

Vinclozolin

TMDI for the European diet was 120% of the ADI. The dried chili peppers' contribution to the intakes of at the proposed MRL of 30 mg/kg ranged from 1% to 5%, the highest being for the European diet.

Other compounds

The IEDI or mixed calculation based on the available STMR and MRL values (Table 3) indicated that the contribution of the residues of other compounds in/on dried chili peppers (carbendazim, chlorpyrifos, diazinon, dinocap, ethephon, ethoprophos, imidacloprid, malathion, methomyl, methoxyfenozide, piperonyl butoxide, pyrethrins, spinosad. tebufenozide, tolyfluanid) to the ADI was < 1%.

Table 3: IEDI calculations for other compounds based on latest JMPR review, incorporating proposed MRLs for dried chili peppers

Compound	ADI, mg/kg bw/day	Long-term intakes (% ADI, Rounded)					Contribution of dried chili peppers at proposed MRL (% ADI, rounded					Reference (JMPR Report)
		Mid-East	Far-East	Africa	Latin America	Europe	Mid-East	Far-East	Africa	Latin America	Europe	
Carbendazim	0.03	3	1	1	2	5	0	0	0	0	0	2003
Chlorpyrifos	0.01	9	3	4	6	30	0	0	0	0	1	2004
Diazinon[1]	0.002	120	60	30	90	180	0	0	0	0	0	1999

Compound	ADI, mg/kg bw/day	Long-term intakes (% ADI, Rounded)					Contribution of dried chili peppers at proposed MRL (% ADI, rounded					Reference (JMPR Report)
		Mid-East	Far-East	Africa	Latin America	Europe	Mid-East	Far-East	Africa	Latin America	Europe	
Dinocap	0.008	2	0	0	1	2	0	0	0	0	0	2001
Ethephon	0.05	10	6	2	6	20	0	0	0	0	0	1999
Ethoprophos[2]	0.0004	7	8	5	10	10	0	0	0	0	0	2004
Imidacloprid[3]	0.06	2	1	1	1	3	0	0	0	0	0	2002
Malathion	0.3	0	0	0	0	0	0	0	0	0	0	2004
Methomyl	0.02	5	4	1	5	20	0	0	0	0	0	2004
Methoxyfenozide	0.1	1	0	0	2	8	0	0	0	0	0	2003
Piperonyl butoxide	0.2	20	40	30	20	20	0	0	0	0	0	2002
Pyrethrins	0.04	1	1	1	1	1	0	0	0	0	0	2003
Spinosad	0.02	20	9	10	20	30	0	0	0	0	0	2004
Tebufenozide	0.02	5	3	1	5	20	0	0	0	0	0	2003
Tolyfluanid	0.08	1	0	0	1	4	0	0	0	0	0	2003

[1] Diazinon – This was a mixed assessment, using STMRs where available and MRLs in most cases.

[2] Ethoprophos - The 2004 JMPR recommended to withdraw CXL for sweet pepper of 0.02 mg/kg and replaced it with an MRL of 0.05 mg/kg. The 2005 CCPR agreed and advanced the MRL of 0.05 mg/kg to Step 5/8. Therefore, for dried chili peppers, the MRL is 0.5 mg/kg. The STMR-P for dried chili peppers was used in the calculation.

[3] Imidacloprid - The 2005 CCPR session decided to change the MRL for imidacloprid on dried chili pepper to 10 mg/kg, as the MRL for peppers of 1 mg/kg was based on a fresh weight basis (para 185, ALINORM 05/28/24). The STMR extrapolated from fresh pepper was used in the calculation.

The TMDI calculations for all uses based on the current MRLs are summarized in Table 4.

Table 4: TMDI calculations for other compounds, based on current MRLs, incorporating proposed MRLs for dried chili peppers

Compound	ADI, mg/kg bw/day	Long-term intakes (% ADI, Rounded)					Contribution of dried chili peppers at proposed MRL (% ADI, rounded					Reference (JMPR Report)
		Mid-East	Far-East	Africa	Latin America	Europe	Mid-East	Far-East	Africa	Latin America	Europe	
Abamectin	0.002	4	1	1	3	8	0	0	0	0	0	1997
Azinphos methyl	0.005	50	10	10	20	80	1	1	2	1	3	1995
Benalaxyl	0.05	2	0	0	1	2	0	0	0	0	0	1993
Bromide ion	1.0	60	50	30	40	50	0	0	0	0	0	1992
Chlorothalonil	0.03	40	8	9	20	40	1	1	2	1	4	1997
Chlorpyrifosmethyl	0.01	120	40	10	40	80	0	0	0	0	1	1994
Cyfluthrin	0.02	4	1	1	2	5	0	0	0	0	0	1992
Cypermethrin	0.05	10	4	3	8	20	0	0	0	0	0	1990

Compound	ADI, mg/kg bw/day	Long-term intakes (% ADI, Rounded)					Contribution of dried chili peppers at proposed MRL (% ADI, rounded					Reference (JMPR Report)
		Mid-East	Far-East	Africa	Latin America	Europe	Mid-East	Far-East	Africa	Latin America	Europe	
Cyromazine	0.02	6	1	2	5	20	0	0	0	0	1	1992
Dithiocarbamates[1]	0.03	50	20	8	40	70	0	0	0	0	1	1996
Fenarimol	0.01	3	2	2	4	8	0	0	0	0	1	1996
Fenpropathrin	0.03	10	4	2	6	30	0	0	0	0	1	1993
Fenvalerate	0.02	100	90	60	70	100	0	0	0	0	0	1990
Metalaxyl	0.08	9	2	2	8	10	0	0	0	0	0	1995
Permethrin	0.05	50	40	20	30	40	0	0	0	0	0	1991
Pirimicarb	0.02	20	5	4	9	30	1	0	1	0	2	1985
Procymidone	0.1	9	1	2	4	10	0	0	0	0	1	1998
Propamocarb	0.1	2	0	0	2	6	0	0	0	0	0	1987
Quintozene	0.01	2	1	1	1	2	0	0	0	0	0	1998
Tebuconazole	0.03	5	1	1	2	8	0	0	0	0	0	1994
Triadimefon	0.03	5	3	1	4	6	0	0	0	0	0	2004
Triadimenol	0.03	20	5	1	7	10	0	0	0	0	0	2004

[1] Dithiocarbamates - Based mainly on maneb, mancozeb, zineb, and metiram, which have a group ADI of 0.03 mg/kg bw/day.

TMDI calculations for all compounds in Table 4, except for chlorpyrifos-methyl, were all within the ADI for all the regional diets. Therefore, long-term intake of residues of these compounds from all uses including those for dried chili peppers is unlikely to present a public health concern.

Chlorpyrifos-methyl

TMDI calculations resulted in the ADI being slightly exceeded for the Middle-Eastern diet (120%), even without dried chili peppers. Dried chili peppers had no contribution to the intakes of any of the five regional diets.

International estimate of short-term dietary intake (IESTI)

The JMPR calculated the short-term intake based on the FAO/WHO consumption data taking into account the 1.75 and 1.67 g/kg bw/day consumption reported for adults and children in France, respectively. Some countries have lower consumption figures for spices: e.g. Australia 0.299 g/kg bw/day for adults; UK 0.1118 g/kg bw/day for adults, USA 97.5th percentile consumption (0.045 g/kg bw/day for adults and 0.087 g/kg bw/day for children 1-6 years); Germany 15.4 g/child/day (0.93 g/kg bw/day); These consumption figures indicate that the short-term intake would not exceed the ARfD in the latter countries.

IESTI for Mevinphos on Spices:

Acute RfD= 0.003 mg/kg bw/day (3 µg/kg bw/day)						
Commodity	STMR or STMR-P mg/kg	Large portion diet Country	Body weight (kg)	Large portion g/kg bw/day	IESTI µg/kg bw/day	% acute RfD rounded
ADULTS						
Spices	2.9	France	62.3	1.75	0.005075	169
	2.9	Australia	67	0.299	0.000867	29
	2.9	UK	76	0.1118	0.000324	11
	2.9	USA	65	0.045	0.0001305	4
CHILDREN						
Spices	2.9	France	17.8	1.67	0.004843	161
	2.9	Germany	16.5	0.93	0.00271	90
	2.9	USA	15	0.087	0.0002523	8

The short-term intake can only be defined at the national level.

2.7 CONSIDERATION OF ALTERNATIVE GAPS

The CCPR, at its 37th Session in 2005 (ALINORM 05/28/24, paragraphs 105, 107, 108, 135 and 243) drew attention to the acute intake concerns for proposals for disulfoton, fenamiphos and aldicarb.

	MRL, mg/kg	Step	IESTI as %ARfD (general population, children)	
74 Disulfoton				
VB 0400 Broccoli	0.1	6	106%, 201%	WHO, 2002 1/
VB 0041 Cabbages, Head	0.2	6	267%, 476%	WHO, 2002
VB 0404 Cauliflower	0.05	6	35%, 103%	WHO, 2002
VL 0482 Lettuce, Head	1	6	698%, 1050%	WHO, 2002
VL 0483 Lettuce, Leaf	1	6	924%, 2300%	WHO, 2002
85 Fenamiphos				
VO 0051 Peppers	0.5	6	100% 110%	JMPR 2003 2/
VO 0448 Tomato	0.5	6	110% 310%	JMPR 2003
VC 0432 Watermelon	0.05 (*)	6	100% 260%	JMPR 2002
117 Aldicarb				
FI 0327 Banana	0.2	6	40%, 110%	JMPR 2002
VR 0589 Potato	0.5	6	230%, 560%	JMPR 2001

1/ CCPR. 2002. 34th Session. 5. Dietary exposure in relation to MRL setting. (A) acute dietary risk assessment. Prepared by WHO. Document CX/PR 02/03, March 2002

2/ IESTI for sweet peppers.

In evaluating supervised trials data to support an MRL, JMPR identifies the maximum GAP in each country, and evaluates trials data from that country and others with similar climate and cultural practices.

JMPR recommends a maximum residue level that relates to the highest residues from a national GAP where there are sufficient supervised trials data.

The CCPR has requested an extension to that procedure, which would become:

JMPR recommends a maximum residue level that relates to the highest residues from a national GAP where there are sufficient supervised trials data and where the residues do not result in an IESTI (international estimate of short-term dietary intake) that exceeds the acute reference dose.

The Meeting agreed that this would be a suitable procedure, because Codex MRLs are used as standards for food in trade, not for enforcement of GAP as in a national registration system where the MRL must be associated with the maximum registered use.

Aldicarb was evaluated by the JMPR in 2001, disulfoton in 1994 and 1998 and fenamiphos in 1999. Some of the registered uses recorded in those evaluations have quite likely been modified since then. The problems of basing an evaluation on obsolete GAP should be noted.

The Meeting sought advice from CCPR on the best way to proceed.

Retrospective approach

CCPR would refer the compound to JMPR and request reconsideration of GAP in specific cases. It would also request the manufacturer(s) and national governments to provide appropriate up-to-date GAP information to support the proposed evaluation.

The advantage of this approach is that reconsideration of GAP would be only at the request of CCPR for specific cases where all other avenues for refinement had been exhausted. The disadvantage is that, because of the elapsed time, the reported GAP may well have changed since the time of the evaluation. A new data submission would be needed.

Prospective approach

During a residue evaluation where the IESTI is exceeded, JMPR should draw attention to available information on alternative GAPs and associated supervised trials data where the IESTI would not appear to be exceeded.

The advantage of this approach is that no time is lost in referral between CCPR and JMPR and the adoption of a Codex MRL would likely occur more quickly. The disadvantage is that the acceptance of alternative GAP would likely become the first action instead of the final resort when other avenues of refinement are exhausted.

2.8 ESTIMATION OF VARIABILITY FACTOR FOR THE USE FOR CALCULATION OF SHORT TERM INTAKE

At its 37th Session the CCPR decided to postpone discussion[1] on the variability factor awaiting the discussion by the 2005 JMPR.

The variability factor, as used in short-term intake assessments when estimating residues in crop units, was defined by an FAO/WHO consultation[2] and refined by an international conference[3] as the ratio of the 97.5th percentile of the residue population in a lot divided by the average residue of that lot. The methods of calculation were further refined by the JMPR[4], which proposed variability factors for different types of commodities. At that time the highest residue in a crop unit, from a sample consisting of a number of crop units at or above 90, was considered to represent the 97.5th percentile of the population in the sampled lot. This method over-estimated the variability in more

than 90% of the cases, because the highest residue can be much higher than the 97.5th percentile ($P_{0.975}$).

As part of its previous discussion, the JMPR considered the work of the International Union of Pure and Applied Chemistry (IUPAC)[5], which also attempted to make best use of the available data, and noted that for the purposes of data analysis the IUPAC project selected only those cases where 95% or higher of the individual units had detectable residues. The initial concern was that the calculated variability would be frustrated if more than a very few of the units were non-detects. It is likely that this selection criterion ruled out most of the "mixed lot" data sets. (Attachment II - Example 2). The probability of contribution, of individual residue values, to the 97.5th percentile was taken into account in the calculation of the best estimate for the variability factor, which led to a generic value of 3. The 2003 JMPR[6] adopted the refined variability factor of 3 based on the scientific evaluation of all available relevant data.

The methodology referred to above[4,7,9] was developed to assess the toxicological acceptability of theoretical short-term intake of residues. The intake estimates were derived using maximum residues levels resulting from GAP reported in *supervised trials*.

The JMPR fully supports the conclusion of the European Food Safety Authority (EFSA) Scientific Panel regarding the unsuitability of monitoring data, based on sample size specified in the Codex sampling procedure and the EU homogeneity studies for estimating variability factor.

The JMPR IESTI procedure *should only be used* for estimation of short-term intake from residues found in crop units taken from a single lot as defined in the Codex sampling procedure.

It is not applicable for residue data obtained from market samples, where the commodities offered for sale are of mixed lots, which may result in a variability factor three to four times higher than the one in the treated lot (Attachment II, Example 1). Consequently, it is not appropriate to attempt to derive a variability factor using residue data of uncertain origin or those clearly indicating that the sampled commodity originated from a mixed lot, i.e., a high CV value, in the estimation of short-term intake based on data from supervised trials.

The JMPR considered the results of the new studies coordinated by the Joint Division of FAO and the International Atomic Energy Agency (IAEA) [7] (summarized in Attachment I) and the data base which was used for preparing the opinion of the EFSA Scientific Panel[8].

The FAO/IAEA project resulted in 11 112 valid residue data in crop units from 13 countries of 3 continents representing 3 small fruits, 5 large crops, 2 medium/large crops and 3 leafy vegetables, and included 25 pesticide active ingredients. Evaluation of these new residue data and the relevant supervised trials (3 new and 8 evaluated previously) carried out by the pesticide manufacturers resulted in an overall average variability factor of 2.8 (IUPAC procedure) and 2.7 obtained with the Harrell-Davis method used by the EFSA Scientific Panel. The values correspond with the average factor (2.8) obtained by EFSA for medium size crops based on supervised trials. Due to the inevitable random nature of the variability factor derived from the combined uncertainty associated with sampling and analysis (Attachment II. Example 3), the best estimate of the variability factor can be gained be meaning the variability factors derived from samples of various crops[9]. This approach was also followed by IUPAC[8].

In order to ascertain the suitability of the variability factor of 3 as currently applied by the JMPR, all data used by the EFSA Scientific Panel, and the new data provided by FAO/IAEA and derived from recent supervised trials, were evaluated. A simple procedure was used and did not apply any prior assumptions. The residues (R_i) measured within an individual data set were divided by the average residues, $R_{ave,}$ of that particular data set. The instances where the ratio was found to be higher than 3 was then recorded. The results are shown below:

	No. of data sets	No. of R_i/R_{ave} values > 3	No. of residue data	% of R_i/R_{ave} > 3
EFSA				
Market samples	69	292	7002	4.2
Supervised trials	22[a]	95	3231	2.9
FAO/IAEA				
Field trials	89	163	11112	1.5
ECPA supervised trials	11[b]	6	1320	0.45
All residue data	191	556	22665	2.45

(a) These data do not include the EPCA grape and lettuce trials with tank mix of pesticides because they were taken into account in the evaluation of the data obtained from the FAO/IAEA Project.
(b) 4 grape and 4 lettuce data sets from the ECPA trials from France and Germany are included in this summary. In the latter case, trials giving the highest variability factors from the tank mix pesticides were selected.

The number of cases where the ratio was higher than 3 provides a measure for the suitability of the current default variability factor of 3 used by the JMPR.

The analysis of all supervised trials and market surveys data available (191 data sets, and 22,665 residue data from crop units) indicated that the R_i/R_{ave} ratio exceeded 3 for only 2.45% of the residue data. The very large amount of actual residue data does not support the conclusion of the EFSA Scientific Panel stating that: variability factors for supervised trials and market surveys will exceed the proposed default value of 3 in 34% and 65% of cases, respectively. In fact, 7002 market samples indicated that only 4.2% of crop units contained residues for which the ratio (R_i/R_{ave}) exceeds 3, and the field and supervised trials (15,663 residue data) gave R_i/R_{ave} ratio > 3 in less than 1.7% of cases.

Taking into account the new residue data and the existing data, suitable for estimating the variability factor as well as the applicability of the IESTI calculation, the Meeting concluded:

- Since theoretically 2.5% of the R_i/R_{ave} values could be above 3 and actually 2.45% of all measured residues exceeded the value of three times the average residue, the current JMPR default value of 3 is a good estimate for the variability factor. That it effectively covers the practical variability of residues likely to be found in a wide range of medium and large sized commodities (fruits and vegetables), and can be used to provide the best estimate currently possible for the short-term intake at the international level.

- The best estimate of the variability factor can be gained from the average of the variability factors calculated for individual crop samples. As the variability factor is estimated at 95% confidence level, it is not appropriate to apply an additional confidence or credibility limit over it.

The JMPR agreed to continue using the default variability factor of 3 for calculation of IESTI, which will be expressed with one significant figure corresponding to its uncertainty.

It is emphasized that the deterministic IESTI calculation used by JMPR should only be applied to residue data derived from supervised trials and single lots. It is not applicable for mixed lots.

ATTACHMENT I

Summary of studies carried out for determining pesticide residues in crop units

When estimating the short-term intake of pesticide residues the variability of the residues in crop units is taken into account. As the vast majority of residue data available was on medium sized crop commodities, the Joint Division of the FAO and the International Atomic Energy Agency (IAEA) initiated a coordinated research programme[3] to undertake field studies to investigate residues in individual items of leafy vegetables as well as small and large crops. The aim being to provide residue data to enable the refinement of the estimates of the variability factor and the uncertainty of associated with sampling.

The results of the project and the relevant data from supervised field trials carried out by the European Crop Protection Association[10], (ECPA), and the company BASF[11] are summarized below.

Within the FAO/IAEA Project field trials were carried out in 13 countries on 13 commodities including 3 small fruits, 5 large crop commodities, 2 medium/large crop commodities and 3 leafy vegetables. The 25 pesticide active ingredients applied represented the dicarboximide (3), organophosphorus (8), synthetic pyrethroids (5), phthalimides (2), organochlorine (1) and other types of pesticides (6). The crop pesticide combinations amounted to 91 combinations, from which 6,116 samples were analysed resulting in 11 112 valid residue data.

In addition, supervised trial data provided by BASF on grapes in Germany and Spain, and 4 grape and 4 lettuce data sets from the ECPA trials from France and Germany are included in this summary. In the latter case, trials giving the highest variability factors from the tank mix pesticides were selected taking into account the conclusion, reached by the EFSA Scientific Panel[1], that the variability factors obtained from a set of pesticides applied in a tank mix may not be independent. These supervised trials included 7 different pesticides analysed in 1320 samples.

The FAO/IAEA field trials represented regular agricultural practice prevailing in different parts of the world, e.g., Europe, Latin and Central America and South-East Asia. They were performed on commercial fields cultivated and treated with pesticides by local farmers as per normal practice. The samples were collected by trained personnel who followed detailed sampling plans. The samples were then analysed using validated methods of known and acceptable performance parameters.

The recoveries obtained during method validation generally ranged between 75 and 110%. In a few cases lower (minimum 63%) and in one case higher (121%) average recoveries were reported. The laboratory reproducibility values, including the error of sample processing CV_L values, were within the acceptable range according to the CCPR GLs[12]. The internal quality control measures confirmed that the analyses of the samples were carried out properly and produced reliable and accurate results.

As the field trials represented normal agricultural practice, based on the performance of the methods it can be concluded that the results reflect the variability of residues to be expected in commodities available in single lots in the market. The results provide a good and reliable basis for estimation of the variability of residues in crop units treated in field trials.

Data sets usually contained detectable residues. In a few cases, where residues < LOQ values were present (< 10%), they were substituted with the half of the lowest reported value only if the replacement did not result in more than 10% difference in the mean residues or the coefficient of variation of the residues, CV_R. The replacement should not significantly affect the estimated CV_R and the variability factor.

Due to the inevitable random nature of the variability factor deriving from the combined uncertainty of sampling and analysis, the best estimate of the variability factor can be gained from the average of the variability factors calculated from samples of various crops[10]. This approach was also followed by Hamilton et al. 2004[8].

The results are summarized in Table 5. Details of the experimental data will be published elsewhere[13].

Table 5. Summary of variability factors for various commodities

Commodity Group	Crop	No. of Compounds	No. of samples	$P_{0.975}/R_{ave}$ [1]	v*[2]	ν H-D[3]
Small fruits[4]	Blackcurrant	2	240	2.99	3.08	3.04
	Cherry	7	840	3.03	3.94	3.68
	Strawberry	6	1183	2.62	3.18	2.93
	Average			**2.82**	**3.46**	**3.23**
Leafy vegetables	Cabbage	4	860	1.85	2.11	2.02
	Chicory leaves	1	242	1.81	2.07	1.96
	Kale	7	1031	2.19	2.43	2.34
	Lettuce	14	1699	2.30	2.64	2.50
	Average			**2.14**	**2.43**	**2.31**
Large crops	Cucumber	11	1360	2.41	3.03	2.81
	Zucchini	1	240	2.33	2.66	2.53
	Grape	15	2426	2.67	3.08	2.89
	Mango	7	1652	2.64	2.71	2.64
	Papaya	4	640	2.24	2.44	2.38
	Squash	2	256	2.39	2.85	2.62
	Average			**2.45**	**2.80**	**2.65**
Average of all commodities				**2.47**	**2.85**	**2.75**

1. Variability factor calculated from the 97.5th percentile/average residue obtained with Excel programme.
2. Variability factor calculated according to Hamilton *et al*. 2004.
3. Variability factor calculated with the Harrell-Davis method applied by the EFSA Scientific Panel.
4. Fruits (average single increment mass 40–225g) were collected from close vicinity to represent approximately the large portion size used in short-term exposure assessment.

ATTACHMENT II: EXAMPLES.

1. Variability of residues in mixed lots/

Experimental data sets were used to illustrate the effect of mixing lots.

Let's assume that the two kale lots treated with indoxacarb (lot 22 and 49) and two grape lots (20 and 17) treated with chlorpyrifos would be mixed with each other, and the grape lot 17 containing 2.37 mg/kg residue would be mixed with untreated fruits in 1:1, 1:2 and 1;3 ratios. The effect of mixing is illustrated in Table 6.

Mixing commodities treated with the same pesticide results in a variability between the two lots, while mixing a treated commodity with untreated one will increase the apparent "variability factor". The larger the residue concentration in the treated lot and lower the LOQ, the larger will be

the new variability factor. Similarly the rate of dilution with untreated commodity will approximately proportionally increase the "variability factor".

Table 6. Effect of mixing commodities on the variability factor

Data sets	Rmin	Rave	Rmax	CV_R	Rmax/Rave	P0.975	P0.975/ave
Kale							
1	0.320	1.138	2.703	0.40	2.38	2.159	1.9
2	0.005	0.482	1.924	0.91	3.99	1.512	3.1
Mixture of 1 and 2	0.005	0.829	2.703	0.67	3.26	2.03	2.5
Grape							
1	0.107	0.517	1.401	0.47	2.71	1.066	2.1
2	2.040	2.373	2.920	0.07	1.23	2.841	1.2
Mixture of 1 and 2	0.107	1.44	2.92	0.954	2.02	2.71	1.9
Mixture[#] : 1:1	0	1.187	2.920	1.01	2.46	2.71	2.4
Mixture[#] : 1:2	0	0.791	2.920	1.42	3.69	2.67	3.6
Mixture[#] : 1:3	0	0.593	2.920	1.74	4.92	2.61	4.8

[#]Grape 2 lot was mixed with other grape lots that did not contain any residue

2. The effect of non-detects on variability of residues

The criterion chosen to minimize the effect of non-detects on the calculations was to make the calculations twice, once with the non-detects = 0 and once with non-detects = LOQ (limit of quantification). If the difference in the calculated variability factor was less than 10%, the data set was accepted (cf. page 18 of EFSA report). This criterion would accept mixed lots, e.g. it would accept a mixture of 90% untreated commodity (LOQ = 0.01 mg/kg) with 10% of treated commodity (residue level = 1 mg/kg).

The summarized data from the 69 relevant data sets in Appendix II of the EFSA paper were examined for the relationship between estimated variability factor and percentage non-detects (Table 7). The estimated values for variability factors appear to be influenced by the percentage of non-detects (when more than about 10%), which suggests either a problem with the calculation method or that these data sets are really mixed lots and the estimated variability factors are not relevant for true lots.

Table 7. The effect of non-detects, and possibly mixed lots, on the estimated variability factor.

		Estimated variability factor	
% detects in data set	Number of data sets	Mean	Range
100%	15	2.9	1.8-4.7
95-99%	13	3.5	2.0-5.8
90-94%	13	3.6	2.2-5.6
70-89%	17	4.5	3.3-10.5
40-69%	11	5.3	2.9-8.7
		3.9 overall mean	

3. Illustration of uncertainty resulted from sampling

To illustrate the variability of the estimated parameters, large test populations (T1-T7) were created from the available residue data.

The parameters of the test populations are given in Table 8. The test populations have variability factors ranging from 2 to 4.6, which cover the range that is likely to occur in practice.

Table 8. Characteristic parameters of the test populations

	T-1[1]	T-2[2]	T-3[1]	T-4[1]	T-5[2]	T-6[2]	T-7[3]
No. of units	2096	2096	2133	3981	10000	10000	10000
R_{min}	0.01	0.00	0.01	0.01	1.30	0.00	0.51
R_{ave}	1.00	0.38	1.00	1.00	2.86	0.15	5.69
R_{max}	8.97	3.89	4.42	7.92	5.82	2.29	35.29
CV	0.83	0.49	0.47	0.61	0.21	1.09	0.65
$P_{0.975}$[4]	2.85	1.74	2.08	2.45	4.230	0.566	15.1
$P_{0.975}/R_{ave}$	2.85	4.62	2.08	2.45	1.48	3.87	2.65
$P_{H\text{-}D0.975}$[5]	2.91	1.75	2.11	2.45	4.226	0.569	1.569

[1] Rescaled populations from measured residues.
[2] The data points are the back-transformed values from a log-normal population derived from original experimental data.
[3] Combined residues from data sets of the same commodity
[4] Calculated with Excel
[5] Calculated with Harrell Davis method

The distribution of residues in the test populations are illustrated in Figures 4 to 6, and show that they are quite different in shape, thus accurately represent the situations that may occur in practice.

Random samples of size 100–120 and 200 were drawn (1000 from each population) from the test populations with replacement. The results indicating the range of estimated variability factors due to the sampling uncertainty are shown in Table 9.

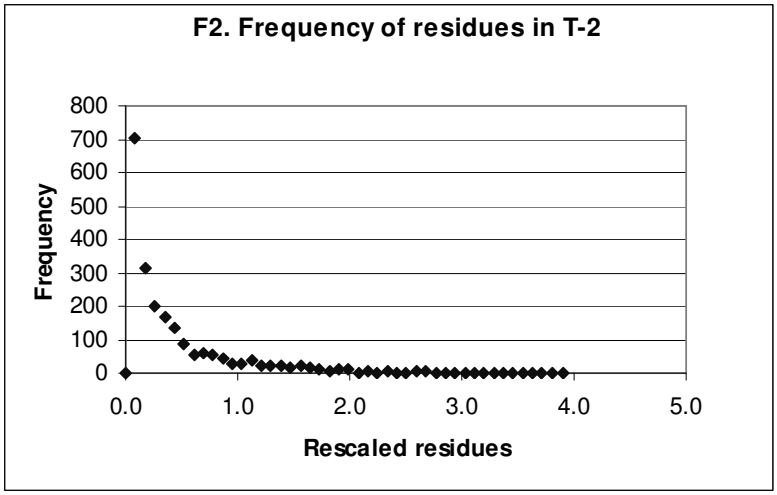


Figure 4. The distribution of residues in the T-2 test population.

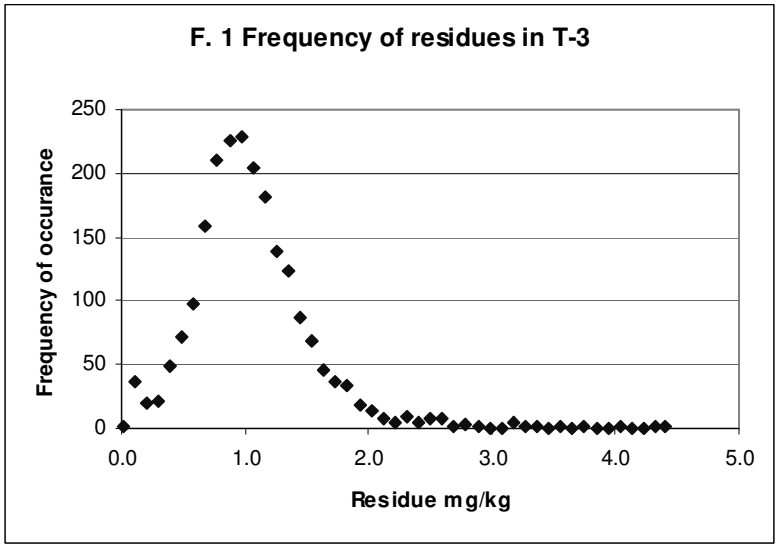


Figure 5. The distribution of residues in the T-3 test population.

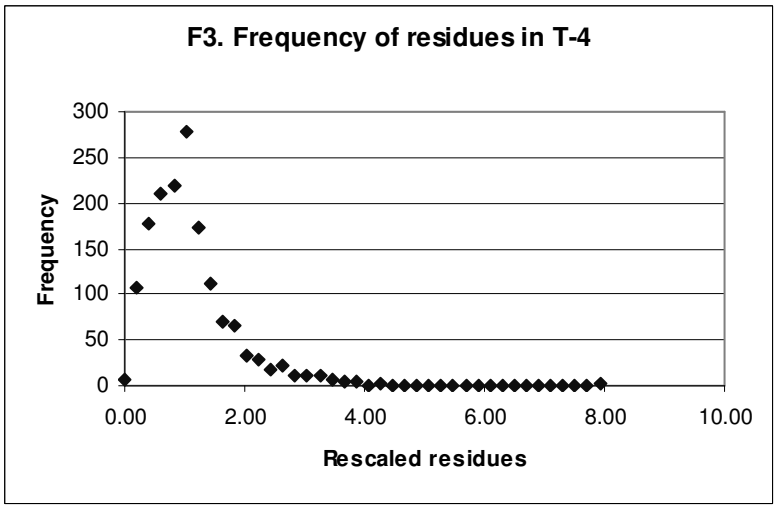


Figure 6. The distribution of residues in the T-4 test population.

Table 9. The relative 95% confidence limits for P0.975/Rave

	$LCLP_{0.975}/R_{ave}$	$P_{0.975}/R_{ave}$	$UCLP_{0.975}/R_{ave}$
T-1 n=100	-0.16	4.62	0.24
T-2 n=120	0.48	2.45	1.33
T-3 n=100	-0.19	2.04	0.33
T-4 n=100	-0.22	2.36	0.23
T-5 n=100	-0.08	1.45	0.09
T-6 n=100	-0.25	3.71	0.33
T-7 n=120	-0.19	2.6	0.29
Average	-0.11	2.75	0.24
Rel. difference	-0.09		0.40

$LCL_{0.025}$ lower confidence limit, $UCL_{0.975}$ upper confidence limit

The percentage deviation of the minimum and maximum variability factors from the mean observed based on 1000 replicate samples in the test populations, is in the similar range and reflects the random variation derived from sampling uncertainty.

The 95% relative confidence intervals of the variability factors estimated from samples of size 100 are practically independent from the variability factors of the parent populations and they are on average in the range of 9% to 40%. This means that an observed range of 2.7–4.2 for a variability factor of 3 can be attributed to the sampling uncertainty at 95% probability level.

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2.9 ESTIMATION OF PROCESSING FACTORS

Processing studies are among the critical supporting studies required for the evaluation of new and periodic review compound.

The *FAO Manual* (2nd edition p. 44) specifies the procedure which has been followed by the FAO Panel. It provides the following options:

a. If more than one processing study has been conducted for a particular pesticide in the same raw agricultural commodity (RAC), the average processing factor for each type of process should be used for each processed commodity.

b. If the processing factors from two trials are irreconcilable, e.g. 10-fold different, the mean is inappropriate because it would not represent either process, then the highest processing factor should be chosen as the default (conservative) value if there is no other reason to choose one or the other.

c. If residues in the processed commodity are undetectable or < LOQ in several studies it may mean that residues in the processed commodity are very low or essentially 0, and the calculated processing factor is merely the reflection of the starting residue level in RAC In this case the best estimate of the processing factor is the lowest "less than" value rather than the mean of the "less than" values.

There are certain cases which are not covered in the above examples

1. Processing studies may result in processing factors including both "less than" and real values, or some high values without any identifiable reasons. In such cases the median value should be taken as the best estimate as the calculation of the mean provides a biased value.

2. Processing factors are determined from the RAC at various days after the last application. In this case the results from the shortest PHI onward should be taken into account. An example is the processing of grape treated with fenhexamid to wine.

PHI (days)	14	21	28-35
Average PF	0.343	0.298	0.366
Median	0.355	0.32	0.36

As the processing factors are not different all data can be considered and the mean or median values could be used as best estimate for the processing factor.

3. However, in cases where the difference between the median and the mean is larger than 20%, the distribution is not close to normal so the median of the valid values would provide the best estimate.

Consequently the median would generally provide the best estimate for the processing factor, and the Meeting decided to use it instead of the average value in the evaluations of the processing studies.

2.10 DEFINITION OF FAT-SOLUBLE PESTICIDES IN MEAT AND FAT

Revisited: Fat-soluble pesticides in meat and fat

As part of the JMPR guidance regarding fat-solubility, physical chemical properties and definition of the residue,[2] one of the factors that should be considered when proposing a residue definition is the *fat solubility of the compound and relevant transformation products*. Due to a number of fat-soluble

[2] Submission and Evaluation of Pesticide Residues Data for the Estimation of Maximum Residue Levels in Food and Feed, FAO, Rome 2002, Chapter 5, p. 40, 47, 52.

compounds being reviewed at this meeting, and in addition to the guidance from the 2004 Meeting regarding MRLs for fat-soluble pesticides in milk and milk products, it was considered timely to revisit the criteria that are important when designating a residue as 'fat-soluble'. A 'residue' is defined as *the combination of the pesticide and its metabolites, derivatives and related compounds to which the MRL or STMR apply*[3].

The designation of a residue as either 'fat-soluble' or non-fat soluble is important for trading purposes and compliance with relevant standards. In trade situations where meat products are sampled at export destinations, the residues of a fat-soluble pesticide measured in meat may be inconsistent due to muscle samples containing different levels of interstitial fat either within a single animal, i.e. a single carcass, or in different animals. From a compliance perspective, it is better to regulate on the residue in the trimmable fat component of the meat, as the residue will be more consistent in fat, when compared to muscle. The 'fat-soluble' status determines the nature of a sample that should be taken for enforcement analysis.

The expression of MRLs for fat-soluble pesticides in meat and animal fat was considered by the Meeting in 1991 and published in a general considerations item[4]. The JMPR chose the octanol-water partition coefficient as the physical property that could indicate solubility of a compound in fat and the Meeting examined a number of compounds with MRLs in animal commodities and their respective P_{ow} values where they were available. The recommendations of the 1991 Meeting were:

The octanol-water partition coefficient (log P_{ow}) should be the prime indicator of fat-solubility, supplemented by inferences that may be drawn from the distribution of residues between muscle and fat tissues, when the residue consists of a single compound.

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

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

The partitioning of residues between fat and muscle as a function of P_{ow} can be predicted. A plot of log P_{ow} versus predicted partitioning in meat between fat and muscle reveals that partitioning is essentially independent of log P_{ow} for compounds with values greater than 3. The Meeting decided to revise the empirical limits recommended by the 1991 JMPR when considering log P_{ow} so that when no evidence is available to the contrary and log P_{ow} exceeds 3, the compound would be designated fat-soluble and when log P_{ow} is less than 3 it would not be so designated.

The partition constant k for fat and muscle (see Figure 7) can be calculated assuming P_{ow} (octanol:water) has the same value as P_{lw}, the partition constant for lipid and water. Further, if it is assumed that muscle contains 5% lipid with the remainder water and that fat is 100% lipid then: P_{lw} = [lipid]/[water] ≈ P_{ow}; k = [fat]/[muscle]; k = [lipid]/(0.05*[lipid] + 0.95*[water]); $k = (1-x)/\{0.05*(1-x) + 0.95*x)\}$ where $x = 1/(1+P_{ow})$.

[3] Submission and Evaluation of Pesticide Residues Data for the Estimation of Maximum Residue Levels in Food and Feed, FAO, Rome 2002, Appendix II, Glossary of Terms.
[4] Pesticide Residues in Food – 1991, 111, p. 15 – 16; General Considerations Item 3.3.

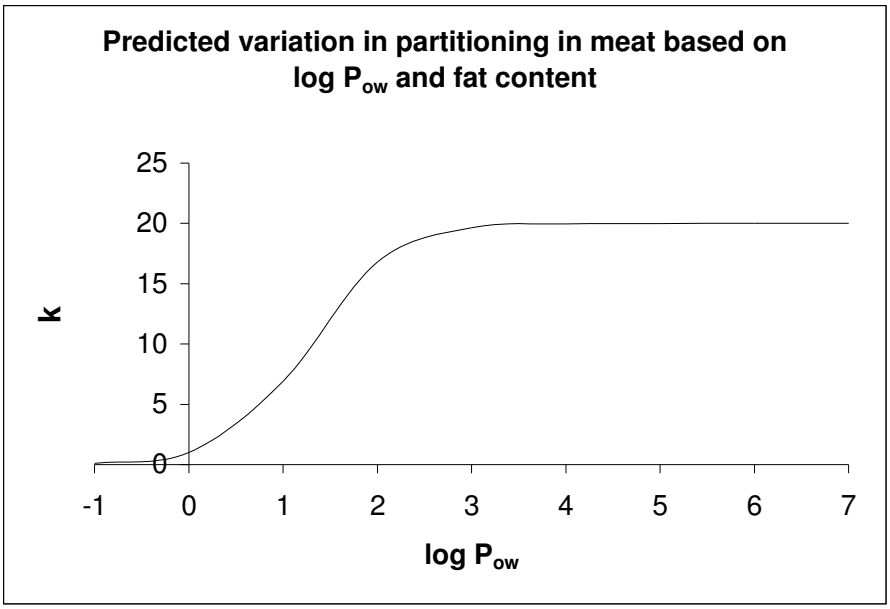

Figure 7. Plot of predicted variation in partitioning in meat based on log P_{ow} and fat content.

It is stated in the *FAO Manual* (2002):

Fat solubility is a property of the residue and is primarily assessed from the octanol-water partition coefficient and the partition of the residue between muscle and fat observed in metabolism and farm animal feeding studies. … Sampling protocols for animal commodities depend on whether a residue is fat-soluble or not [p52].

In general, when log P_{ow} exceeds 4 the compound would be designated fat-soluble and when log P_{ow} is less than 3 it would not be so designated. Pesticides with intermediate log P_{ow} would be considered on a case-by-case basis using the evidence of residue distribution between muscle and fat tissues [p40].

Some worked examples are provided for recently reviewed compounds with log P_{ow} >3 to illustrate different situations and the determinants that may be used to define a residue as being fat-soluble or not fat-soluble for the purposes of JMPR and the estimation of maximum residue levels for meat. Only goats and cattle are considered here, however the same principles apply to hen studies and poultry.

Residue concentrations for the residue definition in both muscle and fat may be compared in the goat metabolism study, where the data allow. These values are compared to the residue concentrations found in the muscle and fat in the corresponding cattle feeding study, and the ratio between muscle and fat may be compared. Data for milk and milk fat may also be considered as an additional factor regarding the fat solubility of a pesticide, although in some instances the residue may be designated fat soluble in meat but not in milk due to differences in partitioning of the individual components included in the residue definition. Examples are discussed below.

Cyprodinil has a log P_{ow} = 4, the residue is defined as parent compound. The residue in goat fat is 75× higher than the residue in muscle in the metabolism study, indicating greater solubility of the residue in fat versus muscle (2003 JMPR). On the basis of the data from the metabolism study, the residue is designated as being fat-soluble.

Flutolanil has a log P_{ow} = 3.17 and the residue is defined as the sum of flutolanil and trifluoromethyl benzoic acid for animal commodities. The cattle feeding study indicates that the

residues in muscle and fat are comparable (2002 JMPR). On the basis of the data provided, the residue as defined for flutolanil is designated as not being fat-soluble.

Haloxyfop-R-methyl ester (active form) has log P_{ow} = 4; haloxyfop methyl (racemate) log P_{ow} = 3.52; haloxyfop acid log P_{ow} = 1.32; the residue of haloxyfop is defined as haloxyfop esters, haloxyfop and its conjugates expressed as haloxyfop. Results from two cattle feeding studies have been reported by the JMPR (1996, 2001); the first by the 1996 JMPR showed residues in fat are higher than in muscle while the second reported by the 2001 JMPR showed residues in fat and muscle were comparable. The results can be explained by the analytical methods utilized in the two studies. Metabolism studies showed haloxyfop was present in fat as a non-polar conjugate that is easily hydrolysed under alkaline conditions to yield haloxyfop; in milk fat the conjugates were identified as conjugates of triacylglycerols. The cattle feeding study reported in the 1996 JMPR utilized an alkaline hydrolysis step to extract residues from all tissues while the later study utilized base extraction for muscle, kidney and liver but not fat. An alkaline extraction is an integral part of the analytical method for both plant and animal matrices and it is clear that the later study reported by the 2001 JMPR should be discounted. On the basis of the cattle feeding study where both fat and muscle samples analysed using an appropriate residue method, the residue should be designated as fat-soluble. This conclusion differs from the recommendation of the 1995 JMPR.

Fipronil has a complex residue definition and the log P_{ow} for fipronil is 3.5 and log P_{ow} for a primary metabolite (MB 46136) is 3.8. The residue concentrations (parent + MB 46136) are 20 to 30× higher in goat fat compared to muscle in the metabolism study (2001 JMPR). In the cattle feeding study, residues (fipronil and MB 46136) were not detected in muscle (< 0.01 mg/kg) following dosing at the equivalent of 0.43 ppm. The individual components of the residue in fat were 3 to 4 × higher for fipronil and were 40 to 50 × higher for MB 46136 than those in muscle (< 0.01 mg/kg). Following combined dermal and oral administration to cattle, levels of fipronil and MB 46136 were < 0.01 mg/kg in muscle, however fipronil levels in fat were 4 to 6 × higher than the muscle LOQ and levels of MB 46136 ranged from 7 to 77 × higher than the muscle LOQ over three fat depots sampled. The data clearly show that the residue as defined (fipronil and MB 46136) is fat-soluble. As is often the case, there are significant differences in residue levels in renal fat compared to abdominal fat illustrating the need for individual fat depots to be analysed in cattle feeding studies.

The above examples demonstrate that log P_{ow} of an individual component of a residue is an initial indicator, however it is not the only factor used to assess fat-solubility.

The considerations applied to the designation of a residue definition as fat soluble or not for meat and fat should also be utilized in the design of any livestock feeding study. Data generated in a livestock study (radiolabelled or transfer) should adequately demonstrate that consideration of the fat-solubility of the chemical and/or metabolites has been taken into account. If the study is not adequately designed, and appropriate samples have not been taken, then it may be difficult to determine whether a residue should be designated as fat-soluble. In addition, if adequate sampling of different fat depots has not taken place, it may be difficult to determine whether MRLs have been recommended at appropriate levels. For the purposes of study design, any residue (compound and/or metabolites) with log P_{ow}> 3 should be considered as potentially being fat-soluble.

The Meeting recommended that in determining “fat solubility” for a residue the following factors should be considered:

- When available, it is the partitioning of the residue (as defined) in muscle versus fat in the metabolism studies and livestock feeding studies that determines the designation of a residue as being “fat soluble”.

- In the absence of useful information on the distribution of residues in muscle and fat, residues with log P_{ow} > 3 are likely to be “fat soluble”.

The Meeting noted that in the design of animal feeding studies, account should be taken of the likely fat solubility of residues with log $P_{ow} > 3$

The Meeting also recommended that the *FAO Manual* be amended as follows to reflect the above discussion:

Page 40 of the FAO Manual:

The solubility of the pesticide is especially of great interest, as the ability of the compound to penetrate plant and animal tissues is dependent on its solubility in water and organic materials.

The JMPR recommended that the distribution of the residue between muscle and fat obtained from livestock metabolism and feeding studies should be the prime indicator of fat-solubility. In some cases the information available on distribution of the residue (parent compound and/or metabolites) from metabolism or feeding studies does not allow an assessment of fat solubility to be made. In the absence of other useful information, the physical property chosen by the JMPR to provide an indication of solubility in fat is the octanol-water partition coefficient, usually reported as log P_{ow}.

It should be noted that there are errors in estimates of log P_{ow}, with differences of one unit for the same compound being reported. Different approaches to the development of these data often give different results. Interpretations must recognize these differences.

The variable composition of some residues, e.g. where the residue is defined as a mixture of parent and metabolites, presents a problem since the fat-solubilities of the metabolites may be different from those of the parent compound. In this case, information on the log P_{OW} of each individual metabolite should be considered if available. The relative concentrations within the mixture are also subject to change and, as a result, the tendency of the mixture to partition into fat will also change.

When no evidence is available to the contrary and log P_{ow} exceeds 3, the compound would be designated fat-soluble and when log P_{ow} is less than 3 it would not be so designated.

Page 52 of the FAO Manual:

Fat-solubility is a property of the residue and is primarily assessed from the octanol-water partition coefficient and the partition of the residue between muscle and fat observed in metabolism and farm animal feeding studies. The section in this chapter, “Physical and chemical properties” provides guidelines for deciding whether a pesticide is fat-soluble. Sampling protocols for animal commodities depend on whether a residue is fat-soluble or not.

The JMPR, for many years, included the qualification “fat-soluble” in the definition of the residues of fat-soluble pesticides, using the expression:

“Definition of the residue: [pesticide] (fat-soluble)”

The 1996 JMPR recommended that “fat-soluble” should no longer be included in the definition of the residue because “fat-soluble” is a qualification of sampling instructions and is not relevant to the dietary intake residue. In order to avoid confusion while conveying the information that a residue is fat-soluble, the JMPR agreed that a separate sentence should indicate that the residue is fat-soluble.

The definition of residues has not always been consistent with these principles, which were first published in the 1995 JMPR Report with a revision published in the report of the 2005 JMPR. Therefore, all residue definitions are re-examined during the periodic review of the compounds.

2.11 JMPR RECOMMENDATIONS FOR ANIMAL FORAGE

Pesticides are needed in the production of animal forage and fodder crops, so residues in the resulting forage and fodder may be expected.

The succulent or high-moisture stages of the crop are known as forage and mostly are grazed directly or are cut and fed to livestock without delay. Examples are: maize forage, alfalfa forage and pea vines.

The dry or low-moisture stages of the crop are known as hay, straw or fodder, which may be readily stored and transported as commodities of trade.

In the past, JMPR has recommended MRLs for forage crops and has used information on their residue status in estimating farm animal dietary burden.

Codex MRLs are used as standards for commodities in international trade. The Meeting was of the opinion that forage was not an item of international trade requiring Codex MRLs and decided not to recommend further forage MRLs.

Fodder MRLs would continue to be evaluated and recommended as previously.

Forage residue data would continue to be evaluated and used in the estimation of farm animal dietary burden.

2.12 RESPONSE TO CCPR REGARDING THE ARfD FOR CARBARYL

At the 37th Session of the CCPR in April 2005, the Australian delegation had raised concern regarding the ARfD for carbaryl established by the JMPR in 2001. The Australian delegation had disagreed with the choice of pivotal study used for setting the ARfD and requested that JMPR review the basis for the ARfD established.

The evaluation of carbaryl by the JMPR

In 2001, the Meeting established an ARfD of 0.2 mg/kg bw based on a NOAEL of 3.8 mg/kg bw per day identified on the basis of inhibition of cholinesterase activity observed at 10 mg/kg bw per day in a 5-week dietary study in dogs, and with the application of a 25-fold safety factor.

The Australian evaluation of carbaryl

The current Australian ARfD of 0.01 mg/kg bw is based on a NOEL of 1 mg/kg bw per day identified on the basis of behavioural indications of autonomic neurotoxicity, and inhibition of brain and plasma erythrocyte cholinesterase activity in a study of developmental toxicity and a 13-week study of neurotoxicity in rats, and using a 100-fold safety factor.

When setting an ARfD for carbaryl, Australia's Office of Chemical Safety (OCS) examined the evaluation made by the JMPR and did not agree with the selection of the pivotal study. The OCS noted that Hayes & Laws (1991) had reported overt acute cholinergic toxicity in a human receiving carbaryl as an oral dose at approximately 2.8 mg/kg bw, a dose that is lower than the NOAEL of 3.8 mg/kg bw per day identified on the basis of inhibition of erythrocyte and brain cholinesterase activity in dogs, which was used as the basis for the JMPR evaluation.

Comments made by the JMPR

In the case of carbaryl, the Meeting noted that the current ARfD of 0.2 mg/kg bw is appropriate and sufficiently protective because it is one-fourteenth of the effect level reported by Hayes & Laws in a study in a single human. The Meeting noted that in general a study based on only one human individual should not serve as the basis for an ARfD, although such a case study may provide supporting information.

In the JMPR toxicological evaluation, it is stated that cholinesterase activities in dogs and rats are considered to be equally sensitive to inhibition by carbaryl. Although the NOAEL of 1 mg/kg bw per day reported in the 13-week study in rats is lower than the NOAEL of 3.8 mg/kg bw per day reported in the 5-week study in dogs, an overall NOAEL was identified by selecting the highest NOAEL below the lowest LOAEL to account for differences in dose spacing in these two studies. Furthermore, inhibition of cholinesterase activity is a sensitive and quantitative biochemical end-point that is adequately protective for other end-points, including neurological symptoms and signs. Lastly, the 25-fold safety factor that was applied to the NOAEL for inhibition of cholinesterase activity in dogs includes an interspecies extrapolation factor that would allow for a fivefold greater sensitivity of humans.

2.13 JOINT FAO/WHO MEETING ON PESTICIDE SPECIFICATIONS

The Meeting was informed about the work and the new working procedure of the Joint FAO/WHO Meeting on Pesticide Specifications (JMPS), and briefly discussed two examples of existing *FAO Specifications and Evaluations for Plant Protection Products*[5]. The Meeting recognized the importance of this activity in developing specifications for the active ingredients of pesticides.

The Meeting considered that it is important to coordinate the activities of the JMPR and the JMPS as far as possible. Therefore the Meeting reiterated the conclusions of the 1999 Meeting, that specifications for the technical material should be developed for a pesticide before it is evaluated within the periodic review programme of the CCPR and for new pesticides, but that this should not delay evaluation of pesticides by the JMPR. The Meeting recognized that there are many compounds on the JMPS agenda that will not lead to residues in food and will therefore not be evaluated by JMPR.

The Meeting noted that the *FAO Specifications and Evaluations for Plant Protection Products* include sections entitled “Hazard summary” and “Appraisal”, which include toxicological information and an appraisal of the hazard potential of the compound. The Meeting expressed concern that the basis for this information and whether the appraisal is a peer-reviewed evaluation of the available information is not indicated in these sections. The Meeting suggested that it should be clearly indicated whether these sections are based on existing national/regional or international evaluations.

The Meeting recommended that if JMPR evaluations exist for a particular pesticide, toxicological information from the summary tables and toxicological evaluations of the JMPR report should be used as the only entry in the relevant toxicological parts of the specifications.

The 2005 JMPR agreed to refer to available JMPS specifications in the JMPR report. However, this reference is not an endorsement of the toxicological information therein (except for JMPR hazard assessments).

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[5] *FAO Specifications and Evaluations for Plant Protection Products:* http://www.fao.org/ag/agp/agpp/pesticid/

2.14 PROJECT TO UPDATE THE PRINCIPLES AND METHODS FOR THE RISK ASSESSMENT OF CHEMICALS IN FOOD

The Meeting briefly discussed the recommendations of the recently held workshop on exposure assessment. This workshop was part of the joint FAO/WHO Project to Update the Principles and Methods for the Risk Assessment of Chemicals in Food, and considered methods for exposure assessment of food chemicals, including pesticide residues, in relation to long-term and acute exposure.

In this context, the advancement of the 13 GEMS/Food cluster diets was discussed. The final cluster diets would be presented at the next Codex Committee on Food Additives and Contaminants (CCFAC) and CCPR meetings, and could be implemented at the next JMPR. The RIVM offered assistance in updating the calculation spreadsheets that the JMPR uses in the dietary risk assessments to replace the current five GEMS/Food regional diets with the 13 cluster diets. This was welcomed by the Meeting.

The Meeting was informed of the next steps of the project, which included a workshop to review current methods for setting MRLs for pesticide residues and veterinary drug residues, and harmonizing to the extent possible. The workshop would be held in November 2005 in the Netherlands, with the support of the RIVM.

A meeting of the Steering Group would be held early next year to review progress on the project, and a final expert consultation to review the final document of the whole project was being planned, as recommended by the Joint FAO/WHO Expert Committee on Food Additives (JECFA). Funding for such a final consultation was currently being sought.

2.15 IPCS FRAMEWORK FOR ANALYSING THE RELEVANCE OF A CANCER MODE OF ACTION FOR HUMANS

The Meeting briefly discussed the draft International Programme on Chemical Safety (IPCS) document *IPCS Framework for Analysing the Relevance of a Cancer Mode of Action for Humans*[6]. To promote the use of mechanistic data, the Meeting noted that the approach laid out in the document should be used in JMPR evaluations. Thus the Meeting recommended that the Secretariat should advise the JMPR Temporary Advisers to use the IPCS framework as guidance in their evaluations of cancer modes of action as appropriate.

The Meeting was informed that the IPCS document would be accompanied by case studies, to illustrate the approach to be used, and that IPCS was encouraging the submission of further examples to be included.

The next planned activity within this project would be to expand the mode of action framework to encompass end-points other than cancer.

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[6] *IPCS Framework for Analysing the Relevance of a Cancer Mode of Action for Humans*: http://www.who.int/ipcs/methods/harmonization/areas/cancer_framework/en/index.html

2.16 PROBABILISTIC MODELLING OF ACUTE DIETARY EXPOSURE

The Meeting noted the conclusions of the 37th Session of CCPR on the proper risk management concerning the safety of Codex MRLs, which was (ALINORM 05/28/24 para 76, italics added):

'The Committee concluded that food containing *residues at the level of the adopted Codex MRL* must be safe for the consumers and that the Committee retains the current policy i.e., when the JMPR notes an ARfD exceedance, the MRLs are not advanced to a higher Step of the Codex Procedure.'

The Meeting reflected that to assess the safety of residues at the level of the adopted Codex MRL the development of probabilistic methodology for JMPR purposes is unnecessary. The deterministic IESTI calculation currently used by JMPR is adequate to determine whether the ARfD might be exceeded. In the IESTI a fixed residue value representing the level of the Codex MRL is combined with a fixed consumption figure, representing a large portion of the commodity being assessed. The large portion is defined as the highest large portion reported from any of the Codex Member States that provided data to GEMS/Food and is represented by the 97.5th percentile of consumption-days only.

However, the Meeting noted that the GEMS/Food consumption database for acute exposure assessments as currently used in the calculations has limited information on the 97.5th percentiles of consumption. Only a few countries have supplied this information to GEMS/Food, and it is not known whether all of them have derived this percentile in the same way.

For example, some countries may have reported the 97.5th percentile consumption of fresh apple only, while others may have included the consumption of apple juice and apple in other foods, e.g. apple pie. Furthermore, to be able to assess the validity of the data provided, there should also be available a list of 97.5th percentiles of consumption figures and the number of person-days behind this percentile, together with more information on the distribution (e.g. geometric mean and geometric standard deviation, or list of percentiles, or preferably all individual data). If a national survey does not contain enough data on a particular commodity to discriminate the 97.5th percentile of consumption, this should be noted.

The Meeting recommended that GEMS/Food and Codex Members put more effort into refinement of the short-term consumption database currently used by JMPR, since anomalies and missing data often cause problems for the IESTI calculations.

2.17 RISK ANALYSIS PRINCIPLES

At the request of the Joint Secretariat, the Meeting provided comments on the *Proposed Draft Risk Analysis Principles applied by the Codex Committee on Pesticide Residues* (ALINORM 05/28/24, Appendix XIII). The current draft was considered to be a concise and accurate description of the tasks assigned to JMPR.

The Meeting stressed that JMPR's contribution to risk analysis is based solely on science whereas the consideration of other legitimate factors relevant to the health protection of consumers and for the promotion of fair practices in food trade is the responsibility of CCPR.

The Meeting also noted that it will continue to propose MRLs for plant and animal commodities based on the available data related to registered uses that reflect national GAPs. The decision whether an adopted CXL for a commodity shall be revoked although sufficient data are available to recommend a MRL, is the responsibility of CCPR, not JMPR.

3. DIETARY RISK ASSESSMENT FOR PESTICIDE RESIDUES IN FOODS

Assessment of risk from long-term dietary intake

Risks associated with long-term dietary intake were assessed for compounds for which MRLs were recommended and STMRs estimated at the present Meeting. International estimated daily intakes (IEDIs) were calculated by multiplying the concentrations of residues (STMRs, STMR-Ps) by the average daily per capita consumption estimated for each commodity on the basis of the GEMS/Food diet [7, 8, 9].

IEDIs are expressed as a percentage of the ADI for a 60 kg person, with the exception of the intake calculated for the Far East, in which a body weight of 55 kg is used[10]. The estimates are summarized in Table 10. The percentages are rounded to one whole number up to 9 and to the nearest 10 above that. Percentages above 100 should not necessarily be interpreted as giving rise to a health concern because of the conservative assumptions used in the assessments. The detailed calculations of long-term dietary intakes are given in Annex 3. A detailed calculation for dimethenamid-P is not included as all the STMRs estimated for these compounds are 0 mg/kg.

Benalaxyl, clofentenzine and propamocarb are evaluated at this Meeting under the periodic review programme. New ADIs for benalaxyl and propamocarb were allocated and the previous ADI for clofentenzine was confirmed. The long-term dietary risk assessment for these compounds will be considered during the periodic review for residues.

The dietary intake of azocyclotin was considered together with cyhexatin as there is a group ADI for these compounds.

The Meeting confirmed the previous ADI for ethoxyquin, however, currently no residue estimations in crops exist for this compound to perform the long-term dietary assessment.

The evaluation of malathion, carbendazim and imazalil performed at this Meeting do not affect the long-term assessment conducted by the previous JMPR for these compounds.

Calculations of dietary intake can be further refined at the national level by taking into account more detailed information, as described in the Guidelines for predicting intake of pesticide residues[7].

Table 10. Summary of long-term dietary of risk assessments conducted by the 2005 JMPR.

CCPR code	Compound Name	ADI (mg/kg bw)	Range of IEDI, as % of maximum ADI
095	Acephate	0–0.03	1–7
67/129	Azocyclotin/ Cyhexatin	0–0.003	0–5
201	Chlorpropham	0–0.05	2–30
214	Dimethenamid-P	0–0.07	0
215	Fenhexamid	0–0.2	0–6

[7] WHO (1997) Guidelines for predicting dietary intake of pesticide residues. 2nd revised edition, GEMS/Food Document WHO/FSF/FOS/97.7, Geneva

[8] WHO (1997) Food consumption and exposure assessment of chemicals. Report of a FAO/WHO Consultation. Geneva, Switzerland, 10-14 February 1997, Geneva

[9] WHO (1998). GEMS/FOOD Regional Diets. Food Safety Issues. WHO/FSF/98.3. Geneva

[10] Codex Alimentarius Commission, 1997, CX/PR 98/5

CCPR code	Compound Name	ADI (mg/kg bw)	Range of IEDI, as % of maximum ADI
158	Glyphosate	0–1	0–1
216	Indoxacarb	0–0.01	1–50
132	Methiocarb	0–0.02	0–2
147	Methoprene	0–0.09	20–40
217	Novaluron	0–0.01	5–40
112	Phorate	0–0.0007	9–20
063	Pyrethrins	0–0.04	1
218	Sulfuryl fluoride	0–0.01	1
167	Terbufos	0–0.0006	10–40

Dried chili peppers

The long-term intake assessment was completed by the 2005 JMPR for all compounds taking into account the use of those compounds on all crops, including dry chili pepper. Details of the calculations are shown on Section 2.6 of this report.

The TMDI estimated ranged from 100 to 690% ADI for dicofol, from 10 to 120% ADI for vinclozolin and from 5 to 40% ADI for profenofos. The highest values were obtained for the European diet. The contribution of chili pepper to the total intake in each case ranged from 1 to 9%.

The IEDIs estimated for acephate, carbaryl, methamidophos and oxamyl ranged from 2 to 70% of ADI and for dimethoate ranged from 30 to 130 (European diet) % ADI. The contribution of chili pepper to the total intake in each case ranged from 1 to 14%.

The IEDI or mixed calculation based on available STMR and MRL were performed for carbendazim, chlorpyrifos, dinocap, ethephon, ethoprophos, imidaclorprid, malathion, methomyl, methoxyfenozide, piperonyl butoxide, pyrethrins, spinosad and tebufenozide and tolyfluanid, monocrotophos, oxamyl, phosphamidon, procymidone, profenofos, tebufenozide and vinclozolin. The intake ranged from 0 to 40% of the ADI. For diazinon, the intake ranged from 30 to 180% ADI. The contribution of chili pepper to the total intake in each case ranged from 0 to 1%.

TMDI calculation were also performed for other compounds based on current MRLs, incorporating proposed MRLs for dried chili peppers (see Table 3 Section 2.6). The total intake ranged from 0 to 120 (chlorpyrifos methyl in middle-eastern diet) % ADI. The contribution of chili pepper to the total intake in each case ranged from 0 to 2% with the exception of azinphos methyl (1–3%) and chlorothalonil (1–4%).

Assessment of risk from short-term dietary intake

Risks associated with short-term dietary intake were assessed for compounds for which STMR and HR values were estimated at the present Meeting and for which acute reference doses (acute RfDs) had been established, in commodities for which data on consumption were available. The procedures for calculating the short-term intake were defined primarily in 1997 at an FAO/WHO Geneva Consultation[8], refined at the International Conference on Pesticide Residues Variability and Acute Dietary Risk Assessment sponsored by the Pesticide Safety Directorate and at subsequent JMPR Meetings. Data on the consumption of large portions were provided by the governments of Australia, France, The Netherlands, Japan, South Africa, the UK and the USA. Data on unit weights and per

cent edible portions were provided by the governments of France, Sweden, the UK and the USA. The body weights of adults and children aged ≤ 6 years were provided by the governments of Australia, France, The Netherlands, South Africa, the UK and the USA. The consumption, unit weight and body weight data used for the short-term intake calculation were compiled by GEMS/FOOD and are available at www.who.int/foodsafety/chem/acute_data The documents are dated 01/01/2003 (large portions and body weights) and 05/02/2003 (unit weights).

The procedures used for calculating the International estimated short-term intake (IESTI) are described in detail in Section 3 of the 2003 JMPR report. A detailed guidance on setting ARfD are described in Section 2.1 of the 2004 JMPR report.

ARfDs were established for benalaxyl, imazalil, ethoxyquin and propamocarb, but short-term intakes were not calculated. The assessment for benalaxyl, imazalil and propamocarb will be considered during the periodic review of residues for these compounds at a subsequent meeting. The assessment was not performed for ethoxyquin, as no STMRs and HRs data was available.

The evaluation of malathion performed at this Meeting did not affect the short-term assessment made by the previous JMPR for this compound.

On the basis of data received by the present or previous Meeting, the establishment of an ARfD for clofentezine, novaluron, fenhexamid, glyphosate and methoprene was considered to be unnecessary. Therefore, the short-term intakes of these compounds were not estimated.

The short-term intakes as percentages of the ARfDs for the general population and for children are summarized in Table 11. The percentages are rounded to one whole number up to 9 and to nearest 10 above that. Percentages above 100 should not necessarily be interpreted as giving rise to a health concern because of the conservative assumptions used in the assessments. The detailed calculations of short-term dietary intakes are given in Annex 4. A detailed calculation for dimethenamid-P is not included as all the STMRs and HRs estimated for this compound are 0 mg/kg.

Table 11: Summary of short-term dietary risk assessments conducted by the 2005 JMPR.

CCPR code	Compound Name	ARfD (mg/kg bw)	Commodity	Percentage of ARfD	
				General population	Children aged ≤ 6 years
095	Acephate	0.1	Apple	160	390
			Broccoli	80	150
			Cauliflower	110	170
			Mandarin	50	160
			Nectarine	60	130
			Peach	80	130
			Pear	90	210
			Peppers, sweet	170	190
			Other commodities	0–50	0–90
67/129	Azocyclotin/Cy-hexatin	0.02*	All commodities	3–10 (only for women of childbearing age)	
214	Dimethenamid-P	0.5	All commodities	0	0
072	Carbendazim	0.5	All commodities	0–11	0–30
		0.1*	All commodities	0–55 (only for women of childbearing age)	
201	Chlorpropham	0.5	All commodities	0–20	0–60

CCPR code	Compound Name	ARfD (mg/kg bw)	Commodity	Percentage of ARfD	
				General population	Children aged ≤ 6 years
216	Indoxacarb	0.1	Cabbages, head	50	130
			Other commodities	0–40	0–60
132	Methiocarb	0.02	All commodities	0–50	0–70
112	Phorate	0.003	Potato	50	120
			Other commodities	0–10	0–20
063	Pyrethrins	0.2	Tree nuts	1	0
218	Sulfuryl fluoride	0.3	All commodities	0–5	0–3
167	Terbufos	0.002	All commodities	0–30	0–60

* For women of childbearing age

Spices

The 2004 JMPR calculated the short-term intake of mevinphos from the consumption of spices based on consumption data from France, and estimated that the intake represented 169% ARfD for adults and 161% for children. At the present Meeting, the calculation was also performed using the diets provided by Australia, Germany, UK and USA. The short-term intake ranged from 4 to 90% of the ARfD. Details of the calculation are reported in section 2.6. The Meeting concluded that national governments should refine this estimation using local consumption data.

4. EVALUATION OF DATA FOR ACCEPTABLE DAILY INTAKE AND ACUTE DIETARY INTAKE FOR HUMANS, MAXIMUM RESIDUE LEVELS AND SUPERVISED TRIAL MEDIAN RESIDUE VALUES

4.1 ACEPHATE (095)

TOXICOLOGY

Acephate is the International Organization for Standardization (ISO) approved name for the organophosphorus insecticide *O,S*-dimethyl acetylphosphoramidothioate, which is a cholinesterase inhibitor. The toxicology of acephate was evaluated by the Joint Meeting in 1976, 1982, 1984, 1987, 1988, 1990 and 2002. The 2002 JMPR established an ADI of 0–0.01 mg/kg bw based on the NOAEL of 10 ppm (equal to 0.58 mg/kg bw per day) in a 13-week study in rats and a safety factor of 50. The 2002 JMPR also established an ARfD of 0.05 mg/kg bw based on the NOAEL of 2.5 mg/kg bw in female rats in a study of acute neurotoxicity. The NOAELs were identified on the basis of inhibition of brain acetylcholinesterase activity. The overall safety factor of 50 ($100/4 \times 2$) was applied, this being a combination of:

- a fourfold reduction in the safety factor because of the absence of relevant sex or species (including humans) differences in inhibition of cholinesterase activity or in kinetics, and the fact that the effect was dependent on the C_{max};
- an additional safety factor of 2 for the marginal but statistically significant inhibition of brain cholinesterase activity observed in rats and dogs at 5 and 10 ppm.

The present Meeting re-evaluated acephate because new data had been submitted, including a study of metabolism in rats, a short-term study of neurotoxicity in rats, a study of developmental neurotoxicity in rats and a 28-day study in humans. The Meeting also reviewed relevant data from the previous evaluations.

All the new studies submitted for consideration by the Meeting complied with good laboratory practice (GLP).

Biochemical aspects

In a new toxicokinetic study in rats given doses of 25 or 100 mg/kg bw by oral administration, acephate was rapidly absorbed with a time to maximum concentration in plasma (T_{max}) of 0.5–1 h. The terminal half-life was 1.4 h. There was no evidence of any persistent accumulation in tissue. Excretion in the urine accounted for 83–89% of the administered dose, most of this appearing in the first 6–12 h after dosing. Elimination via the faeces and as carbon dioxide accounted for about 2% and 5–9% of the administered dose, respectively. Most of the compound excreted in the urine during the first 24 h after dosing was unmetabolized acephate and ≤ 5% was methamidophos. Small amounts of *O*-desmethyl acephate, *O*-desmethyl methamidophos and *O,S*-dimethyl phosphorothioate, have also been identified in the urine.

The pharmacokinetics of acephate was similar in men and women given a single oral dose of 0.35–1.2 mg/kg bw. The T_{max} for plasma was 1–4 h and the terminal elimination half-life was between 3.5 h and 6.6 h. Most of the recovered acephate and methamidophos was found in urine during the first 12 h after dosing. Methamidophos accounted for about 1.3% of the amount recovered in the urine, independently of the dose administered.

A comparison of dose administered and C_{max} in rats and humans is reported in Table 12. There were no relevant differences between humans and rats, considering the different methods used.

Table 12: Relationship between dose administered and C_{max} in rats and humans

	Humans				Rats	
Dose (mg/kg bw)	0.35	0.7	1	1.2	25	100
C_{max} (µg/mL)	0.45	0.8	1.35	1.6	23	90

Toxicological data

Acephate was a slightly more effective inhibitor of brain and erythrocyte acetylcholinesterase activities in rats (IC_{50} = 1.6 and 1.3 mmol/L, respectively) than in cynomolgus monkeys (concentration required to inhibit activity by 50%, IC_{50} = 3.4 and 2.7 mmol/L, respectively) or humans (IC_{50} = 5.4 and 2.7 mmol/L, respectively).

The median lethal dose (LD_{50}) values were 1000–1400 mg/kg bw after oral administration in rats and > 10 000 mg/kg bw after dermal administration in rabbits. The LC_{50} value was > 15 mg/L air (4 h, nose-only) in rats. The clinical signs of toxicity corresponded to those typical of cholinergic poisoning.

In the new short-term study of neurotoxicity in rats fed diets containing acephate at a concentration of 50 to 1000 ppm, brain acetylcholinesterase activity was inhibited at the lowest dietary concentration tested (50 ppm), while erythrocyte acetylcholinesterase activity was reduced at dietary concentrations of 100 ppm and above. This confirms previous observations that in rats in vivo brain acetylcholinesterase is more sensitive to inhibition by acephate than is erythrocyte acetylcholinesterase. No clinical or neurobehavioural effects were observed at any dietary concentration, even the highest tested (1000 ppm), at which brain acetylcholinesterase activity was inhibited by about 80%. No NOAEL could be identified in this study, the LOAEL being 50 ppm (equal to 3.4 mg/kg bw per day).

This difference in enzyme sensitivity was not observed in dogs and monkeys. In a 52-week study, dogs were given diets containing acephate at concentrations of up to 800 ppm. There were no treatment-related clinical signs, no alterations in body weight or food consumption, no changes in ophthalmic parameters and no findings at gross necropsy. Brain and erythrocyte acetylcholinesterase activities were similarly inhibited, as shown in Table 13.

Table 13. Mean percentage inhibition of acetylcholinesterase activity in dogs given diets containing acephate for 52 weeks

Dietary concentration (ppm)	Brain acetylcholinesterase activity		Erythrocyte acetylcholinesterase activity	
	Males	Females	Males	Females
10	17	11	0	0
120	53	49	43	46
800	68	66	86	84

Similarly, the 1984 Meeting reported that in monkeys receiving acephate at a dose of 2.5 mg/kg bw per day by gavage for 33–34 days, the mean inhibition (relative to mean pre-treatment values) of acetylcholinesterase activity was 50% in erythrocytes and 47% in brain.

In the new study of developmental neurotoxicity, acephate was administered via gavage to pregnant rats from day 6 of gestation to postnatal day 6, and to pups from postnatal days 7 to 21. No significant inhibition of brain, erythrocyte or plasma cholinesterase activity was found in pups at postnatal day 4. At postnatal day 21, a significant reduction in brain acetylcholinesterase activity was observed at all doses. The degree of inhibition was found to be lower in erythrocytes and was significant at the highest dose only. A NOAEL could not be identified in this study.

Groups of seven volunteers received acephate as single oral doses at up to 1.2 mg/kg bw (men) and 1 mg/kg bw (women). No inhibition of erythrocyte acetylcholinesterase activity was reported in either sex at any dose. No clinically significant changes were seen in vital signs or on electrocardiography, haematology, clinical chemistry, urine analysis or physical examination. The NOAEL was 1.2 mg/kg bw per day, the highest dose tested.

In the new study in human volunteers, which was conducted according to current ethical standards, 10 men received acephate (purity, 99%) as daily oral doses at 0.25 mg/kg bw per day for 28 consecutive days. There was no inhibition of plasma cholinesterase or erythrocyte acetylcholinesterase activities at any time during the study. There were no treatment-related changes from baseline values for any haematology, clinical chemistry, electrocardiogram or urine analysis parameters, and no changes in vital signs or physical examination. The NOAEL was 0.25 mg/kg bw, the only dose tested.

Toxicological evaluation

To establish the ADI and ARfD, the Meeting considered the following elements derived from the available information:

The critical toxicological effect of acephate is the inhibition of acetylcholinesterase activity in the nervous system, an effect that is dependent on C_{max} rather than on the area under the curve (AUC).

Data on inhibition in vitro indicate that human brain acetylcholinesterase is slightly less sensitive to inhibition by acephate than is rat brain acetylcholinesterase.

Well conducted toxicokinetics studies, available for both rats and humans, show that there is no significant difference between the two species; in particular, C_{max} values have the same relationship to administered dose in the two species, and acephate is rapidly absorbed and eliminated in both species.

Data for rats in vivo indicate that inhibition of brain acetylcholinesterase activity occurs at lower doses than those required for a similar level of inhibition of erythrocyte acetylcholinesterase activity.

Data for dogs and monkeys in vivo indicate that brain and erythrocyte acetylcholinesterase activities are nearly equally inhibited at any given dose, and do not show the difference seen in rats, which might thus be rat-specific.

Well-conducted single- and repeated-dose studies in humans clearly show a NOAEL for inhibition of erythrocyte acetylcholinesterase activity.

Data from animals in vivo do not show sex differences in inhibition of acetylcholinesterase activity or clinical signs.

Studies in which acephate was administered by gavage (such as the study of developmental neurotoxicity in rats), while giving useful information, are not appropriate for setting an ADI because

repeated gavage administration to pups is not relevant to human long-term dietary exposure to residues of acephate.

The Meeting established an ADI of 0–0.03 mg/kg bw based on the NOAEL of 0.25 mg/kg bw per day from the study of repeated doses in humans and an overall safety factor of 10.

The Meeting established an ARfD of 0.1 mg/kg bw on the basis of the NOAEL of 1.2 mg/kg bw from the study of single doses in humans and an overall safety factor of 10.

The overall safety factor of 10 was derived by dividing the default value of 10 by 2 (because inhibition of acetylcholinesterase activity depends on the C_{max}) and by multiplying by 2 (because some uncertainty remains with respect to the in-vivo sensitivity to inhibition of human brain acetylcholinesterase activity relative to that of erythrocyte acetylcholinesterase activity, since brain acetylcholinesterase may be more sensitive than erythrocyte acetylcholinesterase).

An addendum to the toxicological monograph was prepared.

Levels relevant to risk assessment

Species	Study	Effect	NOAEL	LOAEL
Rat	Acute neurotoxicity[a,b]	Toxicity	2.5 mg/kg bw	5 mg/kg bw
	Short-term study of neurotoxicity[c]	Toxicity	50 ppm, equivalent to 3.4 mg/kg bw per day	100 ppm, equivalent to 6.7 mg/kg bw per day
Rabbit	Developmental toxicity[a]	Maternal toxicity	3 mg/kg bw per day	10 mg/kg bw per day
		Embryo- and fetotoxicity	3 mg/kg bw per day	10 mg/kg bw per day
Dog	52-week study of toxicity[c]	Toxicity	10 ppm, equal to 0.27 mg/kg bw per day[d]	120 ppm, equal to 3.1 mg/kg bw per day
Human	Single-dose study[e]	Toxicity	1.2 mg/kg bw[f]	—
	28-day study[e]	Toxicity	0.25 mg/kg bw per day[f]	—

[a] Gavage administration
[b] Tested only in females
[c] Dietary administration
[d] Marginal effects on brain acetylcholinesterase activity, of equivocal toxicological relevance
[e] Oral administration
[f] Highest dose tested

Estimate of acceptable daily intake for humans

0–0.03 mg/kg bw

Estimate of acute reference dose

0.1 mg/kg bw

Information that would be useful for continued evaluation of the compound

Results from epidemiological, occupational health and other such observational studies of human exposures

Critical end-points relevant for setting guidance values for exposure to acephate

Absorption, distribution, excretion and metabolism in mammals	
Rate and extent of oral absorption	Extensive and rapid
Distribution	Widely distributed
Potential for accumulation	None
Rate and extent of excretion	Rapid and nearly completely, mainly via urine
Metabolism in animals	Limited
Toxicologically significant compounds (animals, plants and environment)	Acephate and methamidophos
Acute toxicity	
Rat LD_{50} oral	1000 mg/kg bw
Rabbit LD_{50} dermal	> 2000 mg/kg bw
Rat LC_{50} inhalation	> 15 mg/L air (4 h, nose-only)
Skin irritation	Not irritating
Eye irritation	Not irritating
Skin sensitization (test method used)	Not sensitizing (Magnusson & Kligman)
Short-term studies of toxicity	
Target/critical effect	Nervous system/inhibition of cholinesterase activity
Lowest relevant oral NOAELa	10 ppm, equal to 0.58 mg/kg bw per day (13-week study in rats)
Genotoxicity	
	Unlikely to be genotoxic in vivo
Long-term studies of toxicity and carcinogenicity	
Target/critical effect	Nervous system/inhibition of cholinesterase activity
Lowest relevant NOAEL	5 ppm, equivalent to 0.25 mg/kg bw per day (28-month study in rats)
Carcinogenicity	Not likely to pose a carcinogenic risk to humans
Reproductive toxicity	
Reproduction target/critical effect	Number of pups and postnatal survival decreased at parentally toxic doses
Lowest relevant reproductive NOAEL	50 ppm (equivalent to 3.3 mg/kg bw per day)
Developmental target/critical effect	Decreased fetal body weight and reduced ossification (rats) and slight developmental effects (rabbits) at maternally toxic doses; not teratogenic
Lowest relevant developmental NOAEL	3 mg/kg bw per day (rabbits)
Neurotoxicity/delayed neurotoxicity	
NOAEL for acute neurotoxicity	1.2 mg/kg bw (humans)
NOAEL in short-term study of neurotoxicity	0.25 mg/kg bw per day (humans)
	No signs of delayed polyneuropathy (hens)
Other toxicological studies	
	Toxicokinetic and metabolism data not significantly different from data in rats

Summary

	Value	Study	Safety factor
ADI	0–0.03 mg/kg bw	Human, 28-day study	10
ARfD	0.1 mg/kg bw	Human, single-dose study	10

DIETARY RISK ASSESSMENT

The current Meeting has established an ADI of 0–0.03 mg/kg bw and an ARfD of 0.1 mg/kg bw for acephate. In considering how to best approach the dietary risk assessment of mixed residues of acephate and methamidophos the 2003 JMPR decided that an appropriately conservative approach would be to sum the acephate and methamidophos residues after first scaling the methamidophos residues by a factor to account for the difference in toxicity. The current Meeting utilized the same approach, with relevant factors, for long and short-term intake, derived from the ratios of the acephate and methamidophos ADI and ARfD values; the factors are 7.5 and 10 respectively. Dietary intake estimates for the combined adjusted residues utilizing the new scaling factors were compared with the revised acephate ADI and ARfD.

Long-term intake

The International Estimated Daily Intakes for the 5 GEMS/Food regional diets, based on estimated STMRs were in the range 1–7% of the maximum ADI of 0.03 mg/kg bw (Annex 3). The Meeting concluded that the long-term intake of residues of acephate from uses that have been considered by the 2003 JMPR is unlikely to present a public health concern.

Short-term intake

The IESTI varied from 0% to 170% of the ARfD (0.1 mg/kg bw) for the general population and from 0% to 390% of the ARfD for children aged 6 years and below. The short-term intakes from apple, cauliflower and peppers were 110–170% of the ARfD for the general population and the short-term intakes from apple, broccoli, cauliflower, mandarin, nectarine, pear, peach and peppers were 130–390% of the ARfD for children aged 6 years and below. The information provided to the 2003 JMPR and re-evaluated in the current Meeting precluded a conclusion that the acute dietary intake of pome fruit (e.g. apple, pear) flowerhead brassicas (e.g. broccoli and cauliflower), mandarin, nectarine, peach and peppers would be below the ARfD.

The Meeting concluded that the short-term intake of residues of acephate from uses considered by the 2003 JMPR is unlikely to present a public health concern, with the exception of pome fruit (e.g. apple, pear) flowerhead brassicas (e.g. broccoli, cauliflower), mandarin, nectarine, peach and peppers.

4.2 AZOCYCLOTIN (067) AND CYHEXATIN (129)

TOXICOLOGY

Azocyclotin (tri(cyclohexyl)-1H-1,2,4-triazole-1-yltin) and cyhexatin (tricyclohexyltin hydroxide) are chemically-related organotin compounds that are used as agricultural acaricides. Azocyclotin breaks down to cyhexatin and 1,2,4-triazole. Azocyclotin has similar systemic toxicological properties to cyhexatin and may also have additional properties attributable to the 1,2,4-triazole that is formed.

Toxicological data on cyhexatin were reviewed by the JMPR in 1970, 1973, 1977, 1978, 1980, 1981, 1988, 1989, 1991 and 1994. Azocyclotin was evaluated by the JMPR in 1974, 1981, 1989 and 1991. The Meeting in 1991 considered that the ADI for cyhexatin should also cover exposure to azocyclotin. In 1994, an ADI of 0–0.007 mg/kg bw was established based on a NOAEL of 0.7 mg/kg bw per day for reduced pup survival and decreased pup body-weight gain during lactation in a multigeneration study in rats.

Azocyclotin and cyhexatin were considered by the present Meeting as part of the CCPR periodic review programme.

Several new GLP-compliant studies of cyhexatin were evaluated that had not been previously available, including investigations of absorption, distribution, metabolism and excretion, short-term studies of toxicity, tests for genotoxicity, and a long-term study of combined toxicity/carcinogenicity incorporating a neurotoxicity phase.

Biochemical aspects

Oral doses of azocyclotin and cyhexatin were absorbed to a limited extent in rats. About 12% of azocyclotin or its breakdown products were absorbed from the gut lumen in rats and 1.6–10% in the case of cyhexatin. In rabbits given oral doses of cyhexatin, less than 10% of the administered dose was absorbed from the gut. Azocyclotin was shown to completely break down in aqueous solution to form cyhexatin and 1,2,4-triazole. There were no investigations available on whether 1,2,4-triazole undergoes any metabolism in the body.

Cyhexatin is metabolized by hydroxylation, which splits off cyclohexyl rings to produce dicyclohexyltin and monocyclohexylstannoic acid. The products of the initial reactions can undergo oxidation to produce unidentified polar metabolites. In addition, hydroxylated and destannylated derivatives have been identified in faeces of animals treated with cyhexatin, but it is not clear whether these were the products of bacterial and chemical breakdown in the gut lumen or the products of metabolism of absorbed material that had been excreted in bile. There was extensive distribution of metabolites of azocyclotin and cyhexatin to various organs and tissues of the body, with the highest amounts being found in the liver and the kidneys. Elevated levels of tin and ^{14}C radiolabel were detected in fetuses, amniotic fluid and placenta in pregnant rabbits given oral doses of ^{14}C-labelled cyhexatin.

In all species investigated (rat, rabbit and guinea-pig), excretion of the metabolites of azocyclotin and cyhexatin was mostly in the urine and to a lesser extent in the bile. As a result of poor absorption, large proportions of orally administered doses of azocyclotin and cyhexatin were found in the faeces. Minimal amounts were exhaled as carbon dioxide.

Toxicological data

Azocyclotin and cyhexatin had moderate acute toxicity by the oral route. The LD_{50} values for azocyclotin and cyhexatin in rats were 209 mg/kg bw and 265 mg/kg bw, respectively, when administered by the oral route. Azocyclotin and cyhexatin had very low acute systemic toxicity when applied dermally, with LD_{50} values for rats of 3600 mg/kg bw and > 2000 mg/kg bw, respectively, but high acute toxicity after exposure by inhalation, with LC_{50} values for rats of approximately 0.02 mg/L for azocyclotin and 0.016 mg/L for cyhexatin.

Cyhexatin was a severe irritant to skin and eyes of rabbits. Azocyclotin was more irritant than cyhexatin, being corrosive to rabbit skin. Neither azocyclotin nor cyhexatin caused skin sensitization in tests in guinea-pigs.

Exposure to azocyclotin at a dose of 0.96 µg/L by inhalation caused poorly groomed appearance, impaired breathing and increased lung weight in rats exposed for 6 h per day, 5 days per week, for 3 weeks. The no-observed-adverse-effect concentration (NOAEC) for the study was 0.28 µg/L. Inhalation exposure of rabbits to cyhexatin at 0.21 mg/L or more for 6 h per day, 5 days per week, for 2 weeks, caused inflammation of the respiratory tract, pulmonary congestion and toxicity to the liver and kidneys. The NOAEC was 0.077 mg/L.

No systemic toxicity was seen in rats given azocyclotin at doses of up to 25 mg/kg bw per day applied dermally for 7 h per day, 5 days per week, for 3 weeks. However, increased serum alkaline phosphatase activity was found when cyhexatin at a dose of 1 mg/kg bw per day was applied to the skin of rabbits for 6 h per day, 5 days per week, for 3 weeks. The NOAEL was 0.3 mg/kg bw per day.

In short-term studies with azocyclotin and cyhexatin, the main toxicological effects seen in rats were local effects on the gastric mucosa, haematological changes and hepatotoxicity. However, no treatment-related adverse effects were seen in a 90-day repeat-dose dietary toxicity study that delivered cyhexatin at doses of up to 10 mg/kg bw per day to mice. When cyhexatin was given at doses of 10 or 20 mg/kg bw per day by gavage for 14 or 28 days, erosions and/or ulcers of the glandular gastric mucosa were seen in some animals at both doses. A 28-day dietary study with cyhexatin in rats showed haematological changes related to changes in erythrocyte and blood clotting parameters at 6 mg/kg bw per day. The NOAEL was 3 mg/kg bw per day. In a 90-day study with cyhexatin in rats, there was hepatotoxicity and liver regeneration at dietary concentrations of 50 ppm or more, with a NOAEL of 10 ppm (equal to 0.68 mg/kg bw per day).

Three short-term studies of oral toxicity with azocyclotin were performed in rats, one using gavage dosing and the others using dietary administration. Low body weights were reported in treated animals in all the studies at dietary concentrations of 50 ppm (equal to 2.86 mg/kg bw per day) or more. Decreased total leukocyte counts were reported in two of the studies, with decreased lymphocyte counts in one of these. The NOAEL was 2 mg/kg bw per day. Increased liver weight and increased activities of serum enzymes, such as alkaline phosphatase, alanine aminotransferase and aspartate aminotransferase, were reported in two of the studies. The NOAEL for these effects was 15 ppm (equal to 0.85 mg/kg bw per day).

The toxicity of dietary doses of cyhexatin in dogs was investigated in studies with durations of 90 days, 1 year and 2 years. In the 90-day and 1-year studies, no treatment-related adverse effects were seen at up to the maximum doses tested of 6 and 0.75 mg/kg bw per day, respectively. In the 2-year study, the body weights of the dogs given cyhexatin at a dose of 6 or 12 mg/kg bw per day were reduced compared with those of controls. The NOAEL was 3 mg/kg bw per day.

Feeding studies in dogs given azocyclotin for 90 days or 24 months both showed diarrhoea to be a critical end-point, with a NOAEL of 0.36 mg/kg bw per day. In the 24-month study, diarrhoea was seen in all dogs given azocyclotin at a dose of 1.09 mg/kg bw per day or more. In the 90-day study, there was also a decrease in body-weight gain at 1.73 mg/kg bw per day or more, although this effect was not seen at doses of up to 1.09 mg/kg bw per day in the 24-month study. Thus the NOAEL for decreased body-weight gain was 1.09 mg/kg bw per day. Haematological effects (decreases in erythrocyte count, erythrocyte volume fraction and haemoglobin) were seen in some of the males at 18.3 mg/kg bw per day in the 90-day study. It was considered to be likely that the decreased body weight and diarrhoea were related to the corrosiveness of azocyclotin.

The most sensitive effect seen in long-term studies of toxicity/carcinogenicity with azocyclotin in mice and rats was decreased body weight compared with that of the controls, with NOAELs of 2.12 mg/kg bw per day in mice and 50 ppm (equal to 0.26 mg/kg bw per day) in Wistar rats.

The NOAEL for cyhexatin in a long-term study in mice was 3 mg/kg bw per day on the basis of increased mortality and decreased body weight at 6 mg/kg bw per day. Three long-term studies of toxicity/carcinogenicity were performed with cyhexatin in Sprague-Dawley rats. Increased incidence of retinal atrophy was seen at dietary concentrations of 30 and 180 ppm in one of these studies, with a slight increase in severity at 180 ppm. In the same study there was an increased incidence of minimal to mild bile duct hyperplasia in treated rats. This effect was of equivocal toxicological significance

because there was no progression in severity with increasing doses. The NOAEL was 7.5 ppm (equal to 0.34 mg/kg bw per day) on the basis of retinal atrophy.

Azocyclotin did not produce any tumours in combined long-term studies of toxicity/carcinogenicity in mice and rats. With cyhexatin, no tumours were produced in a long-term study of toxicity/carcinogenicity in mice. In one out of three studies in rats, there were slightly increased incidences of hepatocellular adenomas in both sexes at 30 and 180 ppm. However, only the increased incidence in the females at 180 ppm was statistically significant. As the increased incidence of benign tumours was seen only in one sex at one dose in one of four studies with cyhexatin in rats, and as the effect was not seen in studies with azocyclotin in mice and rats, the Meeting concluded that cyhexatin and azocyclotin were unlikely to be carcinogenic in rodents.

Azocyclotin was not genotoxic in an extensive range of tests for genotoxicity in vitro and in vivo. Cyhexatin gave negative results in most tests for genotoxicity in vitro, but gave positive results in a test for mutation of the xanthine-guanine phosphoribosyl transferase (XPRT) gene in vitro in the presence of metabolic activation, and equivocal results in the absence of metabolic activation. It also gave equivocal results in a test for chromosomal effects in vitro. Cyhexatin gave negative results in a test for micronucleus formation in bone marrow of mice in vivo.

The Meeting concluded that cyhexatin and azocyclotin are unlikely to be genotoxic in vivo.

In the absence of genotoxicity in vivo and with the finding of an equivocal increase in the incidence of benign liver tumours at a high dose in female rats in only one out of four studies of carcinogenicity in rodents, the Meeting concluded that use of azocyclotin or cyhexatin as pesticides is unlikely to pose a carcinogenic risk to humans.

In a multigeneration study in rats given diets containing azocyclotin at concentrations of up to 50 ppm (equivalent to 3.7 mg/kg bw per day), there were no treatment-related adverse effects. The lowest NOAEL identified in any of three studies of reproduction in rats given cyhexatin was 0.5 mg/kg bw per day for maternal hepatotoxicity (periductal inflammation, decreased glycogen content and bile duct hyperplasia) and on the weaning weight and survival to weaning of the pups. In one of the two-generation studies of reproduction with cyhexatin there was delayed eye opening in male and female pups at a dietary concentration of 100 ppm (equal to 7.0 mg/kg bw per day), with an NOAEL of 30 ppm (equal to 2.1 mg/kg bw per day). There were associations between the delayed eye opening and low pup weight at weaning, decreased maternal body weight and decreased maternal feed intake. The Meeting concluded that the pup toxicity was secondary to maternal toxicity.

Two studies of developmental toxicity with azocyclotin in rats treated orally by gavage found no fetotoxicity or teratogenicity at any dose tested up to 30 mg/kg bw per day and no effects on embryotoxicity at doses that were not maternally toxic. The NOAELs for maternal toxicity of azocyclotin administered by gavage, as indicated by effects on body weight, were 3 and 0.3 mg/kg bw per day in rats and rabbits, respectively. Embryotoxicity (increased number of resorptions) was seen in rats given azocyclotin a dose of 30 mg/kg bw per day by gavage. Similarly with cyhexatin, a limited study of developmental toxicity in rats showed no developmental effects at doses of up to 10 mg/kg bw per day and a NOAEL for maternal toxicity of 1 mg/kg bw per day was identified. In addition, a developmental toxicity phase included in one of the two-generation studies of reproduction in rats treated with cyhexatin gave no indication of developmental toxicity at dietary concentrations of up to 100 ppm (equal to 7 mg/kg bw per day).

Six studies of developmental toxicity in rabbits have been performed with cyhexatin and two with azocyclotin. There was no embryotoxicity, fetotoxicity or teratogenicity in rabbits given azocyclotin at doses of up to 1 mg/kg bw per day by gavage. The NOAEL for maternal toxicity was 0.3 mg/kg bw per day. Maternal toxicity caused by cyhexatin, as indicated by reduced body-weight gain, was seen with an overall NOAEL of 1.5 mg/kg bw per day (in rabbits treated by gavage).

Embryotoxicity (postimplantation loss) was seen at a dose of 3 mg/kg bw per day in three of the studies in rabbits given cyhexatin by gavage. The highest NOAEL for embryotoxicity in these studies was 1.5 mg/kg bw per day (in rabbits treated by gavage). In two of the studies in rabbits (Dutchland New Zealand White rabbits from the same supplier) given cyhexatin by oral gavage, there were statistically significant increases in the incidence of hydrocephaly and/or dilated brain ventricles. Equivocal effects were recorded at 0.75 mg/kg bw per day and above in one study. Hydrocephaly was also seen in a study of dermal toxicity in Dutchland New Zealand White rabbits from the same supplier to test the same batch of cyhexatin. Other studies used other batches of cyhexatin either in Charles River New Zealand White rabbits or hybrid Hy/Cr New Zealand White rabbits. In these studies; hydrocephaly and/or dilated ventricles were either not seen at all or seen only at very low incidences at higher doses of cyhexatin. The Meeting concluded that the hydrocephaly observed in two studies was probably a consequence of the unique susceptibility of the substrain of New Zealand White rabbits and/or of a unique toxicity of the batch of cyhexatin used in the study. As a consequence, the finding of hydrocephaly was not relevant to the risk assessment. The Meeting concluded that neither azocyclotin nor cyhexatin were teratogenic or fetotoxic, and that cyhexatin was embryotoxic with a NOAEL of 1.5 mg/kg bw per day.

A 90-day study of neurotoxicity with cyhexatin showed that it was not neurotoxic in rats at dietary concentrations of up to 240 ppm (equal to 13.6 mg/kg bw per day). At the start of the study, the highest dietary concentration had been 360 ppm, but this was reduced to 240 ppm because of high mortality, feed refusal, body-weight loss and adverse clinical signs. There were adverse effects on body-weight gain, food consumption and clinical signs (emaciation, pale extremities, abnormal faeces and hypoactivity) at doses of 180 ppm (equal to 10.9 mg/kg bw per day) or more. The NOAEL for the study was 30 ppm (equal to 1.99 mg/kg bw per day).

The toxicity of the metabolite, dicyclohexyltin oxide, was tested in a 90-day dietary study in rats. No treatment-related adverse effects were seen at any dose up to the highest used, 6 mg/kg bw per day. The results of this study showed that dicyclohexyltin oxide was less toxic than either cyhexatin or azocyclotin.

No health problems were reported in most workers at a factory producing a product that contained 25% azocyclotin. However, one worker who had not worn the recommended personal protective equipment had an exposure that led to “an irritating toxic spastic bronchitis”. Recovery was complete within 3 days. Monitoring of workers at a factory manufacturing cyhexatin over a period of 10 years showed no adverse health effects.

The Meeting concluded that the existing database on azocyclotin and cyhexatin was adequate to characterize the potential hazards to fetuses, infants and children.

Toxicological evaluation

In dogs, azocyclotin caused reduced body weight and clinical signs, including diarrhoea, at dietary concentrations of 30 ppm (equal to1.09 mg/kg bw per day) or more. The NOAEL was 5 ppm (0.16 mg/kg bw per day). These effects were not used in the establishment of an ADI or an ARfD. The Meeting recognized that some of the reported adverse effects of both azocyclotin and cyhexatin were a secondary consequence of an irritating effect on the gastrointestinal mucosa and therefore were not relevant for establishing reference values.

The Meeting established a group ADI for azocyclotin and cyhexatin of 0–0.003 mg/kg bw based on the NOAEL of 0.34 mg/kg bw per day for retinal atrophy in a long-term study of toxicity/carcinogenicity with cyhexatin in rats and using a safety factor of 100.

The Meeting established a group ARfD for azocyclotin and cyhexatin of 0.02 mg/kg bw based on the NOAEL of 1.5 mg/kg bw per day for embryotoxicity in studies of developmental

toxicity with cyhexatin in rabbits, and using a safety factor of 100. The ARfD is applicable to women of childbearing age. No ARfD is necessary for the rest of the population, as the only other acute responses were related to dietary refusal and/or local irritation of the gut.

The Meeting recognized that the ARfD might be conservative, but it was not possible to determine whether the embryotoxicity was the result of systemic toxicity to the conceptus or the result of reduced nutrition caused by reduced maternal food intake and local adverse effects to the maternal gastrointestinal mucosa as a result of the irritant nature of the cyhexatin.

Levels relevant to risk assessment

(i) Studies with azocyclotin

Species	Study	Effect	NOAEL	LOAEL
Mouse	Long-term study of toxicity[c]	Toxicity	15 ppm (equal to 2.12 mg/kg bw per day)	7.58 mg/kg bw per day
		Carcinogenicity	50 ppm (equal to 7.58 mg/kg bw per day) [a]	—
Rat	Long-term study of toxicity[c]	Toxicity	5 ppm (equal to 0.26 mg/kg bw per day)	15 ppm (equal to 0.79 mg/kg bw per day)
		Carcinogenicity	50 ppm (equal to 1.08 mg/kg bw per day) [a]	—
	Multigeneration study[c]	Reproductive toxicity	50 ppm (3.7 mg/kg bw per day) [a]	—
	Developmental toxicity [b]	Maternal toxicity	3 mg/kg bw per day	10 mg/kg bw per day
		Embryotoxicity	10 mg/kg bw per day	30 mg/kg bw per day
		Teratogenicity and fetotoxicity	30 mg/kg bw per day [a]	—
Rabbit	Developmental toxicity[b]	Maternal toxicity (reduced body-weight gain)	0.3 mg/kg bw per day	1.0 mg/kg bw per day
		Developmental effects	1.0 mg/kg bw per day[a]	—

[a] Highest dose tested
[b] Gavage administration
[c] Dietary administration

(ii) Studies with cyhexatin

Species	Study	Effect	NOAEL	LOAEL
Mouse	Long-term study of toxicity/carcinogenicity[d]	Toxicity	3 mg/kg bw per day[b]	6 mg/kg bw per day[b]
		Carcinogenicity	6 mg/kg bw per day[a, b]	—
Rat	Long-term study of toxicity/carcinogenicity [d]	Toxicity (retinal atrophy)	7.5 ppm (equal to 0.34 mg/kg bw per day)	30 ppm (equal to 1.39 mg/kg bw per day)
	Multigeneration study[d]	Toxicity	0.5 mg/kg bw per day[b]	6.0 mg/kg bw per day[b]
		Toxicity	0.5 mg/kg bw per day[b]	6.0 mg/kg bw per day[b]
		Developmental toxicity	7.0 mg/kg bw per day[a, b]	—
	Developmental toxicity[c]	Maternal toxicity	1 mg/kg bw per day	5 mg/kg bw per day
		Developmental toxicity	10 mg/kg bw per day[a]	—
	Neurotoxicity[d]	Toxicity	30 ppm (equal to 1.99 mg/kg bw per day)	180 ppm (equal to 10.94 mg/kg bw per day)
Dog	2-year study[d]	Toxicity	3 mg/kg bw per day	6 mg/kg bw per day

Species	Study	Effect	NOAEL	LOAEL
Rabbit	Developmental toxicity[c]	Maternal toxicity	1 mg/kg bw per day	3 mg/kg bw per day
		Developmental toxicity	1.5 mg/kg bw per day	3 mg/kg bw per day

[a] Highest dose tested
[b] Dietary concentrations were regularly adjusted to achieve set doses
[c] Gavage administration
[d] Dietary administration

Estimate of acceptable daily intake for humans

0–0.003 mg/kg bw

Estimate of acute reference dose

0.02 mg/kg bw for women of childbearing age

Unnecessary for the rest of the population

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

The metabolic fate of the 1,2,4-triazole that splits off from azocyclotin when it breaks down to form cyhexatin is unknown.

Critical end-points for setting guidance values for exposure to azocyclotin

Absorption, distribution, excretion and metabolism in mammals	
Rate and extent of oral absorption	Limited absorption in rats: about 12% absorption of azocyclotin or its breakdown products
Distribution	Extensive, with the largest amounts being found in the liver and kidneys
Potential for accumulation	Accumulation is unlikely
Rate and extent of excretion	Excreted in urine (1% of the administered ^{113}Sn and about 10% of the administered ^{14}C from radiolabelled azocyclotin) and probably also in bile.
	Minimal amounts were exhaled as carbon dioxide.
Metabolism in mammals	Hydrolyses rapidly in aqueous solution to cyhexatin and 1,2,4-triazole.
Toxicologically significant compounds (animals, plants and environment)	Azocyclotin and cyhexatin
Acute toxicity	
Rat LD_{50} oral	209 mg/kg bw for males; 363 mg/kg bw for females
Rat LD_{50} dermal	> 2000 mg/kg bw
Rat LC_{50} inhalation	0.017 mg/L for males; 0.029 mg/L for females
Mouse LC_{50} inhalation	0.035 mg/L
Golden hamster LC_{50} inhalation	0.0055 mg/L for males
Rabbit, skin irritation	Corrosive
Rabbit, eye irritation	Not tested but taken to be corrosive
Skin sensitization (test method used)	No skin sensitization potential in guinea-pigs (Magnusson & Kligman test)
Short-term studies of toxicity	
Target/critical effects	Reduced body-weight gain (rats, rabbits, dogs)
Lowest relevant oral NOAEL	0.3 mg/kg bw per day (rabbits)

Genotoxicity	
	Not genotoxic in vitro or in vivo
Long-term studies of toxicity and carcinogenicity	
Target/critical effects	Low body weight
Lowest relevant oral NOAEL	0.26 mg/kg bw per day (rats)
Carcinogenicity	Unlikely to pose a carcinogenic risk to humans
Reproductive toxicity	
Reproduction target/critical effect	No adverse effects on reproduction at any dose in the multigeneration study
Lowest relevant reproductive NOAEL	3.7 mg/kg bw per day (highest dose tested)
Developmental target/critical effect	Embryotoxicity
NOAEL for maternal toxicity	0.3 mg/kg bw per day (reduced maternal body-weight gain in rabbits)
Lowest relevant developmental NOAEL	10 mg/kg bw per day (embryotoxicity in rats)
Medical data	
Health monitoring of workers	An “irritating toxic spastic bronchitis” reported in one exposed worker in a factory

Critical end-points for setting guidance values for exposure to cyhexatin

Absorption, distribution, excretion and metabolism in mammals	
Rate and extent of oral absorption	Limited absorption in rats (1.6–10%) and rabbits (10%)
Distribution	Extensive, with the largest amounts being found in the liver and kidneys
Potential for accumulation	Accumulation is unlikely
Rate and extent of excretion	Excretion was mainly in the urine and to a lesser extent in bile
Metabolism in mammals	Splitting off of cyclohexyl rings and oxidation to produce a variety of substances (most of which were unidentified)
Toxicologically significant compounds (animals, plants and environment)	Cyhexatin
Acute toxicity	
Rat LD_{50} oral	407 mg/kg bw for males; 265 mg/kg bw for females
Rat LD_{50} dermal	7600 mg/kg bw for males; 3600 mg/kg bw for females
Rabbit LD_{50} dermal	> 2000 mg/kg bw
Rat LC_{50} inhalation	0.016 mg/L
Rabbit, skin irritation	Irritant
Rabbit, eye irritation	Severely irritant
Skin sensitization (test method used)	No skin sensitization potential in guinea-pigs (Buehler test)
Short-term studies of toxicity	
Target/critical effect	Hepatotoxicity (rats); low body weight (dogs)
Lowest relevant oral NOAEL	0.68 mg/kg bw per day (rats)
Genotoxicity	
	Not genotoxic in vivo
Long-term studies of toxicity and carcinogenicity	
Target/critical effects	Mortality and body weight (mice); retinal atrophy (rats)
Lowest relevant oral NOAEL	0.34 mg/kg bw per day for retinal atrophy (rats)
Carcinogenicity	Unlikely pose a carcinogenic. risk to humans

Reproductive toxicity	
Reproduction target/critical effect	Decreased pup weight at weaning and decreased survival to weaning at parentally toxic doses
Lowest relevant reproductive NOAEL	Parents and offspring: 0.5 mg/kg bw per day
	Reproductive toxicity: 7.5 mg/kg bw per day, highest dose tested (rats)
Developmental target/critical effect	Embryotoxicity (postimplantation loss) in rabbits
NOAEL for maternal toxicity	1.5 mg/kg bw per day in studies of developmental toxicity in rabbits (low body-weight gain).
	0.5 mg/kg bw per day in a two-generation study in rats (hepatotoxicity)
Lowest relevant developmental NOAEL	1.5 mg/kg bw per day for embryotoxicity in rabbits.
Medical data	
Health monitoring of workers	No adverse effects seen

Summary for azocyclotin and cyhexatin

	Value	Study	Safety factor
Group ADI	0–0.003 mg/kg bw	Rat, 2-year study, NOAEL	100
Group ARfD*	0.02 mg/kg bw	Rabbit, developmental toxicity, NOAEL	100

* For women of childbearing age, unnecessary for the rest of the population

RESIDUE AND ANALYTICAL ASPECTS

Azocyclotin and cyhexatin are organotin acaricides effective against phytophagous mites. The compounds have been reviewed by the JMPR many times since 1970, the last residue evaluation of azoccyclotin being in 1991 and of cyhexatin in 1992. In 2005, the Meeting established a group ADI of 0–0.003 mg/kg bw and a group ARfD of 0.02 for women of child-bearing age for cyhexatin and azocyclotin.

At the 22nd Session of CCPR, the Committee decided to harmonize the residue definition of azocyclotin and cyhexatin as the sum of both compounds, expressed as cyhexatin. The Committee also decided to have two separate but identical lists of CXLs. At the 33rd Session of CCPR, all CXLs were withdrawn, with the exception of apple, citrus fruits, grapes, meat (from mammals other than marine mammals), milk products, milks and pear for cyhexatin, and citrus fruits, grapes, meat (from mammals other than marine mammals), milk products and milks for azocyclotin. The compounds were listed in the Periodic Re-Evaluation Programme at the 36th Session of CCPR for periodic review by the 2005 JMPR.

The present Meeting received and evaluated information on the identity and physical chemical properties of the compounds, metabolism in farm animals and plants, methods of residue analysis and freezer storage stability for cyhexatin, national use patterns, supervised residue trials and processing studies.

Animal metabolism

Three metabolism studies conducted in farm animals were submitted. One study was conducted in dairy cows dosed with cyclohexyl UL-^{14}C-azocyclotin (gelatin capsule with β-lactose) for 5 consecutive days at a rate of 0.5 mg/kg bw. Kidney, liver, heart, brain, muscle, omental, renal and back fat samples were excised and analysed. More than 98% of the radioactivity present in the tissues

was extracted. Liver, kidney and heart contained the greatest concentration of radioactive residues (0.34, 0.25 and 0.12 mg/kg azocyclotin equivalents (eq), respectively). Muscle, fat and brain contained 0.09, 0.10 and 0.04 mg/kg azocyclotin eq, respectively. Milk collected once or twice a day during the dosing period, reached a maximum residue level at day 4 (0.02 mg/kg azocyclotin eq). Most of the extracted radioactivity (43% TRR in fat, 84% in muscle, and 92% in milk) was assigned as azocyclotin/cyhexatin, as it was stated that no distinction could be made between the compounds in the TLC plate. No cyhexatin standard was, however, applied to the TLC. Dicyclohexyl tin oxide (DCTO) was responsible for up to 23% TRR in fat and up to 15% in loin muscle. From 4% TRR (milk) to 33% (fat) was identified as cyclohexyl stannoic acid (MCTA), which was not detected in heart or muscle.

One study conducted in two lactating goats dosed with ^{119}Sn-cyhexatin for 4 days at 100 ppm in the feed was submitted. On average, 68.5% of the administered radioactivity was recovered from the animals, from which 44% was found in the faeces, 24% in the gastrointestinal (GI) tract and 0.15% in the liver (mean of 1.1 mg/kg cyhexatin eq). Less than 0.1% was found in the other tissues and milk, corresponding, on average, to 0.56 mg/kg cyhexatin eq in kidney, 0.08 mg/kg cyhexatin eq in muscle and up to 0.02 mg/kg eq in milk. Most of the radioactivity found in tissues was cyhexatin (from 70 to 84% TRR in the organic extract), with less than 10% of DCTO and MCTA. Only the parent compound was found in milk.

In one study conducted with laying hens (two groups of six) dosed with ^{119}Sn-cyhexatin for 5 days at 100 ppm in the feed, most of the administered radioactivity (mean of 66.3%) was found in the excreta (63.5%). Liver and kidney had the highest residues (mean of 3.0 and 2.8 mg/kg cyhexatin eq, respectively), followed by muscle (mean of 0.42 mg/kg cyhexatin eq) and fat (0.36 mg/kg cyhexatin eq). Residues in eggs increased during the dose period and were concentrated in the yolk. On day 2, mean residues in the yolk were 0.2 mg/kg cyhexatin eq and in egg white, 0.055 mg/kg. On day 5, residues reached 3.6 and 0.22 mg/kg cyhexatin eq in yolk and white respectively. The organic tissue extracts showed mostly cyhexatin (up to 50% TRR), DCTO (up to 30% TRR) and MCTA (up to 16% TRR). Egg white contained less than 10% TRR of cyhexatin, while only the parent compound was found in the yolk.

Metabolism studies conducted in rats with cyhexatin and azocyclotin and evaluated by the present Meeting (Toxicological evaluation) showed a similar metabolic pathway described for farm animals.

Plant metabolism

Three studies conducted in plants were submitted. Apples, treated with cyclohexyl UL-^{14}C-azocyclotin applied at a rate of 0.03 kg ai/hL, had most of the applied radioactivity in the organic fraction of the acetone wash of the fruits (from 96% at day 0 to 29% at day 21). On average, 78% TRR was azocyclotin/cyhexatin, 9% DCTO and 2% MCTA. On day 21, 11% of the applied radioactivity was found in the peel and < 1% in the pulp. Only 70% TRR found in the peel was characterized, being approximately 9% azocyclotin/cyhexatin and 27% DCTO and MCTA (11% stayed at the TLC origin and 17% remained in the aqueous phase).

In one study conducted with ^{119}Sn cyhexatin on apples at 3.8 kg ai/ha rate, the applied radioactivity was recovered after successive extractions with water, HCl and organic solvents. Most of the radioactivity at 14 days PHI was found in the peel (96% TRR) and whole fruit contained 4% TRR. Peel organic extracts showed approximately 45% TRR as cyhexatin, 25% as inorganic tin, 14% as MCTA and 12% as DCTO.

In one study conducted in grapes treated with U-^{14}C-cyhexatin at 0.3 kg ai./ha, a mean of 86% TRR was found on the fruit surface and 14% in the grape homogenate (acid methanol extraction) at 10 or 28 days after application. Cyhexatin accounted for 77.6 and 59% TRR in the

grape surface after 10 and 28 days, respectively, while DCTO accounted for 7.7 and 14.8%. In the fruit homogenate, only cyhexatin was detected (5% TRR).

In summary, the metabolism of azocyclotin and cyhexatin in animal and plants appears to be similar, and occurs through the loss of the triazole moiety (from azocyclotin) to produce cyhexatin, with subsequent hydrolysis of the cyclohexyl ring to yield DCTO and MCTA.

Environmental fate

One hydrolysis study was conducted in water with [triazole-3,5-^{14}C]azocyclotin and [cyclohexyl-UL-^{14}C]azocyclotin, at a concentration of about 30 µg ai./L in 0.01 M buffer solutions at pH 4, 7 and 9 and in drinking water. The buffer solutions were incubated for 10, 30, and 60 minutes under sterile conditions and the drinking water solution for 10 minutes in the dark at 20°C. Azocyclotin was completely hydrolysed within 10 min ($DT_{90} \leq 10$ min), and cyhexatin and 1,2, 4 triazole were the degradation products identified.

Degradation studies with cyhexatin in soil, field dissipation studies, adsorption/desorption studies in soil and degradation studies in water/sediment system were provided to the Meeting. However, these studies are not relevant to the present evaluation.

Method of analysis

As only cyhexatin and DCTO residues are detected in plants treated with azocyclotin, no analytical method to analyse azocyclotin was submitted.

Complete method validation studies to analyse residues of cyhexatin and DCTO in various crops were submitted. The methodology involves extraction with a mixture of hexane and ethyl acetate in the presence of acetic acid and water, followed by methylation with methyl magnesium chloride to form tricyclohexylmethyltin (TCMT) from cyhexatin and dicyclohexyldimethyltin (DCMT) from DCTO. The extract with the methylated compounds was cleaned-up with florisil, and quantification was performed by gas chromatography with flame photometric detection (GC-FPD) using a sulfur filter or using a tin filter as a primary methodology followed by confirmation using a sulfur filter. No matrix effects were found in the method, regardless of the filter used. The methylated compounds were found to be stable after 7 days stored in the dark at 4°C.

For grapes, oranges, fresh orange juice, peel and molasses, apples, apple pomace (wet) and apple juice, the LOQ for both cyhexatin and DCTO was set at 0.01 mg/kg. The LOQ was 0.02 mg/kg for orange dry pulp, 0.05 mg/kg for apple pomace and 0.10 mg/kg for peel oil and juice concentrate. The limits of detection ranged from 0.005 to 0.013 mg/kg. Recovery at the LOQ level and at 0.1 mg/kg ranged from 71 to 128% for cyhexatin and from 61 to 83% for DCTO.

In some residue trials, a method to analyse only cyhexatin was used. The method involves extraction of the residues with chloroform, clean up with silica gel and quantification by reverse phase high-performance liquid chromatography (HPLC-UV at 215–225 nm. In this methodology, LOQs of 0.05 or 0.1 mg/kg were reported, and recoveries at these levels presented in the trial reports were normally within the 70 to 120% range.

Stability of pesticide residues in stored analytical samples

The stability of stored analytical samples fortified with cyhexatin and DCTO was studied in apples, grapes, raisins and wine. Samples fortified at 0.5 mg/kg were stored up to 12 months at -20° C in the dark. In most cases, residues were stable for up to a year (≥ 70% remained), except for cyhexatin and DCTO in grapes and raisins (approximately 50% remained) and DCTO in apples (62% remained).

Definition of the residue

The hydrolysis study conducted with azocyclotin showed that 90% of this compound degrades to cyhexatin in less than 10 min. Therefore, no residues of azocyclotin are expected to be present in the application solution, and consequently, in treated plants. Metabolism studies conducted in animal and plants with azocyclotin and cyhehatin have shown that cyhexatin is the major residue to be found. Residues of the dicyclohexyltin oxide metabolite (DCTO) can be higher than 10% TRR in some cases, but this metabolite is not considered of toxicological concern.

The log P_{ow} of cyhexatin (6.1 at pH 7) suggests that the compound is fat soluble. However, metabolism studies conducted in cows, goats and hens indicated that cyhexatin does not concentrate in fat.

The Meeting agreed that the residue definition for azocyclotin and cyhexatin in plants and animal products for both enforcement and dietary intake assessment purposes is cyhexatin. The residue definition applies to residues coming from the use of azocyclotin and/or cyhexatin.

Results of supervised trials on crops

Orange and clementine

Thirty four trials were conducted with cyhexatin in oranges in Brazil from 1993 to 1995 using 1 or 2 applications at 0.025 or 0.05 kg ai/hL (GAP is 0.025 kg ai/hL). Residues found, of cyhexatin in whole fruit with a 30 day PHI, in 16 trials conducted according to Brazilian GAP were < 0.01, 0.01 (2), 0.02, 0.03 (2), 0.04 (2), 0.05 (4), 0.06 (2) and 0.07 (2) mg/kg. Residues from trials conducted at double rates reached a maximum of 0.18 mg/kg with a 30 day PHI.

In twenty nine trials (see processing studies), residues were also analysed in peel. On average, residues of cyhexatin in the peel at PHI represented 30% of the residues in the whole fruit.

Three trials were conducted in Spain in 1997 with oranges and three with clementines at 0.36 kg ai/ha (GAP is 0.25 to 0.31 kg ai/hL, 15 days PHI). Residues of cyhexatin from trials conducted according to GAP were < 0.1 mg/kg (0.05 mg/kg) in orange and < 0.1 mg/kg (0.02 and 0.07 mg/kg) in clementine. The LOQ was 0.1 mg/kg, but values below the limit of quantification were reported.

Residues of cyhexatin coming from 17 trials conducted according to GAP in Brazil and Spain in orange were < 0.01, 0.01 (2), 0.02, 0.03 (2), 0.04 (2), 0.05 (4), 0.06 (2) and 0.07 (2) and < 0.1 mg/kg. The Meeting estimated a maximum residue level of 0.2 mg/kg for azocyclotin and cyhexatin in oranges. Considering that 70% of cyhexatin residues in oranges are present in the pulp, and the supervised trial median and highest residue in whole fruit were 0.05 mg/kg and 0.07 mg/kg, respectively, the Meeting estimated an STMR of 0.035 mg/kg and an HR of 0.049 mg/kg in orange pulp.

The Meeting also recommends the withdrawal of the current MRL of 2 mg/kg for azocyclotin and cyhexatin in citrus fruit. The number of trials conducted in clementines according to GAP were not considered sufficient to make any recommendation for this commodity.

Apple and pears

Eight trials were conducted with azocyclotin in apples. In one trial conducted in Brazil (GAP of a maximum of 2 applications at 0.02 to 0.025 kg ai/hL, 30 day PHI) residues of cyhexatin at the 30 day PHI were 0.16 mg/kg. One trial was conducted in Chile (no GAP) and six in Israel. Although azocyclotin is registered in Israel, the trials conducted in this country could not be evaluated as a translated label was not submitted.

Fifty three trials were conducted with cyhexatin in apples in Europe from 1991 to 2001, of which 24 were in France, 21 in Italy and eight in the Netherlands. In 13 trials conducted in France at GAP (0.03 kg ai/hL), residues of cyhexatin at a 30 day PHI were 0.03 (3), 0.04 (4), 0.06 (3), 0.08 (2) and 0.11 mg/kg. In 12 trials conducted at the same GAP in Italy, residues at the 30 day PHI were < 0.1 (4), 0.02 (6) and 0.03 (2) mg/kg.

In six trials conducted in the Netherlands according to Italian and French GAP, residues at the 30 day PHI were 0.02 (5) and 0.03 mg/kg. Currently, there is no GAP for cyhexatin in apple in the Netherlands.

Twenty trials were conducted with cyhexatin in pears in Italy. In 16 trials conducted according to GAP (0.03 kg ai/hL), residues at 30 a day PHI were, < 0.01 (7), < 0.05 (2), 0.01 (2) and 0.02 (3) 0.07 and 0.16 mg/kg.

The Meeting agreed that residues of cyhexatin from the 48 trials conducted according to GAP (apple and pears conducted with cyhexatin in Europe and one trial conducted with azocyclotin in apples in Brazil) can be grouped together as reflecting the use of cyhexatin and azocyclotin. They were, in ranked order < 0.01 (7), 0.01 (2), 0.02 (14), 0.03 (6), 0.04 (4), < 0.05 (2), 0.06 (3), 0.07, 0.08 (2), < 0.1 (4), 0.11 and 0.16 (2) mg/kg.

The Meeting recommended a maximum residue level of 0.2 mg/kg for azocyclotin and cyhexatin in apples and pears. The Meeting also estimated an STMR of 0.025 mg/kg and an HR of 0.16 mg/kg.

The Meeting recommended withdrawal of the current MRLs of 2 mg/kg for cyhexatin in apples and pears.

Grapes

Forty nine trials were conducted with cyhexatin in France (31), Italy (11) and Spain (7) on grapes from 1990 to 2002. GAP rate in France and Spain is similar (0.3 kg ai/ha). In 19 trials conducted at 0.3 kg ai/ha in France, residues of cyhexatin within 30 days PHI were, in rank order, 0.02, 0.04, 0.05, 0.06 (2), 0.07, 0.08, 0.09 (2), 0.10, 0.11 (2), 0.12 (2), 0.15 (2), 0.17 (2) and 0.19, mg/kg. In Spain, residues in the 6 trials conducted according to GAP were 0.02, 0.05, 0.06, 0.08, 0.12 and 0.14 mg/kg.

Cyhexatin is not registered in Italy, but the trials conducted in this country were evaluated against the Spanish GAP. Eleven trials conducted at GAP gave residues at a 30 day PHI of 0.02 (2), 0.04, 0.05, 0.07 (3), 0.08, 0.09 (2) and 0.11 mg/kg

Residues of cyhexatin from 36 trials conducted in Europe according to GAP were grouped as 0.02 (4), 0.04 (2), 0.05 (3), 0.06 (3), 0.07 (4), 0.08 (3), 0.09 (4), 0.10, 0.11 (3), 0.12 (3), 0.14, 0.15 (2), 0.17 (2) and 0.19, mg/kg.

The Meeting recommended a maximum residue level of 0.3 mg/kg, an STMR of 0.085 mg/kg and an HR of 0.19 mg/kg for cyhexatin and azocyclotin in grapes.

The Meeting also recommended the withdrawal of the current MRLs of 0.2 mg/kg for cyhexatin and azocyclotin in grapes.

Stone fruit

Sixteen trials were conducted with cyhexatin in peaches in France and Italy and 6 trials were conducted in plums in France at rates of 0.03 to 0.09 kg ai/hL. GAP rate in France is 0.03 kg ai/hL (30 days PHI) and in Spain is 0.025–0.037 kg ai/hL. There is no registered use of cyhexatin on peaches in Italy. In three trials conducted at 0.03 kg ai/hL in peaches in Italy, residues of cyhexatin

27 days after application were 0.09, 0.21 and 0.41 mg/kg. In 10 French trials conducted at 0.075 kg ai/hL in peaches and at 0.09 kg ai/hL in plums, residues reached a maximum of 0.14 mg/kg at the 30 day PHI.

The number of trials conducted according to GAP was not considered sufficient to recommend maximum residue levels for cyhexatin and azocyclotin in peaches or plums.

Currants, red, black, white

Three trials were conducted with blackcurrants according to French GAP (0.3 kg ai/ha, 28 day PHI). Residues of cyhexatin found 30 days after application were < 0.05 (2) and 0.05 mg/kg. The Meeting recommended a maximum residue level of 0.1 mg/kg and an STMR of 0.05 mg/kg for cyhexatin and azocyclotin in currants, red, black, white.

Dried hops

Nineteen trials were conducted in hops in the United Kingdom and Germany at rates from 0.6 to 1.1 kg ai/ha. Residues of cyhexatin ranged from 63 mg/kg (0 days) to 2.9 (28 days). Cyhexatin has no registered use in UK or Germany, nor is this compound registered for dried hops in other countries in Europe. The Meeting made no recommendation for dried hops.

Fate of residues during processing

Nineteen processing studies were conducted in oranges treated with cyhexatin (0.025 or 0.50 kg ai/ha). Residues of cyhexatin in concentrated juice were all < 0.1 mg/kg. No residues were found in any of the fresh or pasteurized juice samples (< 0.01 mg/kg) produced from orange samples containing from 0.02 to 0.23 mg/kg cyhexatin. A processing factor (PF) of 0.04 (0.01/0.23) was applied to an STMR of 0.05 mg/kg in oranges and the Meeting recommended an STMR of 0.002 mg/kg in orange juice.

Residues of cyhexatin in the peel represented, on average, 30% of residues in the whole fruit. In four trials where molasses samples were analysed, residues of cyhexatin were at or below the LOQ.

Residues of cyhexatin concentrated in dried pulp and in peel oil had mean PFs of 1.6 and 102, respectively. Based on the estimates for oranges, the Meeting estimated a median residue of 0.08 mg/kg for citrus dried pulp.

Twenty three processing studies were conducted in apples. Residues in apples ranged from < 0.01 to 0.12 mg/kg, but none of the juice samples analysed had detectable residues of cyhexatin. A PF of 0.08 (0.01/0.12) was applied to an STMR of 0.025 mg/kg for apple, and the Meeting estimated an STMR of 0.002 mg/kg in apple juice.

Residues of cyhexatin concentrated in wet pomace, with PFs ranging from 1 to > 5 (median of 1.7). The Meeting estimated a median residue of 0.272 mg/kg for cyhexatin in wet pomace. The processing factor for dry pomace ranged from < 0.05 to 4.

Twenty eight processing trials were conducted in grapes. Residues decreased in juice and wine, and were not detected in most of the samples. Median PFs were 0.8 and 0.7 for juice and wine, respectively. These PFs were applied to the STMR on grapes of 0.085 mg/kg. The Meeting recommended STMRs of 0.068 mg/kg for juice and of 0.060 mg/kg for wine.

Processing factors for raisins ranged from 0.3 to 2 (median of 0.9). The Meeting recommended an STMR of 0.076 mg/kg for cyhexatin in grapes, dried (= currants, raisins and sultanas).

Residues of cyhexatin concentrated in all samples of wet and dry pomace with a mean PF of 2.6 and 4.8, respectively.

In three processing studies conducted in dried hops, residues of cyhexatin ranged from 1.9 to 18.2 mg/kg, but no residues of any compound were found in beer.

Farm animal dietary burden

The Meeting estimated the dietary burden of cyhexatin coming from the use of azocyclotin and cyhexatin, in cattle and poultry on the basis of the diets listed in Appendix IX of the *FAO Manual* and the highest and median residues estimated at this Meeting.

Calculation of the dietary burden for maximum residue level and STMR estimation

Commodity	Median residue	Group	% DM	Residues dw	*Diet content (%)*			Residue contribution, mg/kg		
					Beef cattle	*Dairy cows*	*Poultry*	Beef cattle	Dairy cows	Poultry
Apple wet pomace	0.04	AB	40	0.067	*40*	*20*	-	0.027		0
Citrus dried pulp	0.08	AB	91	0.08	*20*	*20*	-		0.016	0
				Total	***40***	***20***	**-**	**0.027**	**0.016**	**0**

Farm animal feeding studies

No animal feeding studies were provided to the Meeting. The calculated cyhexatin dietary burden was 0.027 ppm for mammals and 0 ppm for poultry. No registered direct use of azocyclotin or cyhexatin on animals was provided to the Meeting.

Metabolism studies in goats and hens were conducted at a dose of 100 ppm of ^{119}Sn cyhexatin, approximately 3700 times the calculated dietary burden in goats. In these studies, only total radioactivity was quantified in milk and tissues. Residues in goats were 0.02 mg/kg cyhexatin equivalents in milk, 0.13 mg/kg in muscle, 0.91 mg/kg in kidney and 1.83 mg/kg in liver. In the metabolism study conducted with hens, maximum total radioactivity in tissues and eggs was found in liver (3.0 mg/kg cyhexatin equivalents).

The Meeting concluded that no residues of cyhexatin are expected in animal commodities. No recommendations could be made as no analytical methods for animal commodities were submitted to the Meeting.

DIETARY RISK ASSESSMENT

Long-term intake

The 2005 JMPR established a group ADI of 0–0.003 mg/kg bw for cyhexatin and azocyclotin. The IEDIs were calculated for the five GEMS/Food regional diets from the STMR and STMR-P values for fruits and processed products as estimated by the present Meeting (Annex 3). The group ADI for cyhexatin and azocyclotin is 0.003 mg/kg bw, and the calculated IEDIs ranged from 0 to 5% of the ADI.

The Meeting concluded that these uses of cyhexatin and/or that of azocyclotin resulting in long-term intake of residues of cyhexatin as considered by the JMPR are unlikely to present a public health concern.

Short-term intake

The 2005 JMPR established a group ARfD of 0.02 mg/kg bw for women of childbearing age for cyhexatin and azocyclotin. The IESTI was calculated based on consumption data generated for the general population as no consumption data is available for this group of the population. The IESTI ranged from 3 to 20% ARfD.

An ARfD for the rest of the population was considered unnecessary and no intake calculations were performed for the general population and for children.

The Meeting concluded that the short-term intake of residues of cyhexatin, from uses of cyhexatin and azocyclotin, on commodities that have been considered by the JMPR, is unlikely to present a public health concern.

4.3 BENALAXYL (155)

TOXICOLOGY

Benalaxyl, the ISO approved name for methyl *N*-(2,6-dimethylphenyl)-*N*-(phenylacetyl)-DL-alaninate (a racemic mixture), is a broad-spectrum phenylamide fungicide that inhibits mycelial growth of fungi and germination of zoospores. Benalaxyl was first evaluated by the 1987 JMPR (Annex 1, reference 52), when an ADI of 0–0.05 mg/kg bw was established on the basis of a NOEL of 5.0 mg/kg bw per day for hepatic enlargement in a 13-week dietary study in rats and a safety factor of 100.

Benalaxyl was considered by the present Meeting within the periodic review programme of the CCPR. The Meeting reviewed new data on benalaxyl (studies of toxicokinetics, metabolism, acute toxicity after inhalation, eye irritation, mutagenesis and several studies of toxicity with the two main soil metabolites) that had not been reviewed previously, as well as relevant data from the previous evaluation.

All pivotal studies with benalaxyl were certified as complying with GLP.

Biochemical aspects

Several toxicokinetic studies in rats given ^{14}C-labelled benalaxyl as single and repeated oral doses showed that the active substance is rapidly and extensively absorbed and distributed by all organs and tissues, with the greatest proportion of radioactivity remaining in the intestine and its contents, and in the liver and kidneys (minor quantities). Seven days after treatment, only approximately 0.3% of the administered radiolabelled dose remained in the rat and was distributed among organs and tissues. The half-life of elimination was about 30 h after administration of single doses and 36 h after administration of repeated doses. The pattern of elimination in the urine and faeces was also similar in all situations (administration of single and repeated oral doses) and was not sex-dependent. At 48 h after dosing, the radioactivity was mainly excreted in the faeces (at least 80%), via the bile and in the urine (approximately 8%).

The metabolites of benalaxyl that appeared in the faeces and urine were similar, irrespective of dose and type of administration (single or repeated doses). Unchanged benalaxyl was not detected

in the urine. Eight metabolites were identified and corresponded to approximately 65% of the radioactivity present in the faeces and urine. The identity of three additional very polar metabolites remained unknown, but their proportions were very low compared with those of some other identified compounds. Benalaxyl undergoes extensive metabolism, mainly by oxidation of the methyl group of the aniline ring to a hydroxymethyl group, and finally to the carboxylic acid; minor metabolic pathways were the hydroxylation of the phenyl ring and hydrolysis of the carboxymethyl group.

Toxicological data

Benalaxyl has low acute oral toxicity in rats and mice (LD_{50} values were 4200 mg/kg bw and 680 mg/kg bw, respectively), low acute dermal toxicity in rats and rabbits (LD_{50} values were > 5000 mg/kg bw and > 2000 mg/kg bw, respectively) and low acute toxicity in rats exposed by inhalation (the 4-h LC_{50} value was > 4.2 mg/L, the highest achievable concentration). Although no significant clinical signs were observed in rats treated by oral or dermal administration, signs of intoxication including loss of equilibrium, uncoordinated movements and asthenia occurred in mice treated by oral administration. Benalaxyl is not an irritant to the skin and eyes of rabbits. In a maximization test in guinea-pigs, benalaxyl did not show sensitizing potential.

The toxicity of benalaxyl administered orally was investigated in short-term studies: a 90-day dose range-finding study for a long-term study of toxicity and carcinogenicity in mice, 5-week and 90-day studies in rats, and a 1-year study in dogs. The major target organs were the liver in mice and rats, and the testes in dogs. In the absence of any changes in clinical chemistry or histopathology, the Meeting considered that hepatic enlargement was an adaptive response and not an adverse effect.

In a 90-day study in Swiss mice, a dose-related increase in liver weights occurred at dietary concentrations of 1000 ppm and greater at 96 days and of 2000 ppm and greater at 42 days. There were no histopathological lesions associated with this increase in liver weight. The NOAEL was 5000 ppm, equal to 842 mg/kg bw per day, the highest dose tested.

In a 5-week study in Wistar rats treated by gavage, changes in haematological (coagulation time) and biochemical (increases in cholesterol, albumin and total protein, decreases in aspartate amino transferase and alkaline phosphatase activities) parameters were observed at the highest dose of 800 mg/kg bw per day. The relative weight of the liver was increased in groups treated with benalaxyl at doses of 100 mg/kg bw per day and greater. All these changes had returned to normal relative to values for controls by the end of the 2-week recovery period. The NOAEL was 100 mg/kg bw per day on the basis of changes in haematological and biochemical parameters.

In a study in Sprague-Dawley rats given diets containing benalaxyl at concentrations of up to 10 000 ppm for 13 weeks, or 12 000 ppm for 4 weeks followed by a 9-week recovery period, animals treated at 10 000 and 12 000 ppm had decreased body-weight gain and increased serum cholesterol values relative to those for controls. At 12 000 ppm, there were also some changes in haematological parameters (decreases in erythrocyte count, haemoglobin concentration and erythrocyte volume fraction in both sexes); all changes were reversible after a recovery period. Liver weight was reversibly increased in animals at 1000 ppm (males) and above (both sexes) and lobulation was observed in males in these groups, sometimes associated with rounded edges (this finding was also observed sporadically in other groups). The livers of females at 10 000 ppm were darker than normal, and diffuse steatosis was seen in both sexes at this dietary concentration, although the pattern was more severe in males. The NOAEL was 1000 ppm (equal to 59 mg/kg bw per day).

In a 1-year study in beagle dogs, the only finding that could be attributed to treatment was atrophy of the seminiferous tubules of the testes in two out of six males treated with benalaxyl at the highest dietary concentration of 800 ppm. The NOAEL in males was 200 ppm (equal to 6.5 mg/kg bw per day).

Long-term studies of toxicity and carcinogenicity were carried out in Swiss mice and Sprague-Dawley rats.

In a long-term study of toxicity and carcinogenicity, Swiss mice were given diets containing benalaxyl at concentrations of up to 3000 ppm for 78 consecutive weeks. While there was no effect on survival in female mice, a high incidence of mortality occurred in males at 1000 and 3000 ppm, mainly during the second year of the study. Because 25% of the males at the highest dose survived to termination, this study was considered to be acceptable. In males, body-weight gain was slightly depressed in all treated groups, particularly during the second year of treatment, without a dose-related effect. In females, there was no effect of treatment on body weight. In females at 3000 ppm, absolute and relative weights of the liver were significantly increased (as observed in the 90-day preliminary test). No increase in the incidence of tumours was observed when compared with the control group. The NOAEL was 250 ppm (equal to 43 mg/kg bw per day) on the basis of mortality in males. There was no evidence for carcinogenic potential in Swiss mice treated with benalaxyl for 78 consecutive weeks.

In rats given diets containing benalaxyl at concentrations of up to 1000 ppm for 104 weeks, there was no evidence of neoplastic or non-neoplastic effects related to administration of the test article. Although the incidence of hepatocellular neoplasms was found to be greater in females at the highest dose than in controls, the difference was not statistically significant, no dose–response relationship was observed and the frequency was compatible with that of spontaneous hepatocellular neoplasms. The NOAEL was 1000 ppm (equal to 44 mg/kg bw per day, the highest dose tested), in the absence of any significant findings in either sex.

The Meeting concluded that benalaxyl is not carcinogenic in rodents.

A comprehensive range of studies of genotoxicity in vitro and in vivo with benalaxyl gave consistently negative results. The Meeting concluded that benalaxyl is unlikely to be genotoxic.

In view of the absence of genotoxicity and the lack of carcinogenicity in mice and rats (albeit noting the limitation of the study in rats because the maximum tolerated dose was not attained), the Meeting concluded that benalaxyl is unlikely to pose a carcinogenic risk to humans at dietary doses and anticipated exposures of consumers or workers.

The reproductive toxicity of benalaxyl has been examined in a two-generation study in rats, and in studies of developmental toxicity in rats and rabbits.

In a two-generation (two litters per generation) dietary study of reproductive toxicity in rats, the NOAEL was 1000 ppm (equal to 53 mg/kg bw per day for the F_0 generation) for general toxicity in parent animals (decreased body weight) and adverse effects in pups (decreased pup weight and liver weight) at 5000 ppm, although fertility and reproductive parameters were not affected in the F_0 generation at dietary concentrations of up to 5000 ppm (equal to 289 mg/kg bw per day, the highest dose tested).

In Sprague-Dawley female rats given benalaxyl at doses of up to 200 mg/kg bw per day by gavage from day 6 to day 15 of gestation, no toxicity was apparent in dams. Benalaxyl induced a marginal but statistically significant increase in the delay in ossification of the cranial bones at 50 and 200 mg/kg bw per day (10%, 16%, 18% and 26% of the fetuses in the control group, and at the lowest, intermediate and highest dose, respectively). In addition, in the group receiving the highest dose a statistically significant increase of the percentage of pre-implantation losses was observed. The NOAELs for maternal toxicity, embryotoxicity and developmental toxicity were 200 mg/kg bw per day (the highest dose tested), 50 mg/kg bw per day and 12.5 mg/kg bw per day, respectively.

In female New Zealand White rabbits given benalaxyl by gavage from day 6 to day 27 of gestation, minimal maternal toxicity was manifest as weight loss during late gestation and a low gravid uterus weight at a dose of 250 mg/kg bw per day. There were no treatment-related effects on implantations. No teratogenic potential was seen, but there were statistically significant effects at a dose of 250 mg/kg bw per day on fetal weight and crown–rump lengths and on the incidence of fetuses with delayed skeletal development. The NOAELs for maternal and developmental toxicity were both 50 mg/kg bw per day.

No specific studies of neurotoxicity with benalaxyl were available; however, no evidence of neurotoxicity was apparent from the available studies of toxicity.

No adverse effects were reported in personnel involved in the production and formulation of benalaxyl, or in the use of this product in the field.

The two major soil metabolites, methyl-*N*-malonyl-*N*-2,6-xylyl-DL-alaninate (metabolite A) and *N*-maolonyl-*N*-2,6-xylyl-DL-alanine (metabolite B) were also investigated. The results of studies of acute toxicity and 90-day studies of oral toxicity with both metabolites in rats, showed that both metabolites have very low toxicity (oral LD_{50}s > 2000 mg/kg bw; NOAEL in 90-day dietary studies in rats, 923/1073 and 819/978 mg/kg bw per day for metabolite A and metabolite B, respectively, the highest doses tested) and are thus less toxic than the parent.

The results of a range of studies of genotoxicity, including tests in vitro with metabolite A and metabolite B, and a test for micronucleus formation in vivo with metabolite A, indicated that neither metabolite was genotoxic.

The Meeting concluded that the existing database on benalaxyl was adequate to characterize the potential hazards to fetuses, infants and children.

Toxicological evaluation

The Meeting established an ADI of 0–0.07 mg/kg bw based on a NOAEL of 6.5 mg/kg bw per day for atrophy of the seminiferous tubules occurring at 25 mg/kg bw per day in a 1-year study in dogs and using a safety factor of 100.

Benalaxyl has little acute toxicity and short-term dosing produced no significant general toxicity; however, a delay in ossification of cranial bones was observed at a dose of 50 mg/kg bw per day in the absence of maternal toxicity and of other markers of developmental delay in a study of developmental toxicity in rats. Although statistically significant, this is a marginal effect, but in the absence of data on historical controls, it was considered to be treatment-related. The Meeting established a conservative ARfD of 0.1 mg/kg bw for benalaxyl for women of childbearing age on the basis of a NOAEL of 12.5 mg/kg bw per day in a study of developmental toxicity in rats, and a safety factor of 100. There is no concern regarding the acute toxicity of this compound for the rest of the population, including children.

A toxicological monograph was prepared.

Levels relevant to risk assessment

Species	Study	Effect	NOAEL	LOAEL
Mouse	2-year studies of toxicity and carcinogenicity[a]	Toxicity	250 ppm, equal to 43 mg/kg bw per day	1000 ppm, equal to 174 mg/kg bw per day
		Carcinogenicity	3000 ppm, equal to 522 mg/kg bw per day[c]	—

Rat	2-year studies of toxicity and carcinogenicity[a]	Toxicity	1000 ppm, equal to 44 mg/kg bw per day[c]	—
		Carcinogenicity	1000 ppm, equal to 44 mg/kg bw per day[c]	—
	Multigeneration reproductive toxicity[a]	Parental	1000 ppm, equal to 53 mg/kg bw per day	5000 ppm, equal to 275 mg/kg bw per day
		Offspring toxicity	1000 ppm, equal to 53 mg/kg bw per day	5000 ppm, equal to 275 mg/kg bw per day
		Reproductive toxicity	5000 ppm, equal to 275 mg/kg bw per day[c]	—
	Developmental toxicity[b]	Maternal toxicity	200 mg/kg bw per day[c]	—
		Developmental toxicity	12.5 mg/kg bw per day	50 mg/kg bw per day
Rabbit	Developmental toxicity[b]	Maternal toxicity	50 mg/kg bw per day	250 mg/kg bw per day
		Developmental toxicity	50 mg/kg bw per day	250 mg/kg bw per day
Dog	1-year study of toxicity[a]	Toxicity	200 ppm, equal to 6.5 mg/kg bw per day	800 ppm, equal to 25 mg/kg bw per day

[a] Dietary administration
[b] Gavage administration
[c] Highest dose tested

Estimate of acceptable daily intake for humans

0–0.07 mg/kg bw

Estimate of acute reference dose

0.1 mg/kg bw for women of childbearing age

Unnecessary for the rest of the population

Information that would be useful for continued evaluation of the compound

Results from epidemiological, occupational health and other such observational studies of human exposures.

Critical end-points for setting guidance values for exposure to benalaxyl

Absorption, distribution, excretion and metabolism in mammals	
Rate and extent of oral absorption	Rapid, at least 80% based on biliary and urinary excretion
Distribution	Widely distributed
Potential for accumulation	None
Rate and extent of excretion	Rapid and extensive (> 90% within 72 h, mainly via faeces)
Metabolism in animals	Extensive metabolism, mainly by oxidation and hydroxylation
Toxicologically significant compounds (animals, plants and environment)	Parent compound
Acute toxicity	
Rat LD_{50} oral	4200 mg/kg bw
Mouse LD_{50} oral	680 mg/kg bw
Rabbit LD_{50} dermal	> 2000 mg/kg bw
Rat LC_{50} inhalation	> 4.2 mg/L air (4 h, nose only, aerosol)
Rabbit, skin irritation	Not irritating (24 h)

Rabbit, eye irritation	Not irritating
Skin sensitization (test method used)	Not sensitizing in guinea-pigs (Magnusson & Kligman)
Short-term studies of toxicity	
Target/critical effect	Liver (steatosis in rats), and testes (atrophy seminiferous tubules in dogs)
Lowest relevant oral NOAEL	59 mg/kg bw per day (90-day study in rats) 6.5 mg/kg bw per day (1-year study in dogs)
Lowest relevant dermal NOAEL	No data
Lowest relevant inhalation NOAEC	No data
Genotoxicity	
	Not genotoxic in vitro and in vivo
Long-term studies of toxicity and carcinogenicity	
Target/critical effect	Increased mortality (mice)
Lowest relevant NOAEL	43 mg/kg bw per day (18-month study in mice)
Carcinogenicity	No carcinogenic risk to humans
Reproductive toxicity	
Reproduction target/critical effect	Decreased body-weight gain and increased liver weight of pups at parentally toxic doses
Lowest relevant reproductive NOAEL	Parents and offspring: 53 mg/kg bw per day (rats) Reproductive toxicity: 275 mg/kg bw per day, highest dose tested (rats)
Developmental target/critical effect	Delay in ossification of cranial bones in absence of maternal toxicity (rats) Minor skeletal deviations at maternally toxic doses (rabbits)
Lowest relevant developmental NOAEL	Maternal: 50 mg/kg bw per day (rabbits) Developmental: 12.5 mg/kg bw per day (rats)
Neurotoxicity/delayed neurotoxicity	
	No specific study; no findigs in other studies
Other toxicological studies	
Toxicity of soil and groundwater metabolites	
Metabolite A:	Oral LD_{50}, > 2000 mg/kg bw (rats) NOAEL 90-day study, 923 mg/kg bw per day (rats) Results of studies of mutagenicity in vitro and in vivo: negative
Metabolite B:	Oral LD_{50}, > 2000 mg/kg bw (rats) NOAEL 90-day study, 819 mg/kg bw per day (rats) Results of studies of mutagenicity in vitro: negative
Medical data	
	No adverse effects on health in manufacturing personnel

Summary

	Value	Study	Safety factor
ADI	0–0.07 mg/kg bw	Dog, 1-year study of toxicity	100
ARfD*	0.1 mg/kg bw	Rat, developmental toxicity	100

* For women of childbearing age, unnecessary for the rest of the population

4.4 CARBENDAZIM (072)

TOXICOLOGY

Evaluation for an acute reference dose

Carbendazim is the ISO approved common name for methyl 2-benzimidazole carbamate, a systemically active benzimidazole fungicide that inhibits the synthesis of β-tubulin. Carbendazim was previously evaluated by the Joint Meeting in 1973, 1977, 1983, 1985, and 1995. In 1995, an ADI of 0–0.03 mg/kg bw was established based on the NOAEL of 2.5 mg/kg bw per day in a 2-year study in dogs and a safety factor of 100.

The Meeting had been asked by the CCPR to consider the need for an ARfD for carbendazim. The present Meeting therefore evaluated relevant original studies that had been considered by previous Meetings, and newly submitted data on genotoxicity and reproductive toxicity.

Toxicological data

Carbendazim has low acute toxicity: the oral LD_{50} is > 10 000 mg/kg bw in rats. The clinical signs of toxicity after single high doses were generally nonspecific. Degenerative changes in the testes and epididymides were observed in rats given single oral doses at ≥ 1000 mg/kg bw.

In two short-term studies of toxicity in rats, the overall NOAEL was 2000 ppm (equal to 163 mg/kg bw per day) on the basis of reduced body weight and inhibition of spermatogenesis at 10 000 ppm (equal to 780 mg/kg bw per day) and above. In a 28-day dose range-finding study in dogs, the NOAEL was 500 ppm (equal to 19 mg/kg bw per day) on the basis of liver toxicity at 2500 ppm (equal to 96 mg/kg bw per day).

Carbendazim has been adequately tested in a range of assays for genotoxicity. Carbendazim causes changes in chromosome number (aneuploidy) both in vitro and in vivo (in somatic cells and germ cells) as a result of its interference with mitotic spindle proteins. The effects were seen in tests for the induction of micronuclei or aneuploidy in vivo after single high doses (100 mg/kg bw and above), with a NOAEL of 50 mg/kg bw. The mechanism by which aneuploidy is induced by carbendazim is well understood and consists of inhibition of the polymerization of tubulin, the protein that is essential for the segregation of the chromosomes during cell division. The nature of the mechanism is thus consistent with the identification of a dose that has no toxicological effect. Carbendazim does not cause gene mutations or structural chromosomal aberrations.

The Meeting concluded that the genotoxic effect of carbendazim is a threshold phenomenon.

In a study of developmental toxicity in rats given diets containing carbendazim, the NOAEL for both maternal and developmental toxicity was 10 000 ppm (equal to 747 mg/kg bw per day, the highest dose tested). There was no evidence for embryo- and fetotoxicity or teratogenicity after dietary administration of carbendazim.

Studies of developmental toxicity in rats and rabbits given carbendazim by oral gavage clearly demonstrated that carbendazim is a developmental toxicant and teratogen.

In three studies of developmental toxicity in rats treated by gavage, maternal toxicity (clinical signs, decreased body-weight gain, abortion) was observed at doses of 60 mg/kg bw per day and above. Developmental toxicity consisting of decreased fetal weights and an increased percentage of fetuses with variations per litter was seen at doses of 20 mg/kg bw per day and above. The increased

incidence in variations was largely attributable to delayed development and thus correlated with the reduction in fetal weight. The incidence of malformations including hydrocephaly, anophthalmia, microphthalmia, axial skeletal malformations or malformed scapulae was significantly increased at doses of 30 mg/kg bw per day and above in two studies and at 90 mg/kg bw per day in one study, with a slightly higher incidence of skeletal malformations at 20 mg/kg bw per day than in controls. The threshold for embryo/fetotoxicity and teratogenicity was thus considered to be 20 mg/kg bw per day. For the three studies, the overall NOAEL for maternal toxicity was 30 mg/kg bw per day, while the overall NOAEL for developmental toxicity was 10 mg/kg bw per day.

In a study of developmental toxicity in rabbits treated by gavage, maternal toxicity (reduction of feed consumption and body-weight gain, abortion) was observed at 125 mg/kg bw per day, the highest dose tested. Treatment at 20 and 125 mg/kg bw per day resulted in decreased implantation, increased resorption and decreased size of live litters. Additional effects consisting of decreased fetal body weights and increased incidence of malformations of the cervical vertebrae, ribs and thoracic vertebrae were seen at 125 mg/kg bw per day. The NOAEL for maternal toxicity was 20 mg/kg bw per day and the NOAEL for developmental toxicity was 10 mg/kg bw per day.

In a study of toxicity to the male reproductive system in rats, significant testicular and efferent ductal alterations were seen 2 days after the administration of single doses at 100 mg/kg bw and above by gavage. The major cause of testicular atrophy observed at later times (70 days) after dosing was occlusion of the efferent ductules. The NOAEL was 50 mg/kg bw.

Toxicological evaluation

The Meeting established an ARfD of 0.1 mg/kg bw based on an overall NOAEL of 10 mg/kg bw per day for developmental toxicity from three studies in rats and one study in rabbits, and a safety factor of 100. The Meeting concluded that this ARfD applies only to women of childbearing age.

For the general population, including children, the Meeting established an ARfD of 0.5 mg/kg bw based on the NOAEL of 50 mg/kg bw in the study of toxicity to the male reproductive system in rats and supported by the studies on micronucleus or aneuploidy induction in vivo, using a safety factor of 100.

An additional safety factor for the severity of the effects was considered to be unnecessary, since the underlying mechanism is clearly understood and there is a clear threshold for these effects.

An addendum to the toxicological monograph was prepared.

Levels relevant to risk assessment

Species	Study	Effect	NOAEL	LOAEL
Rat	Developmental toxicity[a]	Maternal toxicity	30 mg/kg bw per day	60 mg/kg bw per day
		Developmental toxicity	10 mg/kg bw per day	20 mg/kg bw per day
	Acute toxicity, special study	Testicular effects	50 mg/kg bw	100 mg/kg bw
Rabbit	Developmental toxicity	Maternal toxicity	20 mg/kg bw per day	125 mg/kg bw per day
		Developmental toxicity	10 mg/kg bw per day	20 mg/kg bw per day

[a] Three studies combined

Estimate of acute reference dose

0.1 mg/kg bw for women of childbearing age

0.5 mg/kg bw for the general population, including children

DIETARY RISK ASSESSMENT

Short-term intake

The International Estimated Short Term Intake (IESTI) for carbendazim, coming from the use of benomyl, carbendazim and thiophanate methyl, was calculated for 31 food commodities for which maximum residue levels were estimated by the JMPR in 1998 and 2003 and for which consumption data was available. These results are shown in Annex 4.

In 2005 the Meeting established for carbendazim an ARfD of 0.5 mg/kg bw for the general population, including children and an ARfD of 0.1 mg/kg bw for women of childbearing age. The IESTI ranged from 0 to 11% ARfD for the general population, from 0 to 30% for children and from 0 to 55% for women of childbearing age. Consumption data generated for the general population was used to assess the intake of women of childbearing age, as no consumption data is available for this group of the population.

The Meeting concluded that the short-term intake of residues of carbendazim from uses of benomyl, carbendazim and thiophanate methyl on commodities that have been considered by the JMPR is unlikely to present a public health concern.

4.5 CHLORPROPHAM (201)

TOXICOLOGY

Chlorpropham is the ISO approved name for 1-methylethyl (3-chlorophenyl) carbamate, which is a plant growth regulator used for pre-emergence and early post-emergence control of grass weeds. It is also used to inhibit potato sprouting. The toxicity of chlorpropham was evaluated by the JMPR in 1963, 1965 and 2000. In 2000, the Meeting established an ADI of 0–0.03 mg/kg bw based on a NOAEL of 10 mg/kg bw per day in a 90-day study of toxicity in Wistar rats, this NOAEL being identified on the basis of a significant decrease in erythrocyte counts and an increase in methaemoglobin formation at the next higher dose of 47 mg/kg bw per day. A safety factor of 300 was applied, which included an additional safety factor of 3 to account for inadequacies in the assessment of methaemoglobinaemia (lack of measurements of methaemoglobin formation at early time-points, a concern since adaptation to this effect can occur), the critical toxicological effect. This ADI also provided an adequate margin of safety for the effects on the thyroid observed in dogs (NOAEL, 5 mg/kg bw per day). An ARfD equal to the maximum ADI was also established.

The sponsor conducted a study of acute toxicity in female beagle dogs in order to refine the ARfD, in order to address concerns with respect to the extent of investigation of methaemoglobinaemia. The 2005 JMPR was asked by the CCPR to review the ARfD for chlorpropham, and as a consequence of this review, the Meeting also reconsidered the ADI.

The new study of acute toxicity complied with GLP.

Toxicological data

In 2000, the JMPR determined that chlorpropham has low acute toxicity: the oral LD_{50} in rats was > 2000–4200 mg/kg bw, and the dermal LD_{50} in both rats and rabbits was > 2000 mg/kg bw. Chlorpropham is also only weakly toxic after inhalation since there were no deaths at 0.47 mg/L, the highest attainable concentration.

Chlorpropham was not irritating to the eyes or skin of rabbits. It did not sensitize the skin of guinea-pigs in a Bühler test, in an open epicutaneous test, or in a Magnusson & Kligman test. Although chlorpropham sensitized the skin of 30% of the guinea-pigs tested in a split adjuvant test, the 2000 JMPR concluded that chlorpropham is unlikely to cause sensitization in humans.

After an evaluation of short- and long-term studies of the effects of chlorpropham in mice, rats, and dogs, the 2000 JMPR determined that the haematopoietic system was the main toxicological target; changes were observed in the morphology and parameters of erythrocytes, including increased formation of methaemoglobin, and changes in the spleen and liver consistent with a haemolytic effect. In a study of dermal toxicity in rabbits, chlorpropham also produced haematopoietic effects. In dogs fed diets containing chlorpropham for 28 days or fed capsules containing chlorpropham for 90 days, effects were also seen on the thyroid gland at doses similar to or lower than those that affected erythrocytes. In dogs given capsules containing chlorpropham for 60 weeks, a NOAEL of 5 mg/kg bw per day was identified on the basis of effects on the thyroid gland, including increased weight, decreased concentrations of thyroxine (in a test for stimulation by thyroid-stimulating hormone), and, occasionally, decreased concentrations of tri-iodothyronine. In 90-day and 2-year dietary studies in rats, reduced thyroid weights were seen at doses higher than those that caused haematotoxic effects.

Chlorpropham was not a reproductive toxicant in rats and was not teratogenic in rats and rabbits. In 2000 the JMPR had concluded that while chlorpropham may be weakly genotoxic in vitro, it was unlikely to present a risk to humans, although it was noted that this conclusion should be validated in adequate studies of genotoxicity in vivo.

The present Meeting evaluated a study of acute oral toxicity in female dogs given capsules containing chlorpropham as single doses at up to 625 mg/kg bw. Chlorpropham produced clinical signs of toxicity manifested as vomiting and reduced activity at 125 mg/kg bw and above, apparent within 2 h after dosing, but these signs were no longer evident by 4–6 h after dosing. The NOAEL was 50 mg/kg bw. Chlorpropham also produced increased formation of methaemoglobin in all treated groups. However, the increases in methaemoglobin levels were very small, reaching a maximum of 0.8% in one of four animals at the highest dose. The effects were possibly treatment-related at 125 and 625 mg/kg bw, but the small increases at 50 mg/kg bw resulted in levels that were no higher and no more prolonged than those seen in control animals. None of the increases in methaemoglobin levels were toxicologically significant at any dose. With respect to the maximum increase in methaemoglobin seen in this study (0.8%), it should be noted that in 2004 the JMPR recommended that for acute exposure to xenobiotics that induce methaemoglobin formation, only an increase in methaemoglobin formation of 4% (or higher) above background in dogs should be considered to be relevant for setting an ARfD.

The primary effects of repeated doses of chlorpropham appear to be on the haematopoietic system and on the thyroid. In rats, haematological effects appeared at lower doses than did thyroid effects, while in dogs thyroid effects appeared at lower doses than did haematological effects. In a 90-day study of toxicity in rats, the NOAEL for increased methaemoglobin formation was 10 mg/kg bw per day, while in a 90-day study of toxicity in dogs, the NOAEL was 25 mg/kg bw per day. These apparent differences in NOAEL are likely to be caused by artefacts of dose selection rather than to any increased sensitivity of rats over dogs. Thus the study of acute toxicity in dogs was considered to be adequate to assess the effects of acute dosing with chlorpropham on the formation of methaemoglobin.

Toxicological evaluation

The Meeting reconsidered the previously established ADI on the basis of the new study providing information on methaemoglobin measurements at early time-points. Because the new study in dogs addressed previous concerns about the induction of methaemoglobin at early time-points, the Meeting established an ADI of 0–0.05 mg/kg bw based on the NOAEL of 5 mg/kg bw per day in a 60-week study in dogs fed with chlorpropham, on the basis of changes in the thyroid at 50 mg/kg bw per day, and using a safety factor of 100. This ADI provided an adequate margin of safety for the haematotoxic effects seen in the studies of repeated doses in rats.

The Meeting established an ARfD of 0.5 mg/kg bw, on the basis of a NOAEL of 50 mg/kg bw in the study of acute toxicity in dogs given capsules containing chlorpropham identified on the basis of clinical signs of toxicity at the higher doses of 125 and 625 mg/kg bw, and using a safety factor of 100. Slight increases in methaemoglobin levels in this study were not considered to be toxicologically significant at any dose.

An addendum to the toxicological monograph was prepared.

Levels relevant to risk assessment

Species	Study	Effect	NOAEL	LOAEL
Mouse	90-day study of toxicity[a]	Toxicity	—	190 mg/kg bw per day
	78-week study of toxicity and carcinogenicity[a]	Toxicity	100 mg/kg bw per day	500 mg/kg bw per day
		Carcinogenicity	1000 mg/kg bw per day[b]	—
Rat	90-day study of toxicity[a]	Toxicity	10 mg/kg bw per day	47 mg/kg bw per day
	24-month study of toxicity	Toxicity and carcinogenicity[a]	—	30 mg/kg bw per day
		Carcinogenicity	500 mg/kg bw per day	1000 mg/kg bw per day
	Two-generation study of reproductive toxicity[a]	Parental and pup toxicity	1000 ppm, equivalent to 50 mg/kg bw per day	3000 ppm, equivalent to 150 mg/kg bw per day
		Reproductive toxicity	10 000 ppm, equivalent to 500 mg/kg bw per day[b]	—
Rabbit	Developmental toxicity[c]	Maternal and fetal toxicity	200 mg/kg bw per day	800 mg/kg bw per day
		Embryotoxicity	200 mg/kg bw per day	800 mg/kg bw per day
	Developmental toxicity[c]	Maternal toxicity	250 mg/kg bw per day	500 mg/kg bw per day
		Embryotoxicity	125 mg/kg bw per day	250 mg/kg bw per day
	Developmental toxicity[c]	Maternal toxicity	125 mg/kg bw per day	250 mg/kg bw per day
		Embryo- and fetotoxicity	250 mg/kg bw per day	500 mg/kg bw per day
Dog	Acute[d]	Toxicity	50 mg/kg bw	125 mg/kg bw
	90-day study of toxicity[d]	Toxicity	25 mg/kg bw per day	125 mg/kg bw per day
	60-week study of toxicity[d]	Toxicity	5 mg/kg bw per day	50 mg/kg bw per day

[a] Dietary administration
[b] Highest dose tested
[c] Gavage administration
[d] Capsule

Estimate of acceptable daily intake for humans

0–0.05 mg/kg bw

Estimate of acute reference dose

0.5 mg/kg bw

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

Results from epidemiological, occupational health and other observational studies of human exposures

Critical end-points for setting guidance values for exposure to chlorpropham

Summary

	Value	Study	Safety factor
ADI	0–0.05 mg/kg bw	Dog, 60-week, toxicity	100
ARfD	0.5 mg/kg bw	Dog, acute toxicity	100

DIETARY RISK ASSESSMENT

Long-term intake

The 2001 JMPR had calculated the International Estimated Daily Intake (IEDI) for chlorpropham for animal products and potatoes (and for their processed fractions) for which MRLs were estimated and for which consumption data was available using the previous ADI of 0–0.03 mg/kg bw.

The Meeting established an ADI of 0–0.05 mg/kg bw for chlorpropham. The IEDIs of chlorpropham, on the basis of the estimated STMRs, were 2-30% of the maximum ADI for the five GEMS food regional diets. The results are shown in Annex 3. The Meeting concluded that long-term intake of residues of chlorpropham from use on potatoes is unlikely to present a public health concern.

Short-term intake

The 2001 JMPR had calculated the International Estimated Short-term Intake (IESTI) for chlorpropham for animal products and potatoes (and their processed fractions) for which MRLs were estimated and for which consumption data was available using the previous ARfD of 0.03 mg/kg bw.

The Meeting established an ARfD of 0.5 mg/kg bw for chlorpropham. The IESTI represented 0–20% of the ARfD for the general population and 0–60% of the ARfD for children. The values of 20 and 60% represent the estimated short-term intake of cooked potatoes with skin.

The Meeting concluded that the short-term intake of residues of chlorpropham from uses that have been considered by the JMPR is unlikely to present a public health concern.

4.6 CLOFENTEZINE (156)

TOXICOLOGY

Clofentezine is an acaricide that is used in plant protection products for the control of spider mites on a wide range of crops. It acts primarily as an ovicide, but it has some activity against early motile stages of mites. The International Union of Pure and Applied Chemistry (IUPAC) chemical name for clofentezine is 3,6-bis(2-chlorophenyl)-1,2,4,5-tetrazine. It was last evaluated by the JMPR in 1986, when an ADI of 0–0.02 mg/kg bw was established based on a NOAEL of 40 ppm (equivalent to 2 mg/kg bw per day) for hepatotoxicity in rats and a NOAEL of 50 ppm (equal to 1.72 mg/kg bw per day) for hepatotoxicity in dogs.

Clofentezine was considered by the present Meeting as part of the periodic review programme of the CCPR. Some GLP-compliant studies of absorption, distribution, metabolism and excretion, toxicity in dogs and effects on the rat thyroid were considered for the first time.

Biochemical aspects

Pharmacokinetic studies in laboratory animals showed that oral doses of clofentezine were quickly absorbed from the gut lumen, with peak concentrations occurring in the plasma after a maximum of 4–6 h in rats. At least half the administered oral dose was absorbed. The liver was the major site for distribution in all species investigated, with high concentrations of radiolabel also being found in the kidneys. Residues were persistent in several tissues, with low concentrations of radiolabel still being present in the liver and adipose tissue of rats at 25 days after the last dose of radiolabelled clofentezine. Radiolabel from orally administered [^{14}C]clofentezine crossed the placental barrier of rats to reach the fetuses of pregnant rats, but concentrations of radiolabel in the fetuses were about five times lower than in the mothers.

Primary metabolism occurred by two major pathways:

- hydroxylation of the phenyl ring at the 3, 4 and/or 5 position;
- hydroxylation at the 3-phenyl position and replacement of the chlorine atom on the same phenyl ring with a methylthio group.

The relative importance of the two pathways differed from species to species, with hydroxylation being the main route in calves and baboon, but methylthiolation being more important in rodents and rabbits. The primary metabolites could be conjugated with glutathione, mercapturic acid or cysteine before excretion in the bile or urine.

Clofentezine and/or its metabolites were found in the urine and faeces of treated animals with up to about three-quarters of an oral dose being voided in the faeces. About 50% of the radiolabel was associated with unchanged clofentezine. The chemical identity of the rest of the radioactivity in the faeces was not investigated. The possible occurrence of enterohepatic circulation was not investigated.

Studies of the effects of oral doses on liver enzymes showed that clofentezine is a potent inducer of several enzymes, including uridine diphosphoglucuronyl transferase (UDPGT) in rats and cytochrome P450 in mice and rats. The NOEL for effects on these enzymes in rats was 1 mg/kg bw per day.

Toxicological data

Clofentezine has low acute oral toxicity in all species tested (mouse, rat, Syrian hamster and dog), causing no serious adverse effects at any dose tested (up to 5200 mg/kg bw in mice and rats). It also has low acute toxicity in rats exposed dermally (LD_{50} > 2100 mg/kg bw) or by inhalation (LD_{50} > 0.89 mg/L).

Clofentezine was not an irritant to the skin of guinea-pigs or the eyes of rabbits. It gave a negative result in a Magnusson & Kligman maximization test for skin sensitization in guinea-pigs.

The main toxicological effects seen in short-term studies in mice, rats or dogs given repeated doses of clofentezine in the diet were hepatotoxicity (changes in histopathology and clinical chemistry) and changes to the thyroid, including follicular hyperplasia. The lowest NOAEL identified from short-term feeding studies was 40 ppm (equal to 2.65 mg/kg bw per day) for effects on the liver in a 90-day study of toxicity in rats. In mice, the NOAEL was 200 ppm (equal to 30.3 mg/kg bw per day) for increased weights of the thyroid and the liver. In dogs, the lowest NOAEL identified was 50 ppm (equal to 1.72 mg/kg bw per day) for hepatotoxicity in a 12-month feeding study.

In a study of carcinogenicity in mice, non-neoplastic changes to the liver included vacuolation and eosinophilia of the hepatocytes. There were no consistent or dose-dependent effects on any tumour type.

The Meeting concluded that there was no evidence of a tumourigenic response in mice.

In the long-term study of toxicity/carcinogenicity in rats, there was limited evidence to suggest that prolonged high doses of clofentezine could cause thyroid follicular cell adenomas and carcinomas in this species. A marginal increase in the incidence of these tumours was seen only in the males at the highest dietary concentration (400 ppm), and was only slightly greater than the incidence in control male rats in a different long-term study of toxicity/carcinogenicity performed in the same laboratory. No changes in the thyroid were seen in the long-term study of toxicity/carcinogenicity in rats at 40 ppm (equal to 1.72 mg/kg bw per day). The results of studies of effects on hormones, enzymes and morphological changes associated with thyroid homeostasis did not clearly establish a mode of action for the development of thyroid tumours.

The Meeting concluded that there was no risk of thyroid tumours developing in rats given oral doses of 1.72 mg/kg bw per day or less.

Clofentezine gave negative results in an adequate range of tests for genotoxicity in vitro and in vivo.

The Meeting concluded that clofentezine is unlikely to be genotoxic.

Noting the absence of genotoxicity, the Meeting concluded that the marginal increase in incidence of thyroid follicular cell tumours in males at the highest dose did not indicate a carcinogenic risk to humans at the levels of exposure likely to be experienced by consumers or workers.

The results of a two-generation study of reproduction in rats showed that exposure to clofentezine at a dietary concentration of 400 ppm caused decreased body-weight gains in pups during lactation, resulting in low body-weights of pups in the weeks following lactation. A transient marginal decrease in pup weight of the F_2 generation males at 40 ppm at 1 week after weaning was not considered to be toxicologically significant. The NOAEL for the study was 40 ppm (equivalent to 2.7 mg/kg bw per day) on the basis of decreased pup weight.

Studies of developmental toxicity in rats and rabbits treated by gavage showed that clofentezine was neither teratogenic nor embryotoxic. The only indication of fetotoxicity was low fetal body weight in rats at maternally toxic doses. The NOAEL for maternal toxicity in these studies was 320 mg/kg bw per day in rats and 250 mg/kg bw per day in rabbits.

No evidence of neurotoxicity was apparent from the available studies of toxicity.

Routine monitoring of workers in a factory producing clofentezine has shown no adverse effects attributable to exposure to clofentezine.

The Meeting concluded that the existing database on clofentezine was adequate to characterize the potential hazards to fetuses, infants and children.

Toxicological evaluation

The Meeting established an ADI of 0–0.02 mg/kg bw based on the NOAEL of 1.72 mg/kg bw per day for thyroid changes in a long-term study of toxicity/carcinogenicity in rats and also for hepatotoxicity in a 12-month study in dogs, and using a safety factor of 100.

The Meeting concluded that it was not necessary to set an ARfD for clofentezine, since clofentezine has low acute toxicity and does not cause developmental toxicity or any other toxicological effect that would be elicited by a single exposure.

A toxicological monograph was prepared.

Levels relevant to risk assessment

Species	Study	Effect	NOAEL	LOAEL
Mouse	Carcinogenicity	Carcinogenicity	500 ppm (51 mg/kg bw per day)[a]	—
Rat	90-day study of toxicity	Liver enlargement	40 ppm (2.65 mg/kg bw per day)	400 ppm (26.2 mg/kg bw per day)
	Long-term study of toxicity/carcinogenicity	Thyroid changes including tumours	40 ppm (1.72 mg/kg bw per day)	400 ppm (17.3 mg/kg bw per day)
	Two-generation study	Decreased weights of pups of the F_2 generation	40 ppm (2.7 mg/kg bw per day)	400 ppm (27 mg/kg bw per day)
	Developmental toxicity [b]	Maternal toxicity (hepatotoxicity)	320 mg/kg bw per day	1280 mg/kg bw per day
Dog	12-month study of toxicity	Hepatotoxicity	50 ppm (1.72 mg/kg bw per day)	1000 ppm (36.0 mg/kg bw per day)
Rabbit	Developmental toxicity [b]	Maternal toxicity (reduced body-weight gain)	250 mg/kg bw per day	1000 mg/kg bw per day

[a] Highest dose tested
[b] Oral gavage administration

Estimate of acceptable daily intake for humans

0–0.02 mg/kg bw

Estimate of acute reference dose

Unnecessary

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

Results from epidemiological, occupational health and other observational studies of human exposures

Critical end-points for setting guidance values for exposure to clofentezine

Absorption, distribution, excretion and metabolism in mammals	
Rate and extent of oral absorption	Rapid with peak levels at 4–6 h after dosing. At least half of an oral dose was absorbed.
Distribution	Extensive. Radiolabel crossed the placental barrier. Radiolabel was persisted in liver and fat for 25 days.
Potential for accumulation	Low
Rate and extent of excretion	In the urine and faeces, with about three-quarters of an oral dose being voided in the faeces.
Metabolism in mammals	By hydroxylation and methylthiolation plus conjugation.
Toxicologically significant compounds (animals, plants and environment)	Clofentezine
Acute toxicity	
Rat LD_{50} oral,	> 3200 mg/kg bw
Rat LD_{50} dermal	> 2100 mg/kg bw
Rat LC_{50} inhalation	> 0.89 mg/L
Guinea-pig, skin irritation	Non-irritant
Rabbit, eye irritation	Non-irritant
Skin sensitization (test method used)	No skin sensitization potential in guinea-pigs (Magnusson & Kligman test)
Short-term studies of toxicity	
Target/critical effects	Hepatotoxicity
Lowest relevant oral NOAEL	1.72 mg/kg bw per day (12-month study in dogs)
Genotoxicity	
	Not genotoxic
Long-term studies of toxicity and carcinogenicity	
Target/critical effects	Hepatotoxicity in mouse. Changes to thyroid of rat.
Lowest relevant oral NOAEL	1.72 mg/kg bw per day (rats)
Carcinogenicity	Thyroid tumours in rats possible at high doses. Non-genotoxic mechanisms are likely. Unlikely to pose a risk to humans.
Reproductive toxicity	
Reproduction target/critical effect	Decreased body weights of pups of the F_2 generation
Lowest relevant reproductive NOAEL	2.7 mg/kg bw per day
Developmental target/critical effects	Not embryotoxic. Not directly fetotoxic. Not teratogenic.
NOAEL for maternal toxicity	250 mg/kg bw per day (reduced body-weight gain in rabbits)
Lowest relevant developmental NOAEL	3000 mg/kg bw per day (highest dose tested in rabbits)
Special studies	
Effects on enzymes	Mouse liver enzymes induced at 40 mg/kg bw per day or more (no NOEL identified). NOEL for induction of rat liver enzymes was 1 mg/kg bw per day.

Medical data	
Health monitoring of workers	No adverse effects reported in production workers

Summary			
	Value	Study	Safety factor
ADI	0–0.02 mg/kg bw	Rat, long-term study of toxicity/carcinogenicity study; dog, 12-month study	100
ARfD	Unnecessary	—	—

4.7 DIMETHENAMID-P (214) / RACEMIC DIMETHENAMIDE

TOXICOLOGY

Dimethenamid-P is the ISO approved common name for *S*-2-chloro-*N*-(2,4-dimethyl-3-thienyl)-*N*-(2-methoxy-1-methylethyl)-acetamide. This compound belongs to the chemical family of chloroacetamides and is used as a pre-emergent or early post-emergent herbicide with a broad spectrum of activity against most annual grasses and some important broad leaf weeds. It is taken up through the coleoptiles (grass seedlings) or the roots and emerging shoots (dicotyledonous seedlings) and reduces cell division and plant growth.

Dimethenamid is a racemic mixture of the M (or *R*) and P (or *S*) stereoisomers. When this compound was originally registered in various countries, all studies of toxicity were conducted with the racemic mixture. Later, it was discovered that only the P (or *S*) enantiomer has useful herbicidal activity. Dimethenamid-P and racemic dimethenamid have not been evaluated previously by the JMPR.

All critical studies complied with GLP.

Biochemical aspects

Racemic dimethenamid was slowly but well absorbed after oral administration and was extensively metabolized by rats. In rats given racemic dimethenamid by gavage, there was no significant difference in the degree of absorption (> 90%) at a low dose of 10 mg/kg bw and a high dose of 1000 mg/kg bw, or between single and multiple doses at 10 mg/kg bw per day. Maximum concentrations in blood were not achieved until about 72 h. Excretion was rapid and primarily via bile, between 45% and 64% of the oral dose being excreted within 7 h by this route; however, biliary elimination appeared to be saturated at 1000 mg/kg bw, because elimination in the urine was increased at this high dose. By 168 h after treatment, an average of 90% of the administered dose was eliminated. In rats, the concentration of radioactivity in blood decreased more slowly than in tissues and was associated with specific binding to globin; however, similar specific binding to blood components did not occur in human blood. Levels in other tissue after 168 h were low regardless of the dose or frequency of dosing. Consequently, there was no evidence of bioaccumulation. There was no significant difference in absorption, distribution and elimination between sexes.

Studies of dermal penetration in vivo in rats demonstrated that dermal penetration of racemic dimethenamid and dimethenamid-P at 24 h was approximately 26%. Based on the results of comparisons of penetration in human and rat skin in vitro, it was concluded that the rate of dermal penetration was lower in humans than in rats.

Metabolism was primarily via the glutathione conjugation pathway, but racemic dimethenamid was also metabolized by cytochrome P450 enzymes via reductive dechlorination, oxidation, hydroxylation, *O*-demethylation, and cyclization pathways, as well as conjugation with glucuronic acid. Unchanged dimethenamid in excreta accounted for only 1–2% of the administered dose, more than 40 metabolites having been detected. At least 20 of these metabolites were structurally identified by mass spectrometry and nuclear magnetic resonance, and confirmed by reference to synthesized standards. There was no significant difference in metabolism between the sexes.

Toxicological data

Although many of the critical studies of toxicity were conducted only with the racemic mixture, some studies were performed with both dimethenamid-P and racemic dimethenamid. These include studies of acute oral toxicity (LD_{50}) in rats, dermal toxicity (LD_{50}) in rats, acute toxicity after inhalation (LC_{50}) in rats, dermal irritation in rabbits, eye irritation in rabbits, dermal sensitization in guinea-pigs, 90-day studies of oral toxicity in rats, prenatal developmental toxicity and teratogenicity in rats, mutagenicity in bacteria and Chinese hamster ovary cells in vitro, chromosome aberrations in Chinese hamster ovary cells in vitro, assays for unscheduled DNA synthesis in rat hepatocytes in vitro, and assays for micronucleus induction in bone-marrow cells in mice in vivo.

The acute toxicities of dimethenamid-P and the racemic mixture are characterized as moderate after oral administration and low after dermal or inhalation administration. The oral LD_{50} values in rats were: dimethenamid-P, 429 mg/kg bw (males) and 531 mg/kg bw (females); racemic dimethenamid, 371 mg/kg bw (males) and 427 mg/kg bw (females). Both substances produced only mild reversible skin and eye irritation. Skin sensitization was produced by dimethenamid-P in guinea-pigs in the Buehler test and by racemic dimethenamid in the Magnusson & Kligman test.

Overall, in short-term studies with racemic dimethenamid, the signs of toxicity observed in mice, rats and dogs were similar, with reduced body-weight gain and liver enlargement being common features. Dimethenamid-P and racemic dimethenamid produced very similar effects in the liver of rats. The Meeting concluded that increased liver weights were indicative of an adaptive response to exposure. Histopathology confirmed the liver as a target organ with observation of hypertrophy of hepatocytes, although this too is indicative of an adaptive response and was accompanied by the induction of several hepatic microsomal enzymes. These hepatic enzyme changes were resolved upon removal from treatment. In addition, however, vacuolization of hepatocytes and dilatation of liver sinusoids occurred in dogs.

The NOAELs for the short-term dietary studies were for dimethenamid-P and racemic dimethenamid, respectively: 90-day study in rats, 500 ppm (equal to 39 mg/kg bw per day) and 500 ppm (equal to 34 mg/kg bw per day); and, for racemic dimethenamid alone: 90-day dietary study in mice, 2000 ppm (equal to 301 mg/kg bw per day); 90-day study in dogs, 92 ppm (equal to 4.6 mg/kg bw per day); 12-month study in dogs, 250 ppm (equal to 10 mg/kg bw per day). In a 3-week study of dermal toxicity with racemic dimethenamid in rabbits, no substance-related systemic findings were detected at 1000 mg/kg bw per day, the highest dose tested.

Long-term feeding studies with racemic dimethenamid in rats and mice demonstrated that the primary target organ was the liver. There was no evidence for a carcinogenic potential in these studies. The NOAELs obtained in long-term studies were: rats, 100 ppm (equal to 7 mg/kg bw per day, on the basis of bile-duct hyperplasia and reduced body-weight gain in females); and mice, 300 ppm (equal to 40 mg/kg bw per day, on the basis of decreased body-weight gain and hepatocellular hypertrophy).

Dimethenamid-P and racemic dimethenamid were tested for genotoxicity in an adequate range of assays, both in vitro and in vivo. No evidence for genotoxicity was observed in any test with

dimethenamid-P. Apart from an equivocal result in one of three assays for unscheduled DNA synthesis in vitro with racemic dimethenamid, none of the assays gave any indication that racemic dimethenamid might be genotoxic. The Meeting concluded that both dimethenamid-P and racemic dimethenamid are unlikely to be genotoxic.

In the absence of genotoxicity and any evidence of carcinogenicity in rodents, the Meeting concluded that dimethenamid-P and racemic dimethenamid are unlikely to pose a carcinogenic risk to humans.

The reproductive toxicity of racemic dimethenamid was investigated in a two-generation study of reproduction in rats and in a study of developmental toxicity in rabbits. The developmental toxicity of both dimethenamid-P and racemic dimethenamid was studied in rats.

Reproductive function was not affected in rats in the two-generation study of racemic dimethenamid and the NOAEL for reproductive function was 2000 ppm (equal to 175 mg/kg bw per day), the highest dose tested. The NOAEL for systemic toxicity in the parental animals in the two-generation study was 500 ppm (equal to 45 mg/kg bw per day). The only effect on pups noted was a decreased body-weight gain during lactation at the highest dose. The NOAEL for developmental toxicity in the F_1 and F_2 litters was 500 ppm (equal to 45 mg/kg bw per day).

In a study of developmental toxicity, rats were given dimethenamid-P at doses of up to 300 mg/kg bw per day. Both maternal and developmental toxicity were observed. There was an increased incidence of clinical signs of toxicity in the group receiving the highest dose. The effects on development included increases in delayed ossifications, but further evaluation demonstrated that these were attributable to unusually low control values and were not related to treatment. The NOAEL for maternal toxicity was 25 mg/kg bw per day on the basis of decreased body-weight increment, and the NOAEL for developmental toxicity was 300 mg/kg bw, the highest dose tested.

In a study of developmental toxicity, rats were given racemic dimethenamid at doses of up to 425 mg/kg bw per day. Signs of maternal toxicity that were recorded included excess salivation at 215 mg/kg bw per day and 425 mg/kg bw per day, and urine-stained abdominal fur at 425 mg/kg bw per day. Fetal body weights were reduced and the frequency of early deaths was increased at doses of 215 mg/kg bw per day and 425 mg/kg bw. The NOAELs for both maternal toxicity and developmental toxicity were 50 mg/kg bw per day.

In a study of developmental toxicity in rabbits given racemic dimethenamid at doses of up to 150 mg/kg bw per day, significant maternal toxicity (body-weight loss preceded by reduced food consumption and associated with dry faeces) was observed at the highest dose and less severe effects were noted at 75 mg/kg bw per day. Abortions in two rabbits at 150 mg/kg bw per day were considered to be treatment-related, but secondary to the clear maternal toxicity. The NOAEL for maternal toxicity was 37.5 mg/kg bw per day and the NOAEL for developmental toxicity was 75 mg/kg bw per day.

No evidence of neurotoxicity was noted in any studies.

The plant and soil oxalamide (M23) and sulfonate (M27) metabolites of racemic dimethenamid, which also occur as products of metabolism in rats, were tested in studies of acute oral toxicity, assays for mutagenicity in bacteria and for micronucleus formation in bone-marrow cells of mice. Both compounds had low acute oral toxicity with LD_{50} values of > 5000 mg/kg bw. Neither compound was mutagenic in bacteria or induced micronucleus formation in bone-marrow cells of mice.

Interviews with and written surveys of 50 people handling racemic dimethenamid and its formulated products over 7 years have been conducted. There were no reported cases of skin irritation or other adverse health effects.

Comparison of racemic dimethenamid with dimethenamid-P has been possible for a number of types of study. These have shown that there is little difference in the toxicological profile or, where appropriate, the NOAELs for these materials. Consequently, the Meeting concluded that data derived from assays with the racemic mixture could be used to supplement data from assays with dimethenamid-P. In the following tables, the actual material tested was identified.

The Meeting concluded that the existing database was adequate to characterize the potential hazards to fetuses, infants and children.

Toxicological evaluation

The Meeting concluded that the toxicology of the *S* enantiomer (dimethenamid-P) is not significantly different from that of the racemic mixture. For the purpose of dietary risk assessment, the residues of concern were defined as parent dimethenamid (*R* and *S* enantiomers); therefore the derivation of a separate ADI or ARfD for dimethenamid-P is not necessary.

An ADI of 0–0.07 mg/kg bw was established for dimethenamid-P and racemic dimethenamid based on the NOAEL of 7 mg/kg bw per day for bile-duct hyperplasia and reduced body-weight gain observed only in female rats in a 24-month study in rats given diets containing racemic dimethenamid, and a safety factor of 100.

The Meeting established an ARfD of 0.5 mg/kg bw for dimethenamid-P and racemic dimethenamid based on an overall NOAEL of 50 mg/kg bw for maternal clinical signs of toxicity and developmental toxicity (fetal body-weight deficits and increases in early deaths) in studies in rats, and a safety factor of 100.

A toxicological monograph was prepared.

Levels relevant to risk assessment

Species	Study	Effect	NOAEL	LOAEL
Mouse	94-week study of toxicity and carcinogenicity with the racemic mixture	Toxicity	300 ppm, equal to 40 mg/kg bw per day	1500 ppm, equal to 200 mg/kg bw per day
		Carcinogenicity	3000 ppm[a], equal to 411mg/kg bw per day	—
Rat	104-week study of toxicity and carcinogenicity with the racemic mixture	Toxicity	100 ppm, equal to 7 mg/kg bw per day	700ppm, equal to 49 mg/kg bw per day
		Carcinogenicity	1500 ppm[a], equal to 80 mg/kg bw per day	—
	Two-generation study of reproductive toxicity with the racemic mixture[b]	Reproductive toxicity	2000 ppm[a] equal to 175 mg/kg bw per day	—
		Parental toxicity	500 ppm, equal to 45 mg/kg bw per day	2000 ppm[a], equal to 175 mg/kg bw per day
		Offspring toxicity	500 ppm, equal to 45 mg/kg bw per day	2000 ppm[a], equivalent to 175 mg/kg bw per day
	Developmental toxicity with dimethenamid-P[c]	Maternal toxicity	25 mg/kg bw per day	150 mg/kg bw per day
		Embryo- and fetotoxicity	300 mg/kg bw[a] per day	—
	Developmental toxicity with the racemic mixture[c]	Maternal toxicity	50 mg/kg bw per day	215 mg/kg bw per day
		Embryo- and fetotoxicity	50 mg/kg bw per day	215 mg/kg bw per day

Rabbit	Developmental toxicity with the racemic mixture[c]	Maternal toxicity	37.5 mg/kg bw per day	75 mg/kg bw per day
		Embryo- and fetotoxicity	75 mg/kg bw per day	150 mg/kg bw per day
Dog	1-year study of toxicity with the racemic mixture	Toxicity	250 ppm, equal to 10 mg/kg bw per day	1500 ppm[a], equal to 49 mg/kg bw per day

[a] Highest dose tested
[b] Measurements of intake of the compound are the mean of the pre-mating phases for F_0 and F_1 females
[c] Gavage administration

Estimate of acceptable daily intake for humans

0–0.07 mg/kg bw

Estimate of acute reference dose

0.5 mg/kg bw

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

Results from epidemiological, occupational health and other such observational studies of human exposures

Critical end-points for setting guidance values for exposure to dimethenamid-P and racemic dimethenamid

Absorption, distribution, excretion and metabolism in mammals	
Rate and extent of oral absorption	Low, plasma T_{max} 7 h; high, > 90% absorbed in rats
Dermal absorption	> 20% (dimethenamid-P and racemic dimethenamid) in rats
Distribution	Distributed throughout the body; higher concentrations in adrenals, pancreas, kidney, liver, spleen and blood
Potential for accumulation	Very low
Rate and extent of excretion	High (determined by the slow absorption); essentially 100% excretion within 168 h
Metabolism in animals	Extensive, about 40 metabolites, little parent compound remaining
Toxicologically significant compounds (animals, plants and environment)	Parent
Acute toxicity	
Rat LD_{50} oral	429 mg/kg bw (dimethenamid-P); 371 mg/kg bw (racemic mixture)
Rat LC_{50} inhalation	> 2.2 mg/L (4 h) (dimethenamid-P and racemic mixture)
Rabbit LD_{50} dermal	> 2000 mg/kg bw (dimethenamid-P and racemic mixture)
Rabbit, skin irritation	Slightly irritating (dimethenamid-P and racemic mixture)
Rabbit, eye irritation	Not irritating (dimethenamid-P and racemic mixture)
Skin sensitization (test method used)	Sensitizing (Buehler test) (dimethenamid-P) and Magnusson & Kligman (racemic mixture)
Short-term studies of toxicity	
Target/critical effect	Body-weight gain decrement, increased absolute and relative liver weight (dimethenamid-P and racemic mixture)
Lowest relevant oral NOAEL	10 mg/kg bw per day: (12-month study in dogs) (racemic mixture)
Lowest relevant dermal NOAEL	1000 mg/kg bw per day (21-day study in rabbits) (racemic mixture)
Lowest relevant inhalation NOAEC	No data available and not required
Genotoxicity	
	Not genotoxic in vivo or in vitro (dimethenamid-P; racemic mixture)

Long-term studies of toxicity and carcinogenicity	
Target/critical effect	Liver, bile-duct hyperplasia (racemic mixture); body weight
Lowest relevant NOAEL	7 mg/kg bw per day (24-month study in rats) (racemic mixture)
Carcinogenicity	Dimethenamid-P and racemic dimethenamid are unlikely to pose a carcinogenic risk to humans
Reproductive toxicity	
Reproductive target/critical effect	None
Lowest relevant reproductive NOAEL	175 mg/kg bw[a, b] per day (racemic mixture)
Developmental target/critical effect	Not teratogenic; reduced fetal body weight (dimethenamid-P); not teratogenic; reduced fetal body weight and increased early deaths (racemic dimethenamid)
Lowest relevant developmental NOAEL	300 mg/kg bwa per day (rat) (dimethenamid-P) and 50 mg/kg bw per day (rat) (racemic mixture)
Neurotoxicity/delayed neurotoxicity	
	No signs of neurotoxicity
Other toxicological studies	
	Liver xenobiotic metabolizing enzyme induction. Strong binding to haemoglobin in rats, but this has no relevance to humans
Medical data	
	There have been no reports of toxicity in workers exposed during manufacture or use

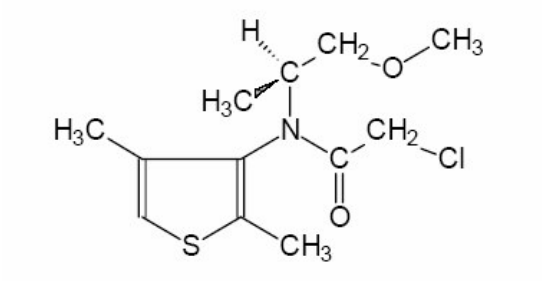
Summary			
	Value	Study	Safety factor
ADI	0–0.07 mg/kg bw	Rat, 2-year study of toxicity and carcinogenicity (racemic mixture)	100
ARfD	0.5 mg/kg bw	Rat, study of developmental toxicity (racemic mixture)	100

[a] Highest dose tested
[b] Measurements of intake of the compound are the mean of the pre-mating phases for P and F_1 females

RESIDUE AND ANALYTICAL ASPECTS

Residue and analytical aspects of the herbicide dimethenamid-P (*S*-dimethenamid) were considered for the first time by the present Meeting. Dimethenamid-P is one of the enantiomers in dimethenamid, the other being the herbicidally inactive dimethenamid-M (*R*-dimethenamid). In this report, the term 'dimethenamid' refers to the 50:50 mixture of *R*-dimethenamid and *S*-dimethenamid while the term 'dimethenamid-P' refers to the herbicidally active *S*-dimethenamid, containing up to 10% of the inactive enantiomer.

When applied as pre-plant, pre-emergent or early post-emergent treatments, this chloroacetamide herbicide is active against germinating broad-leaf and grass weeds, being taken up through the coleoptiles (grass seedlings) or the roots and emerging shoots (dicotyledonous seedlings) and reducing cell division and growth.



Chemical name:

IUPAC: S-2-chloro-N-(2,4-dimethyl-3-thienyl)-N-(2-methoxy-1-methyl-ethyl)acetamide
CAS: (S)-2-chloro-N-(2,4-dimethyl-3-thienyl)-N-[-2-methoxy-1-methyl-ethyl]acetamide

The manufacturer submitted studies on metabolism, analytical methods, supervised field trials, processing, freezer storage stability and rotational crop residues. Most of these studies involved the racemic mixture (dimethenamid) with supporting or bridging studies with dimethenamid-P also being provided. Information on GAP was submitted by the Netherlands.

The following abbreviations are used for the metabolites discussed below:

M7	2-chloro-*N*-(2,4-dimethyl-3-thienyl)-*N*-(2-hydroxy-1-methylethyl) acetamide
M23 (oxalamide)	2,2'-dithiobis(*N*-(2,4-dimethyl-3-thienyl)-*N*-(2-methoxy-1-methylethyl) acetamide)
M25	2-[*N*-(2,4-dimethyl-3-thienyl)-*N*- (2-methoxy-1-methylethyl) amino]-2-oxoethyl-cysteine
M27 (sulfonate)	2-[*N*-(2,4-dimethyl-3-thienyl)-*N*- (2-methoxy-1-methylethyl)-amino]-2-oxoethyl-sulfonic acid
M28	2-[*N*-(2,4-dimethyl-3-thienyl)-*N*- (2-methoxy-1-methylethyl) amino]-2-oxoethyl-sulfonic acid
M29	sulfoxide of 2-[*N*-(2,4-dimethyl-3-thienyl)-*N*-(2-methoxy-1-methylethyl) amino]-2-oxoethyl-N-malonyl cysteine
M30	sulfoxide of 2-[*N*-(2,4-dimethyl-3-thienyl)-*N*-(2-methoxy-1-methylethyl) amino]-2-oxoethyl thiolactic acid
M31	sulfoxide of 2-[*N*-(2,4-dimethyl-3-thienyl)-*N*-(2-methoxy-1-methylethyl) amino]-2-oxoethyl thioglycolic acid

Animal metabolism

The Meeting received animal metabolism studies for dimethenamid on lactating goats and laying hens. Comparison of racemic dimethenamid with dimethenamid-P toxicology has been possible for a number of types of study. These have shown that there is little difference in the toxicological profile or, where appropriate, the NOAEL values of these materials. Consequently, the Meeting concluded that the metabolism studies involving racemic dimethenamid could also apply to dimethenamid-P.

Rats

Dimethenamid was well absorbed and extensively metabolized by rats, with about 90% of the administered dose being eliminated within 168 h and only 1–2% of unchanged dimethenamid was detected in excreta. About 40 metabolites were found in organic extracts using thin layer chromatography (TLC) analysis with 20 of these being identified.

Goats

A lactating goat was orally administered [3-^{14}C-thienyl]dimethenamid for four consecutive days at a dose equivalent to 223 ppm in the diet. In this study, 36% of the administered dose was excreted in either urine or faeces and less than 2.3% TRR remained in animal tissues (0.02% in milk). In milk, residues reached a plateau after 3 days, with a maximum of 0.98 mg/kg dimethenamid equivalents reported 7 h after the third dose. Concentrations in kidney, fat, muscle and liver were 9.9, 1.0, 0.97 and 17 mg/kg, respectively. No residues of the parent compound were found, and metabolites reported at levels higher than 1.0 mg/kg were in kidney (M7 at 2.4 mg/kg) and in liver (M25 at 1.2 mg/kg, M22 at 1.0 mg/kg).

Because of the low recovery rate in this study, partly explained by the loss of a urine sample and reduced faecal production and the exhibition of toxicity symptoms (loss of appetite and decrease in body weight), a supplementary material balance study was also conducted, where a single goat was dosed once with [3-^{14}C-thienyl]dimethenamid (equivalent to 250 ppm in the diet) and radioactivity measured in urine, faeces and milk over the subsequent 5 days. In this second study, more than 59% (urine) and 28% (faeces) of the TRR was excreted by the end of the 5-day study, with 0.09% TRR being measured in milk.

Hens

Laying hens (3) were fed with [3-^{14}C-thienyl]dimethenamid for four days at a dose rate equivalent to 167 ppm in the diet. Elimination of the C^{14} was rapid, with more than 77 % of the total applied dose being found in the excreta, less than 0.5% in liver, between 0.3% and 0.4% in muscle, 0.07% in fat and 0.02% or less in eggs. Radiolabel concentrations in egg white increased from 0.19 mg/kg to 0.3 mg/kg dimethenamid equivalents over the four day period with the related egg yolk residues increasing from 0.01 mg/kg to 0.62 mg/kg over the same period. Residue levels in fat, muscle (breast), muscle (thigh) and liver were 0.29, 0.45, 0.58 and 8.33 mg/kg TRR, respectively.

Residues of dimethenamid were identified in fat (0.1 mg/kg or 36% of the fat radiolabel), with the major identified metabolites being M3 (0.43 mg/kg or 5% liver TRR) and M8 (0.65 mg/kg or 7.8% liver TRR). Up to 21 other metabolites were detected in tissues and eggs, all at less than 10% of the TRR, but these were not identified.

Dimethenamid was extensively metabolized by rats, goats and hens with 1.2% (hens) and 2.3% (goats) of the applied dose remaining in tissues after 4–5 days and 0.02% being found in milk and eggs. The proposed metabolic pathway was via glutathione conjugation, the formation of cysteine, mercapturate thioglycolic sulfoxide conjugates, with other pathways involving demethylation and reductive dechlorination. No residues of the parent compound were reported in milk or any animal tissues except in fat of hens, where dimethenamid residues of about 0.1 mg/kg were reported.

Plant metabolism

The Meeting received plant metabolism studies for dimethenamid in soya beans, maize and sugar beet. While these studies were conducted using dimethenamid, the Meeting considered that dimethenamid-P would exhibit the same metabolic profile and agreed that the plant metabolism studies involving dimethenamid could apply to dimethenamid-P.

Soya beans

In a metabolism study in soya beans treated with radiolabelled dimethenamid to simulate pre-emergence broadcast application (1.68 kg ai/ha and 3.36 kg ai/ha), dimethenamid was rapidly metabolized to a number of polar metabolites (20–30), most being present at low levels (< 0.01 mg/kg or < 3% TRR). No parent compound was detected in any of the samples, even at the 2×

treatment rate. Metabolites present at levels higher than 10% TRR were M23 (17% in forage), M27 (11% in hay) and M30/M31 (12% in mature seeds).

Maize

The metabolic fate of dimethenamid was studied in maize plants, where radiolabelled dimethenamid was applied as a pre-emergence broadcast spray (1.68 kg ai/ha and 4.4 kg ai/ha). Translocation of radiocarbon to grain was minimal. Dimethenamid was rapidly metabolized to several weak acids and other highly polar residues, with many individual fractions present in very small amounts. No dimethenamid residues were found in any of the forage, silage, grain or straw samples, even at the exaggerated (4.4 kg ai/ha) application rate and no metabolites were present at levels greater than 0.05 mg/kg or 10% TRR. The most common metabolites found in foliage were M23, M27 and M30/M31

Sugar beet

In a sugar beet metabolism study, labelled dimethenamid was applied three times to sugar beet plants at a rate equivalent to 0.45 kg ai/ha per treatment. Levels of ^{14}C in roots were about 3.5 times lower than in the tops. No parent residues were detected in any samples, with the major identified metabolites being M23, M27, M28 and M29 in the roots and M27, M29 and M30 in the tops. Numerous polar metabolites were also characterized. All the identified metabolites were present at levels below 10% of the TRR or < 0.01 mg/kg dimethenamid equivalents.

Dimethenamid is rapidly metabolized in plants and metabolism occurs through similar pathways in the three crops studied. The proposed metabolic pathway in plants involves conjugation of dimethenamid with glutathione and hydrolysis to the cysteine conjugate, both being considered transient intermediates undergoing rapid oxidation, deamination and/or decarboxylation to form many relatively polar metabolites, all of which are generally present at levels of < 0.05 mg/kg or less than 10% of the TRR. Bound radiocarbon increased with time, indicating incorporation of residues into the plant matrix. No parent compound was detected in any of the plant tissues at any sampling interval.

Environmental fate

Dimethenamid-P is stable in aqueous buffered solutions at pH 5, 7 and 9 (25°C in the absence of light) for at least 31 days. No information was provided on the formation of hydrolysis products, but it is not expected that hydrolytic processes will be a significant factor in the environmental degradation of dimethenamid-P and dimethenamid.

The Meeting received information on the comparative behaviour and fate of dimethenamid-P and dimethenamid in aerobic soil. No significant differences were observed in the degradation rates of dimethenamid and dimethenamid-P when the soil was mixed with dimethenamid or dimethenamid-P at a concentration of about 2 mg ai/kg (to simulate the concentration within the top 5 cm of soil following a pre-emergence broadcast field application at 1.68 kg ai/ha) and incubated under aerobic conditions at 23°C for 182 days. The calculated DT_{50} value for the aerobic degradation of both compounds in clay loam soil at 23°C was 10 days. After the 182 day incubation period, $^{14}CO_2$ accounted for 28–29% TRR for both treatments. Non-extractable residues were found to increase to 40% TRR.

Soil metabolites, identified following exaggerated rate incubations (21 days, 9.5 mg/kg dry soil), were similar for both dimethenamid and dimethenamid-P, and none of these exceeded 9% of the TRR.

In a confined rotational crop study, labelled dimethenamid was applied to maize and soya bean crops as simulated pre-emergence treatments. The rotational crops used in this study were

winter wheat (planted 141 DAT), spring wheat (planted 322 DAT), lettuce and carrots (planted 332 DAT).

The TRRs for all rotational crop samples from plots treated at a rate equivalent to 1.68 kg ai/ha were between 0.01 mg/kg and 0.06 mg/kg in carrot roots, carrot tops, lettuce leaves, wheat grain and immature wheat plants, with residues of 0.12 mg/kg and 0.17 mg/kg being reported in summer and winter wheat straw respectively. Total radioactive residues in the soya bean samples from the higher (2×) treatment rates were generally twice the above levels while in the high rate (2.6×) maize plots, samples generally contained residues two to three times higher than the above.

Metabolites M23, M27 and M30 were identified in the rotational crops, but all at levels below 0.01 mg/kg. Unidentified metabolites were also < 0.01 mg/kg and residues of dimethenamid were not detected in any samples.

These results indicate that the potential exposure of consumers to residues of dimethenamid from rotational crops is insignificant.

While the above crop rotation study was conducted using dimethenamid, the Meeting considered that dimethenamid-P should exhibit the same metabolic profile as the racemic mixture, and agreed that the results of these crop rotation studies could be applied to dimethenamid-P.

Methods of analysis

The Meeting received information on methods for the analysis of dimethenamid and two metabolites (M23 and M27) in plant and animal tissues. The methods developed for dimethenamid do not differentiate between the isomers and are therefore applicable for analysis of matrices treated with either dimethenamid or dimethenamid-P.

Most of the methods reported to the Meeting and used in the supervised residue trials were based on methanol:water extraction and clean-up using reversed phase C_{18} solid phase extraction columns, partitioning the aqueous eluate with toluene and silica gel column chromatography with ethyl acetate:cyclohexane elution. Analysis in the earlier studies was by CG equipped with thermioinic detector (TSD) and in the later studies, by GC-MS. In animal matrices and most plant matrices, the reported limit of quantification was 0.01 mg/kg, with mean recovery rates of 75% to 105%.

Several earlier methods, designed to measure both the parent compound and the M23 (oxalamide) metabolite also included an additional step to methylate the M23 metabolite by adding diazomethane, but the variable recovery rates in validation studies and in field trials resulted in these methods being discontinued. Supervised residue trials using these methods were not considered in this appraisal.

A multi-residue method, based on the DFG Method S 19 has been developed, involving acetone:water (2:1) extraction, ethyl acetate:cyclohexane (1:1) partitioning, gel permeation and mini silica gel column cleanups and GC-MS analysis. The modification used in this method was the use of ethyl acetate:cyclohexane rather than dichloromethane in the clean-up partitioning step. The reported limit of quantification for this method was 0.01 mg/kg and mean recovery rates were 76–79%.

Stability of pesticide residues in stored analytical samples

The Meeting received information on the stability of dimethenamid and dimethenamid-P in various commodities under freezer storage (-16 to -20 °C). Residue degradation of dimethenamid during storage was less than 20% in maize forage, grain and fodder stored for 21 months, less than 10% in soya bean forage and beans stored for 16 months and no degradation was reported in onion bulbs

stored for 9 months. Dimethenamid-P residues did not degrade in spring onion samples stored at –16 °C for 56 weeks.

Definition of the residue

Metabolism studies in animals (goats and hens) and plants (maize, soya beans) indicate that dimethenamid is rapidly and extensively metabolized, with a number of polar metabolites being produced, all at low levels (less than 10% TRR). The metabolic pathway is similar in the crops investigated. Residues of the parent compound were only found at a low level in poultry fat following administration of a highly exaggerated dose rate.

Based on the available comparative animal and soil metabolism studies and noting that the only difference between dimethenamid and dimethenamid-P was in the enantiomer ratio (50:50 vs 90:10), the residue profile and metabolic behaviour of dimethenamid-P is expected to be the same as for dimethenamid.

The available analytical methods to measure dimethenamid residues are also suitable for measuring dimethenamid-P residues, but they do not differentiate between the enantiomers.

The Meeting noted that national residue definitions for dimethenamid and/or dimethenamid-P included:

"dimethenamid, applied as either the 90:10 or 50:50 *S*:*R* isomers" (USA)

"dimethenamid-P including other mixtures of constituent isomers (sum of isomers)" (EU)

The Meeting concluded that for both animal and plant commodities, the definition of the residue for compliance with MRLs and estimation of dietary intake should be 'dimethenamid-P and its enantiomer' and noted that this residue definition could apply to residues arising from the use of either dimethenamid-P or dimethenamid.

Results of supervised trials on crops

The Meeting received supervised trials involving dimethenamid on onions (bulb), sweetcorn, beans (dry), soya beans, sugar beet, maize, sorghum and peanuts and trials with dimethenamid-P were also provided for spring onions, potato, sugar beet, maize and grass seed crops.

The Meeting agreed that because dimethenamid-P exhibited the same metabolic behaviour as dimethenamid, the results of trials involving dimethenamid could be applied to dimethenamid-P.

The Meeting also agreed that in trials involving pre-plant or pre-emergence applications and where the mature commodities were sampled at normal commercial harvest, the results could be used to support recommendations for MRLs, irrespective of the PHI used in the trials, since the label claims for these treatment methods were more related to crop growth stages (i.e. crop emergence and harvest) than to the number of days between treatment and harvest. In addition, the Meeting agreed that where the reported residues were below the limits of quantification in trials involving application rates higher than GAP and in the case of post-emergence applications where the PHIs were shorter than GAP, these results could be used to support recommendations for MRLs at the limit of quantification.

For commodities where the supporting trials used in the estimation of maximum residue levels all reported residues below the limit of quantification, even at exaggerated rates, the Meeting, taking into account the results of the plant metabolism studies, agreed to estimate STMRs, median residue levels, HRs and highest residue levels of 0 mg/kg, indicating that residues are not expected.

Onion, bulb

Field trials involving single post-emergence treatments with dimethenamid were made available to the Meeting from the USA. In all trials, residues were below the limit of quantification (0.01 mg/kg).

GAP in USA is for post-emergence use (max 1.1 kg ai/ha, PHI 30 days) and while there were no trials available that matched the USA GAP, the Meeting agreed to use the results from 8 dimethenamid trials from the USA with PHIs matching the USA PHI (30 days) but at higher application rates (1.68 kg ai/ha), since these all reported residues of < 0.01 mg/kg. The combined results were < 0.01 (8) mg/kg.

The Meeting estimated an STMR value of 0 mg/kg and a maximum residue level of 0.01 mg/kg (*) for onion, bulb. The HR was 0 mg/kg.

Garlic

The Meeting noted that GAP existed for dimethenamid-P in USA. This GAP is the same as that established for onion, bulb, and the Meeting agreed that the available residue data for onion, bulb could be extrapolated to garlic.

The Meeting estimated an STMR value of 0 mg/kg and a maximum residue level of 0.01 mg/kg (*) for garlic. The HR was 0 mg/kg.

Shallot

The Meeting noted that GAP existed for dimethenamid-P in USA. This GAP is the same as that established for onion, bulb, and the Meeting agreed that the available residue data for onion, bulb could be extrapolated to shallot.

The Meeting estimated an STMR value of 0 mg/kg and a maximum residue level of 0.01 mg/kg (*) for shallot. The HR was 0 mg/kg.

Spring onion

Field trials (6) involving single post-emergence treatments of dimethenamid-P were provided from Canada and USA, all reporting < 0.01 mg/kg, but no matching GAP information was available for dimethenamid-P.

The Meeting agreed not to estimate a maximum residue level, STMR or HR for spring onion.

Sweet corn

Field trials involving single pre-emergence and post-emergence treatments with dimethenamid were made available to the Meeting from Canada (4), France (2) and USA (14). In all trials, residues were below the limit of quantification in sweetcorn cobs (i.e. kernels plus cobs, without husks).

GAP in USA is for use as either a pre-plant, pre-emergence or post-emergence treatment (max 1.1 kg ai/ha, PHI 50 days). GAP in France and Germany is for pre-emergence use (max 1.0 kg ai/ha, PHI 60 days – France).

While there were no trials available that matched the USA pre-emergence GAP for dimethenamid-P, the Meeting agreed to use the results from 14 trials in USA involving dimethenamid with higher application rates (1.68 kg ai/ha) and with PHIs ranging from 70-98 days, since these all reflected residues in mature corn at harvest and reported residues of < 0.01 mg/kg.

Seven early post-emergence trials in USA involving dimethenamid, matching the USA PHI for dimethenamid-P (50 days), but at rates higher than the USA maximum rate for dimethenamid-P (1.1 kg ai/ha) also reported residues of < 0.01 (7) mg/kg.

The combined results from these pre- and post-emergence trials were < 0.01 (21).

The Meeting estimated an STMR value of 0 mg/kg and a maximum residue level of 0.01 mg/kg (*) for sweet corn (corn-on-the-cob). The HR was 0 mg/kg.

Beans, dry

Field trials involving single pre-plant, pre-emergence and post-emergence treatments with Dimethenamid were made available to the Meeting from Canada and USA. In all trials, residues in dry beans were below the limits of quantification (0.01 mg/kg in the USA trials and 0.02 mg/kg in the Canadian trials).

GAP in USA is for use as either a pre-plant, pre-emergence or early post-emergence treatment, up to 1.1 kg ai/ha, PHI 70 days.

While there were no dimethenamid-P trials available that matched the USA GAP for pre-plant or pre-emergence use, the Meeting agreed to use the results from 22 dimethenamid trials with higher application rates and with PHIs ranging from 76–133 days, since these all reflected residues in beans at harvest and reported residues were all below the limits of quantification. Results of these trials were: < 0.01 (14), < 0.02 (8) mg/kg.

While there were no dimethenamid-P trials available that matched the USA GAP for post-emergent use, the Meeting agreed to use the results from post-emergent dimethenamid trials with higher application rates and PHIs that matched the USA PHI (9 trials) as these were all below the limits of quantification. Reported residues in these trials were < 0.01 (9) mg/kg.

The combined results from these pre-plant, pre-emergence and post-emergence trials were < 0.01 (23), < 0.02 (8) mg/kg.

The Meeting estimated an STMR value of 0 mg/kg and a maximum residue level of 0.01 mg/kg (*) for beans, dry. The high residue was 0 mg/kg.

Soya bean, dry

Field trials involving single pre-plant, pre-emergence and post-emergence treatments with dimethenamid were made available to the Meeting from Canada and USA. In all trials, residues in dry beans were below the limit of quantification (0.01 mg/kg).

GAP in USA is for use as either a pre-plant, pre-emergence or post-emergence treatment, up to 1.1 kg ai/ha (applied from 1st to 3rd trifoliate leaf stage BBCH 12–14).

While there were no trials available that matched the USA GAPs for pre-plant or pre-emergence use, the Meeting agreed to use 18 pre-plant trials and 22 pre-emergence trials from Canada and USA involving dimethenamid at higher application rates of 1.68–3.0 kg ai/ha as these were all below the limits of quantification.

The combined results from these pre-plant and pre-emergence trials were < 0.01 (36), < 0.02 (4) mg/kg.

While there were no trials available that matched the USA GAP for post-emergence use, the Meeting agreed to use the results from 22 post-emergence dimethenamid trials with higher

application rates, applied at the 2–4 leaf stage as these were all below the limits of quantification. Reported residues in these trials were < 0.01 (22) mg/kg.

The combined results from these pre-plant, pre-emergence and post-emergence trials were < 0.01 (58), < 0.02 (4) mg/kg.

The Meeting estimated an STMR value of 0 mg/kg and a maximum residue level of 0.01 mg/kg (*) for soya beans, dry. The high residue was 0 mg/kg.

Potato

Field trials involving single pre-plant, pre-emergence and post-emergence treatments with dimethenamid-P were made available to the Meeting from USA. In all trials, residues in tubers were below the limit of quantification (0.01 mg/kg).

GAP in USA is for use as a single pre-emergence treatment, up to 1.1 kg ai/ha with a PHI of 40 days.

One dimethenamid-P trial from USA matched the USA GAP (PHI 40 days) for the pre-emergence use, reporting a residue of < 0.01 mg/kg. Sixteen additional pre-emergence trials from USA, involving longer PHIs (62-128 days), reflecting commercial harvest intervals also reported residues of < 0.01 (16) mg/kg.

In addition, residues were all below the limit of quantification (0.01 mg/kg) in 17 pre-plant USA trials where treatments were made the same day as the above pre-emergence treatments (i.e. the day of planting) and in 34 post-emergence trials from the USA, where tubers were harvested 39–50 days after treatment. While not directly related to the USA GAP (pre-emergence use), the Meeting agreed that these results could be used as supporting data.

The combined results from these pre- and post-emergence trials were < 0.01 (68) mg/kg.

The Meeting estimated an STMR value of 0 mg/kg and a maximum residue level of 0.01 mg/kg (*) for potato. The HR was 0 mg/kg.

Sweet potato

The Meeting noted that GAP existed for dimethenamid-P in the USA. This GAP is the same as that established for potato, and the Meeting agreed that the available residue data for potato could be extrapolated to sweet potato.

The Meeting estimated an STMR value of 0 mg/kg and a maximum residue level of 0.01 mg/kg (*) for sweet potato. The high residue was 0 mg/kg.

Sugar beet

Field trials involving single post-emergent treatments with dimethenamid or dimethenamid-P were made available to the Meeting from France, Germany, Netherlands, Switzerland and USA. In all trials, residues in sugar beet roots were below the limit of quantification (0.01 mg/kg).

GAP in Germany is for a single post-emergent treatment (max 0.65 kg ai/ha), at the 6–8 leaf stage, GAP in Netherlands is for either a single post-emergent treatment (max 0.65 kg ai/ha) or 2–3 split post-emergence applications (max 0.65 kg ai/ha per season). In Belgium, GAP is also for either a single or split (3 applications) post-emergence treatments (max 0.72 kg ai/ha) up to the 8-leaf stage.

GAP in USA is also for either a single or split (2 applications) post-emergence treatments (max 1.1 kg ai/ha per season, up to the 12-leaf stage - PHI 60 days).

Four trials in Germany, France and Netherlands, matching the single post-emergence application GAP of Belgium, Germany and Netherlands reported residues of < 0.01 (4) mg/kg and 12 USA post-emergence trials on sugar beet, matching the USA single-application GAP but with longer PHIs that reflect commercial harvest intervals (80–121 days) also reported residues below the limits of quantification. Combined residues in these trials were < 0.01 (16) mg/kg.

In addition, 5 single post-emergence dimethenamid trials from Germany, France and Switzerland with higher application rates but otherwise matching the Belgium GAP, reported residues of < 0.01 (5) and sixteen multiple-application dimethenamid trials in France, Germany and Switzerland, involving rates higher than the split-application Belgian GAP or with more than 3 treatments per season also reported residues of < 0.01 (16) mg/kg. The Meeting agreed to use the results from these post-emergence dimethenamid trials as residues were all below the limit of quantification and the combined results were < 0.01 (21) mg/kg.

The combined results from all the above post-emergence trials involving dimethenamid or dimethenamid-P were < 0.01 (37) mg/kg.

The Meeting estimated an STMR value of 0 mg/kg and a maximum residue level of 0.01 mg/kg (*) for sugar beet. The high residue was 0 mg/kg.

Beetroot

The Meeting noted that GAP existed for dimethenamid-P in beetroot in USA. This GAP is the same as that established for sugar beet, and the Meeting agreed that the available residue data for sugar beet could be extrapolated to beetroot.

The Meeting estimated an STMR value of 0 mg/kg and a maximum residue level of 0.01 mg/kg (*) for beet root. The high residue was 0 mg/kg.

Maize

Field trials involving single pre-plant, pre-emergence and post-emergence treatments with dimethenamid were made available to the Meeting from Belgium, Canada, France, Germany, Greece, Italy, Netherlands, Spain, Switzerland and USA. In all trials, residues in maize (grain) were below the limit of quantification (0.01 mg/kg).

GAP in USA is for use as a single pre-plant or pre-emergence treatment (max 1.1 kg ai/ha), or either a single or double (split-application) post-emergence treatment, with a maximum rate of 1.1 kg ai/ha per season (up to 30cm plant height). GAP in France is for pre-emergence use (max 1.1 kg ai/ha, PHI 90 days), in Germany, Netherlands and Spain GAP is for a single application, either pre-emergence or post-emergence (max 1.0 kg ai/ha) up to the 6-leaf stage, while the GAP in Belgium is for a post-emergence treatment (max 1.0 kg ai/ha) at the 3–4 leaf stage.

While there were no trials available that matched the GAP for pre-plant use in USA the Meeting agreed to use the results from the pre-plant dimethenamid trials (17) in USA and Canada with higher application rates (1.7–3.0 kg ai/ha), as these were all below the limits of quantification. Reported residues in these trials were < 0.01 (17) mg/kg.

While there were no trials available that matched the GAP for pre-emergence use in France, Germany, Netherlands, Spain and USA, the Meeting agreed to use the results of 11 dimethenamid pre-emergence trials from USA and 20 pre-emergence trials from Belgium, France, Germany, Greece,

Italy and Netherlands, all involving higher rates than the respective GAPs in USA, Belgium and Italy, all reporting residues below the limit of quantification. Combined residues in these trials were < 0.01 (31) mg/kg.

Four *post-emergence* trials with dimethenamid-P in Germany, Italy and France, matching the GAP of Belgium, Germany, Netherlands and Spain reported residues of < 0.01 (4). The Meeting agreed to also use the results from 11 USA post-emergence dimethenamid trials involving higher rates but applied at the recommended USA GAP growth stage and 9 trials from Europe with higher application rates but applied at growth stages matching the GAP of Belgium, Germany or Spain as these were all below the limits of quantification. Reported residues in these trials were < 0.01 (20) mg/kg.

The combined results from all of the above pre-plant, pre-emergence and post-emergence trials with dimethenamid or dimethenamid-P were < 0.01 (72) mg/kg.

The Meeting estimated an STMR value of 0 mg/kg and a maximum residue level of 0.01 mg/kg (*) for maize. The high residue was 0 mg/kg.

Sorghum

Field trials involving single pre-emergence and post-emergence treatments with dimethenamid were made available to the Meeting from USA. In all trials, residues in sorghum grain were below the limit of quantification (0.01 mg/kg).

GAP in USA is for use as either a single pre-plant, pre-emergence or post-emergence treatment, or as split pre-plant/pre-emergence treatments, up to 1.1 kg ai/ha per season, PHI 80 days.

While there were no trials available that matched the USA GAP for pre-emergence use for dimethenamid-P, the Meeting agreed to use the results from pre-emergence dimethenamid trials (14) with higher application rates and longer PHIs (106–155 days), reflecting commercial harvest intervals, with the reported residues in these trials being < 0.01 (14) mg/kg.

While there were no trials available that matched the USA GAP for post-emergence use, the Meeting agreed to use the results from post-emergence dimethenamid trials with higher application rates that matched the USA GAP PHI (8 trials) but with higher application rates (1.68 kg ai/ha) as these were all below the limits of quantification. Reported residues in these trials were < 0.01 (8) mg/kg.

The combined results from the above pre-emergence and post-emergence trials with dimethenamid were < 0.01 (22) mg/kg.

The Meeting estimated an STMR value of 0 mg/kg and a maximum residue level of 0.01 mg/kg (*) for sorghum. The high residue was 0 mg/kg.

Peanut

Field trials involving single pre-emergence and post-emergence treatments with dimethenamid were made available to the Meeting from USA. In all trials, residues in peanut (nuts without shells) were below the limit of quantification (0.01 mg/kg).

GAP in the USA is for a single pre-plant, pre-emergence or post-emergence treatment, or as split pre-plant/pre-emergence treatments (max 1.1 kg ai/ha/season, PHI 80 days).

While there were no trials available that matched the USA GAP for pre-emergence use, the Meeting agreed to use the results from pre-emergence dimethenamid trials (14) with higher

application rates and longer PHIs (121–145 days), reflecting commercial harvest intervals, with the reported residues in these trials being < 0.01 (14) mg/kg.

While there were no trials available that matched the USA GAP for post-emergence use, the Meeting agreed to use the results from 14 post-emergence dimethenamid trials with higher application rates that matched the USA GAP PHI, as these were all below the limits of quantification. Reported residues in these trials were < 0.01 (14) mg/kg.

The combined results from the above pre-emergence and post-emergence trials with dimethenamid were < 0.01 (28) mg/kg.

The Meeting estimated an STMR value of 0 mg/kg and a maximum residue level of 0.01 mg/kg (*) for peanut. The high residue was 0 mg/kg.

Animal feed commodities

Bean forage

Field trials involving single pre-plant, pre-emergence and post-emergence treatments with dimethenamid were made available to the Meeting from Canada and USA. Residues in bean forage were below the limits of quantification (0.01 mg/kg in the USA trials and 0.02 mg/kg in the Canadian trials) except in young plants (at the 6–8 leaf stage (BBCH16-18)) sampled 12–18 days after a late post-emergence treatment.

GAP in USA is for use as either a pre-plant, pre-emergence or post-emergence treatment (max 1.1 kg ai/ha). The PHI for beans is 70 days, with post-emergence use being from 1st to 3rd trifoliate leaf stage BBCH 13–14 Crop stage.

While there were no trials available that matched the USA GAP for pre-plant or pre-emergence use, the Meeting agreed to use the results from 5 pre-plant and 17 pre-emergence dimethenamid trials from Canada and USA with higher application rates (1.3–2.7 kg ai/ha) since the reported residues were all below the limits of quantification. Reported residues in these trials were < 0.01 (14), < 0.02 (8) mg/kg.

There were no trials available that matched the USA GAP for post-emergence use, and the Meeting agreed to use the results from 14 USA trials involving dimethenamid with higher application rates (1.68 kg ai/ha) as residues in mature bean forage (i.e. just before senescence) all reported residues below the limit of quantification. Residues in these trials were < 0.01 (14).

The combined results from these pre-plant, pre-emergence and post-emergence trials were < 0.01 (28), < 0.02 (8) mg/kg.

The Meeting estimated a median residue of 0 mg/kg and a high residue of 0 mg/kg for bean forage.

Bean fodder

Field trials involving single pre-plant, pre-emergence and post-emergence treatments with dimethenamid were made available to the Meeting from Canada and USA. Residues in bean fodder were below the limits of quantification (0.01 mg/kg in the USA trials and 0.02 mg/kg in the Canadian trials)

GAP in USA is for use as either a pre-plant, pre-emergence or post-emergence treatment, up to 1.1 kg ai/ha. The PHI for beans is 70 days, with post-emergence use being from 1st to 3rd trifoliate leaf stage.

While there were no trials available that matched the USA GAP for pre-plant or pre-emergence use, the Meeting agreed to use the results from 22 dimethenamid trials with higher application rates and with PHIs ranging from 76-133 days, since these all reflected residues in bean fodder at harvest and reported residues were all below the limits of quantification. Results of these trials were: < 0.01 (14), < 0.02 (8) mg/kg.

While there were no trials available that matched the USA GAP for post-emergence use, the Meeting agreed to use the results from post-emergence dimethenamid trials with higher application rates and PHIs that matched the USA GAP (14 trials) as these were all below the limits of quantification. Reported residues in these trials were < 0.01 (14) mg/kg.

The combined results from these pre-plant, pre-emergence and post-emergence trials were < 0.01 (28), < 0.02 (8) mg/kg.

The Meeting estimated a median residue of 0 mg/kg and a maximum residue level of 0.01 (*) mg/kg for bean fodder. The highest residue was 0 mg/kg.

Peanut forage

Field trials involving single pre-emergence and post-emergence treatments with dimethenamid were made available to the Meeting from USA. In all trials, residues in peanut forage were below the limit of quantification (0.01 mg/kg).

GAP in USA is for use as either a single pre-plant, pre-emergence or post-emergence treatment, or as split pre-plant/pre-emergence treatments, up to 1.1 kg ai/ha per season, PHI 80 days (hay or straw).

While there were no trials available that matched the USA GAP for pre-emergence use, the Meeting agreed to use the results from pre-emergence dimethenamid trials (14) with higher application rates and longer PHIs (121–145 days), reflecting commercial harvest intervals, with the reported residues in these trials being < 0.01 (14) mg/kg.

While there were no trials available that matched the USA GAP for post-emergence use, the Meeting agreed to use the results from 14 post-emergence dimethenamid trials with higher application rates that matched the USA GAP PHI, as these were all below the limits of quantification. Reported residues in these trials were < 0.01 (14) mg/kg.

The combined results from the pre-emergence and post-emergence trials with dimethenamid were < 0.01 (28) mg/kg.

The Meeting estimated a median residue of 0 mg/kg and a highest residue of 0 mg/kg for peanut forage.

Peanut fodder

Field trials involving single pre-emergence and post-emergence treatments with dimethenamid were made available to the Meeting from USA. In all trials, residues in peanut fodder were below the limit of quantification (0.01 mg/kg).

GAP in USA is for use as either a single pre-plant, pre-emergence or post-emergence treatment, or as split pre-plant/pre-emergence treatments, up to 1.1 kg ai/ha per season, PHI 80 days (hay or straw).

While there were no trials available that matched the USA GAP for pre-emergence use, the Meeting agreed to use the results from pre-emergence dimethenamid trials (14) with higher application rates and longer PHIs (121–145 days), reflecting commercial harvest intervals, with the reported residues in these trials being < 0.01 (14) mg/kg.

While there were no trials available that matched the USA GAP for post-emergence use, the Meeting agreed to use the results from 14 post-emergence dimethenamid trials with higher application rates that matched the USA GAP PHI, as these were all below the limits of quantification. Reported residues in these trials were < 0.01 (14) mg/kg.

The combined results from the pre-emergence and post-emergence trials with dimethenamid were < 0.01 (28) mg/kg.

The Meeting estimated an STMR value of 0 mg/kg and a maximum residue level of 0.01 mg/kg (*) for peanut fodder. The highest residue was 0 mg/kg.

Soya bean forage and fodder

Field trials involving single pre-plant, pre-emergence and post-emergence treatments with dimethenamid were made available to the Meeting from Canada and USA. GAP in USA is for use as either a pre-plant, pre-emergence or post-emergence treatment, up to 1.1 kg ai/ha but with a restriction that treated soya bean forage, hay or straw must not be fed to livestock.

The Meeting agreed not to estimate STMRs, maximum residue levels or highest residues for soya bean forage (green) or soya bean fodder.

Fodder beet

The Meeting noted that GAP existed for use on fodder beet in Belgium and Netherlands. These GAPs were the same as those established for sugar beet, and the Meeting agreed that the available residue data for sugar beet could be extrapolated to fodder beet.

The Meeting estimated an STMR value of 0 mg/kg and a maximum residue level of 0.01 mg/kg (*) for fodder beet. The highest residue was 0 mg/kg.

Hay or fodder (dry) of grasses

Field trials on perennial grass seed crops, involving single post-emergence treatments with dimethenamid-P were made available to the Meeting from the USA. GAP in the USA is for use as post-emergence treatment, up to 1.1 kg ai/ha but with a restriction that livestock must not be grazed on treated areas and that treated grasses, forage, hay, silage, straw, seed or seed screenings must not be fed to livestock.

The Meeting agreed not to estimate STMRs, maximum residue levels or highest residues for hay or fodder (dry) of grasses.

Maize forage

Field trials involving single pre-plant, pre-emergence and post-emergence treatments with dimethenamid (number) and dimethenamid-P (6) were made available to the Meeting from Belgium,

Canada, France, Germany, Greece, Italy, Netherlands, Spain, Switzerland and USA. Residues in maize forage were below the limit of quantification (0.01 mg/kg) in all pre-plant and pre-emergence trials. Residues were detected in some post-emergence trials, ranging from 0.01 mg/kg to 0.04 mg/kg in samples taken 21–43 days after treatment.

GAP in USA is for use as a single pre-plant or pre-emergence treatment (max 1.1 kg ai/ha), or either a single or 2 split-applications post-emergence, with a maximum rate of 1.1 kg ai/ha per season, PHI 40 days. GAP in Germany, Netherlands and Spain is for a single application, either pre-emergence or post-emergence (max 1.0 kg ai/ha) while GAP in Belgium is for a post-emergence treatment, up to 1.0 kg ai/ha and GAP in France is for a pre-emergence use (max 1.1 kg ai/ha, PHI 90 days).

While there were no trials available that matched the USA GAPs for pre-plant and pre-emergence uses, the Meeting agreed to use the results from the pre-plant and pre-emergence dimethenamid trials with higher application rates, as these were all below the limits of quantification.

Trials with dimethenamid from Canada (6) and USA (11), involving higher pre-plant application rates of 1.68-3.0 kg ai/ha and longer PHIs (56–70 days) that reflected commercial forage intervals, reported residues of < 0.01 (17) mg/kg.

Sixteen pre-emergence trials from USA and Canada, involving dimethenamid application rates higher than the USA GAP and with longer PHIs (56-69 days) that reflected commercial forage harvest intervals reported residues of < 0.01 (16). Dimethenamid pre-emergence trials (14) in France, Italy, Spain and Switzerland using rates higher than the GAP of Germany, Netherlands, France and Spain and with PHIs that reflected commercial forage harvest intervals (of about 60–90 days), reported residues of < 0.01 (14) mg/kg.

Six post-emergence trials involving dimethenamid-P in Germany, Italy and France, matching the GAP of Belgium, Germany, Netherlands and Spain, with PHIs of 21-47 days, reported residues of < 0.01 (3), 0.02, 0.03 and 0.04 mg/kg.

The Meeting agreed to combined results from these pre-plant and pre-emergence trials with dimethenamid and the post-emergence trials with dimethenamid-P to give a residue data set of < 0.01 (50), 0.02, 0.03 and 0.04 mg/kg.

Based on a dry matter content of 40%, the Meeting estimated a median residue of 0.025 mg/kg and a highest residue of 0.1 mg/kg for maize forage.

Maize fodder

Field trials involving single pre-plant, pre-emergence and post-emergence treatments with dimethenamid and dimethenamid-P (6) were made available to the Meeting from Belgium, Canada, France, Germany, Greece, Italy, Netherlands, Spain, Switzerland and USA. Residues in maize fodder were below the limit of quantification (0.01 mg/kg) in all trials except one residue of 0.01 mg/kg in fodder treated with dimethenamid, 118 days after a post-emergence treatment (1.43 kg ai/ha) in Belgium.

GAP in USA is for use as a single pre-plant or pre-emergence treatment (max 1.1 kg ai/ha), or either a single or 2 split-applications post-emergence, with a maximum rate of 1.1 kg ai/ha per season, PHI 40 days. GAP in Germany, Netherlands and Spain is for a single application, either pre-emergence or post-emergence (max 1.0 kg ai/ha) while the GAP in Belgium is for a post-emergence treatment, up to 1.0 kg ai/ha and GAP in France is for a pre-emergence use (max 1.1 kg ai/ha, PHI 90 days).

While there were no trials available that matched the GAP for pre-plant use in USA, the Meeting agreed to use the results from the pre-plant dimethenamid trials (17) in USA and Canada with higher application rates (1.7–3.0 kg ai/ha), as these were all below the limits of quantification. Reported residues in these trials were < 0.01 (17) mg/kg.

While there were no trials available that matched the GAP for pre-emergence use in France, Germany, Netherlands, Spain and in USA, the Meeting agreed to use the results of 17 dimethenamid pre-emergence trials from USA and Canada and 8 trials from France, Germany and Switzerland, all involving higher rates than the respective GAPs in USA, Belgium and Italy and all below the limit of quantification. Reported residues in these trials were < 0.01 (25) mg/kg.

Six post-emergence trials in Belgium, Germany, Italy, Netherlands and France, matching the GAPs of Belgium, Germany, Netherlands and Spain, with PHIs of 78–114 days, reported residues of < 0.01 (6).

The Meeting agreed to combined results from these pre-plant and pre-emergence trials with dimethenamid and the post-emergence trials with dimethenamid-P to give a residue data set of < 0.01 (48) mg/kg.

The Meeting estimated an STMR value of 0 mg/kg and a maximum residue level of 0.01mg/kg (*) for maize fodder. The highest residue was 0 mg/kg.

Sorghum forage (green)

Field trials involving single pre-emergence and post-emergence treatments with dimethenamid were made available to the Meeting from USA. In all trials, residues in sorghum forage were below the limit of quantification (0.01 mg/kg).

GAP in USA is for use as either a single pre-plant, pre-emergence or post-emergence treatment, or as split pre-plant/pre-emergence treatments, up to 1.1 kg ai/ha per season, PHI 60 days.

While there were no trials available that matched the USA GAP for pre-emergence use, the Meeting agreed to use the results from pre-emergence dimethenamid trials (14) with higher application rates and longer PHIs (59–107 days), reflecting commercial harvest intervals, with the reported residues in these trials being < 0.01 (14) mg/kg.

While there were no trials available that matched the USA GAP for post-emergence use, the Meeting agreed to use the results from 11 post-emergence dimethenamid trials with higher application rates that matched the USA PHI (60 days), as these were all below the limits of quantification. Reported residues in these trials were < 0.01 (11) mg/kg.

The combined results from these pre-emergence and post-emergence trials with dimethenamid were < 0.01 (25) mg/kg.

The Meeting estimated a median residue of 0 mg/kg and a highest residue of 0 mg/kg for sorghum forage.

Sorghum straw and fodder, dry

Field trials involving single pre-emergence and post-emergence treatments with dimethenamid were made available to the Meeting from USA. In all trials, residues in sorghum fodder were below the limit of quantification (0.01 mg/kg).

GAP in USA is for use as either a single pre-plant, pre-emergence or post-emergence treatment, or as split pre-plant/pre-emergence treatments, up to 1.1 kg ai/ha per season, PHI 80 days.

While there were no trials available that matched the USA GAP for pre-emergence use, the Meeting agreed to use the results from pre-emergence dimethenamid trials (14) with higher application rates and longer PHIs (106–155 days), reflecting commercial harvest intervals, with the reported residues in these trials being < 0.01 (14) mg/kg.

While there were no trials available that matched the USA GAP for post-emergence use, the Meeting agreed to use the results from post-emergence dimethenamid trials with higher application rates that matched the USA GAP PHI as these were all below the limits of quantification. Reported residues in these trials were < 0.01 (8) mg/kg.

The combined results from these pre-emergence and post-emergence trials with dimethenamid were < 0.01 (22) mg/kg.

The Meeting estimated an STMR value of 0 mg/kg and a maximum residue level of 0.01 mg/kg (*) for sorghum fodder. The highest residue was 0 mg/kg.

Sugar beet leaves or tops

Sugar beet field trials involving single post-emergence treatments with dimethenamid or dimethenamid-P were made available to the Meeting from France, Germany, Netherlands, Switzerland and USA. In all trials, residues in sugar beet leaves or tops were below the limit of quantification (0.01 mg/kg) within 30 days after treatment.

GAP in Germany is for a single post-emergence treatment (max 0.65 kg ai/ha) at the 6–8 leaf stage (BBCH 16–18), GAP in Netherlands is for either a single post-emergence treatment (max 0.65 kg ai/ha) or 2–3 split post-emergence applications (max 0.65 kg ai/ha per season). In Belgium, GAP is also for either a single or split (3 applications) post-emergence treatments (max 0.72 kg ai/ha) up to the 8-leaf stage (BBCH 18). GAP in USA is also for either a single or split (2 applications) post-emergence treatments (max 1.1 kg ai/ha per season) up to the 12-leaf stage – PHI 60 days).

Four trials in Germany, France and Netherlands, matching the single post-emergence application GAP of Belgium, Germany and Netherlands reported residues of < 0.01 mg/kg and 12 USA post-emergence trials on sugar beet, matching the USA single-application GAP but with longer PHIs that reflect commercial harvest intervals (80–121 days) also reported residues below the limits of quantification. Combined residues in these trials were < 0.01 (16) mg/kg. In addition, six single-application dimethenamid trials from Germany, France and Switzerland with higher application rates but otherwise matching Belgian GAP, reported residues of < 0.01 (6) mg/kg.

Sixteen multiple-treatment post-emergence dimethenamid trials in France, Germany and Switzerland, involving rates higher than the split-application Belgian GAP or with more than 3 treatments per season also reported residues of < 0.01 mg/kg.

The Meeting agreed to use the results from these single and split-application post-emergence dimethenamid trials as residues were all below the limit of quantification and the combined results were < 0.01 (22) mg/kg.

The combined results from these single or split-application post-emergence trials with dimethenamid-P or dimethenamid were < 0.01 (38) mg/kg.

The Meeting estimated a median residue of 0 mg/kg and a highest residue of 0 mg/kg for sugar beet leaves or tops.

Fodder beet leaves or tops

The Meeting noted that GAP existed in Belgium and Netherlands for fodder beet at the same GAPs established for sugar beet, and agreed that the available residue data for sugar beet could be extrapolated to fodder beet.

The Meeting estimated a median residue of 0 mg/kg and a highest residue of 0 mg/kg for fodder beet leaves or tops.

Fate of residues in storage and during processing

The effect of processing on the level of residues of dimethenamid-P in potatoes and of dimethenamid in soya beans and maize were reported to the Meeting.

Potatoes from a USA field trial where dimethenamid-P was applied twice at an exaggerated (5×) rate of 3.5 kg ai/ha, pre-emergence and post-emergence (PHI 40 days), were processed into chips and flakes using procedures that reflected commercial practice. Dimethenamid residues were not found (LOQ 0.01 mg/kg) in either the initial tubers or in any of the processing fractions (wet peel, chips and flakes).

Soya beans from two USA field trials where dimethenamid was applied pre-emergence at an exaggerated (5×) rate of 8.4 kg ai/ha were processed into oil using procedures that reflected commercial practice. Dimethenamid residues were not found (LOQ 0.01 mg/kg) in either the unprocessed beans or in any of the processing fractions (including hulls, meal, soap stock, crude lecithin, crude oil and refined oil).

Maize from two USA field trials where dimethenamid was applied as either pre-plant or pre-emergence treatments at an exaggerated (5×) rate of 8.4 kg ai/ha was processed into flour, meal and oil using both dry and wet procedures that reflected commercial practice. Dimethenamid residues were not found (LOQ 0.01 mg/kg) in either the unprocessed grain or in any processing fractions (including dust, grits, meal, flour, press cake, soap stock, crude oil and refined oil).

Farm animal dietary burden

The Meeting estimated the dietary burden of dimethenamid-P residues in cattle and poultry on the basis of the diets listed in Appendix IX of the *FAO Manual* (FAO, 2002). Calculations from highest residues provide the levels in feed suitable for estimating animal commodity MRLs, while calculations from STMR or median residue values for feed are suitable for estimating STMRs.

Detectable residues were only reported in maize forage (median residue level of 0.01 mg/kg dry matter, highest residue level 0.1 mg/kg dry matter) and residues were below the limit of quantification (0.01 mg/kg) in all other animal feed commodities considered by the Meeting (STMRs or median residue levels of 0 mg/kg and highest residues of 0 mg/kg).

Estimated maximum dietary burden of farm animals

						Diet content (%)			Residue contribution, mg/kg		
Commodity	Group	Residue (mg/kg)	Basis	% DM	Residue ÷ DM	*Beef cattle*	*Dairy cows*	*Poultry*	Beef cattle	Dairy cows	Poultry
Maize forage	AF	0.04	Highest	40	0.1	*40*	*50*	-	0.04	0.05	-
TOTAL						*40*	*50*	*0*	**0.04**	**0.05**	**0**

Estimated median dietary burden of farm animals

Commodity	Group	Residue (mg/kg)	Basis	% DM	Residue ÷ DM	*Diet content (%)*			Residue contribution, mg/kg		
						Beef cattle	*Dairy cows*	*Poultry*	Beef cattle	Dairy cows	Poultry
Maize forage	AF	0.01	Median	40	0.025	*40*	*50*	-	0.01	0.013	-
TOTAL						*40*	*50*	*0*	**0.01**	**0.013**	**0**

The total dietary burdens for animal commodity MRL estimation (residue levels in animal feeds expressed on dry weight) are 0.04 ppm for beef cattle, 0.05 ppm for dairy cattle, and 0 ppm for poultry. The associated median dietary burden for STMR estimation are 0.01 ppm (beef cattle), 0.013 ppm (dairy cattle) and 0 ppm (poultry).

Animal commodity maximum residue levels

The Meeting noted that in the goat metabolism study, no residues of dimethenamid were found in milk, muscle, fat, liver or kidney of goats dosed for four days with the equivalent of 223 ppm dimethenamid in the diet. As this dosing level is more than 4000 times higher than the maximum estimated dietary burden (0.05 ppm) arising from the uses of dimethenamid-P, the Meeting agreed that residues would not be expected in livestock and estimated STMRs and HRs of 0 mg/kg for meat (from mammals other than marine mammals), edible offal, mammalian and milks.

The Meeting estimated maximum residue levels of 0.01 (*) mg/kg for meat (from mammals other than marine mammals); 0.01 (*) mg/kg for edible offal, mammalian and 0.01 (*) mg/kg for milks.

For poultry, the estimated dietary burden is 0 ppm and the Meeting estimated STMRs and HRs of 0 mg/kg for poultry meat, poultry, edible offal and eggs.

The Meeting estimated maximum residue levels of 0.01 (*) mg/kg for poultry meat; 0.01 (*) mg/kg for poultry edible offal of, and 0.01 (*) mg/kg for eggs.

DIETARY RISK ASSESSMENT

The evaluation of dimethenamid-P has resulted in recommendations for MRLs at the limit of quantification with STMRs and HRs of 0 mg/kg for raw and processed commodities. The Meeting concluded that the long-term and short-term intake of residues of dimethenamid-P from uses that have been considered by the JMPR do not present a public health concern.

4.8 ETHOXYQUIN (035)

TOXICOLOGY

Ethoxyquin is the ISO approved name for 1,2-dihydro-6-ethoxy-2,2,4-trimethylquinoline. It is used primarily as an antioxidant preservative in animal feed and dehydrated storage forage crops and as an

antiscald agent in pears and apples. It is also used as a colour preservative in spices and as an anti-degradation agent in rubber. Ethoxyquin was first evaluated by the Meeting in 1969, when an ADI of 0–0.06 mg/kg bw was established based on the NOAEL in a long-term feeding study in dogs and a study of reproductive toxicity in rats. It was re-evaluated in 1998 within the periodic review programme of CCPR, and an ADI of 0–0.005 mg/kg bw was established on the basis of the minimal-effect level of 2.5 mg/kg bw per day for clinical signs and deposition of pigments in liver in a multigeneration study in dogs, and a 500-fold safety factor to account for the lack of a NOAEL in this study and for the incompleteness of the database. The 1998 Meeting concluded there was no need to establish an ARfD for ethoxyquin. In 1999, the Joint Meeting reviewed the residue chemistry of ethoxyquin and concluded that the plant metabolites/degradation products, C–N and N–N dimers, demethylethoxyquin (DMEQ), methylethoxyquin (MEQ), dehydromethylethoxyquin (DHMEQ) and dihydroethoxyquin (DHEQ) were not formed in rats. In 2000, the Meeting recommended that information on the acute toxicity and genotoxicity of the plant metabolites/degradation products would be necessary to complete the evaluation of ethoxyquin.

The Meeting reviewed new data on the genotoxicity and acute toxicity of ethoxyquin and three of its plant metabolites/degradation products (MEQ, DHMEQ and DHEQ) in dogs, relevant data from previous evaluations and other information from the published literature. DMEQ was not sufficiently stable to permit its synthesis and study.

All the new studies submitted for consideration at the present Meeting complied with GLP.

Biochemical aspects

Previous evaluations have established that ethoxyquin is rapidly absorbed from the gastrointestinal tract of rats and mice, with peak blood concentrations occurring within 1 h. The highest tissue concentrations were found in liver, kidney and adipose tissue. Excretion is predominantly as metabolites via the urine and is rapid, with > 85% of doses of up to 25 mg/kg bw being eliminated within 24 h.

Toxicological data

Previous evaluations have reported that ethoxyquin has low acute toxicity when administered orally (LD_{50} = 1700 mg/kg bw), dermally (LD_{50} > 2000 mg/kg bw) or by inhalation(LC_{50} > 2 mg/L) in rats.

In studies in dogs given ethoxyquin and three plant metabolites/degradation products (MEQ, DHMEQ and DHEQ) as single oral doses, the main target for all four compounds was the liver. Dogs were used in preference to rats as previous studies had shown that dogs are more sensitive to the toxic effects of ethoxyquin.

Dogs were fed capsules containing ethoxyquin, MEQ, DHMEQ or DHEQ as single doses at 50 to 200 mg/kg bw. Ethoxyquin, MEQ and DHEQ caused increases in serum and urinary concentrations of bilirubin at all doses. DHEQ had marginal effects on bilirubin concentrations at the highest dose. Ethoxyquin and MEQ produced changes in the liver indicative of bile stasis and/or accumulation of bile pigment. Similar changes were reported previously in longer-term studies with ethoxyquin. During the 2-week recovery period (two dogs of each sex per group) elevations in serum enzymes for liver function (aspartate aminotransferase and alanine aminotransferase) were noted. After administration of the three metabolites/degradation products, clinical signs, including emesis and oral discharge, were noted. On the basis of the information available, the rank order of the toxic potency for the four compounds was MEQ > ethoxyquin > DHEQ > DHMEQ. The effects observed at 50 mg/kg were minimal to mild, and their toxicological significance is equivocal. The presence of dark-coloured urine at the lowest dose of the compounds was attributed to the presence of a chromophore in the compound or a derivative thereof. The Meeting did not consider that this was

toxicologically significant. The Meeting concluded that the NOAEL for all four compounds was 50 mg/kg bw.

Ethoxyquin and the three plant metabolites/degradation products were evaluated for genotoxicity in an adequate range of tests in vitro and in vivo. All compounds gave negative results in tests for mutagenicity in bacteria, with and without metabolic activation, confirming previous published reports on ethoxyquin. In a test for chromosomal aberrations in Chinese hamster ovary cells, all four compounds gave positive results. Ethoxyquin also gave positive results in a published study in which it was tested for chromosomal aberrations in isolated human peripheral blood lymphocytes. Although there have been positive findings for clastogenicity in vitro, all four compounds gave negative results in a test for micronucleus formation in bone-marrow cells of mice in vivo. This confirms the results of a previous published study of macronucleus formation with ethoxyquin in bone marrow. It has also been reported in a published report that ethoxyquin gave negative results in tests for chromosomal aberrations and for sister chromatid exchange in vivo.

The Meeting concluded that ethoxyquin and the three plant metabolites/degradation products tested do not represent a genotoxic risk in vivo.

The 1969 and 1998 Meetings reviewed a number of published reports in which ethoxyquin had been administered to rodents for a prolonged period of time. These did not reveal any potential for ethoxyquin to produce a tumourigenic response.

In the absence of DNA reactivity and clastogenic effects in vivo and absence of tumours in rodents, the Meeting considered it unlikely that dietary exposures to this compound would pose any carcinogenic risk to humans.

The 1969 Meeting evaluated three studies of reproductive toxicity in which rats received diets containing ethoxyquin at concentrations of up to 1125 ppm. All had non-standard protocols, and the results were contradictory. Two of the studies, including the most extensive, showed no apparent effects on the end-points studied at up to the maximum concentration tested (equivalent to 56 mg/kg bw per day), while the other showed an increased incidence of stillbirths at 1126 ppm and decreased litter size at 375 ppm. The Meeting concluded that the design and reporting of these studies were inadequate.

The 1998 Meeting evaluated a two-generation study of reproductive toxicity in dogs given diets containing ethoxyquin at a concentration of 0, 100, or 225 ppm. There was no effect on reproductive parameters at up to the highest concentration tested (equivalent to 5.6 mg/kg bw per day). Clinical signs observed included dehydration and excess lachrymation. There was evidence of hepatic toxicity, particularly in the females. The effects were seen at 100 ppm, the lowest concentration tested, and were consistent with effects observed in short-term studies in dogs. The lowest concentration tested, 100 ppm (equivalent to 2.5 mg/kg bw per day) was considered to be a minimal-effect level for clinical signs of toxicity and liver effects.

A study of developmental toxicity in rats was evaluated by the 1998 JMPR. Rats were treated with ethoxyquin at doses of up to 350 mg/kg bw per day by gavage. Ethoxyquin was not fetotoxic or teratogenic at doses up to the highest tested. The NOAEL for maternal toxicity was 50 mg/kg bw per day on the basis of reduced body-weight gain at higher doses. No studies of developmental toxicity had been performed in other species.

Toxicological evaluation

The 1998 JMPR established an ADI of 0–0.005 mg/kg bw based on the minimal-effect level of 2.5 mg/kg bw per day for clinical signs in a multigeneration study in dogs and a safety factor of 500, because there was no NOAEL in this study and the database was incomplete owing to the lack of

studies of genotoxicity and long-term studies of toxicity. No additional information was available to this Meeting on the long-term effects of ethoxyquin, although information on the genotoxicity of ethoxyquin and its three metabolites had been provided. It was concluded that these compounds were not genotoxic in vivo. The acute toxicity of the plant metabolites/degradation products DHEQ and DHMEQ was no greater than that of ethoxyquin. The toxicity of the plant metabolite/degradation product MEQ appeared to be slightly greater than that of ethoxyquin. However, the Meeting concluded that a safety factor of 500 would be sufficient to allow for this difference in toxicity. Hence the Meeting confirmed the ADI established by the 1998 JMPR and extended it to cover the three plant metabolites/degradation products, MEQ, DHMEQ and DHEQ.

On the basis of the acute effects of ethoxyquin and its plant metabolites/degradation products in dogs, the Meeting established an ARfD of 0.5 mg/kg bw based on a NOAEL of 50 mg/kg bw for effects on the hepatic biliary system and clinical signs at higher doses from a study in dogs given single doses, and a safety factor of 100. The studies of reproductive toxicity in rats were not considered to be an adequate basis for the derivation of an ARfD. The ARfD established applies to ethoxyquin and to the three plant metabolites/degradation products, MEQ, DHMEQ and DHEQ. It is applicable to the whole population.

An addendum to the toxicological monograph was prepared.

Levels relevant to risk assessment

Species	Study	Effect	NOAEL	LOAEL
Rat	Developmental toxicity[a]	Maternal toxicity	50 mg/kg bw per day	150 mg/kg bw per day
		Fetotoxicity	350 mg/kg bw per day[d]	—
Dog	1-year study of toxicity[a]	General toxicity	3 mg/kg bw per day	10 mg/kg bw per day
	Two-generation[b]	General toxicity	—	100 ppm equivalent 2.5 mg/kg bw per day[e]
		Reproductive performance	225 ppm, equivalent 5.6 mg/kg bw per day[d]	—
	Single oral dose[c] study with parent and plant metabolites	Toxicity	50 mg/kg bw per day	100 mg/kg bw per day

[a] Gavage administration
[b] Dietary administration
[c] Capsule
[d] Highest dose tested
[e] Marginal effects of equivocal toxicological relevance on brain acetylcholinesterase activity

Estimate of acceptable daily intake for humans

0–0.005 mg/kg bw, applicable to ethoxyquin, MEQ, DHMEQ and DHEQ

Estimate of acute reference dose

0.5 mg/kg bw, applicable to ethoxyquin, MEQ, DHMEQ and DHEQ

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

Results from epidemiological, occupational health and other such observational studies of human exposures.

4.9 FENHEXAMID (215)

TOXICOLOGY

Fenhexamid is the ISO approved name for 2',3'-dichloro-4'-hydroxy-1-methylcyclohexanecarboxanilide, which is a hydroxyanilide fungicide that inhibits the growth of fungal spore germ tubes and mycelia.

The Meeting has not previously evaluated fenhexamid.

All pivotal studies with fenhexamid were certified as complying with GLP.

Biochemical aspects

In toxicokinetic studies in rats given single doses (1.0 or 100 mg/kg bw) or repeated doses (1.0 mg/kg bw per day for 14 days) by gavage, radiolabelled fenhexamid was rapidly and completely absorbed from the gastrointestinal tract (> 97%). A peak in plasma concentrations of radioactivity was observed 5–10 min after dosing at 1.0 mg/kg bw. Approximately 96% of the administered dose was eliminated in excreta within 48 h; the major route of excretion was in the faeces (62–81% of the administered dose) with 15–36% of the administered dose being recovered in the urine. Approximately 60% of the administered dose was excreted in bile in the first hour and > 97% within 48 h, primarily as the glucuronide conjugate of the parent compound. A pronounced first-pass effect and extensive enterohepatic circulation was observed with hydrolysis of the glucuronide in the gastrointestinal tract and reabsorption of the parent compound. Only 0.3% of the administered dose was detected in the body at 72 h, with the gastrointestinal tract, kidney and liver having the highest concentrations of radioactivity. The main pathway of biotransformation in rats was conjugation of the aromatic hydroxyl group with glucuronic acid. Limited hydroxylation of the 2, 3 and 4 positions of the cyclohexyl ring also occurred with excretion of these compounds as glucuronide or sulfate conjugates. The main compound detected in excreta was the unchanged parent compound (62–75% of the administered dose). The glucuronic acid conjugate of the parent ranged from about 4% to 23% of the administered dose. Excretion, distribution and metabolite profiles were essentially independent of dose, pre-treatment and sex.

Toxicological data

Fenhexamid has low toxicity when administered by the oral, dermal or inhalation routes. LD_{50} values after oral administration were > 5000 mg/kg bw in rats and mice. The LD_{50} in rats treated dermally was > 5000 mg/kg bw. $LC5_{50}$s in rats treated by inhalation (nose only) was > 0.32 mg/L (aerosol) and > 5.1 mg/L (dust). Fenhexamid was not a skin or eye irritant. Fenhexamid was not a skin sensitizer in guinea-pigs (Buehler test) or in the local lymph node assay, and showed equivocal skin sensitizing potential in a Magnusson & Kligmann (maximization) test in guinea-pigs.

In short-term studies in mice, rats and dogs, very high doses of fenhexamid produced minimal systemic toxicity. In longer-term studies, the major target organ was the kidney in rats and mice and the haematopoietic system in dogs. Slight evidence of liver toxicity was also observed in rats, mice and dogs.

No systemic toxicity was seen in a 28-day study in rats given fenhexamid at doses of up to 1000 mg/kg bw per day by gavage. A 28-day dietary study in dogs given fenhexamid at doses of up to 20 000 ppm (equivalent to 500 mg/kg bw per day) did not produce systemic toxicity.

In a 90-day dietary study of toxicity in mice, increased cholesterol, bilirubin, creatinine, water and food consumption, decreased kidney weights, increased renal protein casts and cellular detritus, and renal tubular basophilia were observed at 10 000 ppm (equal to 3283 mg/kg bw per day). In a second study, similar toxicity in the kidney was observed at the highest dose of 20 000 ppm (equal to 3417 mg/kg bw per day). The lowest NOAEL in these two studies was 1000 ppm (equal to 266.5 mg/kg bw per day).

In a 90-day dietary study of toxicity in rats, decreased body weight and body-weight gains, increased food consumption, reduced food conversion efficiency and decreased liver weights in males (reversible within 4 weeks) were observed at 10 000 ppm (equal to 904 mg/kg bw per day). In females, these findings, plus an increased incidence of mild to moderate focal Kupffer cell proliferation in females, were observed at 20 000 ppm (equal to 2824 mg/kg bw per day). The NOAEL was 5000 ppm (equal to 415 mg/kg bw per day). In a second 90-day dietary study in rats, nephropathy was seen at 50 000 ppm (equal to 5585 mg/kg bw per day). The NOAEL in this study was 5000 ppm (equal to 404 mg/kg bw per day).

In a 90-day study of toxicity in dogs, increases in the number of Heinz bodies were seen at 7000 ppm (equal to 239 mg/kg bw per day) and increases in alkaline phosphatase activity were measured at the highest dose of 50 000 ppm (equal to 1748 mg/kg bw per day). The NOAEL was 1000 ppm (equal to 33.9 mg/kg bw per day). In a 52-week study of toxicity in dogs, increases in the number of Heinz bodies and decreases in erythrocyte count, concentration of haemoglobin, and erythrocyte volume fraction were seen at 3500 ppm (equal to 124 mg/kg bw per day) with increases in alkaline phosphatase activity, adrenal weights and intracytoplasmic vacuoles in females at the highest dose of 25 000 ppm (equal to 918 mg/kg bw per day). The NOAEL was 500 ppm (equal to 17.4 mg/kg bw per day).

No systemic toxicity was seen in a 28-day study of dermal toxicity in rats at 1000 mg/kg bw per day, the highest dose tested. Five-day and 28-day studies of toxicity suggest that high doses administered by inhalation were well tolerated by rats. The NOAEC in the 28-day study was 0.069 mg/L on the basis of an increase in lung weights, grey discolouration of lungs, pigment-laden alveolar microphages and an increase in liver enzymes seen at the lowest-observed-adverse-effect concentration (LOAEC) of 0.487 mg/L.

Fenhexamid gave negative results with or without metabolic activation in an adequate range of studies of genotoxicity in bacteria and cultured mammalian cells in vitro, and in a test for micronucleus formation in mice in vivo.

The Meeting concluded that fenhexamid is unlikely to be genotoxic.

In long-term studies of toxicity and carcinogenicity in mice and rats, there were no treatment-related neoplastic findings. In male mice, decreased kidney weights were observed at 2400 ppm (equal to 807 mg/kg bw per day). Additional effects observed at the highest dose of 7000 ppm (2355 mg/kg bw per day) in males included increased water consumption, increased serum concentrations of creatinine, bilirubin and albumin, decreased body weight, decreased body-weight gain. In females at 7000 ppm (equal to 3178 mg/kg bw per day, the highest dose tested), increased water consumption, decreased kidney weights and increased basophilic cortical tubules in the kidney were observed. The NOAEL for systemic toxicity in mice was 800 ppm (equal to 247 mg/kg bw per day). In rats, only mild treatment-related effects such as increased splenic extramedullary haematopoiesis, increased caecal mucosal hyperplasia, decreased body weights, decreased body-weight gains, decreased food conversion efficiency, and bone marrow hyperplasia were observed. The NOAEL for systemic toxicity was 500 ppm (equal to 28 mg/kg bw per day). Fenhexamid was not carcinogenic in mice or rats.

In view of the lack of genotoxicity and the absence of carcinogenicity in rats and mice, the Meeting concluded that fenhexamid is unlikely to pose a carcinogenic risk to humans.

In a two-generation study of reproduction in rats, reproductive parameters were not affected at the highest dose tested (20 000 ppm, equal to 1814 mg/kg bw per day). The NOAEL for parental systemic toxicity was 500 ppm (equal to 38 mg/kg bw per day) on the basis of lower pre-mating weights, increases in alkaline phosphatase activity and decreases in liver weights and kidney weights in males only. The NOAEL for offspring toxicity was 500 ppm (equal to 38 mg/kg bw per day) on the basis of decreases in body weights during lactation. Fenhexamid was not teratogenic at doses of up to 2000 and 1000 mg/kg bw per day in rats and rabbits, respectively. No systemic toxicity, embryotoxicity or fetotoxicity was observed in the study of developmental toxicity in rats at doses of up to 2000 mg/kg bw per day. At the highest dose tested in rabbits (1000 mg/kg bw per day), a slight decrease in fetal weight of males and delayed ossification (fifth sternal segments, fifteenth caudal vertebrae) was observed in the presence of maternal toxicity. The NOAEL for developmental toxicity in rabbits was 300 mg/kg bw per day.

The Meeting concluded that fenhexamid is not teratogenic nor a reproductive toxicant.

In a study of acute neurotoxicity in rats, doses of up to 2000 mg/kg bw did not produce any systemic toxicity, neurotoxicity or neuropathology findings. There were no treatment-related effects on measures of motor activity, locomotor activity or habituation.

In a study evaluating clinical parameters and physiological functions in rats, mice, and rabbits given fenhexamid as single doses at up to 5000 mg/kg bw by gavage, fenhexamid did not produce marked effects on general condition, behaviour, the nervous system, the respiratory system, the circulatory system, haematopoietic parameters or renal function.

The Meeting concluded that the metabolites of fenhexamid are likely to be less toxic than fenhexamid because the major metabolites are polar glucuronide or sulfate conjugates that are rapidly excreted. Hydrolysis of the glucuronic acid conjugate of the parent can occur in the gastrointestinal tract, with subsequent reabsorption of the parent.

The Meeting concluded that the existing database on fenhexamid was adequate to characterize the potential hazards to fetuses, infants and children.

Toxicological evaluation

The Meeting established an ADI of 0–0.2 mg/kg bw based on a NOAEL of 17.4 mg/kg bw per day for increased adrenal weight and the presence of intracytoplasmic vacuoles in the adrenal cortex of females and haematopoietic effects (increase in the number of Heinz Bodies, decrease erythrocyte count, haemoglobin concentration and erythrocyte volume fraction) seen at higher doses in both sexes in a 52-week study in dogs fed with fenhexamid, and a 100-fold safety factor.

The Meeting concluded that the establishment of an ARfD for fenhexamid was not necessary on the basis of its low acute toxicity, the absence of development toxicity in rats and rabbits, the lack of neurotoxicity after single exposures, and the absence of any other toxicological end-point that would be elicited by a single dose.

A toxicological monograph was prepared.

Levels relevant to risk assessment

Species	Study	Effect	NOAEL	LOAEL
Mouse	104-week study of toxicity and carcinogenicity[a]	Toxicity	800 ppm, equal to 247 mg/kg bw per day	2400 ppm, equal to 807 mg/kg bw per day
		Carcinogenicity	7000 ppm, equal to 2355 mg/kg bw per day[c]	—
Rat	2-year study of toxicity and carcinogenicity[a]	Toxicity	500 ppm, equal to 28 mg/kg bw per day	5000 ppm, equal to 292 mg/kg bw per day
		Carcinogenicity	20 000 ppm, equal to 1280 mg/kg bw per day[c]	—
	Multigeneration study[a]	Parental toxicity/offspring toxicity	500 ppm, equal to 38 mg/kg bw per day	5000 ppm, equal to 406 mg/kg bw per day
	Developmental toxicity[b]	Maternal toxicity	2000 mg/kg bw per day[c]	—
		Embryo- and fetotoxicity	2000 mg/kg bw per day[c]	—
	Acute neurotoxicity[b]	Neurotoxicity	2000 mg/kg bw per day[c]	—
Rabbit	Developmental toxicity[b]	Maternal toxicity	100 mg/kg bw per day	300 mg/kg bw per day
		Embryo- and fetotoxicity	300 mg/kg bw per day	1000 mg/kg bw per day
Dog	1-year study [a]	Toxicity	500 ppm, equal to 17.4 mg/kg bw per day	3500 ppm, equal to 124 mg/kg bw per day

[a] Dietary administration
[b] Gavage administration
[c] Highest dose tested

Estimate of acceptable daily intake for humans

0–0.2 mg/kg bw

Estimate of acute reference dose

Unnecessary

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

Results from epidemiological, occupational health and other such observational studies of human exposures

Critical end-points for setting guidance values for exposure to fenhexamid

Absorption, distribution, excretion, and metabolism in mammals	
Rate and extent of oral absorption	Rapid; maximum reached in blood by 5–10 min; later at higher doses. About 97% absorbed within 48 h
Distribution	Extensive enterohepatic recirculation; highest concentrations in gastrointestinal tract, liver, and kidney
Potential for accumulation	No evidence of significant accumulation; about 0.3% of the total administered dose found in tissues after 72 h

Rate and extent of excretion	Excretion was rapid; approximately 96% excreted in urine (15–36%) and faeces (62–81%) within 48 h.
Metabolism in animals	Extensive; metabolic pathways include conjugation of the aromatic hydroxyl group with glucuronic acid and sulfate. Hydroxylation of the cyclohexyl ring on positions 2, 3 and 4 also occurred. Unchanged fenhexamid in faeces (49–69% of the administered dose).
Toxicologically significant compounds (animals, plants and environment)	Fenhexamid and its glucuronide conjugate
Acute toxicity	
Rat LD_{50} oral	> 5000 mg/kg bw
Rat LD_{50} dermal	> 5000 mg/kg bw
Rat LC_{50} inhalation	> 0.32 mg/L (aerosol) and > 5.1 mg/L (dust) (4-h exposure, nose only)
Rabbit, dermal irritation	Not an irritant
Rabbit, eye irritation	Not an irritant
Skin sensitization (test method used)	Not a skin sensitizer in guinea-pigs (maximization test, Buehler test and local lymph node assay)
Short-term studies of toxicity	
Target/critical effect	Haematopoietic system/increase in Heinz bodies and adrenal effects
Lowest relevant oral NOAEL	17.4 mg/kg bw per day (1-year study in dogs)
Lowest relevant dermal NOAEL	1000 mg/kg bw per day (rats)
Lowest relevant inhalation NOAEL	0.069 mg/L (6 h/day for 5 days per week for 4 weeks; in rats)
Genotoxicity	
	No genotoxic potential
Long-term studies of toxicity and carcinogenicity	
Target/critical effect	Decreases in body weights, body-weight gains, food consumption and food conversion efficiency, increases in cellularity of bone marrow and the presence of splenic extramedullary haematopoiesis
Lowest relevant NOAEL	28 mg/kg bw per day (2-year study in rats)
Carcinogenicity	Unlikely to pose a carcinogenic risk to humans
Reproductive toxicity	
Reproduction target/critical effect	No toxicologically relevant effects were observed
Lowest relevant reproductive NOAEL	1814 mg/kg bw per day in rats; highest dose tested
Developmental target/critical effect	Delayed ossification and decreased male fetal body weights in rabbits at maternally toxic doses
Lowest relevant developmental NOAEL	300 mg/kg bw per day (rabbits)
Neurotoxicity/delayed neurotoxicity	
Acute neurotoxicity	No evidence of neurotoxicity at doses of up to 2000 mg/kg bw (rats)
Other toxicological studies	
Physiological functions	No acute effects after single doses at up to 5000 mg/kg bw in mice, rats and rabbits.
Medical data	
	Limited data; no adverse health effects reported

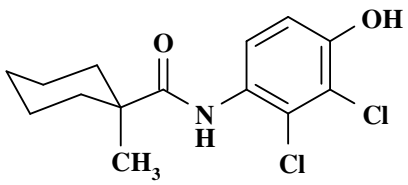
Summary

	Value	Study	Safety factor
ADI	0–0.2 mg/kg bw	Dog, 1-year study of toxicity	100
ARfD	Unnecessary	—	—

RESIDUE AND ANALYTICAL ASPECTS

Residue and analytical aspects of fenhexamid, or 2′,3′-dichloro-4′-hydroxy-1-methylcyclohexane-carboxanilide, were considered for the first time by the present Meeting.

Fenhexamid is a protectant fungicide and has registered uses in many countries on horticultural crops and vegetables. It inhibits spore germ tube development and hyphal growth.



IUPAC: 2′,3′-dichloro-4′-hydroxy-1-methylcyclohexanecarboxanilide

CAS: N-(2,3-dichloro-4-hydroxyphenyl)-1-methylcyclohexane- carboxamide

The Meeting received information on fenhexamid metabolism and environmental fate, methods of residue analysis, freezer storage stability, national registered use patterns, supervised residue trials, fate of residues in processing, and national MRLs. Australia and the Netherlands submitted GAP information and labels to support MRLs for fenhexamid.

Animal metabolism

The metabolism of fenhexamid was investigated in rats and goats.

One lactating goat was dosed with [phenyl-UL-^{14}C]fenhexamid at a rate of 10 mg/kg body weight (equivalent to 133 ppm in the feed) for three consecutive days. Approximately 63.5% of the total radioactivity administered (about 99% of the recovered radioactivity) was excreted within 54 h after the first administration. The major excretory pathway was via the faeces (39% of the applied radioactivity), followed by excretion via the urine (25%). A low amount (0.03%) was secreted with the milk. At sacrifice 6 h after the last dosage, the total radioactive residues (TRR) in the edible tissues and organs accounted for 0.58% of the administrated radioactivity. The major portion and the highest equivalent concentration were observed in the liver (0.47% of the administrated radioactivity).

The metabolism of fenhexamid in the goat is comparable to the metabolism in the rat. Sulfate conjugates of hydroxy-fenhexamid were not observed in the goat but in the rat.

The unchanged parent compound was found in all goat tissue samples and ranged from 19% of the TRR (equiv. to 0.007 mg/kg) in muscle, 21% (equiv. to 0.69 mg/kg) in kidney, 36% (equiv. to 0.031 mg/kg) in fat to 54% (equiv. to 2.5 mg/kg) in liver. No fenhexamid was detected in milk.

4-Hydroxy-fenhexamid was identified as a main metabolite in the goat tissues ranging from 18 to 31.5% of the respective TRR (equiv. to 0.007 mg/kg in muscle and 0.027 mg/kg in fat). The glucuronide of fenhexamid was the predominant metabolite in milk (71% of the TRR, equiv. to 0.13 mg/kg) and a main component in tissues, except liver (9.0 of the TRR in fat, equiv. to 0.008 mg/kg; 24% in muscle, equiv. to 0.009 mg/kg and 31% in kidney, equiv. to 1.01 mg/kg). In addition, the

glucuronide of 4-hydroxy-fenhexamid was detected in kidney (9.4% of the TRR, equiv. to 0.31 mg/kg).

The Meeting concluded that the elimination of fenhexamid in the goat was rapid via conjugation of the phenyl hydroxyl group and hydroxylation of the cyclohexyl ring.

Plant metabolism

The behaviour and metabolism of [phenyl-UL-^{14}C]fenhexamid was investigated under simulated field conditions in grapes, apples, tomatoes, lettuce and field peas using spray application. In addition, separate translocation experiments were carried out for grapes, apples and tomatoes to investigate the possible occurrence of the metabolite 2,3-dichloro-4-hydroxyaniline (DCHA).

The studies demonstrated that the metabolic pathway of fenhexamid is similar in all crops investigated. The rate of degradation in/on plants is quite low and the parent compound was always the major component.

The metabolism of fenhexamid proceeded along two pathways:

conjugation (glucoside) of the parent compound at the phenolic hydroxyl group,

hydroxylation at the 2- and 4-position in the cyclohexyl ring followed by conjugation of the hydroxyl group.

These two metabolic routes occurred only to a limited extent. In the different crop studies it was shown that the majority of radioactivity remained on the surface of the fruits as unchanged parent compound, approaching 90% of the TRR. The sum of all metabolites did not exceed 20% of the TRR, and no single metabolite was present at above 3.2%. Most of the metabolites identified were hydroxy-derivatives of fenhexamid. No DCHA was detected.

Translocation experiments found that fenhexamid was not systemic.

The Meeting concluded that fenhexamid is stable when used as a foliar spray on various food crop plants. There was no appreciable metabolism or degradation under typical GAP conditions.

Nature of residues after hydrolysis under processing conditions

The Meeting received information on the fate and nature of [phenyl-UL-^{14}C]fenhexamid residues during different conditions of hydrolysis (pH 4–6, temperature 90–120°C, time 20–60 min). The results showed that the parent compound is not significantly affected by these processes. At the end of the study the content of fenhexamid was in the range of 96% to 100% of applied radioactivity.

The Meeting concluded that it is unlikely that processing will affect the nature of fenhexamid residue.

Environmental fate

Because fenhexamid is used for foliar spray treatment, only studies of hydrolysis, photolysis and rotational crops were considered.

Fenhexamid is hydrolytically stable at pH 5–9. No formation of hydrolysis products was observed. Considering the degree of hydrolytic stability determined under environmental pH and temperature conditions, it is not expected that hydrolytic processes would contribute to the degradation of fenhexamid in the environment. However, when irridated with a xenon lamp,

fenhexamid underwent photolysis with a half life equivalent to 1.8 h at the equivalent of 40° latitude midday midsummer solar light. Therefore, it can be concluded that while fenhexamid is stable at a range of environmental pHs, rapid photochemical degradation may occur.

The metabolism of [phenyl-UL-^{14}C]fenhexamid was investigated in the rotational crops wheat, Swiss chard and turnips from three consecutive rotations. The TRRs decreased significantly from the first to the third rotation in all raw agricultural commodities. The maximum TRR (0.73 mg/kg) was observed in the first rotation for Swiss chard sown 30 days after soil application. The TRRs of the second rotation were all ≤ 0.1 mg/kg. The TRRs of the third rotation ranged from ≤ 0.01 mg/kg (turnip roots) to 0.08 mg/kg (wheat straw).

The Meeting concluded that residues, from the use of fenhexamid, in succeeding crops are not to be expected.

Methods of analysis

The Meeting received descriptions and validation data for analytical methods for fenhexamid in plant and animal matrices. Plant matrices are extracted with acetone from samples with high water content and with a mixture of water/acetone from dry samples and cleaned up by solid phase extraction. The residues are detected with HPLC/electrochemical detection or HPLC/MS/MS and generally achieved LOQs of 0.02–0.05 mg/kg. The recoveries were in the range of 63–120%.

Animal matrices were extracted with acetonitrile or n-hexane and cleaned-up by liquid-liquid partitioning and finally by column chromatography on a silica gel column. The residues were detected with HPLC-UV and achieve LOQs between 0.01 mg/kg (milk) and 0.05 mg/kg (egg, meat and fat). The recoveries were in the range of 67% to 101%.

Stability of pesticide residues in stored analytical samples

The Meeting received information on the stability of fenhexamid in various plant matrices at freezer temperatures for 5.5–17 months. Fenhexamid residues were generally stable (less than 30% disappearance) for the duration of the testing.

Definition of the residue

The behaviour and metabolism of fenhexamid was investigated in a number of fruiting crops (grape, tomato and apple), leafy crops (lettuce) and oil seed/pulses (peas). The studies demonstrated that the metabolic pathway of fenhexamid is similar in all crops investigated. The rate of degradation on plants is quite low and the parent compound was always the major component. The sum of all metabolites does not exceed 20% of the radioactive residue, and no single metabolite was present at above 3.2%. The residue definition for plants is therefore parent compound only.

Parent fenhexamid is in concentrations from 19 to 54% of TRR detectable in goat tissues where it is hydroxylated to derivatives that form glucuronic acid conjugates. The log P_{OW} of fenhexamid is 3.6 suggesting that it is fat-soluble. This is confirmed by the goat metabolism study which shows a higher residue concentration in fat than in muscle.

The Meeting agreed that the residue definition for compliance with MRLs and for estimation of dietary intake should be fenhexamid per se. The definition applies to plant and animal commodities.

The residue is fat-soluble.

Results of supervised trials on crops

The Meeting received supervised trials data on citrus fruit (oranges, mandarins and lemons), stone fruit (cherries, peaches and nectarines), berries (grapes, strawberries, black currants, blueberries, raspberries and blackberries), kiwi, cucumbers, tomatoes, sweet peppers, lettuce and almonds.

Citrus fruits

The use of fenhexamid as a foliar spray is registered in Japan (GAP of 1–2 applications at rates of 0.03–0.05 kg ai/hL, PHI 14 days).

Seven field trials (reversed decline studies) were conducted in Japan between 1995 and 1997 with fenhexamid on citrus (orange 2 trials, mandarin 2 trials, lemon 3 trials). Fenhexamid was applied twice (orange, lemon) or three times (mandarin) at rates of 0.05 kg ai/hL. The spray interval was 7–8 days. The residues in whole fruits were

Oranges: 0.76, 1.5 mg/kg

Mandarins: 2.2, 2.2 mg/kg

Lemons: 0.10, 0.17, 0.91 mg/kg.

The residues in pulp were

Oranges: 0.04, 0.05 mg/kg

Mandarins: 0.08, 0.11 mg/kg

The Meeting concluded that the data, in particular on oranges and mandarins, were not sufficient to estimate a maximum residue level and STMR for residues in citrus fruits as a major crop.

Stone fruits

Supervised residue trials were presented on cherries, peaches, nectarines and plums. In some trials the residue concentrations were calculated on whole fruit basis and in other cases for the edible portion. The Meeting agreed to use both kinds of data to estimate maximum residue levels and STMRs because the ratio of residue/weight of flesh and whole fruit differed by not more than 20%.

Cherries

Fenhexamid is registered for use on cherries in some European countries as pre-harvest foliar spray treatment. Residue trials were carried out in Germany, France and Italy. The German GAP is 1–3 applications at a rate of 0.25 kg ai/ha per m crown height (equiv. to 0.75 kg ai/ha for a tree with a crown of 3 m) with a 3-days PHI. The residues in whole fruits were 0.68, 0.82, 0.87, 1.0, 1.2, 1.6, 2.1 and 2.8 mg/kg in six German and two French (North) trials on sour and sweet cherries matching the German GAP.

The Italian GAP (1–4 applications at 0.75 kg ai/ha, 1 day PHI) is matched by two trials with residues in whole fruits of 0.63 and 0.91 mg/kg.

In the USA fenhexamid may be used as foliar spray treatment on cherries at 0.84 kg ai/ha with a 0-day PHI after up to 4 applications. In trials matching GAP the fenhexamid residues in the edible portion in ranked order were 1.1, 1.1, 1.1, 1.5, 1.9 and 4.7 mg/kg.

Fenhexamid is also approved in the USA as a post-harvest dip or spray to cherries at a rate of 0.34 kg ai in 378.5 L water to 11,300 kg of fruit (equiv. to 0.09 kg ai/hL or 3 g ai/100 kg fruit). In two trials matching GAP conditions residues found were 1.9 and 2.4 mg/kg. Two further trials were carried out with two pre-harvest spray applications of 0.85 kg ai/ha followed by one post-harvest treatment of 0.09 kg ai/hL. The residues found in the edible portion were 2.3 and 3.7 mg/kg.

The Meeting considered that the data from foliar spray and post-harvest use are from the same pool and decided to combine all cherry residue data. The combined results (n = 20) were 0.63, 0.68, 0.82, 0.87, 0.91, 1.0, 1.1, 1.1, 1.1, 1.2, 1.5, 1.6, 1.9, 1.9, 2.1, 2.3, 2.4, 2.8, 3.7 and 4.7 mg/kg.

The Meeting estimated a maximum residue level of 7 mg/kg and an STMR of 1.35 mg/kg for residues of fenhexamid in cherries.

Peaches and nectarines

Fenhexamid is registered for use on peaches and nectarines in a number of European countries as a pre-harvest foliar treatment. Residue trials were carried out in Spain and Italy. The Italian GAP (maximum of 4 applications at 0.75 kg ai/ha, with a 1 day PHI) was matched by two Spanish trials each on nectarines and peaches with residues found of 0.18, 0.36, 0.36 and 0.44 mg/kg in the whole fruit. The edible portion was analysed in two trials only with residues of 0.22 and 0.39 mg/kg found.

In the USA fenhexamid is approved for use at 0.84 kg ai/ha with a 0-day PHI after four foliar spray applications. In trials on peaches matching GAP, fenhexamid residues in the edible portion were found to be 0.62, 0.66, 0.69, 1.2, 1.3, 1.3, 1.4, 1.9 and 2.1 mg/kg.

Fenhexamid is also approved in the USA as a post-harvest dip or spray at 0.34 kg ai in 378.5 L water to 90,700 kg of fruit (equiv. to 0.09 kg ai/hL or 0.37 g ai/100 kg fruit). In six peach trials matching GAP conditions the residues in the edible portion were 0.65, 1.6, 2.9, 4.1, 4.6 and 5.9 mg/kg. Six further trials were carried out with two pre-harvest spray applications of 0.84 kg/ha followed by one post-harvest treatment at 0.09 kg ai/hL. Residues found in the edible portion were 0.63, 2.8, 3.8, 3.9, 4.8 and 5.7 mg/kg. The combined results were 0.63, 0.65, 1.6, 2.8, 2.9, 3.8, 3.9, 4.1, 4.6, 4.8, 5.7 and 5.9 mg/kg. These residues were considered to belong to a different population from those resulting from foliar spray use.

The Meeting estimated a maximum residue level of 10 mg/kg and an STMR of 3.85 mg/kg on the basis of post-harvest treatment use for fenhexamid residues in peaches and nectarines.

Plums

Fenhexamid is registered for the use on plums in some European countries as pre-harvest foliar treatment. Residue trials were carried out in Germany, UK, the Netherlands, France and Italy. The German GAP consists of a maximum of 3 applications at a rate of 0.25 kg ai/ha per metre of crown height (equiv. to 0.75 kg ai/ha for a 3 m tree) with a three day PHI. In four German, one French (North), two UK and one Dutch trial on plums, matching the German GAP, residues found in the whole fruit were 0.08, 0.14, 0.31, 0.31, 0.37, 0.39, 0.66 and 0.79 mg/kg.

The Italian GAP (maximum of four applications at 0.75 kg ai/ha, with a one day PHI) is matched by two French (South) trials and one Italian trial, residues found in the whole fruit were < 0.05, 0.14 and 0.37 mg/kg.

In the USA, fenhexamid may be used on plums at 0.84 kg ai/ha with a 0-day PHI after 4 foliar applications. In trials matching GAP conditions the fenhexamid residues in the edible portion were < 0.05, 0.06, 0.06, 0.06, 0.06, 0.15, 0.27, 0.33 mg/kg.

All results from pre-harvest foliar treatments, in ranked order were: < 0.05, < 0.05, 0.06, 0.06, 0.06, 0.06, 0.08, 0.14, 0.14, 0.15, 0.27, 0.31, 0.31, 0.33, 0.37, 0.37, 0.39, 0.66 and 0.79 mg/kg.

In the USA fenhexamid is also registered for post-harvest use as dip or spray in plums at a rate of 0.34 kg ai in 378.5 L of water to 90,700 kg of fruit (equiv. to 0.09 kg ai/hL or 0.37 g ai/100 kg fruit). In four trials matching GAP the residues in the edible portion were 0.23, 0.34, 0.38 and 0.65 mg/kg. Four further trials were carried out with two pre-harvest spray applications of 0.84 kg ai/ha followed by one post-harvest treatment with 0.09 kg ai/hL. The residues in the edible portion were 0.33, 0.35, 0.37 and 0.60 mg/kg. The combined residues were 0.23, 0.33, 0.34, 0.35, 0.37, 0.38, 0.60 and 0.65 mg/kg.

The Meeting decided to combine all plum residue data. The combined results (n = 27) were < 0.05, < 0.05, 0.06, 0.06, 0.06, 0.06, 0.08, 0.14, 0.14, 0.15, 0.23, 0.27, 0.31, 0.31, 0.33, 0.33, 0.34, 0.35, 0.37, 0.37, 0.37, 0.38, 0.39, 0.60, 0.65, 0.66 and 0.79 mg/kg.

The Meeting estimated a maximum residue level of 1 mg/kg and an STMR of 0.31 mg/kg for residues of fenhexamid in plums (including prunes).

Apricots

In Italy, Switzerland and the USA the approved use patterns for apricots is identical to that for cherries, peaches and plums. The Meeting agreed to extrapolate from cherries, peaches and plums to apricot. The data on cherries (STMR 1.35 mg/kg), peaches (STMR 3.85 mg/kg) and plums (STMR 0.31 mg/kg) belonged to different populations and could not be combined. Therefore, the extrapolation is based on the peaches data set with the highest STMR.

The Meeting estimated a maximum residue level of 10 mg/kg and an STMR of 3.85 mg/kg for residues of fenhexamid in apricots.

Grapes

The use of fenhexamid in grapes is registered in a number of countries in Europe, North America (Canada, USA), Africa (South Africa), Asia (Japan, South Korea), Australia and New Zealand. Trials on grapes were conducted in Australia, Canada, France, Germany, Japan, Italy, Spain, Portugal, South Africa and the USA.

In the trials grape bunches were the main commodity analysed. However, the portion of the Codex commodity to which the MRL applies and which should be analysed is the "whole commodity after removal of caps and stems." The Meeting therefore decided to use available residue data only from berries/fruits, to estimate the MRL and STMR for grapes.

The highest GAP for northern Europe corresponds to a rate of up to 0.8 kg ai/ha applied up to two times with a PHI of 21 days (Austria, Germany) or a rate of up to 0.75 kg ai/ha applied once with a PHI of 14 days (France). Six trials were conducted using different grape varieties during 1995 and 1998 in Germany (4 trials) and northern France (2 trials). The residues found in berries, 21 days after two applications, were 0.25, 0.27, 0.35, 0.35, 0.44 and 0.47 mg/kg.

The highest GAP for southern Europe corresponds to a rate of up to 0.75 kg ai/ha applied up to two times with a PHI of 7 days (Italy), or up to 0.5 kg ai/ha applied up to 3 times with a PHI of 7 days (Romania). In nine trials from Spain, Italy, Portugal and France (South) matching Italian GAP residues found in berries were 0.37, 0.39, 0.45, 0.47, 0.78, 0.96, 1.1, 1.4 and 1.6 mg/kg.

In two trials from Portugal and Italy fenhexamid was applied 3 times at a rate of 0.5 kg ai/ha and a PHI of 7 days, matching Romanian GAP. The residues in berries were 0.51 and 0.75 mg/kg.

The Meeting considered that the data from northern and southern Europe are from the same population and combined them, resulting in the following ranked order of concentrations in berries of 0.25, 0.27, 0.35, 0.35, 0.37, 0.39, 0.44, 0.45, 0.47, 0.47, 0.51, 0.75, 0.78, 0.96, 1.1, 1.4 and 1.6 mg/kg.

In South Africa fenhexamid is approved for use in table grapes with a maximum of three applications at a rate of 0.038 kg ai/hL with a 3 days PHI. In the trials four to five applications were made rather than three. The residues in the grape bunches were 0.52, 0.54, 1.1, 1.3 and 2.4 mg/kg. Because no berries were analysed, the trials were not included into the evaluation.

In the USA, fenhexamid is approved for use up to 3 times at a rate of 0.56 kg ai/ha with a 0 day PHI. In seven Canadian and 15 USA trials matching USA GAP fenhexamid residues in grape bunches were 0.55, 0.62, 0.71, 0.78, 0.87, 0.91, 0.97, 1.0, 1.1, 1.1, 1.1, 1.2, 1.2, 1.3, 1.4, 1.6, 1.6, 1.8, 1.9, 2.1, 2.2 and 2.8 mg/kg. Because no berries were analysed, the trials were not included into the evaluation.

In Australia, fenhexamid is used on grapes with a maximum of 2 applications at rate of 0.05 kg ai/hL (high volume spray) or 0.25 kg ai/hL (low volume spray) with a 21 days PHI. In five trials matching GAP conditions fenhexamid residues were 1.5, 2.5, 3.5, 4.7 and 6.1 mg/kg in berries.

In Japan, fenhexamid is registered for up to 2 applications at a rate of 0.05 kg ai/hL and a 14 day PHI. Four outdoor and two indoor trials were conducted that matched GAP. The residues in the fruit were 4.3, 6.3, 6.7 and 11 mg/kg in the outdoor trials and 0.14 and 3.2 mg/kg in the indoor trials.

The Meeting compared the data sets from Australia and Japan using the Mann-Whitney U-test (see *FAO Manual*, p. 73) and decided that they belonged to the same population and could be combined. The combined Australian and Japanese residues were 0.14, 1.5, 2.5, 3.2, 3.5, 4.3, 4.7, 6.1, 6.3, 6.7 and 11 mg/kg.

The Meeting considered that the data sets from Australia/Japan and from Europe were from different populations. The Meeting therefore estimated a maximum residue level of 15 mg/kg and an STMR of 4.3 mg/kg for residues in grapes, on the basis of Japanese and Australian data.

Strawberries

A total of 49 trials were conducted with fenhexamid in strawberries in North America, Asia, Australia, northern and southern Europe.

The highest GAP for northern Europe (outdoor) corresponded to a maximum of 3 applications at a rate of 1 kg ai/ha with a PHI of 3 days (Austria). Eight field trials were conducted in northern Europe. The fenhexamid residues found were 0.57, 0.70, 0.78, 0.81, 1.1, 1.2, 1.2 and 1.9 mg/kg.

The highest GAP for southern Europe (outdoor) corresponded to a maximum of 4 applications at a rate of 0.75 kg ai/ha with a PHI of one day (Spain). Eight field trials were conducted in southern Europe. The fenhexamid residues found were 0.48, 0.66, 0.74, 1.0, 1.1, 1.1, 1.3 and 1.5 mg/kg.

Fenhexamid is registered in Italy for indoor (greenhouse) use on strawberries at a rate of 0.75 kg ai/ha with a 1 day PHI but with no apparent restriction on the number of applications indicated. A spray interval of 7–10 days is recommended. Four indoor trials from Italy, with 4 applications at 0.75 kg ai/ha, were considered to match GAP and showed residues of 0.71, 0.81, 1.1 and 1.7 mg/kg.

The USA use pattern on strawberries allows fenhexamid to be sprayed a maximum of 4 times at a rate of 0.84 kg ai/ha with a PHI of 0 days. In 14 trials matching GAP conditions residues found of fenhexamid were 0.35, 0.38, 0.42, 0.49, 0.57, 0.67, 0.97, 1.1, 1.2, 1.2, 1.3, 2.0, 2.1 and 2.3 mg/kg.

Data from two indoor trials were submitted from Japan, in which fenhexamid was applied three times at a rate of 0.05 kg ai/hL. It was decided that the data could not be used for evaluation as the Japanese and Korean GAP specified only outdoor use.

Six further outdoor trials studies were submitted from Australia where five applications were made at rates of 0.4–0.56 kg ai/ha with a PHI of 0 days. The residues found were 0.53, 0.54, 2.7, 3.9, 5.6 and 5.9 mg/kg.

Based on the Australian data, the Meeting estimated a maximum residue level of 10 mg/kg and an STMR of 3.3 mg/kg for residues in strawberries.

Blueberries and black currants

Residue data was received for blueberries and black currants and were evaluated together.

The use of fenhexamid in bilberry and similar berries (incl. blueberry) is registered in the USA with 1–4 spray applications of 0.84 kg ai/ha and a 0-day PHI. Eight residue trials from six US states on blue berry complied with GAP. At the day of treatment, the concentrations of residues were: 1.0, 1.2, 1.4, 1.6, 1.7, 2.6, 2.8 and 2.9 mg/kg.

In Germany and Austria, the GAP for berries (except grapes and strawberries) includes 1- 4 treatments of 1 kg ai/ha and a 7-day PHI. A total of 8 residue trials were performed in Germany and the UK with 4 x 1 kg ai/ha, 0.2 kg ai/hL on black currants. With a 7-day PHI, the fenhexamid residues were: 0.93, 1.0, 1.2, 1.6, 1.7, 1.7, 1.8 and 2.1 mg/kg.

The Meeting noted that the data on blueberries and black currants were similar and could be combined for mutual support. The combined residues were, in rank order: 0.93, 1.0, 1.0, 1.2, 1.2, 1.4, 1.6, 1.6, 1.7, 1.7, 1.7, 1.8, 2.1, 2.6, 2.8 and 2.9 mg/kg.

The Meeting agreed to extrapolate from blueberries and black currants to other bush type berries and estimated a maximum residue level of 5 mg/kg and an STMR of 1.65 mg/kg for residues in bilberries, blueberries, currants (black, red, white), elderberries, gooseberries and juneberries.

Raspberries and blackberries

In Germany and Austria, the GAP for berries (except grapes and strawberries) includes 1- 4 treatments of 1 kg ai/ha and a 7-day PHI. Five residue trials were performed in the UK and 2 in Germany with 4 × 1 kg ai/ha on raspberries. With a 7-day PHI, the fenhexamid residues were: 0.9, 1.1, 1.4, 1.5, 1.6, 2.0 and 4.0 mg/kg.

In the USA, fenhexamid is registered in blackberry and raspberry with 1–4 spray applications of 0.84 kg ai/ha and a 0-day PHI. A total of 6 GAP residue trials were performed with foliar spray application in North America, one on blackberries and two on raspberries in Canada and three on raspberries in the USA. The application rate was 4 × 0.79–0.88 kg ai/ha. The residue concentrations were 0.55, 3.0, 4.0, 5.2, 11 and 11 mg/kg after a 0-day PHI.

The Meeting compared data sets from Europe and the USA by the Mann-Whitney U-test (see *FAO Manual*, p.73) and decided that they belonged to one population and could be combined. The combined residues were, in rank order: 0.55, 0.9, 1.1, 1.4, 1.5, 1.6, 2.0, 3.0, 4.0, 4.0, 5.2, 11 and 11 mg/kg.

The Meeting agreed to extrapolate from raspberries and blackberries to other cane type berries and estimated a maximum residue level and an STMR value for fenhexamid in dewberries (boysenberries, loganberries), raspberries and blackberries of 15 mg/kg and 2.0 mg/kg.

Kiwifruit

Fenhexamid may be used in Europe (Greece and Italy) as post-harvest dip or spray with a 0.05–0.06% solution on kiwifruit with a 60 day PHI. Four trials were performed in Italy with dipping in a 0.075% solution. The residues were 60 days after treatment in whole fruits 3.5, 4.0, 4.8 and 6.3 mg/kg.

In the USA fenhexamid is registered for post-harvest use by 30 s dipping in a solution of 0.09% or as a packing line spray at a rate of 0.37 g ai/100 kg fruits. Three trials were performed with dipping (0.09%) and two with spraying (0.375 g ai/100 kg fruits). The residues were 3.5, 6.3, 6.5, 9.5 and 11 mg/kg.

The Meeting compared both kiwifruit data sets from Europe and the USA by the Mann-Whitney U-test (see *FAO Manual*, p.73) and decided that they belonged to one population and could be combined. The combined residues were, in rank order: 3.5, 3.5, 4.0, 4.8, 6.3, 6.3, 6.5, 9.5 and 11 mg/kg.

The Meeting estimated a maximum residue level and an STMR value for fenhexamid in kiwifruit of 15 mg/kg and 6.3 mg/kg.

Cucumber, gherkin and summer squash

The highest GAP for indoor uses in Europe in/on cucumber corresponds to 0.75 kg ai/ha, applied up to 3 times with a PHI of 3 days (Austria) or sprayed at 0.05 kg ai/hL with a PHI of 1 day in the Netherlands, where no maximum number of application is stated. The GAP for Israel is the same as for Austria without specifying the maximum number of applications, but because cucumbers are harvested continuously and spray intervals were 7 days or more it is unlikely that the same fruit received more than 3 applications. The fenhexamid residues in cucumbers from 16 European indoor trials (3 Belgium, 3 German, 1 Dutch, 2 French, 2 Italian, 3 Spanish, 2 Greek) meeting these conditions were 0.10, 0.12, 0.14, 0.14, 0.14, 0.15, 0.16, 0.18, 0.19, 0.19, 0.20, 0.20, 0.21, 0.29, 0.33 and 0.65 mg/kg with a 1-day PHI.

The registered use in The Netherlands on gherkin and summer squash is the same as on cucumber. The Meeting agreed to extrapolate the cucumber values to gherkin and summer squash.

The Meeting estimated a maximum residue level of 1 mg/kg and an STMR of 0.185 mg/kg for residues in cucumber, gherkin and summer squash.

Tomato

The highest GAP for outdoor and indoor uses in Europe in tomato corresponds to 0.75 kg ai/ha, 0.05–0.075 kg ai/hL with a PHI of 1 day (Italy) and spray intervals of 10–14 days, no maximum number of applications is stated.

Seven outdoor trials (4 French, 1 Italian, 2 Portuguese) on tomato matching the GAP with a rate of 3 x 0.75 kg ai/ha were submitted with residues of 0.29, 0.32, 0.34, 0.42, 0.62, 0.63 and 0.93 mg/kg.

A total of 17 tomato residue trials (1 Spain, 2 France, 4 Italy, 4 Germany, 3 Belgium, 1 Greece, 2 Netherlands) were performed indoor according to Italian GAP in Europe in 1995/96/98/99.

In each trial, 3 applications (interval 7 days) were made. All applications were carried out approximately at the highest label application rate (0.75 kg ai/ha). At the 1-day PHI, the concentrations of residues were: 0.17, 0.24, 0.24, 0.25, 0.27, 0.32, 0.34, 0.34, 0.39, 0.40, 0.41, 0.42, 0.54, 0.63, 0.72, 0.80 and 0.86 mg/kg.

The Meeting considered that the data from indoor and outdoor trials on tomato are from the same pool and combined them, resulting in a ranked order as follows (n = 24): 0.17, 0.24, 0.24, 0.25, 0.27, 0.29, 0.32, 0.32, 0.34, 0.34, 0.34, 0.39, 0.40, 0.41, 0.42, 0.42, 0.54, 0.62, 0.63, 0.63, 0.72, 0.80, 0.86 and 0.93 mg/kg.

The Meeting estimated a maximum residue level of 2 mg/kg and an STMR of 0.395 mg/kg for residues of fenhexamid in tomato.

Peppers

The highest GAP for indoor uses in Europe in/on peppers corresponds to 0.75 kg ai/ha, applied up to 3 times with a PHI of 3 days (Austria) or sprayed at 0.05 kg ai/hL with a PHI of 1 day in the Netherlands, where no maximum number of application is stated. The GAP for Israel is the same as for Austria without specifying the maximum number of applications, but because peppers in greenhouse are harvested continuously and spray intervals were 7 days or more it is unlikely that the same fruit received more than 3 applications.

The fenhexamid residues in sweet peppers from 18 European indoor trials (3 Belgium, 3 German, 3 Dutch, 2 French, 4 Italian, 2 Spanish, 1 Portuguese) meeting these conditions were 0.38, 0.41, 0.43, 0.45, 0.48, 0.63, 0.66, 0.67, 0.67, 0.75, 0.76, 0.84, 0.86, 0.89, 0.90, 0.92, 1.0 and 1.5 mg/kg with a 1-day PHI.

The Meeting agreed to extrapolate from data for sweet pepper on the whole subgroup including chili and sweet peppers and estimated a maximum residue level of 2 mg/kg and an STMR of 0.71 mg/kg for residues of fenhexamid in peppers.

Egg plant

The registered use on egg plant is the same as on tomato and peppers in the Netherlands. The Meeting agreed to extrapolate from tomato and sweet pepper to egg plant. The data on tomato and peppers belonged to different populations and could not be combined. Therefore, the extrapolation based on the sweet pepper data set.

The Meeting estimated a maximum residue level of 2 mg/kg and an STMR of 0.71 mg/kg for residues of fenhexamid in egg plant.

Lettuce

The Austrian use pattern for lettuce grown indoor and outdoor allows fenhexamid to be sprayed 2 times at 0.75 kg ai/ha with a PHI of 7 days.

Eight outdoor trials on head lettuce from northern European countries (3 Germany, 3 Netherlands, 2 UK) matching maximum GAP with a rate of 2 × 0.75 kg ai/ha were submitted with fenhexamid residues at day 7 of 0.10, 0.11, 0.24, 0.30, 0.47, 1.1, 2.0 and 5.3 mg/kg.

Eight further outdoor trials on head and leaf lettuce were carried out in southern Europe (2 Spain, 3 Italy, 2 Portugal, 1 France-South) under the same application conditions. The residues were in head lettuce < 0.05, 0.07, 0.69, 0.84 and 2.0 mg/kg and in leaf lettuce 0.48, 0.94 and 2.7 mg/kg.

Six indoor trials on head lettuce from European countries (4 Germany, 2 Italy) matching maximum GAP with a rate of 2× 0.75 kg ai/ha were submitted with fenhexamid residues at day 7 of

1.3, 2.7, 6.4, 11, 12 and 17 mg/kg. Two further indoor trials on leaf lettuce were carried out under the same application conditions in Italy with residues of 14 and 19 mg/kg at day 7.

The Meeting compared both data sets from indoor and outdoor use by the Mann-Whitney U-test (see FAO Manual, p.73) and decided that they belonged to different populations and could not be combined. The Meeting decided to use the greenhouse lettuce data to support the evaluation.

In summary, fenhexamid residues in lettuce from greenhouse trials in rank order were: 1.3, 2.7, 6.4, 11, 12, 14, 17 and 19 mg/kg.

The Meeting noted that the 24 trials covered 15 varieties of lettuce and decided to make recommendations for both head and leaf lettuce.

Based on the indoor data set, the Meeting estimated a maximum residue level and an STMR value for fenhexamid in head and leaf lettuce of 30 mg/kg and 11.5 mg/kg.

Almonds

Fenhexamid is registered in the USA for use on almonds up to 4 times at 0.84 kg ai/ha up to 4 times at 0.84 kg ai/ha up to 28 days after petal fall.

Five trials on almonds from the USA with 4 treatments at 0.85 kg ai/ha and a 142−173 days PHI matching the GAP for foliar spray up to 28 days after petal fall were reported. The fenhexamid residues in almond nuts without shells were all < 0.02 (5) mg/kg.

The Meeting estimated a maximum residue level and an STMR value for fenhexamid in almonds of 0.02*mg/kg and 0.02 mg/kg.

Almond hulls

From the five trials described above the fenhexamid residues in almond hulls were 0.15, 0.47, 0.54, 0.77 and 1.1 mg/kg (fresh weight).

The Meeting estimated a maximum residue level of 2 mg/kg, a highest residue of 1.2 and an STMR of 0.6 mg/kg on dry weight basis.

Fate of residues during processing

The effect of processing on the level of residues of fenhexamid has been studied in cherries, plums, grapes, strawberries and tomatoes. The processing factors (PF) shown below were calculated.

In Australian grape processing studies, five PF values for juice, wine, wet pomace and raisin could be calculated per trial. In these cases, only the maximum PF per trial was used for the evaluation. The mean PF was calculated from two values, otherwise the median PF was calculated.

RAC	Processed product	No.	PF	Mean/median PF
Cherries	Juice	1	0.02	0.02
	Preserve	2	0.198, 0.27	0.23
Grapes	Juice	16	0.045, < 0.06, < 0.17, 0.29, 0.39, 0.44, 0.49, 0.51, 0.51, 0.55, 0.66, 0.68, 0.78, 0.79, 0.80, 1.35	0.51
	Must	6	0.19, 0.24, 0.40, 0.43, 0.53, 0.9	0.415

RAC	Processed product	No.	PF	Mean/median PF
	Wine	19	0.20, 0.20, 0.20, 0.21, 0.22, 0.23, 0.23, 0.24, 0.27, 0.28, 0.29, 0.31, 0.34, 0.40, 0.42, 0.46, 0.50, 0.90, 0.90	0.28
	Raisin	11	1.41, 1.47, 1.58, 1.69, 1.82, 1.86, 2.42, 3.0, 3.15, 3.68, 4.23	1.86
Strawberry	Jam	1	0.29	0.29
Tomato	Juice	2	0.30, 0.38	0.34
	Paste	2	4.12, 6.25	5.2
	Preserve	2	0.29, 0.30	0.30

Cherries (RAC residues 0.86, 1.0 mg/kg) were processed into juice and preserve with processing factors of 0.02 and 0.23. Based on the STMR value of 1.35 mg/kg for cherries, the STMR-Ps were 0.03 mg/kg for cherry juice and 0.31 mg/kg for preserves.

Plums (RAC residues < 0.05 mg/kg) were processed into sauce and dried prunes. No detectable residues were reported in sauce but 0.1 mg/kg in prunes. As the concentration of residues was at the LOQ in the RAC, no STMR-P values could be estimated.

Grapes were processed into juice, must, wine and dried fruit (raisins) with processing factors of 0.51, 0.415, 0.28 and 1.86 respectively. Based on the STMR value of 4.3 mg/kg for grapes, the STMR-P for juice was 2.2 mg/kg, for must 1.8 mg/kg, for wine 1.2 mg/kg and for raisins (dried grapes) 8.0 mg/kg. Based on the highest fenhexamid residue of 11 mg/kg, the Meeting estimated a maximum residue level of 25 mg/kg for residues in raisins (dried grapes).

Strawberries (RAC residues 0.66 mg/kg) were processed into jam with a processing factor of 0.29. Based on the STMR value of 3.3 mg/kg for strawberries, the STMR-P value was 0.96 mg/kg for residues in strawberry jam.

Tomatoes (RAC residues 0.34, 0.96 mg/kg) were processed into juice, paste and preserve with processing factors of 0.34, 5.2 and 0.3, respectively. Based on the STMR value of 0.395 mg/kg for tomato, the STMR-Ps were 0.13 mg/kg, 2.05 mg/kg and 0.12 mg/kg for residues in tomato juice, paste and preserves, respectively.

Lettuce head Two processing-type studies were performed with fenhexamid on head lettuce. The trials were designed to determine the extent of the residue deposits on the outer leaves as well as the effect of washing on residue levels. Processing was conducted using household practices. The residues measured in different plant parts indicate variations in the distribution of fenhexamid on the plant.

The residue levels of fenhexamid in lettuce head RACs sampled on day 3 after the last applications were 1.3–6.0 mg/kg. Values of 4.2–11.0 mg/kg were measured in the outer leaves, which demonstrate that the major portion of the residues was deposited on the surface, as is to be expected. The residue level in the inner head samples (heads without outer leaves) from these trials were 1.5–2.6 mg/kg, and those in the inner leaf samples ranged from 1.5–3.5 mg/kg. The residues in "inner leaves, washed" ranged from 0.35–0.99 mg/kg and from 0.27–0.91 mg/kg in the washing water.

The studies demonstrated that the residues of fenhexamid are concentrated on the outer leaves (factors 1.7, 3) and washing reduces the concentration of residues on leaves.

Residues in animal commodities

Fenhexamid treated raw agricultural commodities are not fed to farm animals. The only processed feedstuff might be almond hulls. The dietary burden of fenhexamid for beef and dairy cattle arising from almond hulls is very low: 0.12 mg/kg for the maximum and 0.06 mg/kg for the median animal dietary burden.

Estimated maximum dietary burden of farm animals

Commodity	Codex Commodity Group	Residue (mg/kg)	Basis	% Dry matter	Residue, on dry wt (mg/kg)	Chosen diets, %			Residue contribution (mg/kg)		
						Beef cattle	Dairy cattle	Poultry	Beef cattle	Dairy cattle	Poultry
Almond hulls	AM	1.1	Highest residue	90	1.2	10	10	-	0.12	0.12	-

Estimated median dietary burden of farm animals

Commodity	Codex Com-modity Group	Residue (mg/kg)	Basis	% Dry matter	Residue, on dry wt (mg/kg)	Chosen diets, %			Residue contribution (mg/kg)		
						Beef cattle	Dairy cattle	Poultry	Beef cattle	Dairy cattle	Poultry
Almond hulls	AM	0.54	STMR	90	0.6	10	10	-	0.06	0.06	-

No feeding studies of fenhexamid on farm animals were received. The Meeting noted that in the metabolism study on a goat dosed for three days with the equivalent of 133 ppm fenhexamid in the feed the residues in all tissue samples were low and ranged from 0.007 mg/kg in muscle, 0.69 mg/kg in kidney, 0.031 mg/kg in fat to 2.5 mg/kg in liver. No fenhexamid was detected in milk.

As this dosing level is more than 1100 times higher than the maximum estimated dietary burden of 0.12 ppm, the Meeting agreed that residues would not be expected in animal commodities and estimated STMRs and HRs of 0 for meat (from mammals other than marine mammals), edible offal (mammalian) and milks.

The Meeting estimated maximum residue levels of 0.01* (F) mg/kg for milks, 0.05*(fat) mg/kg for meat (from mammals other than marine mammals) and 0.05* mg/kg for edible offal (mammalian).

DIETARY RISK ASSESSMENT

Long-term intake

The International Estimated Daily Intakes (IEDIs) of fenhexamid, based on the STMRs estimated for 30 commodities, for the five GEMS/Food regional diets were in the range of 0% to 6% of the maximum ADI (Annex 3). The Meeting concluded that the long-term intake of residues of fenhexamid resulting from its uses that have been considered by JMPR is unlikely to present a public health concern.

Short-term intake

The 2005 JMPR decided that an ARfD is unnecessary. The Meeting therefore concluded that the short-term intake of fenhexamid residues is unlikely to present a public health concern.

4.10 GLYPHOSATE (158)

RESIDUE AND ANALYTICAL ASPECTS

Glyphosate is a herbicide with uses on many crops. Glyphosate has been evaluated several times with the initial evaluation in 1986 and the latest in 1997. It was listed under the Periodic Re-evaluation Programme of the 34th Session of the CCPR for residue review by 2005 JMPR (ALINORM 03/24). The Meeting received information on glyphosate metabolism and environmental fate, methods of residue analysis, freezer storage stability, national registered use patterns, supervised residue trials on conventional and glyphosate tolerant crops and national MRLs.

The 2004 JMPR concluded that the metabolite AMPA is of no greater toxicological concern than the parent glyphosate and established an ADI for the sum of glyphosate and AMPA of 0-1 mg/kg bw. The same meeting considered an ARfD unnecessary.

Some information on GAP and national MRLs were submitted by Australia and The Netherlands.

The following abbreviations are used for the metabolites discussed below:

AMPA	aminomethyl phosphonic acid
N-methyl AMPA	[(*N*-methylamino)methyl]phosphonic acid

Glyphosate is available in a variety of different salt forms including as the sodium, potassium, ammonium and isopropylamine salts. To assist uniform interpretation of GAP application rates have been expressed in terms of glyphosate acid equivalents (ae). Applications of glyphosate can be made at different stages of crop growth. The following abbreviations are used for the main stages of application:

PRE = pre-emergent or pre crop emergence

EPO = early post-emergence

LPO = late post-emergence

PH = pre-harvest, specifically within a few weeks prior to harvest

Animal metabolism

The Meeting received metabolism studies for glyphosate in rats, lactating goats and laying hens.

The biotransformation and degradation pathways in the goat and hen are similar to those established in rat metabolism. In animals, ^{14}C-labelled glyphosate is excreted unchanged. The only residue identified in tissues of goats and laying hens was glyphosate although there were indications that small amounts of AMPA may be formed. A significant proportion of the ^{14}C in the goat and hen metabolism experiments was retained on columns used for separation and characterization. The possible identity of the retained ^{14}C activity was not explored. Metabolism studies on rats samples were analysed both with and without clean-up on cation and anion columns detecting only unchanged glyphosate and small amounts of AMPA. Experiments on rats determined that no AMPA was formed following intravenous administration suggesting that microbial degradation on oral administration may be responsible for the minor amounts of AMPA detected.

Plant metabolism

The Meeting received plant metabolism studies for glyphosate on coffee, corn, cotton, soya beans, wheat, pasture grasses and alfalfa as well as on the glyphosate tolerant crops cotton, soya beans and sugar beet. Pre-emergent application of [^{14}C]glyphosate at application rates equivalent to 4.5 kg ae/ha resulted in low levels of ^{14}C in plants collected 4–8 weeks after application. Control plants also contained ^{14}C probably from incorporation of $^{14}CO_2$ liberated during soil microbial degradation of [^{14}C]glyphosate.

For the same crops grown hydroponically and exposed to sublethal doses of [^{14}C]glyphosate in the growth solution, glyphosate was the major component of the total radioactive residue (TRR) in the aerial parts of the plants (21–69%). Other compounds identified were AMPA (4.2–28%), *N*-methyl AMPA (0–2.0%) as well as small amounts of natural products. The proportion of ^{14}C extracted with water was higher for aerial parts (70–90%) compared with roots (36–87%). In the case of roots, glyphosate was the major compound detected (7.6-57%) together with smaller amounts of AMPA (2.8–7.4%), *N*-methyl AMPA (0–0.4%) and natural products (1–11%). In summary, several minor metabolites were present at < 2% TRR (N-methyl AMPA, methylphosphonic acid and *N*-methyl glyphosate) though their origin was unclear; in vivo metabolism, microbial degradation or impurities in the material administered.

The metabolism of [^{14}C]glyphosate on both immature and mature coffee plants following uptake from soil, from hydroponic solution, stem injection and foliar application was studied. ^{14}C was translocated from the sites of application. In all cases glyphosate was the major component of the ^{14}C residue. For example 5 weeks after foliar application to mature coffee plants glyphosate comprised 72–99% of the residue in leaves, 91% in stems, 96% in roots and 94% in beans. Residues of AMPA were 5% or less of the TRR and were generally present in ratios with glyphosate comparable to that present in the administered formulation.

Only low levels of radioactivity were recovered in grasses, alfalfa and clover grown on [^{14}C]glyphosate treated soil or in soil into which [^{14}C]glyphosate treated quackgrass was incorporated. Glyphosate was the only component of the ^{14}C residue of foliar treated grass and alfalfa extracted with water, a process that recovered > 95% of the TRR. Small amounts of AMPA were detected in grass samples following foliar application of [^{14}C]glyphosate. Drying grass and alfalfa to form hay did not alter the ^{14}C residues.

Metabolism studies have been completed in glyphosate tolerant soya beans, sugar beet, and cotton crops that contain the CP4-EPSPS gene. In tolerant soya beans, glyphosate is metabolized substantially to AMPA, the latter can be conjugated with natural plant constituents to give trace level

metabolites, or degraded to one carbon fragments that are incorporated into natural products. None of the trace level metabolites account for greater than 2% of the TRR in any soya bean raw agricultural commodity. Glyphosate plus AMPA account for at least 66% of the total radioactive residues in forage, hay, and grain. Glyphosate residues differ among the plant components accounting for about 90% of the TRR in forage but only about 25% of the TRR in grain. AMPA accounted for only 6.8% of the TRR in forage, but was the major ^{14}C compound in grain accounting for up to 49% of the TRR. About 9% of the TRR in grain was shown to be due to incorporation of ^{14}C into natural products; in the oil as fatty acids, in the aqueous extract as soluble components, and in the acid hydrolysate of the extracted grain as amino acids and natural organic acids.

In glyphosate tolerant cotton, glyphosate and AMPA account respectively for 91–95% and 0.7–1.6% of the TRR in forage. In cottonseed, glyphosate is the major extractable radiolabeled compound (12–24 % of the TRR) and only trace levels of AMPA are present (< 2% of the TRR). A significant fraction of the residues in the seed are attributed to incorporation into natural products; 10–12% of the TRR was characterized as saponifiable fatty acids in oil and 54–75% of the TRR was present as natural products.

The metabolism of [^{14}C]glyphosate in tolerant sugar beet was very similar to soya beans and cotton. Glyphosate is partially metabolized to AMPA and low levels of AMPA conjugates. Glyphosate and AMPA together account for at least 99 and 81% of the TRR in roots and tops, respectively. AMPA is further converted, to a limited degree, to low levels of simple conjugates. In addition to conjugation, ^{14}C is broadly incorporated into a wide variety of natural products and plant constituents.

The results of all the studies demonstrate that the metabolic fate of glyphosate in tolerant plants is the same as in non-tolerant plants.

Environmental fate

The Meeting received information on the behaviour and fate of glyphosate during solution photolysis and aerobic soil metabolism. Consistent with the policy outlined by the 2003 JMPR only the environmental fate data relevant to the residues of glyphosate in crops were evaluated.

Crop rotation studies were not provided. However, aerobic soil metabolism of glyphosate was rapid with inferred degradation half-lives of 3.6–25 days depending on the soil system studied. The major metabolite formed was AMPA which was further degraded to CO_2. In aqueous solution glyphosate is stable to hydrolysis. The rate of degradation in field and in aquatic environments is such that glyphosate is not expected to persist in the environment.

Methods of analysis

Glyphosate and AMPA residues are measured as derivatives following clean-up of aqueous extracts by cation and anion exchange, the derivatization reaction varying with the chromatographic method used for separation (GC, HPLC) and detection system employed (FPD in phosphorous mode, fluorescence detector, UV, MS and MS/MS). Satisfactory recoveries at the LOQs of 0.05 mg/kg for both glyphosate and AMPA were reported for numerous commodities.

Stability of pesticide residues in stored analytical samples

The Meeting received information on the stability of glyphosate residue samples during storage of analytical samples at freezer temperatures. The available storage stability data indicate that residues of glyphosate and AMPA are stable under frozen storage conditions (-20°C) in/on the following commodities (storage interval in parentheses): beans, rape and linseed (18 months), wheat grain and straw, rye grain and straw (1349 days), pasture grass (362 days), soya bean seed (183 days) soya bean

straw (398 days), corn grain (944 days), sorghum forage (958 days), sorghum straw (958 days), clover (944 days) and tomatoes (938 days). Residues were stable in animal commodities (pig, cow and chicken tissues and milk) for at least 700 days. For eggs residues were stable for 431 days.

Residues of AMPA are stable under frozen storage conditions (-20 °C) in/on the following commodities (storage interval in parentheses): pasture grass (362 days), soya bean seed (183 days) soya bean straw (398 days), corn grain (944 days), sorghum forage (958 days), sorghum straw (958 days), clover (944 days) and tomatoes (938 days). Residues were stable in animal commodities (pig, cow and chicken tissues and milk) for at least 700 days. For eggs residues were stable for 431 days.

Definition of the residue

The metabolism studies in coffee, corn, cotton, soya beans, wheat, pasture grasses and alfalfa as well as on the glyphosate tolerant crops cotton, soya beans and sugar beet patterns of metabolites were similar in different species of plants. The main metabolite found in plant metabolism studies was AMPA. The Meeting agreed that glyphosate together with AMPA should be regarded as the residues of toxicological concern.

For the purposes of estimation of dietary intake and to enable comparison of the calculated intakes with the ADI it is preferable to express the residues in terms of glyphosate (glyphosate = 1.5 × AMPA).

Currently, the residue definition for glyphosate is “glyphosate”. In national systems the residue definition for glyphosate is generally also the parent compound.

The Meeting agreed that the residue definition applicable to glyphosate would continue to be the parent compound. As for estimation of dietary intake and the risk assessment component relating to exposure, the 2004 JMPR concluded that AMPA was of no greater toxicological concern than its parent compound and set a group ADI of 0–1 mg/kg bw for the sum of glyphosate and AMPA.

For glyphosate STMR estimation, residue = glyphosate + 1.5 × AMPA

Definition of glyphosate residue (for compliance with MRLs): *glyphosate*

Definition of glyphosate residue (for estimation of dietary intake): *sum of glyphosate and AMPA, expressed as glyphosate.*

These definitions apply to plant and animal commodities.

Results of supervised trials on crops

The Meeting received data from supervised trials on the following crops: olives, bananas, kiwifruit, beans (dry), peas (dry), lentils, soya beans (conventional and tolerant), sugar beet (glyphosate tolerant), barley, maize (conventional and tolerant), oats, rye, sorghum, wheat, sugarcane, almonds, pecan, macadamia, walnuts, cotton (conventional and tolerant), linseed, mustard, rape, sunflower, coffee, tea, alfalfa and grasses.

Glyphosate may be applied prior to crop emergence (pre-emergence = PRE), shortly after crop emergence (early post-emergence = EPO), between EPO and a few weeks before harvest (late post-emergence = LPO) and prior to harvest (pre-harvest = PH). In addition glyphosate may be applied to weeds in the crop as a spot treatment or by wiper application to weeds in which case the area treated is generally less than 10% of the area planted and a directed sprays in which the crop is not exposed. The Meeting considered these later methods of application as unlikely to result in

significant residues in crops. As such spot, wiper and directed sprays (e.g., hooded sprayers) were not included in consideration of GAP.

When applied as pre-harvest residues in the raw agricultural commodity (RAC) are mainly determined by applications made when the plant is growing and transport from the application site to the RAC occurs, rather than applications made to senescing crops where the RAC is protected from the spray, such as beans in pods. For commodities that are exposed and glyphosate is applied as a pre-harvest application to senescent crops, it is the pre-harvest spray that has the greatest influence on residues. If a range of application protocols involving different numbers of sprays, timing and application rates were used for a crop grown at a single location, the highest residue from any trial at the location and carried out with numbers of applications and rates within the range permitted by GAP was selected.

The limits of detection of glyphosate and AMPA are typically 0.05 mg/kg. When glyphosate and AMPA were summed, AMPA was converted to glyphosate equivalents (AMPA mg/kg × 1.5). If AMPA residues are < 0.05, they are not summed with glyphosate, because they are typically much less than glyphosate residues. If both glyphosate and AMPA are < LOQ, then sum is < LOQ of glyphosate. The exception is where there is evidence that AMPA residues are comparable to glyphosate residues such as for soya beans in which case the residues are summed and if both glyphosate and AMPA residues are < LOQ, the sum is less than the combined LOQs for glyphosate and AMPA.

Olives

Trials on olives were conducted in Greece (no GAP provided), Italy (GAP 4.3 kg ae/ha; no PHI specified) and Spain (directed sprays/spot sprays GAP 2.5 kg ae/ha, PHI not specified, assumed 0 days or 4.3 kg ae/ha, PHI 7 days for fruit on the ground, the lower rate, shorter PHI was taken to be the critical use for Spain). Two trials from Italy and two from Spain matched Italian GAP. Glyphosate residues found in fruit, harvested from the ground one or more days after application were 0.39 and 0.66 mg/kg, for the Italian trials, and 0.17 and 0.12 mg/kg for the Spanish trials. Residues of AMPA were not measured in these trials. Four trials from Spain matched that countries GAP (2.5 kg ae/ha). Residues in fruit collected from the ground were 6.7, 12, 12 and 12 mg/kg for glyphosate. Residues of AMPA were all < 0.05 mg/kg; the sum of glyphosate and AMPA residues were 6.7, 12, 12 and 12 mg/kg.

The Meeting decided that the residues from trials complying with the GAP of Italy and Spain were from different populations and that they could not be combined for estimating a maximum residue level. The Meeting agreed that the number of residue trials was insufficient to estimate a maximum residue level for olives.

Bananas

Trials on bananas were conducted in Brazil (GAP of 4.3 kg ae/ha, with a PHI of 30 days), Honduras, Panama, Colombia and Ecuador (no GAP supplied). For three trials from Brazil that matched Brazilian GAP residues found of glyphosate and AMPA were < 0.05 mg/kg. In four trials conducted in Honduras, Panama, Colombia and Ecuador, at applications rates higher than Brazilian GAP, residues found in pulp and peel, when expressed as whole bananas, were < 0.05 mg/kg for both glyphosate and AMPA. The Meeting decided to utilize the trials at higher application rates in support of the Brazil trials to recommend a maximum residue level of 0.05 (*) for glyphosate in bananas. The HR and STMR for total residues are both 0.05 mg/kg.

Kiwifruit

Trials on kiwifruit were conducted in Italy (GAP of 4.3 kg ae/ha ground directed spray, with no PHI specified). None of the trials matched GAP. The Meeting agreed to withdraw its previous recommendation of 0.1 (*) mg/kg for kiwifruit.

Beans, dry

Trials on beans, dry were conducted in Belgium (no GAP provided), Denmark (no GAP provided), the UK (GAP of 1.4 kg ae/ha when grain moisture is <30% generally applied 7–14 days before harvest), the USA (GAP 0.43–4.2 kg ae/ha pre-emergent). The Netherlands GAP is 0.72–2.2 kg ae/ha, PHI 7 days. In Canada GAP is 0.9 kg ae/ha when grain moisture is < 30% generally 7–14 days before harvest. Trials from Belgium and Denmark were evaluated against UK GAP.

Five trials from the UK matching GAP had residues of 0.11, 0.12, 0.16, 0.20 and 1.8 mg/kg. One trial each from Belgium and Denmark matched UK GAP with residues of < 0.05 and 0.17 mg/kg respectively. Residues of AMPA were < 0.05 mg/kg.

None of the USA trials matched GAP for that country and were evaluated against the GAP of Canada. Thirteen trials conducted in the USA approximated Canadian GAP. Residues found in beans (dry) were < 0.05, 0.07, 0.09, 0.10, 0.11, 0.13, 0.19, 0.30, 0.32, 0.37, 0.38, 0.68 and 1.6 mg/kg. Residues of AMPA were all < 0.05 mg/kg.

The Meeting considered that the field trials conducted according to the GAP of the UK and the USA were from similar residue populations and could be combined for the purposes of estimating a maximum residue level. Glyphosate residues, in ranked order were (n = 19) : < 0.05, < 0.05, 0.07, 0.09, 0.10, 0.11, 0.12, 0.13, 0.16, 0.17, 0.19, 0.20, 0.30, 0.32, 0.37, 0.38, 0.68, 1.6 and 1.8 mg/kg. The Meeting confirmed its previous recommendation of a maximum residue level for glyphosate in beans (dry) of 2 mg/kg.

As residues of AMPA were < 0.05 mg/kg, total residues for the purposes of estimating an STMR and highest residues are the same as the glyphosate values. The highest residue and STMR are estimated to be1.8 and 0.17 mg/kg respectively.

Peas, dry

Trials on peas, dry were conducted in Belgium (no GAP provided), Canada (GAP of 0.9 kg ae/ha, when grain moisture is < 30% generally applied, 7–14 days before harvest), Denmark (no GAP provided), the UK (GAP 1.4 kg ae/ha, when grain moisture is < 30% generally 7–14 days before harvest) and the USA (GAP 0.43–4.2 kg ae/ha pre-emergent). The Netherlands GAP is 0.72–2.2 kg ae/ha, PHI 7 days. Trials from Belgium and Denmark were evaluated against UK GAP.

Residues in six UK trials that approximated GAP of that country were 0.13, 0.16, 0.17, 1.7, 1.8 and 2.1 mg/kg. Residues in a single trial from Belgium and Denmark that approximated the UK GAP were 0.17 and 0.5 mg/kg respectively. When measured, residues of AMPA were < 0.05 (4) mg/kg.

In four trials from Canada that approximated GAP of that country, residues of glyphosate were 0.5, 0.82, 1.4 and 8.9 mg/kg. AMPA residues were < 0.05 mg/kg.

The Meeting considered that the field trials conducted according to the GAP of the UK and Canada were from similar residue populations and could be combined for the purposes of estimating a maximum residue level. Glyphosate residues, in ranked order were (n = 11): 0.13, 0.16, 0.17, 0.17,

0.5, 0.5, 0.82, 1.4, 1.7, 1.8 and 2.1 mg/kg. The Meeting estimated a maximum residue level for glyphosate in peas (dry) of 5 mg/kg confirming its previous recommendation.

As residues of AMPA were < 0.05 mg/kg, total residues for the purposes of estimating an STMR and highest residue are the same as the glyphosate values. The STMR is estimated to be 0.5 mg/kg and highest residue 2.1 mg/kg.

Lentils

Trials on lentils were conducted in Canada (GAP of 0.9 kg ae/ha, when crop has < 30% grain moisture content and lowermost pods (bottom 15%) are brown and seeds rattle, with a 7-14 days PHI). Two trials matched GAP of Canada with residues of glyphosate of < 0.05 and 3.0 mg/kg and AMPA of < 0.05 mg/kg. The total residues were < 0.05 and 3.0 mg/kg.

The Meeting considered there were insufficient trials to recommend a maximum residue level for lentils.

Soya beans

Trials on conventional soya beans were conducted in the USA (GAP of 4.2 kg ae/ha PRE, 4.2 kg ae/ha PH, with a PHI of 7 days). Four trials approximated GAP for the USA had glyphosate residues of 0.45, 5.4, 13 and 17 mg/kg. Corresponding AMPA residues were < 0.05, 1.2, 1.9 and 1.8 mg/kg respectively.

Additionally, trials were conducted on glyphosate tolerant soya beans (GAP of 0.43–4.2 kg ae/ha PE, 1.7 kg ae/ha LPO, 0.83 kg ae/ha PH, combined LPO+PH < 2.5 kg ae/ha, PHI 14 days). GAP allows pre-harvest applications together with post-emergent directed sprays as well as pre-harvest over the top sprays. The Meeting considered that a single pre-harvest application made close to harvest would not give rise to residues in beans (dry) representative of GAP as when the last application is made the crop has entered into senescence, limiting transport of residues to the seed. Only trials that included pre-emergent and in-crop applications were considered as compliant with USA GAP. The Meeting also noted that in trials conducted in the USA the pre-emergent application was typically at a higher rate than permitted by GAP, 6.4 versus 4.2 kg ae/ha, but considered the difference in application rates to account for less than 10% difference in the residue at harvest and that the later post-emergent sprays determined the residue. In a metabolism study on soya beans residues in seed after a single pre-emergent application at 5.4 kg ae/ha were < 0.01 mg/kg. While residues found after one or two post-emergent applications at 0.84 or 1.7 kg ae/ha, with the last application occurring 61 days prior to harvest, were 0.04 and 4.4 mg/kg respectively. Thirty-two trials from the USA approximated GAP of that country. Residues of glyphosate were 0.27, 0.28, 0.34, 0.37, 0.42, 0.44, 0.51, 0.56, 0.60, 0.70, 1.0, 1.1, 1.4, 1.4, 1.5, 1.7, 1.8, 1.9, 1.9, 1.9, 2.0, 2.6, 2.7, 2.7, 3.0, 3.3, 3.5, 3.6, 3.7, 4.4, 5.3 and 5.6 mg/kg. Total residues were 0.59, 0.78, 0.89, 1.0, 1.1, 1.1, 1.2, 1.2, 1.5, 1.6, 2.4, 3.2, 4.0, 4.0, 4.3, 4.7, 4.9, 5.1, 5.4, 5.7, 6.2, 6.6, 7.1, 7.6, 7.6, 7.9, 8.2, 8.5, 11, 11, 11 and 17 mg/kg.

The Meeting considered that the field trials conducted on conventional and glyphosate tolerant soya beans according to the GAP of the USA to be from similar residue populations and could be combined for the purposes of estimating a maximum residue level. Glyphosate residues, in ranked order were (n = 36): 0.27, 0.28, 0.34, 0.37, 0.42, 0.44, 0.45, 0.51, 0.56, 0.60, 0.70, 1.0, 1.1, 1.4, 1.4, 1.5, 1.7, 1.8, 1.9, 1.9, 1.9, 2.0, 2.6, 2.7, 2.7, 3.0, 3.3, 3.5, 3.6, 3.7, 4.4, 5.3, 5.4, 5.6, 13 and 17 mg/kg. The Meeting confirmed its previous recommendation of a maximum residue level for glyphosate in soya beans (dry) of 20 mg/kg.

Total residues were (n = 36): 0.45, 0.59, 0.78, 0.89, 1.0, 1.1, 1.1, 1.2, 1.2, 1.5, 1.6, 2.4, 3.2, 4.0, 4.0, 4.3, 4.7, 4.9, 5.1, 5.4, 5.7, 6.2, 6.6, 7.1, 7.2, 7.6, 7.6, 7.9, 8.2, 8.5, 11, 11, 11, 16, 17 and 20 mg/kg. The highest residue and STMR for total residues are 20 and 5.0 mg/kg respectively.

No residue data was available for immature seed and the Meeting agreed to recommend withdrawal of its previous recommendation for soya bean (immature seed) of 0.2 mg/kg.

Sugar beet (glyphosate tolerant)

Trials on sugar beet (glyphosate tolerant) were conducted in the USA (GAP of 0.43–4.2 kg ae/ha PRE, 1.3 kg ae/ha EPO from emergence to 8-leaf stage, 0.87 kg ae/ha from 8-leaf stage to canopy closure, 3.8 kg ae/ha combined maximum rate for all applications from emergence to harvest, PHI 30 days). The metabolism study indicated that pre-emergent applications of glyphosate do not make a significant contribution to the residue in sugar beet roots at harvest. An examination of the trial data indicated that it was probable that the last application contributed most to the residue at harvest. The Meeting considered that none of the trials matched GAP.

Cereal grains

The Meeting decided to evaluate the residue trial data for barley, maize, oats, rye, sorghum and wheat for a possible cereal grains recommendation. Estimates of values for total residues (HR and STMR) that are required for dietary intake and animal dietary burden calculations are discussed under each commodity while maximum residue level estimation is discussed at the end after wheat.

Barley

Trials on barley were conducted in Belgium (no GAP provided), France (no GAP provided) and the UK (GAP of 0.54–1.4 kg ae/ha, when grain moisture is < 30% generally 7–14 days before harvest). Trials conducted in Belgium and France were evaluated against the GAP of the Netherlands (GAP of 0.72–2.2 kg ae/ha, with a PHI of 7 days).

Residues of glyphosate in four UK trials approximating UK GAP were 1.4, 3.3, 4.4 and 11 mg/kg. Total residues were 1.4, 3.3, 4.4 and 11 mg/kg. Residues in two trials from Belgium (10 and 20 mg/kg), two from the UK (6.3 and 8.4 mg/kg) and nineteen from France (1.5, 2.2, 2.8, 2.9, 3.3, 5.5, 5.9, 6.3, 6.7, 7.2, 7.9, 8.5, 9.6, 13, 14, 15, 19, 19 and 19 mg/kg) approximated the GAP of the Netherlands.

The Meeting considered the trials to all be from similar populations and decided to combine the results for the purpose of maximum residue level recommendation. Glyphosate residues in rank order were (n = 27): 1.4, 1.5, 2.2, 2.8, 2.9, 3.3, 3.3, 4.4, 5.5, 5.9, 6.3, 6.3, 6.7, 7.2, 7.9, 8.4, 8.5, 9.6, 10, 11, 13, 14, 15, 19, 19, 19 and 20 mg/kg. Total residues (where glyphosate and AMPA were reported) were (n = 22): 1.1, 2.2, 2.8, 3.0, 3.3, 3.3, 4.4, 5.6, 6.0, 6.8, 7.3, 8.0, 8.6, 9.7, 10, 11, 14, 15, 19, 19, 19 and 20 mg/kg. The Meeting estimated a high residue and STMR for total residues in barley of 20 and 7.65 mg/kg respectively.

Maize

Trials on conventional maize were conducted in the USA (GAP of 0.43-4.2 kg ae/ha PRE, 0.87 kg ae/ha directed spray when the crop is > 30 cm tall and 2.5 kg ae/ha PH when grain moisture is < 35%, with a PHI of 7 days).

Trials on conventional maize were conducted in the USA (GAP of 0.43–4.2 kg ai/ha PRE, 0.87 kg ai/ha directed spray when crop > 30 cm tall and 2.5 kg ai/ha PH grain moisture < 35%, with a PHI of 7 days). From 21 trials that approximated USA GAP, which involved a single pre-harvest application to conventional maize residues of < 0.05 (12), 0.05 (2), 0.06 (2), 0.07, 0.09, 0.19, 0.54 and 3.0 mg/kg were found. Corresponding total residues were < 0.12 (11), < 0.14 (2), 0.14, < 0.16, 0.19, < 0.23, < 0.25, < 0.26, < 0.62 and 3.0 mg/kg respectively.

Additionally, trials were conducted on glyphosate tolerant maize (GAP 0.43–4.2 kg ae/ha PRE, 0.83 kg ae/ha EPO, 1.7 kg ae/ha LPO, total EPO and LPO applications < 2.5 kg ae/ha, 0.87 kg ae/ha PH < 35% grain moisture, PHI 7 days). None of the trials on glyphosate tolerant maize incorporated a pre-harvest application. Trials on conventional maize showed that pre-harvest applications made a significant contribution to the final residues found. The Meeting considered that none of the trials on glyphosate tolerant maize matched GAP of the USA.

Oats

Trials on oats were conducted in Canada (GAP of 0.18–4.3 kg ae/ha PRE, 0.9 kg ae/ha PH, application at < 30% grain moisture typically 7–14 days before harvest), Denmark (no GAP provided) and the UK (GAP 0.54-1.4 kg ae/ha, < 30% grain moisture typically 7–14 days before harvest). Three trials from Canada matched GAP of that country with glyphosate residues of 0.70, 3.1 and 4.6 mg/kg (total residues 0.70, 3.2 and 4.8 mg/kg). Eight trials from the UK and three from Denmark approximated UK GAP with glyphosate residues of 0.9, 3.4, 3.4, 4.1, 4.9, 4.9, 5.2, 6.0, 8.1, 8.6 and 14 mg/kg. Total residues in three trials that also measured AMPA levels were 3.5, 6.1 and 8.4 mg/kg.

The Meeting considered the trials approximating GAP in Canada and the UK to be from the same population and decided to combine the results for the purpose of estimating the maximum residue level and STMR. Residues of Glyphosate in ranked order were (n = 14): 0.7, 0.9, 3.1, 3.4, 3.4, 4.1, 4.6, 4.9, 4.9, 5.2, 6.0, 8.1, 8.6 and 14 mg/kg. AMPA residues were only measured in six of the fourteen trials considered giving total residues of 0.7, 3.2, 3.5, 4.8, 6.1 and 8.4 mg/kg. The Meeting estimated a high residue of 14 mg/kg and an STMR of 4.15 mg/kg.

Rye

Trials on rye were conducted in Denmark (no GAP provided) and were evaluated against the GAP of the UK (GAP 0.54–1.4 kg ae/ha, < 30% grain moisture PHI 7–14 days). Three trials approximated UK GAP with glyphosate residues of 1.6, 1.6 and 2.2 mg/kg (AMPA not measured).

The Meeting considered three trials insufficient to estimate a maximum residue level for rye.

Sorghum

Trials on sorghum were conducted in the USA (GAP of 0.43–4.2 kg ae/ha PRE, 0.87 kg ae/ha directed spray when crop > 30 cm tall and 1.7 kg ae/ha PH grain moisture < 35%, PHI 7 days). Thirteen trials matched GAP for the USA with glyphosate residues of 1.1, 1.3, 1.4, 1.7, 1.8, 4.4, 4.6, 5.3, 6.0, 6.3, 6.4, 12 and 13 mg/kg (total residues 1.1, 1.4, 1.6, 1.8, 1.8, 4.5, 4.8, 5.4, 6.2, 6.6, 6.6, 12 and 13 mg/kg). The Meeting estimated a highest residue of 13 mg/kg and an STMR of 4.8 mg/kg for total residues in sorghum grain.

Wheat

Trials on wheat were conducted in Belgium (no GAP provided), France (no GAP provided) and the UK (GAP of 0.54–1.4 kg ae/ha, < 30% grain moisture with a PHI of 7 days). Trials conducted in Belgium and France were evaluated against the GAP of the Netherlands (GAP is 0.72–2.2 kg ae/ha, PHI 7–14 days). Seven trials approximated GAP of the UK with glyphosate residues of 0.1, 0.1, 0.3, 0.3, 0.5, 0.7 and 1.0 mg/kg (residues of AMPA were all < 0.05 mg/kg). Two trials from Belgium (1.7 and 3.6 mg/kg), two from the UK (1.1 and 1.2 mg/kg) and nineteen from France (0.16, 0.53, 0.66, 0.80, 0.90, 0.99, 1.1, 1.2, 1.3, 1.5, 1.7, 2.1, 2.4, 3.8, 3.9, 4.0, 4.9, 6.3 and 9.5) approximated GAP of the Netherlands.

The Meeting decided that the residues conducted according to GAP of the Netherlands and the UK could be combined for the purposes of STMR and maximum residue level recommendation.

Residues of glyphosate in rank order were (n = 30): 0.1, 0.1, 0.16, 0.3, 0.3, 0.5, 0.53, 0.66, 0.7, 0.80, 0.90, 0.99, 1.0, 1.1, 1.1, 1.2, 1.2, 1.3, 1.5, 1.7, 1.7, 2.1, 2.4, 3.6, 3.8, 3.9, 4.0, 4.9, 6.3 and 9.5 mg/kg. Total residues were (n = 24): 0.1, 0.1, 0.24, 0.3, 0.3, 0.5, 0.53, 0.66, 0.7, 0.80, 0.90, 1.0, 1.1, 1.1, 1.2, 1.5, 1.9, 2.2, 3.7, 3.8, 3.9, 4.0, 4.9 and 6.5 mg/kg where measured. The Meeting recommended a high residue of 9.5 mg/kg and an STMR of 1.05 mg/kg for total residues in wheat grain.

Data are available for a large range of cereal grains and the Meeting considered it appropriate to estimate a group maximum residue level for cereal grains. As the residues of glyphosate in maize are much lower than in the other cereal grains due to the protection afforded by the husk and also the absence of data for rice, the Meeting decided to recommend a group maximum residue level for cereal grain except maize and rice of 30 mg/kg. The estimated maximum residue level replaces the previous recommendations for barley, oats and sorghum of 20 mg/kg and wheat of 5 mg/kg.

Total residues for cereal grains except maize and rice were (n = 65) 0.1, 0.1, 0.24, 0.3, 0.3, 0.5, 0.53, 0.66, 0.7, 0.7, 0.80, 0.90, 1.0, 1.1, 1.1, 1.1, 1.1, 1.2, 1.4, 1.5, 1.6, 1.8, 1.8, 1.9, 2.2, 2.2, 2.8, 3.0, 3.2, 3.3, 3.3, 3.5, 3.7, 3.8, 3.9, 4.0, 4.4, 4.5, 4.8, 4.8, 4.9, 5.4, 5.6, 6.0, 6.1, 6.2, 6.5, 6.6, 6.6, 6.8, 7.3, 8.0, 8.4, 8.6, 9.7, 10, 11, 12, 13, 14, 15, 19, 19, 19 and 20 mg/kg. The Meeting estimated an STMR of 3.7 mg/kg for total residues in cereal grains except maize and rice. This STMR value will be used in the dietary intake calculations for cereal grain commodities other than barley, maize, oats, sorghum and wheat.

Using the results for conventional maize of (n = 21) < 0.05 (12), 0.05 (2), 0.06 (2), 0.07, 0.09, 0.19, 0.54 and 3.0 mg/kg and corresponding total residues of < 0.12 (11), < 0.14 (2), 0.14, < 0.16, 0.19, < 0.23, < 0.25, < 0.26, < 0.62 and 3.0 mg/kg, the Meeting recommended a maximum residue level of 5 mg/kg for maize. The Meeting estimated highest residue and STMR levels for total residues in maize of 3.0 and < 0.12 mg/kg respectively.

Sugarcane

Trials on sugarcane were conducted in the USA (GAP of 0.49 kg ae/ha, PHI 21–35 days, 0.84 kg ae/ha; PHI 28–70 days). Seven trials from the USA matched GAP with residues 0.07, 0.13, 0.21, 0.27, 0.28, 0.69 and 0.97 mg/kg (total residues 0.07, 0.13, 0.21, 0.27, 0.28, 0.69 and 0.97 mg/kg).

The Meeting recommended a maximum residue level of 2 mg/kg for residues of glyphosate in sugarcane. The high residue and STMR levels for total residues are 0.97 and 0.27 mg/kg respectively.

Tree nuts

Trials on tree nuts (almonds, pecans, macadamias and walnuts) were conducted in the USA (GAP 0.43–4.3 kg ae/ha, directed applications, PHI 3 days). None of the trials matched GAP.

Cottonseed

Trials on conventional cotton were conducted in the USA (GAP of 0.43–4.2 kg ae/ha PRE, 0.43–4.2 kg ae/ha directed spray and 0.43–1.7 kg ae/ha PH, PHI 7 days). No trials matched GAP for conventional cotton.

Additionally, trials were conducted on glyphosate tolerant cotton (USA GAP of 0.43–4.2 kg ae/ha PRE do not exceed 4.2 kg ae/ha/season for pre-emergent application, 0.83 kg ae/ha for in-crop directed applications which must not exceed 3.3 kg ae/ha/season, 1.7 kg ae/ha PH do not exceed 1.7 kg ae/ha/season for pre-harvest application; combined applications must not exceed 6.6 kg ae/ha/season, PHI 7 days). USA GAP allows pre-harvest applications together with post-emergent directed sprays as well as pre-harvest over the top sprays. The Meeting considered that a single pre-harvest application would not give rise to residues in cottonseed representative of GAP as the timing

last application coincides with crop senescence, limiting potential transport of residues to the seed. Only trials that included pre-emergent and in-crop applications were considered as compliant with USA GAP.

Twenty-three trials from the USA approximated USA GAP with glyphosate residues of 0.46, 0.50, 0.69, 1.2, 1.3, 2.5, 2.8, 3.6, 4.2, 4.6, 4.9, 5.0, 7.2, 7.5, 9.7, 13, 16, 18, 18, 18, 21, 22 and 28 mg/kg (total residues 0.46, 0.58, 0.69, 1.2, 1.4, 2.5, 2.9, 3.7, 4.4, 4.6, 5.1, 5.2, 7.5, 7.9, 9.8, 14, 17, 18, 19, 19, 22, 23 and 28 mg/kg). The Meeting estimated a maximum residue level of 40 mg/kg for glyphosate to replace its previous recommendation of 10 mg/kg and estimated a highest residue of 28 mg/kg and an STMR of 5.2 mg/kg for total residues in cottonseed.

Linseed (flax)

Trials on linseed were conducted in the UK (GAP 1.1–1.4 kg ae/ha, < 30% grain moisture PHI 7–28 days). Two trials from the UK matched GAP from that country with glyphosate residues of 2.0 and 4.6 mg/kg. The Meeting agreed the number of trials was insufficient for the purposes of estimating a maximum residue level.

Mustard seed

Trials on mustard were conducted in the UK (GAP 1.1–1.4 kg ae/ha, < 30% grain moisture, with a PHI of 8–10 days). Two trials matched GAP in the UK with glyphosate residues of 0.25 and 2.6 mg/kg (total residues 0.25 and 2.6 mg/kg). The Meeting considered two trials insufficient to estimate a maximum residue level.

Rape (Canola)

Trials on rape were conducted in Belgium (no GAP provided), Canada (0.18–4.3 kg ae/ha PRE; 0.9 kg ae/ha PH, < 30% grain moisture, with a PHI of 7–14 days), Denmark (no GAP provided), Finland (no GAP provided) France (no GAP provided), Sweden (no GAP provided) and the UK (GAP 1.1–1.4 kg ae/ha, < 30% grain moisture with a PHI of 14–21 days). Trials from Belgium, France, Denmark, Finland and Sweden were evaluated against the GAP of the UK.

Four trials from Canada matched GAP of that country with residues found of 0.61, 1.8, 2.1 and 3.6 mg/kg (total residues 0.61, 1.8, 2.1 and 3.7 mg/kg). Two trials from Belgium (0.23 and 4.6 mg/kg), ten trials from France (0.21, 0.23, 0.35, 0.50, 0.87, 0.93, 0.96, 1.4, 1.9 and 5.6 mg/kg), ten from the UK (0.16, 0.4, 0.35, 0.60, 0.7, 0.7, 0.80, 0.9, 1.5 and 2.7 mg/kg), five from Denmark (4.1, 6.7, 8.6, 10 and 12 mg/kg), one from Finland (1.5 mg/kg) and three from Sweden (0.40, 2.0 and 2.8 mg/kg) approximated GAP from the UK. The Meeting agreed that the residue populations for trials approximating the GAP of Canada and the UK could be combined for the purpose of recommending maximum residue levels and STMRs.

Residues of glyphosate in ranked order were (n = 35): 0.16, 0.21, 0.23, 0.23, 0.4, 0.35, 0.35, 0.40, 0.50, 0.60, 0.61, 0.7, 0.7, 0.80, 0.87, 0.9, 0.93, 0.96, 1.4, 1.5, 1.5, 1.8, 1.9, 2.0, 2.1, 2.7, 2.8, 3.6, 4.1, 4.6, 5.6, 6.7, 8.6, 10 and 12 mg/kg. The Meeting recommended a maximum residue level of 20 mg/kg for glyphosate residues in rape seed. The new recommendation replaces the previous recommendation of 10 mg/kg.

Total residues in rank order were (n = 31): 0.16, 0.21, 0.23, 0.23, 0.35, 0.35, 0.4, 0.40, 0.50, 0.60, 0.7, 0.7, 0.80, 0.87, 0.9, 0.93, 0.96, 1.4, 1.5, 1.6, 1.9, 2.0, 2.7, 3.0, 4.1, 4.6, 5.7, 6.7, 8.6, 10 and 12 mg/kg. The Meeting estimated a highest residue of 12 mg/kg and an STMR of 0.93 mg/kg for total residues in rape seed.

Sunflower

Trials on sunflowers were conducted in Hungary (GAP 0.54–4.3 kg ae/ha PRE, 1.8 kg ae/ha PH 20-30% grain moisture, with a PHI of 6 days if rate is 0.54 kg ae/ha PH, otherwise a PHI of 21 days). Eight trials matched GAP of Hungary with glyphosate residues of < 0.05, < 0.05, 0.16, 0.39, 0.40, 3.7, 4.9 and 5.6 mg/kg. Total residues in the three trials that also measured AMPA were < 0.05, < 0.05 and 0.39 mg/kg. The Meeting estimated a maximum residue level of 7 mg/kg for residues in sunflower seed. Available evidence suggests residues of AMPA in sunflower seed are unlikely to exceed 10% of the glyphosate residue. The Meeting decided to utilize the glyphosate residues to estimate a highest residue and an STMR for total residues in sunflower seed of 5.6 and 0.395 mg/kg respectively.

Coffee beans

Trials on coffee were conducted in Brazil (no GAP provided), Columbia (no GAP provided), Costa Rica (no GAP provided) and the USA (GAP 0.43-4.3 kg ae/ha PRE and as directed sprays, with a PHI of 28 days). All trials were evaluated against the GAP of the USA yielding four trials that approximated GAP with glyphosate residues of < 0.05, < 0.05, 0.30 and 0.58 mg/kg (total residues < 0.05, < 0.05, 0.30 and 0.58 mg/kg). The Meeting considered four trials insufficient to estimate a maximum residue level for coffee beans.

Tea

Trials on tea were conducted in China (no GAP provided), India (no GAP provided), Sri Lanka (no GAP provided) and Japan (GAP single application at 0.9–2.3 kg ae/ha directed spray, with a PHI of 7 days). All trials were evaluated against the GAP of Japan. Four trials from Sri Lanka matched GAP for Japan with glyphosate residues of 0.12, 0.21, 0.27 and 0.42 mg/kg (total residues 0.12, 0.21, 0.27 and 0.42 mg/kg). The Meeting considered four trials insufficient to estimate a maximum residue level for tea.

Alfalfa

Trials on alfalfa were conducted in Canada (GAP of 0.9-1.8 kg ae/ha, PHI not specified but typically 3–7 days before last cut before rotation of renovation) and the USA (GAP 0.43-4.3 kg ae/ha PRE, 1.7 kg ae/ha PH for renovation, PHI 1.5 days).

Twenty trials approximated the GAP of the USA with glyphosate residues (as received) in forage of 54, 54, 55, 57, 58, 61, 64, 66, 70, 74, 76, 77, 85, 94, 98, 99, 107, 114, 122 and 153 mg/kg. Total residues were 54, 54, 55, 57, 58, 61, 64, 66, 71, 74, 76, 78, 86, 95, 99, 100, 108, 115, 123 and 154 mg/kg. The Meeting estimated a high residue of 154 mg/kg together with a median residue of 75 mg/kg for total residues in alfalfa forage all on an as received basis. The Meeting agreed to withdraw its previous recommendation for alfalfa forage.

Three trials from Canada matched GAP of that country with glyphosate residues in fodder (hay) of 57, 77 and 78 mg/kg (total residues 58, 78 and 79 mg/kg). Residues in hay from USA trials that matched GAP were 0.45, 83, 97, 97, 117, 131, 148, 187, 189, 195, 196, 204, 208, 214, 219, 256, 257, 280, 335 and 341 mg/kg. Total residues were: 0.79, 84, 98, 98, 119, 132, 149, 188, 190, 197, 197, 206, 210, 215, 221, 260, 259, 282, 338 and 344 mg/kg.

Residues of glyphosate in alfalfa fodder (hay) in ranked order were (n = 23): 0.45, 57, 77, 78, 83, 97, 97, 117, 131, 148, 187, 189, 195, 196, 204, 208, 214, 219, 256, 257, 280, 335 and 341 mg/kg (as received). Total residues in rank order were; 0.79, 58, 78, 79, 84, 98, 98, 119, 132, 149, 188, 190, 197, 197, 206, 210, 215, 221, 260, 259, 282, 338 and 344 mg/kg.

The Meeting recommended maximum residue level of 500 mg/kg (dry weight basis) for glyphosate in alfalfa fodder based on a high residue of 383 mg/kg (341 mg/kg ÷ 0.89 default dry matter content) together with highest residue and median residue levels of 344 and 190 mg/kg (as received) respectively for total residues.

Grass pasture

Trials on grass pasture were conducted in the USA (GAP of 0.31–4.3 kg ae/ha PRE, 4.3 kg ae/ha PH for pasture renovation, if application is less than 2.3 kg ae/ha no grazing or harvest interval is required, if > 2.3 kg ae/ha a waiting period 8 weeks applies before grazing or harvesting). Thirteen trials matching USA GAP were provided. Residues of glyphosate found in forage (from grass 15–20 cm high to boot stage) were 431, 456, 527, 616, 657, 664, 689, 713, 773, 869, 881, 884 and 1093 mg/kg (dry weight basis). Total residues were 435, 460, 530, 623, 660, 668, 691, 718, 777, 875, 881, 891 and 1099 mg/kg. The Meeting decided to utilize the averages of residues over 7 days (263, 273, 311, 333, 348, 430, 431, 449, 449, 478, 511, 612 and 615 mg/kg) to estimate a highest residue level of 615 mg/kg and a median residue of 431 mg/kg for total residues in grass forage, both on a dry weight basis.

Residues found in hay, cut when the grass was at boot to early head growth stage, were (n = 13): 7.3, 38, 66, 75, 100, 122, 187, 203, 212, 215, 233, 244 and 259 mg/kg (as received). Total residues were: 9.9, 39, 67, 77, 101, 124, 190, 210, 214, 218, 240, 248 and 262 mg/kg. The Meeting recommended a maximum residue level of 500 mg/kg (dry weight basis) for glyphosate based on a high residue of 294 mg/kg (259 mg/kg ÷ 0.88 default dry matter content) and highest and median residue levels of 262 and 190 mg/kg (as received) respectively for total residues in hay or fodder (dry) of grasses. The recommended maximum residue level replaces the previous recommendation of 50 mg/kg.

Bean fodder

Trials on beans haulm/straw were conducted in Belgium (no GAP provided) and the UK (GAP of 1.4 kg ae/ha, with a PHI of 7 days). Trials from Belgium were evaluated against UK GAP. Residues of glyphosate in haulm/straw at harvest were (n = 10): 3.4, 4.4, 7.8, 16, 17, 28, 46, 50, 51 and 93 mg/kg. AMPA was measured in four of the trials, with AMPA residues found to be less than 10% of the glyphosate residues. The therefore, Meeting agreed to use glyphosate residues to estimate the high and median residue levels. The Meeting estimated a maximum residue level of 200 mg/kg (dry weight basis) based on a highest residue of 103 mg/kg (93 mg/kg ÷ 0.90 default dry matter content) and high and median residue levels of 93 and 22.5 mg/kg (as received) for bean fodder.

Pea fodder

Trials on pea haulm/straw were conducted in Belgium (no GAP provided), Canada (GAP of 0.9 kg ae/ha, when the crop has < 30% grain moisture content and lower most pods (bottom 15%) are brown and seeds rattle, with a 7–14 days PHI) and the UK (GAP of 1.4 kg ae/ha, with a PHI of 7 days). Some trials from the UK conducted at higher rates were evaluated against the GAP of the Netherlands (0.72–2.2 kg ae/ha, PHI 7 days). Trials from Belgium were evaluated against the GAP of the UK. Residues in pea straw from Canada (16, 19, 20 and 28 mg/kg) appeared to be from a different population to that data approximating the GAP of the UK and the Netherlands; the latter were used for the purposes of maximum residue level estimation. Residues in ranked order were (n = 10): 27, 27, 31, 78, 79, 125, 154, 179, 200 and 320 mg/kg (as received). Total residues were 79, 80, 127, 155 and 181 mg/kg. AMPA was measured in five of the trials, with AMPA residues found to be less than 10% of the glyphosate residues. The Meeting therefore agreed to use glyphosate residues to estimate the high and median residue levels. The Meeting estimated a maximum residue level of 500 mg/kg (dry weight basis) based on a highest residue of 364 mg/kg (320 mg/kg ÷ 0.88 default dry matter content) and high and median residue levels of 320 and 102 mg/kg (as received) respectively for pea hay or fodder (dry).

Lentil fodder

Trials on lentil straw were conducted in Canada (GAP of 0.9 kg ae/ha, when crop has < 30% grain moisture content and lowermost pods (bottom 15%) are brown and seeds rattle, with a 7–14 days PHI). Residues of glyphosate were < 0.05 and 11 mg/kg. The Meeting considered two trials inadequate for the purposes of estimating an MRL for lentil straw.

Soya bean forage and fodder

Trials on conventional soya beans were conducted in the USA (GAP 3.7 kg ae/ha for PH use, do not graze or harvest treated hay or fodder for livestock feed within 25 days of last application. If application rate for PH is less than 0.74 kg ae/ha the livestock feed interval is reduced to 14 days after last application). The Meeting considered that pre-harvest application would give rise to residues in bean forage and fodder representative of GAP. Four trials approximating GAP for the USA had glyphosate residues in hay of 2.5, 3.4, 8.5 and 9.9 mg/kg (as received). Corresponding AMPA residues were 0.16, 0.18, 0.30 and 0.1 mg/kg respectively. The Meeting considered four trials insufficient to estimate a maximum residue level for soya bean hay. The Meeting agreed to withdraw its previous recommendation of 200 mg/kg for soya bean fodder.

Additionally, trials were conducted on glyphosate tolerant soya beans (GAP 1.7 kg ae/ha LPO; 0.83 kg ae/ha PH, do not graze or harvest treated hay or fodder for livestock feed within 14 days of last application). Residues of glyphosate in forage in trials that approximated USA GAP were 4.1, 4.5, 9.1, and 12 mg/kg (as received). No trials matched GAP for hay. The Meeting considered four trials inadequate for the purpose of estimating a maximum residue level and agreed to withdraw the previous recommendation of 5 mg/kg for soya bean forage.

Sugar beet tops

Trials were provided on sugar beet (glyphosate tolerant) from the USA (GAP 0.43–4.2 kg ae/ha PRE, 0.43–1.3 kg ae/ha LPO, 0.43-0.87 kg ae/ha PH, PHI 30 days). No trials matched GAP.

Barley straw

Trials on barley straw were conducted in Belgium (no GAP provided), France (no GAP provided) and the UK (GAP of 0.54–-1.4 kg ae/ha, PHI 7 days). Trials conducted in Belgium, France as well as some UK trials were evaluated against the GAP of the Netherlands (GAP is 0.72–2.2 kg ae/ha, PHI 7 days). Residues in straw in four UK trials that matched the GAP of that country were 13, 41, 47 and 62 mg/kg. In twenty-three trials that matched GAP of the Netherlands residues of glyphosate in straw were 29 and 86 mg/kg for Belgium trials, 6.0, 6.9, 12, 15, 17, 33, 39, 40, 43, 59, 71, 80, 96, 102, 110, 126, 140, 147 and 160 mg/kg for trials conducted in France and 22 and 56 mg/kg for two UK trials.

The Meeting considered the residues to be from the same population and decided to pool the results. Residues of Glyphosate in barley straw in ranked order were (n = 27): 6.0, 6.9, 12, 13, 15, 17, 22, 29, 33, 39, 40, 41, 43, 47, 56, 59, 62, 71, 80, 86, 96, 102, 110, 126, 140, 147 and 160 mg/kg (as received). Total residues, where measured, were: 6.1, 6.9, 13, 14, 15, 17, 22, 30, 34, 39, 41, 42, 44, 48, 56, 61, 64, 73, 82, 89, 100, 105, 115, 126, 142, 151 and 162 mg/kg (as received). The Meeting recommended a maximum residue level for glyphosate of 400 mg/kg (dry weight basis) based on a highest residue of 180 mg/kg (160 mg/kg ÷ 0.88 default dry matter content) and highest and median residue levels for total residues of 162 and 48 mg/kg (as received) for residues in barley straw.

Maize forage and fodder

Trials on conventional maize were conducted in the USA (GAP 4.2 kg ae/ha PRE; 0.87 kg ae/ha hooded sprayers, Do not graze or feed maize forage or fodder following hooded sprayer applications; 2.5 kg ae/ha PH grain moisture < 35%, PHI 7 days). Glyphosate residues in stover/fodder 7 days after

a pre-harvest application according to USA GAP were 2.1, 2.6, 3.4, 3.7, 4.8, 6.7, 8.4, 8.8, 11, 18, 23, 28, 35, 43, 43, 44, 53, 54, 55, 82, and 92 mg/kg. Total residues were: 2.1, 2.6, 3.5, 3.8, 4.8, 6.8, 8.8, 9.0, 11, 18, 24, 29, 36, 44, 45, 45, 54, 55, 56, 83 and 93 mg/kg.

Additionally, trials were conducted on glyphosate tolerant maize (GAP 4.2 kg ae/ha PRE; 1.7 kg ae/ha LPO, allowing a minimum of 50 days between application and harvest of corn forage; 0.87 kg ae/ha PH < 30% grain moisture, combined LPO+PH < 2.5 kg ae/ha, PHI 7 days). Seventeen trials on forage but no trials on tolerant maize fodder matched GAP. Glyphosate residues were (n = 17): 0.30, 0.50, 0.54, 0.66, 0.73, 0.79, 0.87, 0.92, 1.1, 1.1, 1.2, 1.3, 1.3, 1.8, 1.8, 2.2 and 4.6 mg/kg. Total residues were: 0.35, 0.50, 0.54, 0.75, 0.78, 0.84, 0.92, 0.98, 1.2, 1.2, 1.3, 1.4, 1.4, 1.9, 1.9, 2.4 and 4.7 mg/kg.

Using the residue trials for conventional maize crops, the Meeting recommended a maximum residue level of 150 mg/kg (dry weight basis) for maize fodder based on a highest residue of 111 mg/kg (92 mg/kg ÷ 0.83 default dry matter content). The Meeting also estimated a highest residue of 93 mg/kg and a median residue of 24 mg/kg for total residues in maize fodder, both on an as received basis.

The highest and median residues for total residues in maize forage were 4.7 and 1.2 mg/kg respectively, both on an as received basis. The Meeting considered that maize forage is not traded and agreed to withdraw its previous recommendation of 1 mg/kg.

Oat straw

Trials on oats straw were conducted in Canada (GAP 0.9 kg ae/ha PH, PHI growth stage dependent < 30% grain moisture 7–14 days) and the UK (GAP 0.54–1.4 kg ae/ha, < 30% grain moisture PHI 7–14 days). Residues in the trials from Canada conducted according to GAP were 3.5, 27 and 33 mg/kg. Residues in the UK trials were 12, 16, 21, 25, 33, 35, 49 and 64 mg/kg. Total residues where AMAP residues were also measured were: 26, 28, 34, 37 and 50 mg/kg. In all cases AMPA residues were much less than 10% of the glyphosate residue. The Meeting decided to pool the data from the Canada and UK trials to estimate a maximum residue level for glyphosate in oat straw of 100 mg/kg (dry weight basis weight) based on a highest residue of 71 mg/kg (64 mg/kg ÷ 0.90 default dry matter content) and to utilize the glyphosate residues to estimate highest and median residue levels of 64 and 27 mg/kg (as received).

Rye straw

Trials on rye straw were conducted in Denmark (no GAP provided) and were evaluated against the GAP of the UK (GAP 0.54–1.4 kg ae/ha, < 30% grain moisture PHI 7-14 days). No trials matched GAP.

Sorghum fodder and hay

Trials on sorghum were conducted in the USA (GAP of 1.7 kg ae/ha PH grain moisture < 35%, PHI 7 days). Residues of glyphosate in fodder (stover) in trials approximating USA GAP were (n = 10): 2.9, 7.0, 8.2, 16, 16, 21, 28, 29, 30 and 33 mg/kg (total residues 2.9, 7.1, 8.4, 16, 16, 22, 28, 29, 30 and 33 mg/kg). The Meeting recommended a maximum residue level for residues of glyphosate in sorghum fodder of 50 mg/kg (dry weight basis) based on a highest residue of 37.5 mg/kg (33 mg/kg ÷ 0.89 default dry matter content) and total residues highest and median levels of 33 and 19 mg/kg (as received) respectively.

Wheat straw

Trials on wheat were conducted in Belgium (no GAP provided), France (no GAP provided) and the UK (GAP of 0.54-1.4 kg ae/ha, < 30% grain moisture PHI 7 days). Trials conducted in Belgium,

France and some UK trials were evaluated against the GAP of the Netherlands (GAP is 0.72–2.2 kg ae/ha, PHI 7–14 days).

Five trials in the UK matched GAP of that country with residues in straw of 6.3, 7.3, 18, 47 and 47 mg/kg (total residues 6.5, 7.8, 18, 48 and 48 mg/kg).

In four trials conducted in the UK according to GAP of the Netherlands residues in straw were 23, 27, 68 and 109 mg/kg. Two trials from Belgium matched GAP of the Netherlands with residues of 103 and 198 mg/kg (total residues 105 and 202 mg/kg). In eighteen trials conducted in France matching the GAP of the Netherlands glyphosate residues in straw were 7.8, 16, 20, 23, 24, 25, 25, 32, 46, 58, 70, 77, 90, 96, 98, 107, 120 and 130 mg/kg (total residues 7.9, 17, 23, 24, 25, 26, 26, 33, 60, 71, 78, 90, 101, 111, 123 and 132 mg/kg).

The Meeting considered the residues from trials conducted according to the GAP of the UK and the Netherlands to be from the same population and to combine the residues for the purposes of estimation of a maximum residue level and STMR. Residues in wheat straw, in rank order were (n = 29): 6.3, 7.3, 7.8, 16, 18, 20, 23, 23, 24, 25, 25, 27, 32, 46, 47, 47, 58, 68, 70, 77, 90, 96, 98, 103, 107, 109, 120, 130 and 198 mg/kg (where measured total residues were 6.5, 7.8, 7.9, 17, 18, 23, 24, 25, 26, 26, 33, 48, 48, 60, 71, 78, 90, 101, 105, 111, 123, 132 and 202 mg/kg). The Meeting recommended a maximum residue level for glyphosate in wheat straw of 300 mg/kg (dry weight basis) based on a highest residue of 225 mg/kg (198 mg/kg ÷ 0.88 default dry matter content) as well as highest and median values for total residues of 202 and 48 mg/kg respectively, both on an as received basis.

The Meeting agreed to withdraw its previous recommendation for straw and fodder (dry) of cereal grains of 100 mg/kg.

Almond hulls

Trials on tree nuts (almonds, pecans, macadamias and walnuts) were conducted in the USA (GAP of 0.43–4.3 kg ae/ha, directed applications, with a PHI of 3 days). No trials matched GAP.

Cotton gin by-products

Trials on conventional cotton were conducted in the USA (GAP of 1.7 kg ae/ha, with a PHI of 7 days). No trials matched GAP for conventional cotton.

Trial data on glyphosate tolerant cotton (GAP 1.7 kg ae/ha, PHI 7 days) was also submitted. Residues of glyphosate in cotton gin by-products were found to be (n = 16): 5.8, 8.6, 16, 19, 21, 31, 34, 36, 37, 41, 42, 67, 70, 84, 91 and 126 mg/kg (total residues 5.9, 8.7, 16, 19, 21, 31, 35, 37, 37, 41, 42, 68, 71, 85, 92 and 128 mg/kg).

The Meeting estimated a highest residue level for cotton by-products of 128 mg/kg and a median level of 37 mg/kg, both on an as received basis.

Rape straw

Trials on conventional rape were conducted in the Sweden (No GAP) and were evaluated against the GAP of the UK (GAP 1.4 kg ae/ha, PHI 14 days). One trial matched GAP of the UK with residues in straw of 30 mg/kg The Meeting considered a single trial insufficient for estimation of a maximum residue level.

Fate of residues duiring processing

The Meeting received processing studies for glyphosate in olives, soya beans, sugar beet, barley, maize, oats, sorghum, wheat, cotton seed, linseed, rape seed, sugarcane, coffee beans and tea leaves,

investigating the effects of washing and further processing on incurred residues of glyphosate and AMPA in a range of processing fractions. Only the processing studies relevant to commodities for which maximum residue levels were estimated are reported below.

In trials from the USA conventional and glyphosate tolerant *soya beans* were processed according to simulated commercial practices into hulls, meal and oil (crude and refined). Median processing factors for hulls, meal and oil prepared according to commercial procedures were 4.5 (n = 3, range 3.8–5.2) for hulls, 1.0 (n = 3, range 0.8–1.0) for meal and < 0.01 (n = 4, range < 0.01–0.02) for crude and refined oil. Median processing factors for total residues were 4.1 (n = 3, range 2.1–5.0) for hulls, 0.89 (n = 3, range 0.83–0.95) for meal and < 0.02 (n = 4, range 0.01–< 0.04) for crude and refined oil.

The Meeting considered that using the median processing factors from the various studies would be appropriate, to reflect the different commercial practices, and estimated soya bean processing factors for glyphosate of 4.5 in hulls, 1.0 in meal and < 0.01 in oil. For total residues, processing factors of 4.1 in hulls, 0.89 in meal and < 0.02 in oil are established. As residues did not concentrate in oil the Meeting did not consider it necessary to recommend a maximum residue level.

Processing studies for *barley* to beer and distilled spirit were reported however the reported processing factors would exceed the theoretical maximum transfer and the results were not considered further.

In a study on processing (wet and dry milling) of glyphosate tolerant maize, processing factors for aspirated grain dust were 1.6 for both glyphosate and total residues. For bran, the processing factor for dry milling was 1.2 and for wet milling 0.45. Flour and meal had processing factors of 1.1 for glyphosate and total residues while the processing factors for gluten, starch and refined oil were all < 0.05 for glyphosate and < 0.33 for total residues.

Median processing factors for glyphosate in oat processed commodities for hulls, kernels and rolled oats were 1.8 (n = 4, range 1.5–2.3), 0.2 (n = 4, range 0.2-0.2) and 0.2 (n = 4, range 0.1–0.3) respectively.

Sorghum was processed in a study that approximated commercial practices to yield bran, flour, germ, grain dust, grits (medium) and starch. Mean processing factors (n = 2) for glyphosate residues were 5.0, 0.34, 0.02, 4.9, 0.47 and 0.01 respectively for bran, flour, germ, grain dust, grits (medium) and starch.

Four wheat processing studies were made available to the Meeting. Median glyphosate or best estimates of processing factors for bran, whole meal, flour and whole meal bread were 1.7, 0.46, 0.105 and 0.36. As residues concentrate in bran, the Meeting decided to estimate highest anticipated residues in bran based on the highest residue found from trials used to estimate the maximum residue level and mean processing factor. The Meeting confirmed its previous recommendation of a maximum residue level for wheat bran (unprocessed) of 20 mg/kg based on a high glyphosate residue of 9.5×1.7 = 16 mg/kg. The Meeting agreed to withdraw its recommendations for other processed commodities for which residues did not concentrate, i.e., wheat flour and wheat wholemeal.

Data on processing of sugar cane approximating commercial practices were made available to the Meeting. Although the application rates used on the cane processed to bagasse, molasses, raw and refined sugar were higher than the current GAP in the USA the Meeting decided to use the processing data for cane harvested 28 to 35 days after the last application. Median or best estimates of glyphosate processing factors for bagasse, molasses, raw and refined sugar were: 0.275, 8.25, 0.80 and 0.24 respectively. Using the STMR of 0.27 and high residue of 0.97 for sugar cane and the relevant processing factors, the Meeting estimated a maximum residue level for glyphosate of 10 mg/kg for sugar cane molasses together with a median residue of 2.3 mg/kg for total residues.

In a cotton processing study approximating commercial practices glyphosate processing factors for kernels, hulls, meal, crude oil, refined oil and bleached oil were 0.07, 0.33, 0.11, < 0.1, < 0.1 and < 0.1 respectively. As residues of AMPA were all below the limit of quantification, the processing factors for total residues are the same as for glyphosate. Residues did not concentrate in cotton seed oil. The Meeting agreed to withdraw its previous recommendations for the commodities cotton seed oil (crude) and cotton seed oil (edible).

Processing factors and high residue values relevant to maximum residue estimation (glyphosate) and STMR and median residue based on total residues are summarized below.

Commodity	$HR_{glyphosate}$ (mg/kg)	$PF_{glyphosate}$	High residue (mg/kg)	$STMR_{total}$ (mg/kg)	$PF_{total\ residue}$	STMR-P/ median residue (mg/kg)
Soya beans	17			5.0		
Meal		1.0			0.89	4.45
Hulls		4.5			4.1	20.5
Crude oil		< 0.01			< 0.02	< 0.1
Maize	3.0			< 0.12		
Aspirated grain dust		1.6			1.6	0.19
Bran		1.2	3.6		1.2	0.14
Flour		1.1	3.3		1.1	0.13
Meal		1.1			1.1	0.13
Gluten		< 0.05			< 0.33	0.04
Refined oil		< 0.05			< 0.33	0.04
Starch		< 0.05			< 0.33	0.04
Oats	14			4.75		
Hull		1.8				8.55[1]
Kernel		0.2				0.95[1]
Rolled oats		0.2				0.95[1]
Sorghum	13			4.8		
Bran		5.0	65		5.0	24
Flour		0.34			0.32	1.5
Germ		0.02			< 0.03	0.14
Grain dust		4.9			4.8	23
Grits		0.47			0.46	2.2
Starch		0.01			< 0.03	0.14
Wheat	9.5			1.05		
Whole meal		0.46			0.46	0.48
Flour		0.105			0.105	0.11
Bran		1.7	16		1.7[2]	1.8
Whole meal bread		0.36			0.36	0.38
Cottonseed	28			5.2		
Kernels		0.07			0.07	0.36
Hulls		0.33			0.33	1.7
Meal		0.11			0.11	0.57
Crude oil		< 0.1			< 0.1	0.52
Refined oil		< 0.1			< 0.1	0.52
Bleached oil		< 0.1			< 0.1	0.52

Commodity	$HR_{glyphosate}$ (mg/kg)	$PF_{glyphosate}$	High residue (mg/kg)	$STMR_{total}$ (mg/kg)	$PF_{total\ residue}$	STMR-P/ median residue (mg/kg)
Rape	12			0.93		
Seedcake		2.5				2.3a
Crude oil		< 0.1				
Refined oil		< 0.1				
Sugarcane	0.97			0.27		
Raw sugar		0.8			0.8	0.216
Refined sugar		< 0.24			< 0.24	0.065
Molasses		8.25	8.29		8.65	2.3
Bagasse		0.275			0.275	0.074

[1] Processing factors for total residues were not available, however residue data suggests AMPA is either present at less than 10% of the glyphosate residue level or not detected at levels above the limit of quantitation. In these cases the glyphosate processing factors and total residue processing factors would not be significantly different

[2] Where residues of AMPA were measured they were <LOQ. The Meeting decided to use the larger database of glyphosate processing factors to estimate the median processing factor for total residues

Farm animal dietary burden

The Meeting estimated the farm animal dietary burden of glyphosate residues using the diets in Appendix IX of the *FAO Manual* (FAO 2002).

The calculation from the MRLs provides the feed levels suitable for animal commodity MRL estimation, while the calculation from feed STMRs is suitable for estimation of animal commodity STMRs. DM is dry matter. The percent dry matter (DM) is taken as 100% where MRLs and STMRs are already expressed on a dry weight.

Calculation of the dietary burden for maximum residue estimation

Commodity	Highest residue/ STMR	Group	% DM	HR/STMR ÷DM	Diet content (%)				Residue contribution, mg/kg			
					Beef cattle	Dairy cows	Swine	Poul-try	Beef cattle	Dairy cows	Swine	Poul-try
Alfalfa forage	154	AL	35	440								
Alfalfa hay	344	AL	89	383								
Barley grain	20	GC	88	22.73	15	15	80	75	3.41	3.41	18.18	17.05
Barley straw	162	AS	89	182								
Maize grain	3	GC	88	3.41								
Maize aspirated grain fractions	0.19	CF	85	0.22								
Maize milled by-products (meal)	0.13	CF	85	0.15								
Maize fodder (stover)	43	AS	83	51.8								
Maize forage	4.7	AF	40	11.7								
Cotton seed	28	SO	88	33.38	25	25			8.35	8.35		
Cotton gin by-products	37	AM	90	41.11								
Cotton seed meal	0.57	AM	89	0.64								
Cotton seed hulls	1.7	AM	90	1.89								
Grass forage	615	AS		615	60	60			369	369		

Commodity	Highest residue/ STMR	Group	% DM	HR/STMR ÷DM	Diet content (%)				Residue contribution, mg/kg			
					Beef cattle	Dairy cows	Swine	Poul-try	Beef cattle	Dairy cows	Swine	Poul-try
Grass hay	262	AS	88	298								
Oats grain	14	GC	89	15.73								
Oats straw	64	AS	90	71.11								
Pea seed	2.1	VD	90	2.33								
Pea hay	320	AL	88	363.64								
Sorghum grain	13	GC	86	15.12								
Sorghum fodder (stover)	33	AS	88	37.50								
Sorghum aspirated grain fraction	23	CF	85	27								
Soya bean grain	20	VD	89	22.5			20	20			4.5	4.5
Soya bean meal	4.45	AL	92	4.84								
Soya bean hulls	20.5	AL	90	22.78				5				1.14
Sugar cane molasses	2.3	DM	75	3.07								
Wheat grain	9.5	GC	89	10.67								
Wheat straw	202	AS	88	230								
Wheat milled by-products (bran)	1.8	CF	88	2.05								
TOTAL					100	100	100	100	**381**	**381**	**22.7**	**22.7**

Calculation of the dietary burden for STMR estimation

Commodity	STMR/ STMR-P residue	Group	% DM	STMR/ STMR-P ÷DM	Diet content (%)				Residue contribution, mg/kg			
					Beef cattle	Dairy cows	Swine	Poul-try	Beef cattle	Dairy cows	Swine	Poultry
Alfalfa forage	75	AL	35	214.29								
Alfalfa hay	190	AL	89	213.5								
Barley grain	7.65	GC	88	8.69	20	20	80	75	1.74	1.74	6.95	6.52
Barley straw	48	AS	89	53.9								
Maize grain	0.12	GC	88	0.14								
Maize aspirated grain fractions	0.19	CF	85	0.22								
Maize milled by-products (meal)	0.14	CF	85	0.16								
Maize fodder (stover)	24	AS	83	28.92								
Maize forage	1.2	AF	40	3.0								
Cotton seed	5.2	SO	88	5.91								
Cotton gin by-products	37	AM	90	41.11								
Cotton seed meal	0.57	AM	89	0.64								
Cotton seed hulls	1.7	AM	90	1.89								
Grass forage	431	AS		431	60	60			258.6	258.6		
Grass hay	190	AS	88	215.9								

Commodity	STMR/ STMR-P residue	Group	% DM	STMR/ STMR-P ÷DM	Diet content (%)				Residue contribution, mg/kg			
					Beef cattle	Dairy cows	Swine	Poul-try	Beef cattle	Dairy cows	Swine	Poultry
Oats grain	4.15	GC	89	4.66								
Oats straw	27	AS	90	30								
Pea seed	0.5	VD	90	0.56								
Pea hay	102	AL	88	115.91								
Sorghum grain	4.8	GC	86	5.58								
Sorghum fodder (stover)	19	AS	88	21.59								
Sorghum aspirated grain fraction	23	CF	85	27	20	20			5.41	5.41		
Soya bean grain	5.0	VD	89	5.62				5				0.28
Soya bean meal	4.45	AL	92	4.84								
Soya bean hulls	20.5	AL	90	22.78			20	20			4.56	4.56
Sugar cane molasses	2.3	DM	75	3.07								
Wheat grain	1.05	GC	89	1.18								
Wheat straw	48	AS	88	54.55								
Wheat milled by-products (bran)	1.8	CF	88	2.05								
TOTAL					100	100	100	100	**266**	**266**	**11.5**	**11.4**

The glyphosate dietary burdens for animal commodity MRL and STMR estimation (residue levels in animal feeds expressed on dry weight, figures in brackets are for STMRs) are: beef and dairy cattle 381 (266) ppm, swine 23 (11.5) ppm and poultry 23 (11.4) ppm.

Farm animal feeding studies

The Meeting received information on the residue levels arising in animal tissues and milk when dairy cows were fed rations containing a 9:1 mixture of glyphosate and AMPA at total combined daily dietary levels of 40, 100 and 400 ppm. No residues were detected in milk from animals receiving the highest feed level. Tissue residues in single animals slaughtered after 28 days of feeding treated rations were < 0.05 mg/kg at all feed levels in fat and muscle for both glyphosate and AMPA. Glyphosate residues in liver were 0.06, 0.07 and 0.21 mg/kg for the 40, 100 and 400 ppm feed levels respectively (total residues 0.06, 0.07 and 0.47 mg/kg). In kidney, glyphosate residues were 0.32, 0.82 and 3.3 mg/kg for the three feed levels (total residues 0.42, 1.2 and 4.5 mg/kg). By 28 days after feeding treated rations ceased, residues in tissues were < 0.05 mg/kg in all tissues and milk.

The Meeting also received information on the residue levels arising in tissues when pigs were fed a ration with glyphosate and AMPA in a 9:1 ratio for 28 days at 40, 120 and 400 ppm in the diet. No residues above LOQ were detected in fat at any feed level. Maximum residues in tissue samples were for animals fed at 400 ppm and were liver 0.72 (total residue 1.4) mg/kg, kidney 9.1 (11) mg/kg, muscle 0.06 (0.06) mg/kg and fat < 0.05 (< 0.05) mg/kg. At the 40 ppm feed level, maximum residues were liver 0.06 (total residue 0.06) mg/kg, kidney 0.32 (0.42) mg/kg, muscle < 0.05 (< 0.05) mg/kg and fat < 0.05 (< 0.05) mg/kg. Residues in tissues were < 0.05 mg/kg for all feed levels at 28 days after access to treated feed was stopped.

A residue study on laying hens fed a diet incorporating glyphosate and AMPA in a 9:1 ratio at 40, 120 and 400 ppm for periods of up to 28 days was made available to the Meeting. At the highest feeding levels, maximum glyphosate residues in eggs were 0.12 (total residues 0.16) mg/kg, no residues were detected in eggs at the lowest feeding level. Maximum residues in tissues at the highest feeding level were < 0.05 mg/kg for fat and muscle and 0.61 (total residue 1.1) mg/kg for

liver and 4.3 (4.8) mg/kg for kidney. At the lowest feed level of 40 ppm maximum residues in tissues were < 0.05 mg/kg for fat and muscle and 0.06 (total residue 0.06) mg/kg for liver and 0.35 (0.35) mg/kg for kidney

Animal commodity maximum residue levels

The dietary burdens used for maximum residue and STMR estimation for beef and dairy cattle at 381 and 266 ppm are close to the maximum feed level of 400 ppm and this feed level was used to estimate residue levels in milk and cattle tissues. Maximum residues of glyphosate expected in tissues are: fat < 0.05 mg/kg, muscle < 0.05 mg/kg, liver 0.20 mg/kg, kidney 3.1 mg/kg and the mean residue for milk < 0.05 mg/kg. The STMR dietary burden for beef and dairy cattle is 266 ppm. The Meeting estimated STMR values for total residues from the mean total residues obtained at the 400 ppm feeding level. The estimated STMRs were: meat < 0.05 mg/kg, fat < 0.05 mg/kg, kidney 2.9 mg/kg, liver 0.29 mg/kg and milks < 0.05 mg/kg.

Dietary burden (mg/kg)[1]		Residues[3] (mg/kg)								
Feeding level [ppm][2]		Milk	Fat		Muscle		Liver		Kidney	
		Mean	HR	Mean	HR	Mean	HR	Mean	HR	Mean
MRL beef	(381)		*(< 0.05)*		*(< 0.05)*		*(0.20)*		*(3.1)*	
	[400]		< 0.05		< 0.05		0.21		3.3	
MRL dairy	(381)	*(< 0.05)*								
	[400]	< 0.05								
STMR beef	(266)			*(< 0.05)*		*(< 0.05)*		*(0.29)*		*(2.9)*
	[400]			< 0.05		< 0.05		0.43		4.3
STMR dairy	(266)	*(< 0.05)*								
	[400]	< 0.05								

[1] Values in parentheses are the estimated residues at the dietary burdens

[2] Values in square brackets are the actual feeding levels in the transfer study

[3] Residue values in parentheses in italics are obtained from the dietary burden, feeding levels in the transfer study and the residues found in the transfer study. Mean is mean animal tissue (or milk) residue in the relevant feeding group. The residues for HR calculations are glyphosate residues while those for STMR calculations are total residues (glyphosate + 1.5×AMPA).

The maximum dietary burden for pigs is 23 ppm. The levels of residues in tissues other than kidney all expected to be < 0.05 mg/kg for both glyphosate and AMPA when fed at this level. Residues in kidney at the 40 ppm feed level were a maximum of 0.6 mg/kg (total residues 0.72 mg/kg, mean total residues 0.43 mg/kg). Residues of glyphosate in kidney of animals fed at 23 ppm in the diet are estimated to be 0.345 mg/kg. Mean total residues in kidney of animals fed at 11.5 ppm in the diet are estimated to be 0.12 mg/kg. The STMR values for pig meat and pig edible offal as estimated to be 0 and 0.12 mg/kg.

The Meeting estimated a maximum residue level of 0.5 mg/kg for pig edible offal. The Meeting also estimated maximum residue levels for meat (from mammals other than marine mammals) of 0.05 (*) mg/kg; edible offal mammalian [except pigs] of 5 mg/kg and milks 0.05 (*) mg/kg. The recommendations replace the previous recommendations of 0.1 (*) mg/kg for cattle meat, 2 mg/kg for cattle edible offal, 0.1 (*) mg/kg for cattle milk, 0.1 (*) mg/kg for pig meat and 1 mg/kg for pig, edible offal.

The maximum dietary burden for poultry is 23 ppm. The levels of glyphosate and AMPA residues in fat, muscle and eggs are all expected to be < 0.05 mg/kg when fed at this level. Residues

of glyphosate in liver and kidney at the 40 ppm feed level were 0.06 mg/kg for liver and 0.35 mg/kg for kidney. Mean total residues in liver and kidney at the 40 ppm feed level were 0.055 and 0.31 mg/kg respectively. Residues of glyphosate in liver and kidney of birds fed at 23 ppm in the diet are estimated to be < 0.05 and 0.20 mg/kg. Mean total residues in liver and kidney of birds fed at 11.4 ppm are estimated to be < 0.05 and 0.088 mg/kg.

The Meeting estimated maximum residue levels for poultry meat 0.05 (*) mg/kg; poultry edible offal 0.5 and eggs 0.05 (*) mg/kg. The recommendation for poultry meat and eggs replace the previous recommendation, both 0.1 (*) mg/kg. As no residues are expected at the dietary burden for STMR estimation, the poultry meat and eggs STMRs are zero. The STMR for liver and kidney are estimated to be 0.05 and 0.088 mg/kg respectively.

DIETARY RISK ASSESSMENT

Short-term intake

The 2004 JMPR concluded that it was unnecessary to establish an ARfD for glyphosate. The Meeting therefore concluded that short-term dietary intake of glyphosate residues is unlikely to present a risk to consumers.

Long-term intake

The evaluation of glyphosate has resulted in recommendations for MRLs and STMRs for raw and processed commodities. Consumption data was available for 32 food commodities and were used in the dietary intake calculation. The results are shown in Annex 3.

The International Estimated Daily Intakes for the 5 GEMS/Food regional diets, based on estimated STMRs were in the range 0-1% of the maximum ADI of 1 mg/kg bw for the sum of glyphosate and AMPA (Annex 3). The Meeting concluded that the long-term intake of residues of glyphosate and AMPA from uses that have been considered by the JMPR is unlikely to present a public health concern.

4.11 IMAZALIL (110)

TOXICOLOGY

Evaluation for an acute reference dose

Imazalil (synonym: enilconazole, a pharmaceutical), 1-[2-(2,4-dichlorophenyl)-2-(2-propenyloxy)ethyl]-1*H*-imidazole), was first evaluated by the JMPR in 1977 when a temporary ADI of 0–0.01 mg/kg bw was established. The ADI of 0–0.01 mg/kg bw was reaffirmed in 1986 on the basis of the NOAEL in a 2-year study in dogs. In 1991, the JMPR reconsidered imazalil and a new ADI of 0–0.03 mg/kg bw was established based on a NOAEL for clinical signs, decreased body-weight gain and food consumption, decreased serum concentration of calcium, increased alkaline phosphatase activity, and increased liver weight in a study in dogs. In 2000, the JMPR reaffirmed the ADI and concluded that an ARfD was unnecessary.

The present Meeting was asked to reconsider the need for an ARfD by the Codex Committee on Pesticide Residues in view of refinements to the criteria used to establish ARfD values since 2000.

The present Meeting considered six new studies of acute toxicity (investigating end-points such as death and irritation) that were submitted by the sponsors. The Meeting also reconsidered the existing database on imazalil as previously evaluated and described in the monograph; however, the original studies were not available to the Meeting.

All the studies submitted complied with the essential elements of the applicable test guidelines and GLP requirements.

Toxicological data

The present Meeting evaluated the following studies:

The acute oral LD_{50} of imazalil technical and its salts in rats ranged between 200 and 664 mg/kg bw. Clinical signs that were observed at 160 mg/kg bw and above in survivors were ataxia, piloerection, hypotonia, hypothermia, and ptosis.

Imazalil was a slight irritant to the skin of rabbits and was moderately irritating to the eye. It had sensitizing potential when tested by the Magnusson & Kligman method.

The 2000 JMPR evaluated the following studies:

In a series of studies of developmental toxicity in mice, rats and rabbits, the lowest NOAEL for maternal toxicity after dosing by gavage was 5 mg/kg per day on the basis of reduced food consumption at higher doses. No teratogenicity was seen in any species. The lowest NOAEL for fetal toxicity in rabbits was 5 mg/kg bw per day on the basis of an increased number of resorptions and a reduced number of live pups.

In a two-generation study, the NOAEL for maternal toxicity was 20 mg/kg bw per day on the basis of reduced body-weight gain. The NOAEL for fetotoxicity was 20 mg/kg bw per day on the basis of a decreased number of live pups and an increased number of stillbirths at 80 mg/kg bw per day. A statistical re-examination on a litter basis showed that the rate of mortality of F_1 pups during lactation was significantly increased at the highest dose of 80 mg/kg bw per day.

In two studies of developmental toxicity in mice, the overall NOAEL for maternal toxicity (reduced body-weight gain) and fetotoxicity (reduced number of live fetuses, body weight and number of resorptions) was 10 mg/kg bw per day.

A published case study involving only one woman indicated that imazalil used to treat a fungal infection was well tolerated after oral ingestion at high doses (50 mg per day progressing to 1200 mg per day over 6 months). The only adverse effect noted was nausea.

Toxicological evaluation

The Meeting considered that an ARfD was necessary on the basis of mortality at doses of less than 1000 mg/kg bw, and acute clinical signs at and above 160 mg/kg bw.

On the basis of the data reviewed and previous evaluations, the Meeting established an ARfD of 0.05 mg/kg bw, using the NOAEL of 5 mg/kg bw per day for maternal and fetal toxicity in a study of developmental toxicity in rabbits and a safety factor of 100. It was considered that this ARfD would also be protective of the potential effects observed during gestation and lactation. The Meeting concluded that it would be inappropriate to use a human case study with only one individual for the purpose of establishing an ARfD.

The Meeting recognized that an ARfD based on maternal and fetal toxicity would be conservative for the general population, but that in the absence of a more suitable study this value was considered appropriate.

An addendum to the toxicological monograph was prepared.

Levels relevant to risk assessment

Species	Study	Effect	NOAEL	LOAEL
Rat	Two-generation reproduction study[a]	Maternal toxicity	20 mg/kg bw per day	80 mg/kg bw per day
		Fetotoxicity	20 mg/kg bw per day	80 mg/kg bw per day
Rabbit	Developmental[b]	Maternal toxicity	5 mg/kg bw per day	10 mg/kg bw per day
		Developmental toxicity	5 mg/kg bw per day	10 mg/kg bw per day

[a] Dietary administration at a nominal concentration
[b] Gavage administration

Estimate of acute reference dose

0.05 mg/kg bw

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

Additional end-points relevant for establishing an ARfD

4.12 INDOXACARB (216)

TOXICOLOGY

Indoxacarb is the ISO approved name for a new oxadiazine insecticide, methyl (*S*)-*N*-[7-chloro-2,3,4a,5-tetrahydro-4a-(methoxycarbonyl)indeno[1,2-*e*][1,3,4]oxadiazin-2-ylcarbonyl]-4′-(trifluoromethoxy)carbanilate (IUPAC), also known as methyl (4a*S*)-7-chloro-2,5-dihydro-2-[[(methoxycarbonyl)[4-(trifluoromethoxy)phenyl]amino]carbonyl]indeno[1,2-*e*][1,3,4]oxadiazine-4a(3*H*)-carboxylate (CAS).

The indoxacarb racemate contains two enantiomers (*S*:*R*), designated DPX-KN128 and DPX-KN127, but only the *S* enantiomer has insecticidal activity. The ISO approved common name applies only to the insecticidally active *S* enantiomer. The indoxacarb racemate DPX-JW062 has been used in several toxicological studies. Subsequent refinements in the chemical synthesis process have enabled commercial production of a mixture enriched approximately 3:1 with the insecticidally active enantiomer. This enriched mixture has the code DPX-MP062 and is the active ingredient in all currently formulated products. The database contains a series of studies with DPX-MP062 to demonstrate its toxicological equivalence with DPX-JW062.

Indoxacarb has not previously been considered by the Meeting.

All pivotal studies were performed by GLP-certified laboratories and complied with the relevant OECD test guidelines.

Biochemical aspects

The kinetics and metabolism of racemic or enantiomer-enriched indoxacarb appeared to be very similar in rats. Indoxacarb administered by gavage at low doses (5 mg/kg bw) is extensively, albeit slowly, absorbed (69–81%), but at higher doses (150 mg/kg bw) saturation kinetics becomes evident (8–14% absorption). There was a considerable difference in the time required to achieve the maximal concentration in blood between the sexes. In males it was 5 h at a low dose and 3 h at a high dose, while in females it was 8 h and 27 h respectively. In-vitro evidence from rat hepatic microsome preparations showed that while females metabolized indoxacarb more slowly than males, they produced almost tenfold more of the toxic metabolite IN-JT333. This metabolite, which contains the chiral centre, showed evidence of stereospecific uptake into fat. Elimination (probably caused by the preferential accumulation of metabolites in fat and erythrocytes) was slow, with the half-life in plasma ranging between 92 h and 114 h in males and females respectively.

In rats, indoxacarb is biotransformed to yield the arylamine metabolite 4-trifluoromethoxyaniline. This metabolite, which does not contain a chiral centre, was present in the urine and erythrocytes. The *N*-hydroxy derivative of 4-trifluoromethoxyaniline, while not being detected in excreta or erythrocytes, has been implicated as the causative agent responsible for haemolytic effects observed in all repeat-dose studies because of its ability to effectively oxidize glutathione in erythrocytes in vitro. The haemolytic potential of the arylamine metabolite (4-trifluoromethoxyaniline) observed in the erythrocytes of treated rats was not tested.

The major metabolites in the faeces were formed by hydrolysis of the carboxymethyl group from the amino nitrogen of the trifluoromethoxyphenyl portion of the parent compound, and hydroxylation of the inandione ring. No parent compound was detected in bile and no single metabolite accounted for more than 4% of an administered dose. An oxadiazine ring-opened metabolite formed by hepatic microsomal enzymes is likely to be a precursor for several metabolites found in urine. The eight minor urinary metabolites in rats accounted in total for less than 5% of the administered dose.

Toxicological data

Indoxacarb (DPX-MP062) has low acute oral toxicity (LD_{50} = 1730 mg/kg bw) in male rats and moderate oral toxicity (LD_{50} = 268 mg/kg bw) in female rats, and low dermal (LD_{50} > 5000 mg/kg bw) and inhalation toxicity (DPX-JW062; LC_{50} = 4200 mg/m^3 (4.2 mg/L) in rats. The difference in oral toxicity between the sexes is thought to arise from the more efficient biotransformation of indoxacarb to an acutely toxic metabolite IN-JT333 in females (LD_{50} = 52 mg/kg bw and 39 mg/kg bw in males and females respectively). Purified indoxacarb (DPX-KN128) and its insecticidally-inactive enantiomer (DPX-KN127) are almost equally toxic by the oral route. Although DPX-KN128, like DPX-MP062, showed a difference in oral toxicity between the sexes (i.e. LD_{50} = 843 mg/kg bw and 179 mg/kg bw in males and females respectively), the absence of a sex difference for DPX-KN127 (LD_{50} = 444 mg/kg bw and 480 mg/kg bw in males and females respectively) may be attributable to the dose selection.

Indoxacarb (DPX-MP062) was a moderate eye irritant in rabbits, was not a skin irritant in rabbits, but was a skin sensitizing agent in the maximization test in guinea-pigs.

Although indoxacarb has been shown to block neuronal sodium channels in insects, clear evidence of neurotoxicity in mammals occurred only at high acute doses (200 mg/kg bw) at which ataxia, reduced motor activity, forelimb grip strength and decreased foot splay were observed in male rats. Clinical signs suggestive of neurotoxicity were noted in short-term repeat-dose dietary studies in mice and included abnormal gait/mobility and head tilt at high doses (30 mg/kg bw per day and greater). Long-term exposure to indoxacarb at doses of 22 mg/kg bw or greater in mice caused

neuronal degeneration in the piriform cortex and hippocampus. Higher doses resulted in death. In contrast, a repeat-dose study of neurotoxicity in rats showed no effects on motor activity or functional observational battery assessments, and no histological evidence of neurotoxicity at doses of up to 12 mg/kg bw per day in males and 6 mg/kg bw per day in females.

In studies in mice, rats and dogs, the two main toxicological findings after repeated dosing with indoxacarb were mild haemolysis and reduced body-weight gain. Both effects occurred at similar doses in short-term repeat-dose studies, irrespective of the ratio of enantiomers. The reduction in body-weight gain was usually associated with a concomitant decrease in food consumption and food efficiency. In long-term studies in dogs and rats, the effect levels were similar (NOAELs were approximately 1–2 mg/kg bw per day respectively, and LOAELs were approximately 3–4 mg/kg bw per day). In a long-term study, mice were found to be insensitive to haematological effects and slightly less sensitive to reductions in body-weight gain (the NOAEL was 2.6 mg/kg bw per day, and the LOAEL was 13.8 mg/kg bw per day). The mild haemolysis observed in rats and dogs was characterized by reduced erythrocyte count, erythrocyte volume fraction, haemoglobin concentration, and a secondary physiological response involving increased haemopoiesis and deposition of haemosiderin in the spleen and liver. While the reductions in erythrocyte numbers through oxidative damage of haemoglobin occurred with a rather shallow dose–response curve, they achieved statistical significance relative to concurrent controls. In rats, early mortalities in groups receiving the highest dose and necropsy at 2 years revealed haemosiderin pigment in renal tubule cells and/or lumens, suggesting that haemolysis may have been a factor; these animals showed atrophy of the spleen, thymus and/or bone marrow, which was attributable to loss of lymphoid and haemopoietic cells. In mice (short-term exposure only) and dogs, haemoglobin within erythrocytes was oxidized/denatured (Heinz bodies). At high doses (> 17 mg/kg bw per day), morphological changes (Howell-Jolly bodies, polychromasia and hypochromasia) of the erythrocytes were observed in dogs.

There was no evidence of carcinogenicity at dietary concentrations of up to 125 ppm (22–30 mg/kg bw per day) in mice and up to 125 ppm (females only) and 250 ppm (8 mg/kg bw per day) in rats.

Indoxacarb (DPX-MP062) and two of its major metabolites, IN-JT333 and IN-KG433, gave negative results in an adequate battery of studies of genotoxicity in vitro and in vivo.

In view of the absence of any carcinogenic potential in rodents and the lack of genotoxic potential in vitro and in vivo, the Meeting concluded that indoxacarb is unlikely to pose a carcinogenic risk to humans.

In a two-generation study of reproductive toxicity in rats, adults given indoxacarb at a dose of 3.8 mg/kg bw per day had reduced body-weight gain and food consumption while the pups had lower body-weight gain during lactation. The NOAEL for effects in the parents and pups was 1.3 mg/kg bw per day. There were no effects on reproductive performance.

In studies of developmental toxicity in rats and rabbits, indoxacarb was not teratogenic but caused reduced fetal body weight when dams also showed reduced body weight and food consumption. The NOAEL for these effects was 2 mg/kg bw per day in rats and 1 mg/kg bw per day in rabbits.

The Meeting concluded that the existing database on indoxacarb was adequate to characterize the potential hazards to fetuses, infants and children.

In a study of acute neurotoxicity in rats, reduced body-weight gain and food consumption occurred at doses of 50 mg/kg bw and above in females and 200 mg/kg bw in males. The NOAEL was 12.5 mg/kg bw. In females, evidence of neurotoxicity, such as slightly reduced motor activity,

was observed at 100 mg/kg bw. In males, a reduced forelimb grip strength and decreased foot splay was observed at 200 mg/kg bw.

In-vitro data indicated that glucose-6-phosphate dehydrogenase-deficient individuals were slightly more sensitive (the concentration of agonist that elicits a response that is 50% of the possible maximum, EC_{50} = 55.5 µmol/L relative to 75.5 µmol/L for controls) to the oxidative effects of *N*-hydroxy-4-trifluoromethoxyaniline. The Meeting considered that the application of the normal tenfold safety factor for intraspecies variability would also be protective for glucose-6-phosphate dehydrogenase-deficient individuals.

Toxicological evaluation

It should be recognized that the ADI and ARfD applies to indoxacarb (*S* enantiomer) and its *R* enantiomer. The Meeting established an ADI of 0–0.01 mg/kg bw per day based on a NOAEL of 1.1 mg/kg bw per day for erythrocyte damage and the secondary increase in haematopoiesis in the spleen and liver in a 1-year dietary study in dogs and using a 100-fold safety factor. This NOAEL is supported by a similar value (1.3 mg/kg bw per day) in a two-generation study of reproduction in rats in which reduced body weight and food consumption in dams was observed. The pups lost body weight during lactation at this dose.

The Meeting established an ARfD of 0.1 mg/kg bw based on the NOAEL of 12.5 mg/kg bw for reduction in body-weight gain and food intake after a single administration of indoxacarb in a study of neurotoxicity in rats, and using 100-fold safety factor.

A toxicological monograph was prepared.

Levels relevant to risk assessment

Species	Study	Effect	NOAEL	LOAEL
Rat	3-month study of toxicity [a] (Indoxacarb 1:1 DPX-JW062)	Reduced body-weight gain; haemolysis	30 ppm, equal to 2.3 mg/kg bw per day	60 ppm, equal to 4.6 mg/kg bw per day
	3-month study of toxicity[a] (Indoxacarb 3:1 DPX-MP062)	Reduced body-weight gain; haemolysis	25 ppm, equal to 2.1 mg/kg bw per day	50 ppm, equal to 3.8 mg/kg bw per day
	3-month study of toxicity [a] (Indoxacarb 1:0 DPX-KN128)	Reduced body-weight gain; haemolysis	20 ppm, equal to 1.7 mg/kg bw per day	50 ppm, equal to 4.1 mg/kg bw per day
	2-year study of toxicity and carcinogenicity[a] (Indoxacarb 1:1 DPX-JW062)	Reduced body-weight gain; haemolysis	40 ppm, equal to 2.1 mg/kg bw per day	60 ppm, equal to 3.6 mg/kg bw per day
	Acute neurotoxicity[b] (DPX-MP062)	Reduced body-weight gain and food consumption	12.5 mg/kg bw	50 mg/kg bw
	Two-generation study of reproductive toxicity[a]	Maternal toxicity: reduced maternal body weight and food consumption Fetal toxicity: reduced maternal body weight during lactation	20 ppm, equal to 1.3 mg/kg bw per day	60 ppm, equal to 4 mg/kg bw per day
	Developmental toxicity[b]	Reduced maternal body-weight gain, food consumption and reduced fetal body weight	2 mg/kg bw per day	4 mg/kg bw per day

Species	Study	Effect	NOAEL	LOAEL
Rabbit	Developmental toxicity[b]	Reduced maternal body-weight gain, food consumption, clinical signs, decreased weight and number of live fetuses	10 mg/kg bw per day	100 mg/kg bw per day
Dog	12-month study of toxicity[a] (Indoxacarb 1:1 DPX-JW062)	Haemolysis	40 ppm, equal to 1.1 mg/kg bw per day	80 ppm, equal to 2.3 mg/kg bw per day

[a] Dietary administration
[b] Gavage administration

Estimate of acceptable daily intake for humans

0–0.01 mg/kg bw

Estimate of acute reference dose

0.1 mg/kg bw

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

Results from epidemiological, occupational health and other such observational studies of human exposure

Critical end-points for setting guidance values for exposure to indoxacarb

Absorption, distribution, excretion and metabolism in mammals	
Rate and extent of oral absorption	Rapid, approximately 70–80% at 5 mg/kg bw. Absorption rate and extent declines with dose, i.e. saturation kinetics evident.
Distribution	Distributed throughout the body with the highest levels in fat and erythrocytes.
Rate and extent of excretion	In both sexes, most of the administered dose was excreted within 72 to 96 h after single oral doses. The elimination half-life in plasma after a single dose ranged between 92 h and 114 h.
Potential for accumulation	Up to 9% of the administered dose retained in fat 7 days after a single dose. The elimination half-life in fat after dosing for 14 days was 18 days.
Metabolism in mammals	Extensive, no unchanged indoxacarb excreted in bile or urine
Toxicologically significant compounds (animals, plants and the environment)	Parent compound (*S*, *R* enantiomers), racemic metabolites IN-JT333 and IN-KG433
Acute toxicity (DPX-MP062 tested except for inhalation toxicity, DPX-JW062)	
Rat LD_{50} oral	1730 mg/kg bw (males); 268 mg/kg bw (females)
Rat LD_{50} dermal	> 5000 mg/kg bw (no deaths)
Rat LC_{50} inhalation (dust)	4.2 mg/L (4200 mg/m^3)
Rabbit, skin irritation	Non-irritant
Rabbit, eye irritation	Moderate irritant
Skin sensitization (test method)	Sensitizer in guinea-pigs (Magnussen & Kligman)
Acute toxicity (enantiomers)	
DPX-KN128: rat LD_{50} oral	843 mg/kg bw (males); 179 mg/kg bw (females)
DPX-KN127: rat LD_{50} oral	444 mg/kg bw (males); 480 mg/kg bw (females)
DPX-KN128: rat LD_{50} dermal	> 5000 mg/kg bw

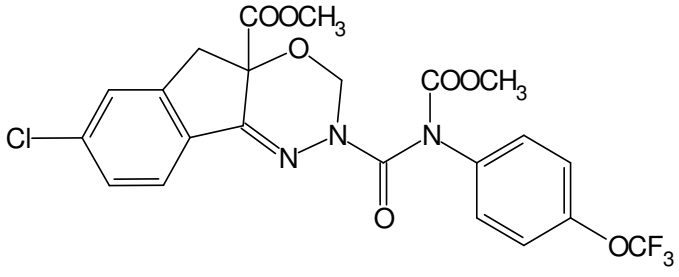
Short-term studies of toxicity	
Target/critical effect	Reduced body-weight gain, haemolysis in rats and dogs
Lowest relevant oral NOAEL	1.1 mg/kg bw per day (12-month study in dogs; DPX-JW062)
Lowest relevant dermal NOAEL	50 mg/kg bw per day in rats (DPX-MP062)
Lowest relevant inhalation NOAEC	No data
Genotoxicity	
	Unlikely to pose a genotoxic risk in vivo
Long-term studies of toxicity and carcinogenicity	
Target/critical effect	Reduced body-weight gain and haemolysis
Lowest relevant NOAEL	2.1 mg/kg bw per day in a 2-year dietary study in rats (DPX-JW062)
Carcinogenicity	Not carcinogenic in rats or mice; unlikely to pose a carcinogenic risk to humans
Reproductive toxicity	
Reproduction target/critical effect	Reduced pup weight gain at parentally toxic doses
Lowest relevant reproductive NOAEL	20 ppm, equal to 1.3 mg/kg bw per day
Developmental target/critical effect	Reduced fetal body weight at parentally toxic doses
Lowest relevant developmental NOAEL	2 mg/kg bw per day (rats)
Neurotoxicity/delayed neurotoxicity	
	Evidence of neurotoxicity at high doses (100 mg/kg bw in females and 200 mg/kg bw in males)
Lowest relevant NOAEL	12.5 mg/kg bw (for reduced body-weight gain and food consumption)
Other toxicological studies	
	Studies on a plant metabolite of indoxacarb indicated that it was no more toxic than the parent compound.
Medical data	
	No data

Summary

	Value	Study	Safety factor
ADI	0–0.01 mg/kg bw	Dog, 1-year study	100
ARfD	0.1 mg/kg bw	Rat, acute neurotoxicity	100

RESIDUE AND ANALYTICAL ASPECTS

Indoxacarb was considered for the first time by the present Meeting. It is an indeno-oxadiazine insecticide that is used for control of lepidoptera and other pests.



Indoxacarb, chemical name (IUPAC) (*S*)-7-chloro-3-[methoxycarbonyl-(4-trifluoromethoxy-phenyl)-carbamoyl]-2,5-dihydro-indeno[1,2-e][1,3,4]oxadiazine-4a(3*H*)-carboxylic acid methyl ester, is a new insecticidal active ingredient.

Indoxacarb was originally marketed as a racemic mixture of indoxacarb with its *R* enantiomer. Subsequently, a commercial technical material was developed that contained 3 parts indoxacarb and 1 part *R* enantiomer. For the purposes of this report the original material will be described as "racemic indoxacarb" and the later material will be described as "indoxacarb 3*S*+1*R*". Residues, where the two enantiomers are not in a defined ratio, will be described as "indoxacarb + *R* enantiomer".

Animal metabolism

The Meeting received the results of animal metabolism studies in rats, lactating dairy cows and laying hens.

When rats were orally dosed with indoxacarb it was readily absorbed followed by extensive metabolism and excretion. Loss of a methoxycarbonyl group produced IN-JT333 (methyl 7-chloro-2,5-dihydro-2-[[[4-(trifluoromethoxy)phenyl]amino]carbonyl]indeno[1,2-e][1,3,4]oxadiazine-4a(3*H*)-carboxylate) a major metabolite in the fat (see the toxicology report for more details of laboratory animal metabolism.)

When lactating dairy cows were orally dosed with labelled racemic indoxacarb (labelled in the indanone ring or the trifluoromethoxyphenyl ring) for 5 consecutive days at 200 mg/animal/day, equivalent to 10 ppm in the feed, most of the administered ^{14}C was excreted in the faeces (53–60%) and urine (19–20%). ^{14}C recovery was adequate (74% and 82% for the two labels). Residues in milk and tissues accounted for 0.7–0.8% and 0.79–0.84% of the dose respectively.

Parent compound was the major identified component of the residue in milk and each of the tissues. Chiral HPLC analysis of parent compound in milk (day 5 and pooled) and kidneys showed S:R enantiomer ratios of 2:1 and 2-2.5:1 respectively, a change from the starting ratio of 1:1.

The concentration of parent compound was substantially higher in the perirenal fat than in the other tissues suggesting that indoxacarb is a fat-soluble compound.

Metabolite IN-JT333 was present in perirenal fat at levels equivalent to 7% and 11% of parent compound levels. A number of other metabolites were identified in the liver.

When laying hens were orally dosed with labelled racemic indoxacarb (labelled in the indanone ring or the trifluoromethoxyphenyl ring) for 5 consecutive days at 1.2 mg/bird/day, equivalent to 10 ppm in the feed, most of the administered ^{14}C was excreted in the faeces (87–88%). ^{14}C recovery was 89% and 90%. Residues in eggs and tissues accounted for 0.28–0.4% and 1.3–1.4% of the dose respectively.

More residue appeared in the egg yolk than in the egg white, suggesting a tendency for fat solubility of the residue components. Parent compound constituted 3-4% of the total ^{14}C in egg yolk. Major metabolites in egg yolk were IN-KG433 + IN-KT319 ((*E*)- and (*Z*)-methyl 5-chloro-2,3-dihydro-2-hydroxy-1-[[[(methoxycarbonyl)[4-(trifluoromethoxy)phenyl]amino]carbonyl]hydrazono]-1*H*-indene-2-carboxylate) at 18-26% of total ^{14}C and Metabolite F (proposed identification as 1-(3-(6-chloro-1-hydroxy-2-methoxycarbonylindene)-4-(4-trifluoromethoxyphenyl)-1,2,4-triazole-2,3,4,5-tetrahydro-3,5-dione) at 7-14% of total ^{14}C.

Fat contained the highest concentration of residue, where the main component, Metabolite F constituted 45 and 38% of the total ^{14}C in the fat. Parent compound constituted 5 and 6% of the total

^{14}C in the fat. Metabolite IN-JT333 constituted 16 and 18% of the total ^{14}C in the fat. Residues in breast muscle and thigh muscle were generally too low for metabolite identification. Parent compound accounted for approximately 4-5% of the total ^{14}C in liver.

The residue in hens was fat-soluble but the residue composition in poultry fat was somewhat different from the residue composition in dairy cow fat.

Although there were similarities in the metabolic pathways in dairy cows and in poultry, there were also notable differences, e.g. a major metabolite, metabolite F in chicken fat, was not identified in dairy cow fat. In dairy cow fat, parent compound comprised 65–80% of the total residue with IN-JT333 the only identifiable metabolite at 5–7% of the total residue. In poultry fat, parent compound comprised 4–6% of the total residue with metabolite IN-JT333 at 17% of total residue. Other identified metabolites comprised 69–76% of the total residue.

Plant metabolism

The Meeting received plant metabolism studies with racemic indoxacarb on cotton, lettuce, grapes and tomatoes.

In each crop tested, parent compound mostly represented more than 90% of the total ^{14}C residue and was essentially the only compound detected. In grapes and tomatoes the residue was found to be mostly a surface residue. Chiral HPLC analysis of the residues in tomatoes showed that the enantiomers remained in a 1:1 ratio.

When cotton plants were treated with a single application of formulated [^{14}C]racemic indoxacarb, labelled in the indanone ring or the trifluoromethoxyphenyl ring, parent compound mostly represented more than 90% of the total ^{14}C residue in plant samples taken 7, 14, 30, 59 and 90 days after treatment. Chiral analysis of parent compound demonstrated that it remained racemic.

When lettuce plants were treated with a single application of formulated [^{14}C]racemic indoxacarb, labelled in the indanone ring or the trifluoromethoxyphenyl ring, parent compound mostly represented more than 95% of the total ^{14}C residue in plant samples taken 0, 7, 14, 21, 28 and 35 days after treatment. Even on day 0 less than half of the residue was on the leaf surface and the percentage on the surface decreased further with time after treatment.

Grape vines at the early fruit development stage were treated with a single foliar application of formulated [^{14}C] racemic indoxacarb, labelled in the indanone ring or the trifluoromethoxyphenyl ring. Most of the residue associated with fruit sampled on days 0, 14, 46 and 66 days (mature) post-treatment was surface residue, with 52% and 75% still surface residues 66 days after treatment. Parent compound was essentially the only component of the residue at all times.

When tomato vines were treated with 4 foliar applications, approximately 6–10 days apart, of formulated [^{14}C]racemic indoxacarb, labelled in the trifluoromethoxyphenyl ring, the majority of the residue associated with the fruit sampled 3, 7 and 14 days after the final application was surface residue, mostly around 90% of the residue. Parent compound was essentially the only component of the residue at all times. Parent compound isolated from leaf extracts from the samples collected before the second application and at harvest, 14 days after final application, were subjected to chiral HPLC analysis, which demonstrated that the two enantiomers remained in a 1:1 ratio.

Environmental fate in soil

The Meeting received information on the environmental fate of indoxacarb in soil, including studies on aerobic soil metabolism, field dissipation and crop rotational studies.

When [^{14}C]racemic indoxacarb labelled in the indanone ring or the trifluoromethoxyphenyl ring was incubated with a silt loam soil under aerobic conditions in the dark at 25°C, indoxacarb degraded quickly (half-life approximately 2-3 days). Identifiable metabolites were a minor part of the residue and mostly also degraded relatively quickly. IN-JT333 and IN-KG433 were the main metabolites in the first few days. IN-MK643 (1,2-dihydro-5-(trifluoromethoxy)-2*H*-benzimidazol-2-one) was identified as a longer term metabolite. The indanone ring was mineralized more quickly (26% in 120 days) than the trifluoromethoxyphenyl ring (5.4% in 120 days). The non-extractable ^{14}C had begun to decline within 90 days.

Very little of the applied indoxacarb moved below the top 15 cm of the soil during field dissipation trials of duration up to 18 months with [^{14}C]labelled racemic indoxacarb applied to 4 different soils. Indoxacarb (+ R enantiomer) concentrations declined to half of their initial values in seven days to six months.

In a field persistence and mobility study at two sites with racemic indoxacarb, residues of indoxacarb + R enantiomer disappeared from the top 15 cm of soil with half-lives of 55 and 60 days. Residues did not occur at lower depths except occasionally and intermittently. Metabolite IN-JT333 reached its peak concentration on days 14 and 100 at the 2 sites. Metabolite KG-433 was detected at a low concentration at one site.

In a confined rotational crop study in USA, soil was treated directly with [^{14}C]racemic indoxacarb labelled in the indanone ring or the trifluoromethoxyphenyl ring. Crops of carrots, lettuce, wheat and soybeans were sown into the treated soil at intervals of 36, 90 and 125 days after treatment and were grown to maturity and harvested for analysis. No parent compound or potential metabolite (IN-JT333) was detected. Low levels (≤ 0.05 mg/kg) of unidentifiable components were observed, with different patterns for the two different label positions suggesting that the parent compound was fragmented.

Methods of analysis

The Meeting received descriptions and validation data for analytical methods for residues of indoxacarb in raw agricultural commodities, processed commodities, feed commodities, animal tissues, milk and eggs.

Methods rely on HPLC-UV, GC-ECD and GC-MSD for analysis of indoxacarb in the various matrices. Indoxacarb and its R enantiomer are determined and reported together in all these methods. Signal enhancement by extracts of some matrices may require the preparation of standards in matrix extracts for measurement at low concentrations. A method with LOQ values of 0.2–0.3 mg/kg and not requiring that standards are prepared in control matrix solutions was provided as suitable for enforcement. A method suitable for enforcement for animal commodities (LOQ values 0.01–0.03 mg/kg) was adapted from existing method DFSG S19.

Numerous recovery data on a wide range of substrates were provided from validation testing of the methods, which showed that the methods were valid over the relevant concentration ranges.

Extraction efficiency has been proven with various solvent mixtures on [^{14}C]indoxacarb incorporated into or incurred in crop and animal commodities. Extraction procedures used either ethyl acetate – water or acetonitrile – hexane.

Stability of pesticide residues in stored analytical samples

The Meeting received information on the freezer storage stability of residues of racemic indoxacarb and indoxacarb 3S+1R in alfalfa, apple juice, apple pomace, apples, fat, grape pomace, grapes,

lettuce, liver, milk, muscle, peanut hay, peanut kernels, peanut meal, peanut oil, sweet corn, sweet corn forage, sweet corn stover, tomatoes and wine.

Residues were stable (less than 30% disappearance) during the storage intervals tested, mostly 6 months, 12 months or 18 months. Storage data was available for some animal commodities for only shorter intervals, 2–3 months, but which were suitable for the purpose of demonstrating stability of the residues in samples from the studies.

Definition of the residue

The composition of the residue in the metabolism studies, the available residue data in the supervised trials, the toxicological significance of metabolites, the capabilities of enforcement analytical methods and the national residue definitions already operating all influence the decision on residue definition. [Check the significance of metabolites with WHO Group].

Residues of indoxacarb are described as the sum of indoxacarb and its R enantiomer in national residue definitions.

In crop residue situations, parent compound comprises most of the residue and, at least in some situations, its enantiomer composition is unchanged.

In dairy cows, particularly in the fat, milk and kidney, parent compound is the major part of the residue. In liver, parent is the major identified compound in the residue. The parent residue becomes more enriched in S enantiomer (indoxacarb) in some animal commodities. Metabolite IN-JT333 was present in fat at levels of 7–11% of parent compound levels. Because of its toxicity, it should be included in the residue definition for risk assessment for animal commodities.

In poultry tissues and eggs, parent compound is a minor component of the residue and no single metabolite would be a good indicator of the residue level. Under the present dietary burden, even the total residues in poultry are estimated to be very low and unlikely to be detectable.

Available analytical methods and supervised trial data suggest that “indoxacarb and its R enantiomer” is a practical residue definition.

In the animal metabolism studies, the concentration of residue was clearly higher in the fat than in other tissues. In milk the residue partitioned into the lipid phase. The octanol-water partition coefficient (log P_{OW} = 4.65) also suggests that indoxacarb is a fat-soluble compound.

The Meeting recommended a residue definition for indoxacarb for plants and animals.

Definition of the residue (for compliance with the MRL for all commodities and for estimation of dietary intake for plant commodities): sum of indoxacarb and its R enantiomer. The residue is fat soluble.

Definition of the residue (for estimation of dietary intake for animal commodities): sum of indoxacarb, its R enantiomer and methyl 7-chloro-2,5-dihydro-2-[[[4-(trifluoromethoxy)phenyl]amino]carbonyl]indeno[1,2-e][1,3,4]oxadiazine-4a(3H)-carboxylate, expressed as indoxacarb.

Results of supervised trials on crops

The Meeting received supervised trials data for indoxacarb uses on apples, pears, stone fruits, grapes, cabbages, cauliflowers, broccoli, Brussels sprouts, lettuce, cucumbers, courgettes, melons, tomatoes,

peppers, sweet corn, pulses (adzuki beans, chickpeas mung beans), soybeans, potato, peanuts, cotton seed, sweet corn forage, legume animal feeds, alfalfa and cotton gin trash.

In most trials, duplicate field samples from an unreplicated plot were taken at each sampling time and were analysed separately. For the purposes of the evaluation, the mean of the two results was taken as the best estimate of the residue from the plot.

In some trials the formulation was based on racemic indoxacarb and in others indoxacarb 3S+1R was used. In all situations, the application rate and spray concentration were expressed in terms of the active ingredient, indoxacarb. In all cases residues were measured and expressed as indoxacarb + R enantiomer.

Parallel trials (same place, same application rate, same operator, etc) between products based on racemic indoxacarb and products based on indoxacarb 3S+1R compared the resulting residues on apple, broccoli, cabbage, cauliflower, cotton, lettuce and tomato. Residue levels from the 3S+1R treatments were approximately 50% of those with the racemic treatments. Therefore, supervised residue trials with racemic indoxacarb were not used as GAP trials for MRL evaluation, except for cases like sweet corn where residues were below LOQ.

The Meeting was informed that racemic indoxacarb is currently registered in only one country.

Processing trials with racemic material were considered valid because the processing factors should not be influenced by higher residues than achieved by GAP. It is common practice to apply a pesticide at exaggerated rates in processing trials to achieve measurable levels in processed commodities.

In some trials residues were measured on samples taken just prior to the final application as well as just after it (the “zero day” residue). The residue just prior expressed as a % of zero day residue provides a measure of the contribution of previous applications to the final residue in the use pattern followed in the trial.

For apples, the average carryover of residue was 45% (Europe, n = 12). For peaches, the average carryover of residue was 38% (Europe, n = 6). For grapes, the average carryover of residue was 41% (Australia, n = 12) and 44% (Europe, n = 20). For cabbages, the average carryover of residue was 44% (Europe, n = 6) and 25% (South Africa, n = 4). For cauliflower, the average carryover of residue was 27% (Europe, n = 7). For broccoli, the average carryover of residue was 23% (Europe, n = 6). For lettuce, the average carryover of residue was 26% (Europe, n = 6). For melons-peel, the average carryover of residue was 36% (Europe, n = 10). For tomatoes, the average carryover of residue was 48% (Europe, n = 12). For peppers, the average carryover of residue was 49% (Europe, n = 9).

The final 3 applications would be expected to influence the final residue level where the carryover is approximately 50%, which means that if GAP specified a maximum of 4 applications, trials with only 1 or 2 applications would not be maximum GAP. The final 2 applications would be expected to influence the final residue level for a carryover of approximately 30-40%. Earlier applications should not have a significant influence.

Residue data was evaluated only where labels (or translations of labels) describing the relevant GAP were available to the Meeting.

Apples

Residue trials on apples were available from Australia, Belgium, France, Germany, Greece, Hungary, Italy, South Africa and USA with racemic indoxacarb or indoxacarb 3*S*+1*R*. The trials from Hungary could not be evaluated because the PHI in the trials did not match the label PHI.

Indoxacarb is registered in Australia for use on apple trees at a spray concentration of 0.0075 kg ai/hL with a PHI of 14 days. In four Australian trials in 1996 and 1998 approximating GAP (0.0075–0.009 kg ai/hL and PHI 14–15 days) residues of indoxacarb + *R* enantiomer were: 0.28, 0.45, 0.50 and 0.85 mg/kg.

In Belgium, indoxacarb may be used on apple trees at 0.075 kg ai/ha with harvest 7 days after the final application. In three apple trials in Belgium with application rates of 0.075 ± 30%, i.e. 0.053 to 0.098 kg ai/ha and 7 days PHI, indoxacarb + *R* enantiomer residues were 0.06, 0.07 and 0.09 mg/kg. In five trials in France within ± 30% of the Belgian application rate and a PHI of 7 days, the indoxacarb + *R* enantiomer residues were: 0.05, 0.08, 0.11, 0.13 and 0.14 mg/kg.

In Germany, indoxacarb may be used on pome fruit at 0.077 kg ai/ha with a PHI of 7 days. In three apple trials in Germany with application rates of 0.077 ± 30%, i.e. 0.054–0.100 kg ai/ha and 7 days PHI, indoxacarb + *R* enantiomer residues were 0.10, 0.16 and 0.24 mg/kg.

Indoxacarb is allowed for use on apples in Greece at 0.1 kg ai/ha with a PHI of 7 days. In four trials in Greece with application rates of 0.10 ± 30%, i.e. 0.070–0.13 kg ai/ha and 7 days PHI, indoxacarb + *R* enantiomer residues were 0.03, 0.06, 0.10 and 0.23 mg/kg.

In Italy, indoxacarb may be used on apple trees at 0.075 kg ai/ha with harvest 7 days after the final application. In 3 apple trials in Italy with application rates of 0.075 ± 30%, i.e. 0.053 to 0.098 kg ai/ha and 7 days PHI, indoxacarb + *R* enantiomer residues were 0.07, 0.07 and 0.21 mg/kg.

In summary, the European data for 18 trials in rank order, median underlined, were: 0.03, 0.05, 0.06, 0.06, 0.07, 0.07, 0.07, 0.08, <u>0.09</u>, <u>0.10</u>, 0.10, 0.11, 0.13, 0.14, 0.16, 0.21, 0.23 and 0.24 mg/kg.

Indoxacarb is registered for use on apples in South Africa with a spray concentration of 0.0075 kg ai/hL with a PHI of 28 days. In a trial at 0.0068 kg ai/hL and PHI of 28 days indoxacarb + *R* enantiomer residues were 1.1 mg/kg.

Indoxacarb is registered for use in USA on apples at 0.12 kg ai/ha with a PHI of 14 days. In 14 trials in USA with application rates of 0.12 ± 30%, i.e. 0.085–0.156 kg ai/ha, residues of indoxacarb + *R* enantiomer in rank order, median underlined, were: 0.087, 0.11, 0.12, 0.13, 0.15, 0.20, <u>0.21</u>, <u>0.21</u>, 0.21, 0.22, 0.23, 0.23, 0.26 and 0.30 mg/kg.

The Meeting decided that the data from Australia and South Africa were insufficient to use on their own. The Australian data was significantly different from the USA data on a Mann-Whitney test. The USA data was also significantly different from the European data (Mann-Whitney test) and so could not be combined.

The Meeting estimated a maximum residue level and STMR and HR values for indoxacarb in apples, based on the USA data, of 0.5, 0.21 and 0.30 mg/kg respectively.

Pears

Indoxacarb residue trials on pears were available from Australia, South Africa and USA. The South African trials could not be evaluated because the spray concentrations used in the trials were too high compared with GAP concentrations.

Indoxacarb is registered for use on pears in Australia at a spray concentration of 0.0075 kg ai/hL with a PHI of 14 days. In one trial in Australia matching those conditions, residues of indoxacarb + *R* enantiomer were 0.30 mg/kg, but one trial is insufficient.

Indoxacarb is registered for use in USA on pears at 0.12 kg ai/ha with a PHI of 28 days. In 6 trials in USA with application rates of 0.12 ± 30%, i.e. 0.085-0.156 kg ai/ha, and with PHIs of 24 and 28 days, residues of indoxacarb + *R* enantiomer in rank order, median underlined, were: 0.042, 0.051, <u>0.051</u>, 0.065, 0.067 and 0.11 mg/kg.

The Meeting estimated a maximum residue level and STMR and HR values for indoxacarb in pears, based on the USA data, of 0.2, 0.051 and 0.11 mg/kg respectively.

Stone fruits

Indoxacarb residue trials on apricots, nectarines and peaches were available from Australia, France, Greece, Italy and Spain.

Indoxacarb is registered for use on apricots, nectarines and peaches in Australia at a spray concentration of 0.0075 kg ai/hL with a PHI of 7 days. In an apricot trial in Australia matching those conditions, residues of indoxacarb + *R* enantiomer were 1.5 mg/kg. In two nectarine trials in Australia matching those conditions, residues of indoxacarb + *R* enantiomer were 0.20 and 0.29 mg/kg. In one peach trial matching GAP, residues of indoxacarb + *R* enantiomer were 0.86 mg/kg.

In Greece, indoxacarb may be used on peach trees at 0.1 kg ai/ha with a PHI of 7 days. In three trials in Greece with application rates of 0.1 ± 30%, i.e. 0.07–0.13 kg ai/ha, residue of indoxacarb + *R* enantiomer were 0.12, 0.13 and 0.18 mg/kg.

In Italy, indoxacarb may be used on peach trees at 0.075 kg ai/ha with a PHI of 7 days. In four trials in Italy with application rates of 0.075 ± 30%, i.e. 0.053–0.098 kg ai/ha, residues of indoxacarb + *R* enantiomer were 0.06, 0.07, 0.11 and 0.16 mg/kg. In a peach trial in Spain matching Italian GAP, residues of indoxacarb + *R* enantiomer were 0.05 mg/kg. In a peach trial in France matching Italian GAP, residues of indoxacarb + *R* enantiomer were 0.10 mg/kg.

In summary, residues of indoxacarb + R enantiomer in peaches from the nine European trials in rank order, median underlined, were: 0.05, 0.060, 0.070, 0.10, <u>0.11</u>, 0.12, 0.13, 0.16 and 0.18 mg/kg.

The Australian data was insufficient to support a recommendation.

The Meeting estimated a maximum residue level and STMR and HR values for indoxacarb in peaches, based on the European data, of 0.3, 0.11 and 0.18 mg/kg respectively.

Grapes

Indoxacarb residue trials on grapes were available from Australia, France, Germany, Greece, Hungary, Italy, Spain and USA.

In Australia, indoxacarb may be sprayed on grapes at a concentration of 0.0051 kg ai/hL with harvest 56 days after the final treatment. In three grape trials in Australia with application

concentrations of 0.0051 ± 30%, i.e. 0.0036–0.0066 kg ai/hL, and PHIs of 60 and 61 days, residues of indoxacarb + *R* enantiomer were 0.04, 0.18 and 0.33 mg/kg.

In France, indoxacarb may be used on grapes at 0.038 kg ai/ha with harvest 10 days after the final application. In 15 grape trials in France with application rates of 0.038 ± 30%, i.e. 0.027–0.049 kg ai/ha and a PHI of 10 days, residues of indoxacarb + *R* enantiomer in rank order were: 0.02, 0.02, 0.02, 0.03, 0.03, 0.03, 0.04, 0.04, 0.04, 0.04, 0.04, 0.04, 0.05, 0.05 and 0.07 mg/kg. In one German trial matching French GAP, residues were 0.03 mg/kg.

In Germany, indoxacarb may be used on wine grapes at 0.056 kg ai/ha with harvest 14 days after the final application. In three grape trials in Germany with application rates of 0.056 ± 30%, i.e. 0.039–0.073 kg ai/ha and 14 days PHI, residues of indoxacarb + *R* enantiomer in rank order were: 0.04, 0.06 and 0.11 mg/kg.

Indoxacarb is registered in Greece for use on grapes at 0.068 kg ai/ha with a PHI of 10 days. In a Greek trial where indoxacarb was used at 0.052 kg ai/ha with a PHI of 9 days, residues of indoxacarb + *R* enantiomer were 0.12 mg/kg. In a Spanish trial in line with Greek GAP, residues of indoxacarb + *R* enantiomer were 0.13 mg/kg. In three Italian trials at 0.56–0.58 kg ai/ha, comparable to Greek GAP, residues 10–11 days after the final application were 0.13, 0.17 and 0.22 mg/kg.

Indoxacarb is registered in Hungary for use on grapes at 0.038 kg ai/ha with a PHI of 3 days. In two trials in Hungary with application rates of 0.045 kg ai/ha (18% above label rate) and a PHI of 3 days, residues of indoxacarb + *R* enantiomer were 0.12 and 0.46 mg/kg.

Indoxacarb is registered in Italy for use on grapes at 0.038 kg ai/ha with a PHI of 10 days. In four trials in Italy with application rates of 0.038 ± 30%, i.e. 0.027–0.049 kg ai/ha and PHIs of 10–11 days, residues of indoxacarb + *R* enantiomer were 0.06, 0.11 and 0.13 mg/kg. In 2 Spanish trials in line with Italian GAP, residues of indoxacarb + *R* enantiomer were 0.14 and 0.19 mg/kg.

In summary, residues in the 32 European grape trials in rank order, median underlined, were: 0.02, 0.02, 0.02, 0.03, 0.03, 0.03, 0.03, 0.04, 0.04, 0.04, 0.04, 0.04, 0.04, 0.04, 0.05, 0.05, 0.06, 0.06, 0.07, 0.11, 0.11, 0.12, 0.13, 0.13, 0.13, 0.14, 0.14, 0.17, 0.19, 0.22, 0.22 and 0.46 mg/kg.

In USA, indoxacarb may be used on grapes at 0.12 kg ai/ha with harvest 7 days after the final application. In 13 grape trials in USA matching GAP conditions, residues of indoxacarb + *R* enantiomer in rank order, median underlined, were: 0.09, 0.16, 0.17, 0.18, 0.26, 0.28, 0.32, 0.39, 0.42, 0.44, 0.75, 1.4 and 1.5 mg/kg.

The USA grape data and the European grape data was significantly different populations (Mann-Whitney test) and could not be combined. The USA grape data and the Australian grape data was not significantly different populations (Mann-Whitney test) and could be combined. In summary, the combined USA and Australian data set for grapes is 0.04, 0.09, 0.16, 0.17, 0.18, 0.18, 0.26, 0.28, 0.32, 0.33, 0.39, 0.42, 0.44, 0.75, 1.4 and 1.5 mg/kg.

The Meeting estimated a maximum residue level and STMR and HR values for indoxacarb in grapes, based on the USA data, of 2, 0.30 and 1.5 mg/kg respectively.

Cabbages

The Meeting received information on supervised residue trials on cabbages in Australia, Belgium, Denmark, France, Germany, Greece, India, Netherlands, Portugal, Italy, South Africa, Spain, UK and USA.

In Australia, indoxacarb is registered for use on cabbages with an application rate of 0.075 kg ai/ha and a PHI of 7 days. In two Australian trials matching GAP, residues of indoxacarb + *R* enantiomer were < 0.02 and 0.21 mg/kg.

Indoxacarb may be used in India on cabbages at 0.04 kg ai/ha with a PHI of 7 days. In three trials in India matching GAP, residues of indoxacarb + *R* enantiomer were < 0.01 (2) and 0.02 mg/kg.

In South Africa, indoxacarb may be used on cabbage at 0.045 kg ai/ha with harvest 3 days after the final treatment. In four South African trials with application rates at 0.053 kg ai/ha and a PHI of 3 days, residues of indoxacarb + *R* enantiomer were 0.40, 0.47, 0.83 and 2.0 mg/kg.

In France, indoxacarb is registered for use on cabbages with an application rate of 0.026 kg ai/ha and a PHI of 3 days. In seven trials in France with conditions aligned with GAP, residues of indoxacarb + *R* enantiomer were: < 0.02 (4), 0.02, 0.05 and 0.08 mg/kg. In three trials in The Netherlands with conditions aligned with French GAP, residues were < 0.02 (2) and 0.09 mg/kg. In three trials in Belgium, Denmark and UK with conditions aligned with French GAP, residues were < 0.02 (3) mg/kg.

In Germany, indoxacarb is registered for use on cabbages with an application rate of 0.026 kg ai/ha and a PHI of 3 days. In three trials in Germany matching GAP, residues of indoxacarb + *R* enantiomer were < 0.02 (3) mg/kg.

In Italy, indoxacarb is registered for use on cabbages with an application rate of 0.026 kg ai/ha and a PHI of 3 days. In three trials in Italy matching GAP, residues of indoxacarb + *R* enantiomer were < 0.02 (3) mg/kg. In a trial in Greece with conditions matching Italian GAP, residues were < 0.02 mg/kg.

In Spain, indoxacarb is registered for use on cabbages with an application rate of 0.025 kg ai/ha and a PHI of 3 days. In a trial in Spain matching GAP, residues of indoxacarb + *R* enantiomer were < 0.02 mg/kg. In a trial in Portugal under conditions matching Spanish GAP, residues were < 0.02 mg/kg.

In summary, the residues in the 22 cabbage trials from Europe, in rank order, were: < 0.02 (18), 0.03, 0.05, 0.08 and 0.09 mg/kg.

In USA, indoxacarb may be used on cabbage at 0.073 kg ai/ha with harvest 3 days after the final application. In four USA trials matching GAP, residues of indoxacarb + *R* enantiomer in cabbages with wrapper leaves were: 0.21, 0.34, 0.38 and 2.7 mg/kg.

The USA and South African cabbage data appeared to be similar populations and were combined. The European data and the combined USA and South African data was significantly different populations (Mann-Whitney test). In summary, the combined USA and South African data set for cabbage was 0.21, 0.34, 0.38, 0.40, 0.47,0.83, 2.0 and 2.7 mg/kg.

The Meeting estimated a maximum residue level and STMR and HR values for indoxacarb in head cabbages of 3, 0.435 and 2.7 mg/kg respectively, based on the USA and South African data.

Broccoli

The Meeting received information on supervised residue trials on broccoli in Australia, France, Italy, South Africa, UK and USA.

Indoxacarb is registered for use on broccoli in Australia at 0.075 kg ai/ha with a PHI of 7 days. In three trials on broccoli with conditions in line with GAP, residues of indoxacarb + *R* enantiomer were 0.08, 0.12 and 0.23 mg/kg.

Indoxacarb is registered for use on broccoli in France at 0.026 kg ai/ha with a PHI of 3 days. In three trials on broccoli in France under conditions of GAP, residues of indoxacarb + *R* enantiomer were: < 0.02, 0.04 and 0.08 mg/kg. In a UK trial on broccoli in line with French GAP, residues were 0.05 mg/kg.

Indoxacarb may be used on broccoli in Spain at 0.025 kg ai/ha with harvest 3 days after the final treatment. In four indoxacarb trials on broccoli in Italy under conditions of Spanish GAP, residues were 0.03, 0.06, 0.10, and 0.14 mg/kg.

In summary, residues in broccoli in nine European trials were < 0.02, 0.03, 0.04, 0.05, 0.06, 0.08, 0.10, 0.13 and 0.14 mg/kg.

Indoxacarb may be used in South Africa at 0.045 kg ai/ha on broccoli, with a PHI of 3 days. In two broccoli trials in South Africa in line with GAP conditions, residues of indoxacarb + *R* enantiomer were 0.22 and 0.31 mg/kg.

Indoxacarb is registered for use on broccoli in USA at 0.073 kg ai/ha with a 3 days PHI. In two trials in the USA in line with the registered use, residues of indoxacarb + *R* enantiomer were: 0.25, and 0.39 mg/kg.

The numbers of trials from Australia, South Africa and USA were too small, so the evaluation was based on the European data with the lower residue values. In summary, the European residue data for broccoli are: < 0.02, 0.03, 0.04, 0.05, 0.06, 0.08, 0.10 and 0.14 mg/kg.

The Meeting estimated a maximum residue level and STMR and HR values for indoxacarb in broccoli, based on the European data, of 0.2, 0.055 and 0.14 mg/kg respectively.

Cauliflower

The Meeting received information on supervised residue trials on cauliflowers in Australia, Denmark, France, Germany, Greece, Italy, Netherlands, South Africa and Spain.

Indoxacarb is registered for use on cauliflowers in Australia at 0.075 kg ai/ha with a PHI of 7 days. In a trial on cauliflower with conditions in line with GAP, residues of indoxacarb + *R* enantiomer were < 0.01 mg/kg.

Indoxacarb is registered for use on cauliflowers in France at 0.026 kg ai/ha with a PHI of 3 days. In seven trials on cauliflowers in France under conditions of GAP, residues of indoxacarb + *R* enantiomer were: < 0.02 (4), 0.01, 0.05 and 0.14 mg/kg. In a cauliflower trial in Denmark under conditions of French GAP, residues were 0.03 mg/kg. In 2 cauliflower trials in The Netherlands under conditions of French GAP, residues were < 0.02 and 0.09 mg/kg.

Indoxacarb is registered for use on cauliflowers in Germany at 0.026 kg ai/ha with a PHI of 3 days. In three trials on cauliflowers in Germany under conditions of GAP, residues of indoxacarb + *R* enantiomer were < 0.02, 0.03 and 0.07 mg/kg.

Indoxacarb may be used on cauliflowers in Italy at 0.026 kg ai/ha with harvest 3 days after the final treatment. In a trial in Italy in line with GAP, residues of indoxacarb + *R* enantiomer were 0.02 mg/kg. In a cauliflower trial in Greece in line with Italian GAP, residues were < 0.02 mg/kg.

Indoxacarb may be used on cauliflowers in Spain at 0.025 kg ai/ha with harvest 3 days after the final treatment. In a trial in Spain on cauliflowers according to GAP conditions, residues of indoxacarb + *R* enantiomer were < 0.02 mg/kg.

In summary, residues in cauliflowers in 16 European trials, in rank order, median underlined, were: 0.01, < 0.02 (8), 0.02, 0.03, 0.03, 0.05, 0.07, 0.09 and 0.14 mg/kg.

Indoxacarb may be used in South Africa at 0.045 kg ai/ha on cauliflowers, with a PHI of 3 days. In two cauliflower trials in South Africa in line with GAP conditions, residues of indoxacarb + *R* enantiomer were < 0.01 and 0.04 mg/kg.

The data from the cauliflower trials from Australia (1) and South Africa (2) appear to be of the same population as the European data and may be combined: < 0.01 (2), 0.01, < 0.02 (8), 0.02, 0.03, 0.03, 0.04, 0.05, 0.07, 0.09 and 0.14 mg/kg.

The Meeting estimated a maximum residue level and STMR and HR values for indoxacarb in cauliflowers, based on the European, South African and Australian data, of 0.2, 0.02 and 0.14 mg/kg respectively.

Brussels sprouts

The Meeting received information on supervised residue trials on Brussels sprouts in Australia.

Indoxacarb is registered in Australia for use on Brussels sprouts at 0.075 kg ai/ha with a PHI of 7 days. In two trials in Australia where the use was in line with GAP, residues of indoxacarb + *R* enantiomer were 0.03 and 0.07 mg/kg.

Because two trials are insufficient, the Meeting was unable to recommend a maximum residue level for indoxacarb on Brussels sprouts.

Cucumbers and summer squash

The Meeting received information on supervised residue trials on cucumbers in France, Greece, Italy and Spain. The Meeting also received information on 2 supervised trials on courgettes (summer squash) from Italy.

Indoxacarb is registered in Spain for field or greenhouse use on cucurbits at 0.038 kg ai/ha with a 1-day PHI. In two field trials on cucumbers in Spain under conditions matching GAP, residues of indoxacarb + *R* enantiomer were < 0.02 and < 0.02 mg/kg. In four greenhouse trials on cucumbers in Spain with conditions matching GAP (one trial with application rate of 0.047 kg ai/ha), residues were < 0.02 (2), 0.02 and 0.10 mg/kg. In two field trials on cucumbers in Italy under conditions matching Spanish GAP, residues were < 0.02 and < 0.02 mg/kg. In four greenhouse trials on cucumbers in France under conditions matching Spanish GAP, residues were < 0.02 (2), 0.02 and 0.03 mg/kg.

Indoxacarb is registered in Greece for field or greenhouse use on cucumbers at 0.038 kg ai/ha with a 1-day PHI. In two greenhouse trials on cucumbers in Greece with conditions matching GAP, residues of indoxacarb + *R* enantiomer were < 0.02 and < 0.02 mg/kg.

Indoxacarb may be used in Hungary for field or greenhouse use on cucumbers at 0.051 kg ai/ha with a 1-day PHI. In two greenhouse trials in France and one in Spain on cucumbers under conditions in line with Hungarian GAP, residues in indoxacarb + *R* enantiomer were 0.03, 0.03 and 0.05 mg/kg.

In summary, residues in cucumbers in four field trials from Europe were < 0.02 (4), and residues from 13 greenhouse trials in rank order, median underlined, were < 0.02 (6), 0.02, 0.02, 0.03, 0.03, 0.03, 0.05 and 0.10 mg/kg.

The Meeting agreed to use the greenhouse data set to support the MRL.

The Meeting estimated a maximum residue level and STMR and HR values for indoxacarb in cucumbers, based on the European greenhouse data, of 0.2, 0.02 and 0.10 mg/kg respectively.

Residues in the courgettes (summer squash) from the 2 field trials (0.07 and 0.09 mg/kg) were apparently different from the residues in cucumbers (< 0.02 (4)) in the field trials, so the data could not be combined to support a summer squash recommendation.

Melons

The Meeting received information on supervised residue trials on melons in France, Greece, Italy and Spain. Residues were measured on peel and pulp separately and the residue levels for whole fruit were calculated from the measured residues and the weights of peel and pulp.

Indoxacarb is registered in Spain for field or greenhouse use on cucurbits at 0.038 kg ai/ha with a 1-day PHI. In one field trial and 3 greenhouse trials on melons in Spain under conditions matching GAP, residues of indoxacarb + *R* enantiomer were 0.04 mg/kg (field) and 0.02, 0.03 and 0.04 mg/kg (greenhouse).

In four field trials and 3 greenhouse trials on melons in France with conditions matching Spanish GAP, residues of indoxacarb + *R* enantiomer were 0.02, 0.03, 0.03 and 0.05 mg/kg (field) and 0.02, 0.024 and 0.03 mg/kg (greenhouse).

In two field trials and 1 greenhouse trial on melons in Greece with conditions matching Spanish GAP, residues of indoxacarb + *R* enantiomer were 0.03 and 0.04 mg/kg (field) and 0.085 mg/kg (greenhouse).

In two field trials and two greenhouse trials on melons in Italy with conditions matching Spanish GAP, residues of indoxacarb + *R* enantiomer were 0.03 and 0.03 mg/kg (field) and 0.03 and 0.04 mg/kg (greenhouse).

In summary, the 9 field trials on melons produced residues of 0.02, 0.03 (5), 0.04, 0.04 and 0.05 mg/kg and the 9 greenhouse trials produced residues of 0.02, 0.02, 0.024, 0.03 (3), 0.04, 0.04 and 0.085 mg/kg.

The two data populations, field and greenhouse, are not significantly different (Mann-Whitney test) and can be combined for evaluation: 0.02 (3), 0.024, 0.03 (8), 0.04 (4), 0.05 and 0.085 mg/kg.

The Meeting estimated a maximum residue level for indoxacarb in melons, except watermelon, of 0.1 mg/kg.

Indoxacarb residues were below LOQ (0.02 mg/kg) in every sample of pulp in all the trials, so residues are unlikely to occur. In the absence of additional evidence that residues do not occur in the pulp, the Meeting estimated STMR and HR values of 0.02 mg/kg for melons.

Tomatoes

The Meeting received information on supervised residue trials on tomatoes in Australia, France, Greece, Italy, Spain and USA.

In Australia, indoxacarb may be applied to tomatoes at 0.075 kg ai/ha with a 3-days PHI. In two trials from Australia matching GAP conditions, residues of indoxacarb + *R* enantiomer were 0.09 and 0.12 mg/kg.

In France, indoxacarb may be applied to tomatoes in the field at 0.038 kg ai/ha with a 3-days PHI. In six trials on tomatoes in France matching GAP conditions, residues of indoxacarb + R enantiomer were < 0.02 (3), 0.03, 0.05 and 0.05 mg/kg.

In Greece, indoxacarb may be applied to tomatoes in the field or greenhouse at 0.038 kg ai/ha with a 1-day PHI. In one field trial and two greenhouse trials on tomatoes in Greece with conditions matching GAP, residues of indoxacarb + *R* enantiomer were 0.03 mg/kg (field) and 0.02 and 0.04 mg/kg (greenhouse).

In Spain, indoxacarb may be applied to tomatoes in the field or greenhouse at 0.038 kg ai/ha with a 1-day PHI. In three greenhouse trials on tomatoes in Spain with conditions matching GAP, residues of indoxacarb + *R* enantiomer were < 0.02, 0.03 and 0.03 mg/kg. In four field trials on tomatoes in Italy with conditions matching Spanish GAP, residues were 0.03, 0.03, 0.04 and 0.07 mg/kg. In one field trial and four greenhouse trials on tomatoes in France with conditions matching Spanish GAP, residues were < 0.02 mg/kg (field) and 0.02, 0.02, 0.065 and 0.065 mg/kg (greenhouse).

In summary, residues on tomatoes from 13 field trials in Europe were < 0.02, (4), 0.025, 0.03, 0.03, 0.033, 0.04, 0.045, 0.045, 0.050 and 0.070 mg/kg, and from 9 greenhouse trials < 0.02, 0.02, 0.02, 0.02, 0.03, 0.035, 0.04, 0.065 and 0.065 mg/kg. The two populations were not significantly different and could be combined: < 0.02, < 0.02, < 0.02, < 0.02, < 0.02, 0.02, 0.02, 0.02, 0.025, 0.03, 0.03, 0.03, 0.033, 0.035, 0.04, 0.04, 0.045, 0.045, 0.050, 0.065, 0.065 and 0.070 mg/kg.

In USA, indoxacarb is registered for use on tomatoes at 0.073 kg ai/ha with harvest 3 days after the final application. In six trials on tomatoes in USA under conditions matching GAP, but with intervals after treatment longer than PHI when residues were greater, residues of indoxacarb + *R* enantiomer in rank order, median underlined, were: 0.02, 0.05, 0.06, 0.13, 0.13 and 0.30 mg/kg.

The tomato residue data populations from Europe and US were significantly different (Mann-Whitney test) and could not be combined. The residue data from the Australian trials and the USA trials appeared to be similar populations and were combined resulting in an eight trial data-set: 0.02, 0.05, 0.06, <u>0.09</u>, <u>0.12</u>, 0.13, 0.13 and 0.30 mg/kg.

The Meeting estimated a maximum residue level and STMR and HR values for indoxacarb in tomatoes, based on the USA and Australian data, of 0.5, 0.11 and 0.30 mg/kg respectively.

Peppers

The Meeting received information on supervised residue trials on peppers in Australia, France, Greece, Italy, Portugal, Spain and USA.

In Australia, indoxacarb is registered for application to peppers at 0.075 kg ai/ha with harvest permitted 3 days after the final application. In three trials on sweet peppers with conditions matching GAP, residues of indoxacarb + *R* enantiomer were 0.03, 0.06 and 0.41 mg/kg.

In Greece, indoxacarb may be applied to peppers in the field or in greenhouses at 0.038 kg ai/ha with harvest 1 day after the final application. In two peppers trials in the field and two in greenhouses in Greece with conditions matching GAP, residues of indoxacarb + *R* enantiomer were 0.03 and 0.05 mg/kg (field) and 0.06 and 0.21 mg/kg (greenhouse).

In two peppers trials in the field and three in greenhouses in France with conditions matching GAP in Greece, residues of indoxacarb + R enantiomer were < 0.02 and < 0.02 mg/kg (field) and < 0.02 (2) and 0.02 mg/kg (greenhouse).

In three peppers trials in the field in Italy with conditions matching GAP in Greece, residues of indoxacarb + *R* enantiomer were < 0.02, 0.045 and 0.05 mg/kg.

In one peppers trial in the field in Portugal with conditions matching GAP in Greece, residues of indoxacarb + *R* enantiomer were 0.035 mg/kg.

In four peppers trials in the field and four in greenhouses in Spain with conditions matching GAP in Greece, residues of indoxacarb + *R* enantiomer were 0.03, 0.06, 0.075 and 0.19 mg/kg (field) and 0.035, 0.04, 0.085 and 0.09 mg/kg (greenhouse).

In summary, residues in peppers from 12 field trials in Europe were < 0.02 (3), 0.03, 0.03, 0.035, 0.045, 0.05, 0.05, 0.06, 0.075 and 0.19 mg/kg, and in 9 greenhouse trials < 0.02 (2) 0.02, 0.035, 0.04, 0.06, 0.085, 0.09 and 0.21 mg/kg.

In USA, indoxacarb is registered for use on peppers at 0.073 kg ai/ha with harvest 3 days after the final application. In nine trials with both bell peppers and non-bell peppers in USA with conditions matching GAP, residues of indoxacarb + *R* enantiomer in rank order, median underlined, were < 0.02 (3), 0.02, 0.02, 0.04, 0.067, 0.076 and 0.096 mg/kg.

The residue data populations from the European field trials and greenhouse trials are not significantly different (Mann-Whitney test) and may be combined. The populations of the European data set and the USA field trial data are not significantly different (Mann-Whitney test) and may all be combined for evaluation. A single value from three trials in Australia was higher than all the 30 values from USA and Europe suggesting a different data population. Combined European and USA data in rank order, median underlined: < 0.02 (8), 0.02, 0.02, 0.02, 0.03, 0.03, 0.035, 0.035, 0.04, 0.04, 0.045, 0.05, 0.05, 0.06, 0.06, 0.067, 0.075, 0.076, 0.085, 0.09, 0.096, 0.19 and 0.21 mg/kg.

The Meeting estimated a maximum residue level and STMR and HR values for indoxacarb in peppers, based on the combined data, of 0.3, 0.038 and 0.21 mg/kg respectively.

Egg plant

In USA, indoxacarb is registered for use on egg plant at 0.073 kg ai/ha with harvest 3 days after the final application, the same use pattern as on tomatoes and peppers. The Meeting decided to extrapolate the tomato recommendations to egg plant.

The Meeting estimated a maximum residue level and STMR and HR values for indoxacarb in egg plant of 0.5, 0.11 and 0.30 mg/kg respectively.

Sweet corn

The Meeting received information on supervised residue trials on sweet corn in USA.

Indoxacarb is registered for use on sweet corn in the USA with an application rate of 0.073 kg ai/ha and harvest 3 days after the final application. In six sweet corn trials in USA in line with GAP, residues of indoxacarb + *R* enantiomer in kernel + cob with husk removed were below LOQ (0.01 mg/kg). The six trials are supported with data from 12 USA trials with racemic indoxacarb. In 12 sweet corn trials with racemic indoxacarb, which is expected to give higher residues than the 3*S*+1*R* indoxacarb, residues were below LOQ (0.01 mg/kg) in 11 trials and close to LOQ in the remaining one (0.012 mg/kg).

The Meeting estimated a maximum residue level and STMR and HR values for indoxacarb in sweet corn (corn-on-the-cob) of 0.02, 0.01 and 0.012 mg/kg respectively.

Lettuce

The Meeting received information on supervised residue trials on lettuce in France, Greece, Italy, Spain and USA.

In Spain, indoxacarb may be applied to lettuce in field or greenhouse at 0.038 kg ai/ha with harvest permitted 1 day after the final application. In four field trials in Spain in line with GAP, residues of indoxacarb + *R* enantiomer in the head lettuce were 0.19, 0.25, 0.39 and 0.52 mg/kg.

In two field trials on head lettuce in Italy under conditions in line with Spanish GAP, residues of indoxacarb + *R* enantiomer were 0.16 and 0.88 mg/kg.

In three field trials on lettuce in France with conditions matching Spanish GAP, residues of indoxacarb + *R* enantiomer were 0.54 mg/kg for head lettuce and 0.52 and 0.86 mg/kg for leaf lettuce.

In a field trial on lettuce in Greece with conditions matching GAP (same as for Spain), residues of indoxacarb + *R* enantiomer were 1.65 mg/kg for leaf lettuce.

In summary, the residues on head lettuce from the European trials were 0.16, 0.19, 0.25, 0.39, 0.52, 0.54 and 0.88 mg/kg, while the residues on leaf lettuce were 0.52, 0.86 and 1.65 mg/kg.

In the USA, indoxacarb is registered for application to lettuce at 0.12 kg ai/ha with harvest 3 days after the final application. In nine field trials with head lettuce where conditions matched GAP conditions, residues of indoxacarb + *R* enantiomer were in rank order, median underlined, 0.61, 2.1, 2.5, 2.7, <u>2.8</u>, 3.2, 3.8, 4.0 and 4.3 mg/kg and for nine field trials on leaf lettuce, residues were 2.8, 3.6, 4.1, 6.1, <u>6.6</u>, 7.2, 7.4, 8.2 and 8.4 mg/kg.

The USA and European residue data populations for head lettuce were significantly different (Mann-Whitney test) and should not be combined. The same conclusion was reached for the leaf lettuce.

The Meeting estimated a maximum residue level and STMR and HR values for indoxacarb in head lettuce, based on the USA data, of 7, 2.8 and 4.3 mg/kg respectively.

The Meeting estimated a maximum residue level and STMR and HR values for indoxacarb in leaf lettuce, based on the USA data, of 15, 6.6 and 8.4 mg/kg respectively.

Pulses – adzuki beans, chickpeas and mungbeans

The Meeting received information on supervised residue trials on adzuki beans, chickpeas, mungbeans and soybeans from Australia. The adzuki bean data could not be evaluated because there is no registered indoxacarb use on adzuki beans.

In Australia, indoxacarb is registered for a single application to chickpeas at 0.045 kg ai/ha 28 days before harvest. In four chickpea trials in Australia with conditions matching GAP, residues of indoxacarb + *R* enantiomer in the chickpea grain were < 0.01, 0.02, 0.02 and 0.13 mg/kg.

In Australia, indoxacarb is registered for a single application to mungbeans at 0.060 kg ai/ha 28 days before harvest. In three mungbean trials in Australia with conditions matching GAP, residues of indoxacarb + *R* enantiomer in the mungbean grain were < 0.01 (2) and 0.02 mg/kg.

The Meeting combined the data from the three pulse crops for mutual support. Residues in the seven trials in rank order, median underlined, were: < 0.01 (3), <u>0.02</u> (3) and 0.13 mg/kg.

The Meeting estimated a maximum residue level and an STMR value for indoxacarb in chickpeas and mungbeans, based on the Australian data, of 0.2 and 0.02 mg/kg respectively.

Soybeans

The Meeting received information on supervised residue trials on soybeans from USA and Australia.

In Australia, indoxacarb is registered for a single application to soybeans at 0.060 kg ai/ha 28 days before harvest. In three soybean trials in Australia with conditions matching GAP, residues of indoxacarb + *R* enantiomer in the soybean grain were < 0.01 (2) and 0.06 mg/kg.

In the USA, indoxacarb is registered for use on soybeans at an application rate of 0.12 kg ai/ha with harvest 21 days after the final application. In 20 supervised trials in USA with a use pattern matching GAP, residues of indoxacarb + *R* enantiomer in rank order, with median underlined, were: 0.008, 0.009, 0.010, 0.010, 0.010, 0.011, 0.012, 0.014, 0.020, <u>0.024</u>, <u>0.030</u>, 0.032, 0.032, 0.039, 0.17, 0.24, 0.25, 0.29, 0.29 and 0.45 mg/kg.

The Australian data appear to be a different population from the USA data. The Meeting estimated a maximum residue level and an STMR value for indoxacarb in soybeans, based on the USA data, of 0.5 and 0.027 mg/kg respectively.

Potato

The Meeting received information on supervised residue trials on potatoes from USA.

In USA, indoxacarb is registered for use on potatoes at an application rate of 0.12 kg ai/ha with harvest 7 days after the final application. In 17 potato trials in USA with application rates of 0.15 kg ai/ha (25% above label rate) and PHI of 7 days, residues of indoxacarb + *R* enantiomer in rank order, median underlined, were: < 0.01 (17) mg/kg.

The Meeting estimated a maximum residue level and STMR and HR values for indoxacarb in potatoes of 0.02, 0.01 and 0.01 mg/kg respectively. Residue levels exceeded the detection limit (0.003 mg/kg) in some trials, so it is not a nil residue situation. Regulatory analytical methods for indoxacarb may not be practical for the low concentrations measured in the trials. The estimated maximum residue level of 0.02 mg/kg is based on the capabilities of the reviewed analytical methods.

Peanuts

The Meeting received information on supervised residue trials on peanuts from the USA.

In the USA, indoxacarb may be used on peanuts at 0.12 kg ai/ha with harvest 14 days after the final treatment. In 13 peanut trials in USA with conditions matching GAP, residues of indoxacarb + *R* enantiomer in peanut kernels were below LOQ (0.01 mg/kg) in every sample tested. Residue levels did not exceed the detection limit (0.003 mg/kg) in any trial. It should be noted that the PHI for peanuts is the interval between final treatment and digging, in this case 14 days. In the trials, peanuts were dug and allowed to dry in the field for 3 to 13 days before sampling.

The Meeting estimated a maximum residue level and STMR and HR values for indoxacarb in peanuts of 0.02*, 0.01 and 0.01 mg/kg respectively. Regulatory analytical methods for indoxacarb may not be practical for the low concentrations measured in the trials. The estimated maximum residue level of 0.02 mg/kg is based on the capabilities of the reviewed analytical methods.

Cotton

The Meeting received information on supervised residue trials on cotton from the USA.

In the USA, indoxacarb is registered for use on cotton at 0.12 kg ai/ha with harvest permitted 14 days after the final application. In seven cotton trials in USA with application rates of 0.15 kg ai/ha (25% above label rate) and PHI of 13–17 days (with intervals after treatment longer than PHI when residues were greater), residues of indoxacarb + *R* enantiomer in cotton seed in rank order, median underlined, were: 0.067, 0.26, 0.27, <u>0.36</u>, 0.37, 0.65 and 0.92 mg/kg.

The Meeting estimated a maximum residue level and STMR and HR values for indoxacarb in cotton seed of 1, 0.36 and 0.92 mg/kg respectively.

Legume animal feeds – chickpea, mungbean and soybean fodder

The Meeting received information on residues in legume fodder from the supervised residue trials in Australia.

In Australia, the indoxacarb label instruction for fodder of chickpeas, mungbeans and soybeans is: Do not graze or cut for stock food for 28 days after application. See previous section on pulses for GAP in Australia.

In four trials in Australia in line with GAP, residues of indoxacarb + *R* enantiomer in "chickpea trash" were: 0.78, 0.78, 1.1 and 1.2 mg/kg. In three trials in line with Australian GAP, residues in "mungbean trash" were: 1.3, 1.7 and 5.6 mg/kg. In 3 trials in line with Australian GAP, residues in "soybean trash" were: 0.07, 0.11 and 0.20 mg/kg.

The fodder data from the three crops appear not to be of the same population and so cannot be combined. The number of trials for each crop on its own is insufficient to recommend a fodder MRL.

Peanut hay

The Meeting received information on residues in peanut hay from the supervised residue trials in USA.

See previous section on peanuts for GAP in the USA. In 12 peanut trials in the USA matching the conditions of GAP, residues of indoxacarb + *R* enantiomer in peanut hay in rank order, median underlined, were: 2.1, 2.5, 8.9, 9.7, 11, <u>11</u>, <u>12</u>, 13, 15, 18, 21 and 33 mg/kg. Moisture levels were measured on 13 samples of peanut hay (mean = 28%, range = 19-36%). Residues in peanut hay expressed on dry weight (i.e. adjusted for 28% moisture) were: 2.9, 3.5, 12, 13, 15, <u>15</u>, <u>17</u>, 18, 21, 25, 29 and 45 mg/kg.

The Meeting estimated a maximum residue level and STMR and highest residue values for indoxacarb in peanut fodder (= hay) of 50, 16 and 45 mg/kg respectively.

Alfalfa

The Meeting received information on residues in alfalfa from supervised residue trials in the USA.

In USA, indoxacarb is registered for use on alfalfa at 0.12 kg ai/ha, once per cutting, with cutting permitted 7 days after application. In 12 trials on alfalfa with conditions matching GAP, residues were measured in each trial after each of 3 or 4 cuttings. From each cutting, the 7 days residue (or later if it was higher) was chosen for evaluation. Residues of indoxacarb + *R* enantiomer in the alfalfa forage (fresh weight) from the 43 cuttings were: 0.94, 1.5, 1.6, 1.8, 1.9, 2.1, 2.2, 2.4, 2.4, 2.5, 2.5, 2.7, 2.9, 2.9, 3.1, 3.1, 3.1, 3.2, 3.3, 3.3, 3.4, 3.4, 3.8, 3.8, 3.9, 3.9, 3.9, 4, 4.2, 4.4, 4.4, 4.5, 4.8, 5.3, 5.3, 5.6, 5.7, 6, 6.2, 6.6, 7, 7.5 and 9.7 mg/kg. Residues expressed as dry weight in rank order, median underlined, were: 4.7, 6.0, 8.0, 9.4, 9.6, 10, 10, 11, 11, 12, 12, 13, 13, 13, 14, 15, 15, 15, 16, 16, 16, <u>16</u>, 16, 17, 17, 17, 18, 18, 18, 18, 19, 19, 20, 21, 22, 22, 23, 24, 24, 26, 26, 27 and 28 mg/kg.

Residues of indoxacarb + *R* enantiomer in the alfalfa hay (fresh weight) from the 43 cuttings were: 2.4, 5.8, 6.1, 6.3, 6.7, 6.8, 7, 7.5, 7.7, 7.7, 8.2, 8.2, 8.2, 8.6, 9.1, 9.2, 9.2, 10, 10, 10, 10, 11, 12, 15, 15, 15, 16, 16, 16, 16, 17, 18, 18, 19, 20, 20, 20, 21, 23, 24, 25, 26 and 26 mg/kg. Residues expressed as dry weight in rank order, median underlined, were: 7.3, 7.5, 9.1, 10, 10, 11, 12, 12, 12, 12, 13, 13, 13, 14, 14, 14, 15, 15, 15, 16, 16, 17, 18, 19, 19, 20, 20, 20, 21, 23, 24, 25, 25, 25, 25, 26, 27, 31, 32, 33, 33, 33 and 43 mg/kg.

The Meeting estimated an STMR and a highest residue value for indoxacarb in alfalfa forage of 16 and 28 mg/kg respectively.

The Meeting estimated a maximum residue level and STMR and highest residue values for indoxacarb in alfalfa fodder (= hay) of 60, 18 and 43 mg/kg respectively.

Maize fodder

The Meeting received information on residues in sweet corn fodder (= maize fodder) from the supervised residue trials in USA.

See previous section on sweet corn for GAP in the USA. The PHI for fodder and stover is 35 days. In five sweet corn trials in the USA with application rates matching GAP, residue data on stover (mature dried stalks from which the grain or whole ear (cob + grain) have been removed) were accepted with PHIs of 28–66 days. Residues, expressed as fresh weight, of indoxacarb + *R* enantiomer in maize fodder were: 1.6, 1.9, 3.7, 5.3 and 9.8 mg/kg.

Moisture levels were measured on six samples of stover (3 of the 6 were in the GAP trials), giving a range and mean of 23–68% and 43% dry matter respectively. Residue levels were adjusted to dry weight in maize fodder using the measured dry matter for the 3 samples directly and the average dry matter for the other two. Residue levels in maize fodder, expressed as dry weight, in rank order, median underlined, were: 4.4, 4.8, 7.8, 8.6, and 15 mg/kg.

A set of five trials is rather a limited data set to support an MRL. However, the Meeting decided that it was best to take into account the residues occurring in the fodder from sweet corn when assessing farm animal dietary burden and therefore estimated a maximum residue level for maize fodder.

The Meeting estimated a maximum residue level and STMR and highest residue values for indoxacarb in maize fodder of 25, 7.8 and 15 mg/kg respectively.

Cotton fodder

The Meeting received information on residues in cotton gin trash (= cotton fodder) from the supervised residue trials in USA.

See previous section on cotton for GAP in USA. In seven trials on cotton in USA with an indoxacarb application rate of 0.15 kg ai/ha (25% above label rate) with harvest 13–17 days after the final application, residues of indoxacarb + *R* enantiomer in cotton gin trash in rank order, median underlined, were: 3.6, 6.6, 6.7, 8.0, 8.4, 8.4 and 11 mg/kg.

Moisture levels were measured on several samples of cotton gin trash from these and associated trials, giving a range and mean of 77–96% and 91% dry matter (n = 9) respectively. Because moisture levels were low (average < 10%) no adjustment was made for dry matter content.

The Meeting estimated a maximum residue level and STMR and highest residue values for indoxacarb in cotton fodder of 20, 8.0 and 11 mg/kg respectively.

Fate of residues during processing

Information on the fate of indoxacarb residues during food processing was available for apples, peaches, grapes, tomatoes, potatoes and soybeans. Processing factors for potato products could not be estimated because residues in the raw agricultural commodity were less than the LOQ.

Racemic indoxacarb was generally stable to hydrolysis under pasteurization conditions. Approximately 7–30% was lost during baking and boiling conditions. The products of hydrolysis were minor and polar.

Racemic indoxacarb was used in some of the processing studies. It is quite suitable for processing studies because it is the relative residue levels that are important.

Calculated processing factors and the mean or best estimate are summarized in the following table.

Raw agricultural commodity (RAC)	Processed commodity	Calculated processing factors.	Median or best estimate
Apples	Wet pomace	2.1, 2.6, 2.4, 2.6, 1.6, 3.6, 3.3	2.6
	Apple Juice	< 0.02, < 0.01, < 0.02, < 0.3, 0.14, < 0.3, < 0.2	0.05[1]
	Apple Sauce	< 0.3, < 0.14, < 0.3, < 0.2	0.2
Peach	Peach juice	< 0.08, < 0.11, < 0.20	0.08
	Canned peaches	< 0.08, < 0.11, < 0.20	0.08
Grapes	Raisins	2.7, 1.9, 3.5	2.7
	Grape juice	0.007	0.007
	Wine	0.037, 0.08, < 0.1, < 0.1, < 0.07	0.06
Tomatoes	Tomato puree	0.91, 0.23, 0.75, 2.0	0.83
	Tomato paste	3.2, 0.62	1.9
	Tomato juice	< 0.2, < 0.6	0.2
Undelinted cotton seed	Cotton seed hulls	0.026	0.026
	Cotton seed meal	0.0014	0.0014
	Cotton seed refined oil	0.036	0.036
Peanut kernels	Peanut oil	1	1
	Peanut meal	0.39	0.39
Soybean grain	Soybean hulls	8.5	8.5
	Soybean meal	< 0.14	0.14
	Soybean refined oil	0.66	0.66

[1] Mean of 0.14, and the 3 smaller “less-than” values.

The processing factors for wet apple pomace (2.6), apple juice (0.05) and apple sauce (0.2) were applied to the estimated STMR for apples (0.21 mg/kg) to produce STMR-P values for wet apple pomace (0.55 mg/kg), apple juice (0.011 mg/kg) and apple sauce (0.042 mg/kg).

The processing factors for peach juice (0.08) and canned peaches (0.08) were applied to the estimated STMR for peaches (0.11 mg/kg) to produce STMR-P values for peach juice (0.009 mg/kg) and canned peaches (0.009 mg/kg).

The processing factors for raisins (2.7), grape juice (0.007) and wine (0.06) were applied to the estimated STMR for grapes (0.30 mg/kg) to produce STMR-P values for raisins (0.81 mg/kg), grape juice (0.002 mg/kg) and wine (0.018 mg/kg). The processing factor for raisins (2.7) was applied to the HR for grapes (1.5 mg/kg) to produce an HR-P value for raisins (4.1 mg/kg).

The Meeting estimated a maximum residue level for indoxacarb in dried grapes (= currants, raisins, sultanas) of 5 mg/kg.

The processing factors for tomato puree (0.83), tomato paste (1.9) and tomato juice (0.2) were applied to the estimated STMR for tomatoes (0.11 mg/kg) to produce STMR-P values for tomato puree (0.09 mg/kg), tomato paste (0.21 mg/kg) and tomato juice (0.022 mg/kg).

The processing factors for cotton seed hulls (0.026), cotton seed meal (0.0014) and cotton seed refined oil (0.036) were applied to the estimated STMR for cotton seed (0.36 mg/kg) to produce STMR-P values for cotton seed hulls (0.0094 mg/kg), cotton seed meal (0.0005 mg/kg) and cotton seed refined oil (0.013 mg/kg). The estimated residue in cotton seed oil would be less than the highest residue in cotton seed because the processing factor is 0.036.

The Meeting agreed not to recommend a residue level suitable for establishing an MRL for cotton seed oil, because the level would not exceed the value recommended for the RAC, cotton seed.

The processing factors for peanut oil (1) and peanut meal (0.39) were applied to the estimated STMR for peanuts (0.003 mg/kg) to produce STMR-P values for peanut oil (0.003 mg/kg) and peanut meal (0.0012 mg/kg). The estimated residue in peanut oil would be the same as the highest residue in peanuts because the processing factor is 1.

The Meeting agreed not to recommend a residue level suitable for establishing an MRL for peanut oil, because the level would not exceed the value recommended for the RAC, peanuts.

The processing factors for soybean hulls (8.5), soybean meal (0.14) and soybean refined oil (0.66) were applied to the estimated STMR for soybean (0.027 mg/kg) to produce STMR-P values for soybean hulls (0.23 mg/kg), soybean meal (0.0038 mg/kg) and soybean refined oil (0.018 mg/kg). The estimated residue in soybean oil would be less than the highest residue in soybean because the processing factor is 0.66.

The Meeting agreed not to recommend a residue level suitable for establishing an MRL for soybean oil, because the level would not exceed the value recommended for the RAC, soybean.

Residues in animal commodities

Farm animal feeding

The Meeting received a lactating dairy cow feeding study, which provided information on likely residues resulting in animal tissues and milk from residues in the animal diet.

Lactating Holstein cows were dosed with indoxacarb 3*S*+1*R* at the equivalent of 7.5 (low dose), 22.5 (medium dose) and 75 (high dose) ppm in the dry-weight diet for 28 consecutive days. Milk was collected throughout and tissues were collected for residue analysis (as indoxacarb + *R* enantiomer) and as metabolite IN-JT333 from animals slaughtered on day 29.

Residues in milk reached a plateau within about 4 days and levels of residue were approximately proportional to the dose. Highest residues in the milk at the 3 dosing levels were:

0.021 mg/kg (low dose), 0.054 mg/kg (medium dose) and 0.19 mg/kg (high dose). Highest residues in cream were: 0.22 mg/kg (low dose), 0.60 mg/kg (medium dose) and 2.2 mg/kg (high dose).

Metabolite IN-JT333 was below LOQ (< 0.01 mg/kg) for almost all the milk samples, but was present in cream from the 3 dosing levels on day 28 at 0.018 (low dose), 0.027 (medium dose) and 0.075 (high dose) mg/kg, representing about 3–8% of the parent compound concentration.

Indoxacarb is fat-soluble. The residue concentration in cream was found to be 10.8 times the residue in the milk (regression line for 40 data points).

In the tissues, the mean residues (indoxacarb + *R* enantiomer) at the 3 dosing levels were: muscle (< 0.01, < 0.01, 0.066 mg/kg); fat (0.22, 0.45, 1.9 mg/kg); liver (< 0.01, 0.01, 0.018 mg/kg); kidney (< 0.01, 0.017, 0.039 mg/kg).

Metabolite IN-JT333 was below LOQ (< 0.01 mg/kg) in muscle, kidney and liver from all doses. Metabolite IN-JT333 was present in fat at approximately 4–7% of the parent compound concentration.

Residues depleted quickly from the milk of a high-dose animal after dosing was stopped, falling below LOQ (0.01 mg/kg) after 5 days. Residues depleted to 0.079 mg/kg in the fat of the animal subjected to a 75 ppm dose for 28 days and then no dose for 15 days, i.e. depletion by approximately 96% from the value at day 28.

Farm animal dietary burden

The Meeting estimated the dietary burden of indoxacarb in farm animals on the basis of the diets listed in Appendix IX of the *FAO Manual*. Calculation from highest residue and STMR-P values provides the levels in feed suitable for estimating MRLs, while calculation from STMR and STMR-P values for feed is suitable for estimating STMR values for animal commodities. The percentage dry matter is taken as 100% when the highest residue levels and STMRs are already expressed as dry weight.

Estimated maximum dietary burden of farm animals

Commodity	CC	Residue	Basis	DM	Residue dw	*Diet content (%)*			Residue contribution (mg/kg)		
		mg/kg		%	mg/kg	*Beef cattle*	*Dairy cows*	*Poultry*	Beef cattle	Dairy cows	Poultry
Alfalfa fodder	AL	43	highest residue	100	43	*45*	*10*		19.4	4.3	
Alfalfa forage	AL	28	highest residue	100	28						
Apple pomace, wet	AB	0.55	STMR-P	40	1.38		*5*			0.07	
Chick-pea (dry)	VD	0.13	highest residue	100	0.13						
Cotton fodder, dry	AM	11	highest residue	90	12.2	*5*	*20*		0.61	2.4	
Cotton seed	SO	0.92	highest residue	88	1.05						
Cotton seed hulls	AM	0.0094	STMR-P	90	0.0104						
Cotton seed meal		0.0005	STMR-P	89	0.0006			*15*			0.00008

Commodity	CC	Residue mg/kg	Basis	DM %	Residue dw mg/kg	*Diet content (%)*			Residue contribution (mg/kg)		
						Beef cattle	*Dairy cows*	*Poultry*	Beef cattle	Dairy cows	Poultry
Maize fodder	AS	15	highest residue	100	15	*25*	*15*		3.8	2.3	
Peanut fodder	AL	45	highest residue	100	45	*25*	*50*		11.3	22.5	
Peanut meal		0.0012	STMR-P	85	0.0014			*25*			0.00035
Potato culls	VR	0.0085	highest residue	20	0.043						
Soya bean (dry)	VD	0.45	highest residue	89	0.51			*20*			0.101
Soybean hulls	AL	0.23	STMR-P	90	0.26			*20*			0.051
Soybean meal	AL	0.0038	STMR-P	92	0.0041			*20*			0.00083
Total						*100*	*100*	*100*	35.0	31.6	0.15

Estimated mean dietary burden of farm animals

Commodity	CC	Residue mg/kg	Basis	DM %	Residue dwmg/kg	*Diet content (%)*			Residue contribution (mg/kg)		
						Beef cattle	*Dairy cows*	*Poultry*	Beef cattle	Dairy cows	Poultry
Alfalfa fodder	AL	25.5	STMR	100	25.5	*70*	*60*		17.9	15.3	
Alfalfa forage	AL	22.5	STMR	100	22.5						
Apple pomace, wet	AB	0.55	STMR-P	40	1.38		*5*			0.07	
Chick-pea (dry)	VD	0.015	STMR	100	0.015						
Cotton fodder, dry	AM	8	STMR	90	8.89	*20*	*20*		1.78	1.8	
Cotton seed	SO	0.36	STMR	88	0.41						
Cotton seed hulls	AM	0.0094	STMR-P	90	0.0104						
Cotton seed meal		0.0005	STMR-P	89	0.0006			*15*			0.00008
Maize fodder	AS	7.8	STMR	100	7.80	*10*	*15*		0.8	1.2	
Peanut fodder	AL	16	STMR	100	16						
Peanut meal		0.0012	STMR-P	85	0.0014			*25*			0.00035
Potato culls	VR	0.003	STMR	20	0.015						
Soya bean (dry)	VD	0.027	STMR	89	0.03			*20*			0.006
Soybean hulls	AL	0.23	STMR-P	90	0.26			*20*			0.051
Soybean meal	AL	0.0038	STMR-P	92	0.0041			*20*			0.00083
Total						*100*	*100*	*100*	20.4	18.3	0.06

Animal commodities, MRL estimation

For MRL estimation, the high residues in the tissues were calculated by interpolating the maximum dietary burden between the relevant feeding levels from the dairy cow feeding study and using the

highest tissue concentrations from individual animals within those feeding groups. The high residues for milk and cream were calculated similarly except that the mean milk and cream concentrations from the relevant groups were used instead of the highest individual values.

The STMR values for the tissues, milk and cream were calculated by interpolating the STMR dietary burdens between the relevant feeding levels from the dairy cow feeding study and using the mean tissue and milk concentrations from those feeding groups. The concentrations of Metabolite IN-JT333 in the tissues, milk and cream were expressed as indoxacarb and added to the concentrations of indoxacarb and its enantiomer, which caused a slight change in concentrations in cream and fat, but not in milk or the other tissues.

In the table, dietary burdens are shown in round brackets (), feeding levels and residue concentrations from the feeding study are shown in square brackets [] and estimated concentrations related to the dietary burdens are shown without brackets. Residue concentrations from the feeding study and estimated concentrations related to the dietary burdens include metabolite IN-JT1333.

Dietary burden (ppm) Feeding level [ppm]	Milk	Cream	Cream	Muscle	Liver	Kidney	Fat	Fat
MRL			Includes IN-JT333					Includes IN-JT333
	mean	mean	mean	highest	highest	highest	highest	highest
MRL beef cattle (35.0) [22.5, 75]				0.03 [<.01, 0.093]	0.014 [0.013, 0.019]	0.027 [0.020, 0.049]	0.86 [0.54, 1.9]	0.91 [0.57, 2.0]
MRL dairy cattle (31.6) [22.5, 75]	0.081 [0.058, 0.19]	0.88 [0.60, 2.2]	0.91 [0.62, 2.3]					
STMR								
	mean	mean	mean	mean	mean	mean	mean	mean
STMR beef cattle (20.4) [7.5, 22.5]				< 0.01 [< 0.01, < 0.01]	0.01 [< 0.01, 0.01]	0.016 [< 0.01, 0.017]	0.42 [0.22, 0.45]	0.44 [0.22, 0.48]
STMR dairy cattle (18.3) [7.5, 22.5]	0.048 [0.021, 0.058]	0.49 [0.21, 0.60]	0.51 [0.21, 0.62]					

The Meeting estimated dietary burdens for indoxacarb + *R* enantiomer in dairy cows to be 31.6 and 18.3 ppm (maximum and mean). By interpolation, the highest residue and STMR for milk were estimated as 0.081 and 0.048 mg/kg. Similarly, the STMR for cream was estimated 0.51 mg/kg. On the assumption of 50% milk fat in cream, these values become 1.82 and 1.02 mg/kg for milk fat. The highest residue for parent compound only in cream was 0.88 mg/kg, i.e. 1.76 mg/kg in milk fat.

The Meeting estimated a maximum residue level and an STMR value for indoxacarb in milk of 0.1 and 0.048 mg/kg, respectively.

The Meeting estimated a maximum residue level and an STMR value for indoxacarb in milk fat of 2 and 1.0 mg/kg, respectively.

The Meeting estimated dietary burdens for indoxacarb + *R* enantiomer in beef cattle to be 35.0 and 20.4 ppm (maximum and mean). By interpolation, the highest residues for muscle, liver, kidney and fat were estimated as 0.03, 0.014, 0.027 and 0.91 respectively, with corresponding STMR values of < 0.01, 0.01, 0.016 and 0.44 mg/kg. The highest residue of parent only in fat was 0.86 mg/kg.

The Meeting estimated maximum residue levels of 1 (fat) and 0.05 mg/kg for indoxacarb in mammalian meat and edible offal respectively.

The Meeting estimated STMR values for indoxacarb in muscle tissue, mammalian fat and edible offal of 0.01, 0.44 and 0.016 respectively, with corresponding HR values of 0.03, 0.91 and 0.027 mg/kg, respectively.

The Meeting estimated dietary burdens for indoxacarb + *R* enantiomer in poultry to be 0.15 and 0.006 ppm (maximum and mean). The dosing level in the laying hen metabolism study was equivalent to 10 ppm in feed. Indoxacarb (+ *R* enantiomer) was not a major component of the identified residue in poultry commodities so estimates were made of both the total ^{14}C residue and the indoxacarb residue resulting from exposure to the dietary burden feed levels. Calculations were made on the assumption that residues at the dietary burden level were proportional to residues in the laying hen metabolism study, based on relative intakes.

For a dietary burden of 0.15 ppm, estimated equivalent total residues were calculated as 0.0073, 0.0005, 0.0035, 0.0020 and 0.0048 mg/kg in fat, muscle, skin + fat, liver and eggs (yolk) respectively. Estimated residues of indoxacarb + *R* enantiomer were: 0.0004, < 0.0002, 0.0005, 0.0002 and 0.0002 mg/kg in fat, muscle, skin + fat, liver and eggs (yolk) respectively. All of these values are below the LOQ of the analytical method (0.01 mg/kg).

The Meeting recommended maximum residue levels of 0.01*(fat), 0.01* and 0.01* for indoxacarb in poultry meat, poultry offal and eggs, respectively. The Meeting recommended STMR and HR values of 0 mg/kg for poultry fat, muscle, offal and eggs, respectively.

DIETARY RISK ASSESSMENT

Long-term intake

The evaluation of indoxacarb resulted in recommendations for MRLs and STMR values for raw and processed commodities. Data on consumption were available for 37 food commodities and were used to calculate dietary intake. The results are shown in Annex 3.

The IEDIs in the five GEMS/Food regional diets, based on estimated STMRs were 1–50 % of the maximum ADI of 0.01 mg/kg bw. The Meeting concluded that the long-term intake of residues of indoxacarb from uses that have been considered by the JMPR is unlikely to present a public health concern.

Short-term intake

The IESTI of indoxacarb calculated on the basis of the recommendations made by the JMPR represented 0–130% of the ARfD (0.1 mg/kg bw) for children and 0-50 % for the general population. The IESTI for head cabbage for children was 130% of the ARfD.

It should be noted that unit weight data are not available for leaf lettuce in the GEMS/Food data base. Availability of a realistic unit weight would improve the estimate of short-term intake.

The Meeting concluded that the short-term intake of residues of indoxacarb resulting from uses that have been considered by the JMPR, except the use on head cabbages, is unlikely to present a public health concern.

The information provided to the JMPR precludes an estimate that the dietary intake would be below the ARfD for consumption of head cabbages by children.

4.13 MALATHION (049)

RESIDUE AND ANALYTICAL ASPECTS

Malathion was evaluated in the periodic review programme by the JMPR in 1999 and re-evaluated in 2004. At its 37th Session, the CCPR decided to advance the MRLs for apple, citrus and grapes for adoption at step 5. The CCPR also decided to return all other MRLs associated with animal feeds, including cotton seed, maize and wheat, to Step 6 pending review by JMPR of animal feeding studies. These studies were listed as desirable in the 1999 JMPR report, but no data was submitted to the Meeting. In the 2004 JMPR, residues from trials conducted on alfalfa according to GAP confirmed the previous recommendations for this crop.

At this Meeting, animal dietary burden was calculated for cattle and poultry based on the recommendations on animal feed made by the previous Meetings. In addition, animal metabolism studies submitted to the 1999 JMPR were evaluated in light of the calculated dietary burden. No additional GAP information was provided to this Meeting.

Estimated maximum dietary burden of farm animals

Commodity	Residue	Basis	Group	% DM*	Residues, dw	*Diet content (%)*			Residue contribution mg/kg		
						Beef cattle	*Dairy cows*	*Poultry*	Beef cattle	Dairy cows	Poultry
Alfalfa forage	98	hr	AL	22	445	***70***	***60***	-	**312**		
Alfalfa fodder	175	hr	AL	89	196	*70*	*60*	-			
Clover	95	hr	AL	19	500	*30*	*60*				
Clover hay	120	hr	AL	89	135	*30*	*60*				
Grass forage	190	hr	AF	25	760	*30*	*60*	-		**456**	
Hay or fodder (dry) of grasses	260	hr	AS	88	295	*60*	*60*	-			
Maize grain	0.02	HR	GC	88	0.023	*80*	*40*	*80*			
Maize fodder	24	hr	AS	83	29	*25*	*15*	-			

Commodity	Residue	Basis	Group	% DM*	Residues, dw	*Diet content (%)*			Residue contribution mg/kg		
						Beef cattle	*Dairy cows*	*Poultry*	Beef cattle	Dairy cows	Poultry
Maize forage	2.4	hr	AF	40	6.0	*40*	*50*	-			
Sorghum	2.2	HR	GC	86	2.6	*40*	***10***	*80*		0.26	2.0
Wheat	0.28	HR	GC	89	0.31	*50*	*40*	*80*			
Wheat forage	2.4	hr	AF	22	11	*25*	*60*	-			
Wheat straw and fodder, dry	34	hr	AS	88	38	*10*	*10*	-			
Cotton seed meal	0.34	Median-p	-	89	0.38	*15*	*15*	***20***			0.08
Cotton seed hulls	10.8	hr-p	AM	90	12	*20*	*15*	-			
Citrus dried pulp	0.2	Median-p	AB	91	0.22	*20*	*20*	-			
Turnip tops	3.4	HR	AV	30	11	***30***	***30***	-	3.4	3.4	
Turnip roots	0.13	HR	VR	15	0.87	*75*	*20*	-			
Total						**100**	**100**	**100**	**315**	**460**	**2.1**

DM= dry matter; dw= dry weight; hr= highest residue for animal feed; m= median residues for animal feed; p=processing commodity, *information from the trials or from the *FAO Manual*

Metabolism studies in animals

Two metabolism studies were evaluated by the 1999 JMPR. In one study conducted with goats dosed at 115 ppm diet for 5 days, malathion was found to be used as a carbon source, with the radioactivity being incorporated in fatty acids, glycerol, tricarboxylic cycle acid intermediates and protein. No malathion or any products arising from primary metabolism of malathion were observed at levels above 0.05 mg/kg in any sample analysed.

In one study conducted in hens, dosed at 25 ppm diet for 4 days, malathion was also found to be used as a carbon source. No malathion or any products of immediate metabolism were observed at levels exceeding 0.02 mg/kg in any of the samples, except the white from one egg on day 1, where significant activity as malathion carboxylic acid was detected.

Residues in animal products

The *FAO Manual* (2002) states that feeding studies in animals are required where significant residues (> 0.1 mg/kg) occur in crops or commodities fed to animals and metabolism studies indicate that significant residues (> 0.01 mg/kg) may occur in edible tissues. Residues in commodities fed to animals estimated by the JMPR are significant and the calculated dietary burden for ruminants (460 ppm) is much higher than the dose used in the metabolism study in goats. The Meeting concluded that the metabolism study could not be used to estimate the level of malathion residues in commodities from ruminant animals, and confirms that feeding studies with malathion on ruminant animals are desirable.

The Meeting noticed that the highest contribution to the dietary burden of malathion came from crops grown specifically for feed. Residues of malathion in other feed and food commodities, including cereal grains and citrus dried fruit, are low (< 1 mg/kg) and are not expected to make any significant contribution to the animal dietary burden. Although currently there is no recommendation for apple pomace, the recommended HR for apple is 0.28 mg/kg, and the Meeting agreed that the expected residues in apple pomace should also not contribute significantly to the animal dietary burden.

The metabolism study conducted in hens at approximately 10 times the calculated dietary burden indicates that no residues of malathion are expected to be found in tissues and eggs. The Meeting concluded that a feeding study in hens is not necessary. However, no recommendations could be made in poultry commodities as no analytical method in animal products was submitted to this or previous Meetings.

4.14 METHIOCARB (132)

RESIDUE AND ANALYTICAL ASPECTS

Methiocarb, an insecticide, acaricide, molluscicide and bird repellent, was first reviewed by the Meeting in 1981. Since then, it was evaluated a number of times both for toxicology and residues.

It was reviewed under the Periodic Review Programme in 1998 for toxicology and in 1999 for residues. The 1998 JMPR allocated a new ADI of 0-0.02 mg/kg body weight and ARfD of 0.02 mg/kg body weight. The 1999 JMPR concluded that the residue should be defined both for enforcement of MRLs and for the estimation of dietary intake as "the sum of methiocarb, methiocarb sulfoxide and methiocarb sulfone, expressed as methiocarb".

The 1999 JMPR estimated provisional maximum residue levels and STMRs for strawberry, leek, cabbages, cauliflower, cucumber, melons, pepper, tomato, pea, maize and hazelnuts. However, due to the lack of appropriate storage stability studies it decided to withdrew the existing Codex MRLs for the above-mentioned commodities (except strawberry) and other commodities for which no data had been submitted to the Meeting.

Methiocarb was identified by the 36th Session of the CCPR in 2004 for evaluation by the 2005 JMPR. The current Meeting received data to support MRLs for artichoke, barley, Brussels sprout, cabbages, cauliflower, cucumber, grapes, hazelnut, leek, lettuce, maize, melons, onion, pea, pepper, potato, sugar beet, sunflower, tomato and wheat. The data of some crops had been submitted to the 1999 JMPR which reviewed them and made provisional recommendations based on them. The Meeting, however, agreed that these data should be reviewed along with new data in view of new GAP information and new JMPR policies established for evaluation since 1999.

Methods of analysis

The Meeting received information on a new HPLC method which was developed after the last evaluation and used in supervised trials conducted in recent years. Information on the validation of previously reviewed method, Bayer method number 00014, for the determination of methiocarb, methiocarb sulfoxide and methiocarb sulfone in grape and melon pulp and peel was also provided.

The new method determines methiocarb, methiocarb sulfoxide and methiocarb sulfone in plant materials separately using HPLC-MS/MS. The analytical procedure includes extraction with either a mixture of acetonitrile/water (samples with low lipid content) or acetonitrile saturated with n-hexane followed by partition with n-hexane (samples with high lipid content), clean-up on a non-polar column, analysis by a reverse phase HPLC with an acidic acetonitrile/water eluent on a silica based C_{18} column and detection by tandem mass spectrometry with electrospray ionization. In the case of starch-containing sample materials, a cysteine solution was added for stabilization. The product ions of 169, 122 and 185 *amu* were used for quantification of methiocarb, methiocarb sulfone and methiocarb sulfoxide respectively. The limit of quantitation (LOQ) was 0.01 mg/kg for each of the three compounds in matrices in supervised trials except in the analysis of barley straw and wheat

straw for which the LOQ was 0.05 mg/kg. Mean recoveries of these compounds from matrices in supervised trials with fortification at LOQ and 10 x LOQ were in the range of 72 to 104% for these compounds with relative standard deviations below 17%.

The above method is generally more sensitive than other methods but as HPLC-MS/MS is not considered common equipment in the world, this HPLC-MS/MS method could not be recommended for enforcement purposes at the international level.

Bayer method number 00014 with the modification M001 (reported in the 1999 JMPR Evaluation; HPLC method with post-column derivatization) was successfully validated for grape with the LOQ at 0.02 mg/kg for each of the three compounds and mean recoveries of these compounds at the fortification levels of 0.02, 0.10 and 1.0 m/kg ranged between 79–107%. This method was also successfully validated for melon pulp and melon peel with the LOQ at 0.02 mg/kg for each of the three compounds and mean recoveries of these compounds at the fortification levels of 0.02, 0.10 and 1.0 mg/kg ranged between 81 and 126%.

Stability of pesticide residues in stored analytical samples

A 2-year deep-freezer storage stability study was conducted with methiocarb, methiocarb sulfone and methiocarb sulfoxide in matrices of plant origin. Shredded samples of grape (bunch), field peas, potato and rapeseed were fortified with methiocarb, methiocarb sulfone and methiocarb sulfoxide at 0.20 mg/kg. The samples were stored at -18°C or below for up to 733–734 days. Methiocarb, methiocarb sulfone and methiocarb sulfoxide were analysed by the HPLC-MS/MS method mentioned above. During the storage period, the sum of methiocarb, methiocarb sulfone and methiocarb sulfoxide did not decrease significantly except in the case of rapeseed, where a 25% decrease was observed, which was still within the acceptable range. In the case of potato, some conversion from the parent compound to sulfoxide was shown.

The Meeting concluded that these results indicate that the data from supervised trials were acceptable for estimating maximum residue levels, STMRs and HRs as samples had been stored no longer than 2 years.

No information was available on the storage stability of these compounds in matrices of animal origin.

Results of supervised trials on crops

The Meeting received supervised trials involving methiocarb on artichoke, barley, Brussels sprout, cabbage, cauliflower, cucumber, grape, hazelnut, leek, lettuce, maize, melon, onion, pea, pepper, potato, sugar beet, sunflower, tomato and wheat.

A number of the residue trials were carried out using a 50 wettable powder (WP) or a 500 soluble concentrate (SC) formulation. These formulations are considered to be interchangeable with regard to the residue behaviour of the methiocarb active ingredient. The Meeting concluded that the data generated with either of the two formulations could be used to support the other.

For spreader applications, ready-to-use (RTU) bait formulations (containing 2, 3 or 4 percent methiocarb) were used in the residue trials. The bait formulations are designated as either RB or GR. Both names refer to the same formulation and the designation RB is used in this review.

Residues were determined as methiocarb sulfone and calculated and expressed as methiocarb (a GLC method using oxidation by permanganate), or determined separately and the sum of the three components was expressed as methiocarb (HPLC methods). For the calculation of total residues, the Meeting took a similar approach as the 1999 JMPR as indicated in the following table.

Methiocarb	Methiocarb sulfone	Methiocarb sulfoxide	Total residues
< 0.05	< 0.05	< 0.05	< 0.05
0.15	< 0.05	< 0.05	0.15
0.15	< 0.05	0.06	0.21
0.15	0.05	0.06	0.25

The 1999 Meeting considered that a practical LOQ for enforcement purposes was 0.05 mg/kg for commodities of plant and animal origin except for milk for which the practical LOQ was 0.005 mg/kg. The current Meeting concluded that where total residues arising from supervised trials for a crop were all below LOQ which is smaller than 0.05 mg/kg, a maximum residue level should be recommended at 0.05 * mg/kg.

For commodities where the supporting trials used in the estimation of maximum residue levels all reported residues below the limit of quantification, even at exaggerated rates, the Meeting, taking into account the results of the plant metabolism studies, agreed to estimate STMRs, median residue levels, HRs and highest residue levels of 0 mg/kg, indicating that residues are not expected.

Grapes

A total of eight trials were conducted in France (1), Greece (4), Italy (1), Portugal (1) and Spain (1). These trials were carried out with 2 or 3 spray applications at 1 kg ai/ha.

Registered use patterns for grapes related to the supervised trials are as follows:

Country	Form.	Method	No.	Rate kg ai/ha	PHI
Greece	50 WP	Spraying	2	1.0	42
Italy	50 WP	Spraying	2	1.0	21
Portugal	50 WP	Spraying	1	0.5	#
Spain	50 WP	Spraying	2	1.0	#

Last application before flowering

In a total of five trials, one each in France, Greece, Italy, Portugal and Spain, methiocarb was applied three times instead of twice as specified by GAP in Greece, Italy or Spain. The analysis of grapes taken immediately before the last application and 21 days after the last application indicates that one extra application did not have a significant effect on residue concentrations taken at the PHI. The Meeting agreed to use the results of trials with three applications for estimating a maximum residue level, STMR and HR.

All eight trials were evaluated against GAP in Italy. Among all eight trials, five trials (one each in France, Greece, Italy, Portugal and Spain) were in accordance with Italian GAP. Total residues in ranked order, were: 0.13, 0.16, 0.24, 0.27 and 0.34 mg/kg. The Meeting considered it inadequate to estimate a maximum residue level for grapes on a basis of five valid trials.

The Meeting also evaluated these eight trials against the Greek GAP, with a PHI of 42 days. Seven trials were in accordance with Greek GAP and total residues in ranked order, were: 0.04(2), 0.07, 0.10, 0.12, 0.16 and 0.20 mg/kg. The Meeting concluded that seven valid trials were not sufficient to estimate a maximum residue level for grapes.

Leek

Eight supervised residue trials were conducted on leek in France using the 50WP formulation and four trials in the Netherlands using the 500 SC formulation. In each trial, 3 spray treatments at approximately 0.75 kg ai/ha were carried out.

Registered use patterns for leek related to the supervised trials are as follows:

Country	Form.	Method	No.	Rate kg ai/ha	PHI
Belgium	500 SC	Spraying	-	0.75	21
France	50 WP	Spraying	3	0.75	21

No GAP information was available from the Netherlands but the results of trials conducted in the Netherlands were reviewed against the GAP of Belgium.

Eight trials conducted in France were in accordance with GAP in France. Residues in leek in these trials were in rank order: 0.07, 0.09, 0.10, 0.13, 0.17, 0.17, 0.21 and 0.33 mg/kg.

Four residue trials conducted in the Netherlands were in accordance with Belgian GAP. Residues in leek in these trials were: < 0.02 (3) and 0.03 mg/kg.

As residues arising from French trials and those from Dutch trials did not appear to belong to the same population, the results from French trials were used to estimate a maximum residue level, STMR and HR. The Meeting estimated a maximum residue level, STMR and HR for leek at 0.5, 0.15 and 0.33 mg/kg respectively.

Onion, bulb

Eight supervised trials were conducted using the 50 WP formulation in France, Greece, Portugal and Spain. In each trial 2 kg ai/ha was applied twice.

Registered use pattern for onion related to the supervised trials is as follows:

Country	Form.	Method	No.	Rate kg ai/ha	PHI
Belgium	500 SC	Spraying	3	0.75	21

In all of eight trials, methiocarb was applied only twice instead of three times as specified in the Belgian GAP and the application rate was 1.0 kg ai/ha instead of the 0.75 kg ai/ha GAP rate. As the analysis of samples taken immediately before the last application indicated that no carry-over of residues was expected, the Meeting decided to use these trial data for estimating a maximum residue level. All eight trials reviewed were regarded as in accordance with Belgian GAP and total residues were in ranked order: < 0.01 (4), 0.04, 0.05, 0.06 and 0.35 mg/kg.

The Meeting estimated a maximum residue level, STMR and HR for onion, bulb at 0.5, 0.025 and 0.35 mg/kg respectively.

Brussels sprouts

A total of eight supervised trials were conducted in Belgium (1), France (2), Germany (2), the Netherlands (1) and the UK (2) using 4RB formulation (ready to use bait).

Registered use patterns for Brussels sprouts related to the supervised trials are as follows:

Country	Form.	Method	No.	Rate kg ai/ha	PHI
Ireland	4 RB	Spreading	2	0.20	14
Ireland	3 RB	Spreading	2	0.15	14
Poland	2 RB	Spreading	2	0.10	14
UK	2 RB	Spreading	2	0.15	14

As no GAP information was provided for Belgium, France, Germany and the Netherlands, the results of trials conducted in these countries were reviewed against the Irish GAP for the 4RB formulation. From the six trials conducted in accordance with Irish GAP no quantifiable residues of methiocarb, methiocarb sulfone and methiocarb sulfoxide were found: < 0.01 mg/kg (6).

The two UK trials were also in accordance with the Irish GAP for the 4RB and total residues found were: < 0.01 mg/kg (2).

The Meeting estimated a maximum residue level, STMR and HR for Brussels sprouts at 0.05*, 0.01 and 0.01 mg/kg respectively.

Cabbages, Head

Eight supervised trials were conducted on cabbage with methiocarb 500 SC or 50 WP applied as a spray in Belgium, Germany and the Netherlands. An additional 14 trials were conducted in Belgium, France, Germany, the Netherlands and the UK where the RTU bait formulation of methiocarb was applied.

Registered use patterns for cabbages related to the supervised trials are as follows:

Country	Form.	Method	No.	Rate kg ai/ha	PHI
Belgium	500 SC	Spraying	4	0.50	14
France	4 RB	Spreading	-	0.12	15
Germany	2 RB	Spreading	2	0.10	14
Ireland	3 RB	Spreading	1	0.12	14
Ireland	4 RB	Spreading	-	0.22	7
Italy	75 WP	Spraying	2	0.75	21
Poland	4 RB	Spreading	2	0.12	14
UK	3 RB 2 RB	Spreading	1	0.12	14

In two trials conducted in Belgium, two in Germany and four in the Netherlands, methiocarb was sprayed three times at rates ranging from 0.70 to 0.75 kg ai/ha. These trials were regarded as matching the maximum GAP in Belgium by the 1999 JMPR when the GAP at the time permitted a maximum of three applications at a rate of 0.75 kg ai/ha. Due to a change in GAP, which permits a maximum of four applications at a rate of 0.50 kg ai/ha, the trials were no longer in accordance with the maximum GAP of Belgian. In these trials, total residues at a PHI of 14 days ranged from < 0.02 to 0.05 mg/kg. The application rates of these trials were comparable to the Italian GAP (a maximum of 2 applications) but some trials indicate potential carry-over of residues from earlier application and therefore these trials were not used for estimating a maximum residue level.

All six trials conducted in Germany with the application rate of 0.12 kg ai/ha using 4 RB formulation were regarded as in accordance with the maximum GAP of Germany and residues found were: < 0.05 mg/kg (6).

Of eight trials, one conducted with two applications at the rate of 0.20 kg ai/ha in Belgium, one in France, four in Germany, one in the Netherlands and one in the United Kingdom, four trials were in accordance with Irish GAP (application number not specified; 0.22 kg ai/ha, PHI 7 days) the residues found were: < 0.01 (3) and 0.08 mg/kg. In the other four trials, no samples were taken at the PHI of 7 days but all three components were below or at the LOQ of 0.01 mg/kg even on day 0.

Combined residue results in ranked order were: < 0.01 (3), < 0.05 (6) and 0.08 mg/kg. The Meeting estimated a maximum residue level, STMR and HR for cabbages, head at 0.1, 0.05 and 0.08 mg/kg respectively.

Cauliflower

Four supervised trials were conducted on cauliflowers in Germany using a RTU bait formulation. Residues were determined as methiocarb sulfone and calculated as methiocarb.

Registered use patterns for cauliflower related to the supervised trials are as follows:

Country	Form.	Method	No.	Rate kg ai/ha	PHI
France	4 RB	Spreading	-	0.12	15
Germany	2 RB	Spreading	2	0.10	14
Ireland	3 RB	Spreading	2	0.12	14
Ireland	4 RB	Spreading	-	0.22	7
Italy	1 RB	Spreading	-	0.10	21
Poland	2 RB	Spreading	2	0.10	14
Poland	4 RB	Spreading	2	0.12	14
UK	2 RB 3 RB	Spreading	2	0.12	14

The four trials were conducted in accordance with the maximum GAP of Germany. However, in one trial the cauliflower florets were not analysed. Residues from the three valid trials were all < 0.05 mg/kg.

The Meeting agreed that three trials were insufficient for estimating a maximum residue level and STMR for cauliflower. The 1999 JMPR concluded that the data on cabbages could be extrapolated to cauliflowers as the GAP is identical and the treatments are applied to the ground, not foliar where differences in plant structure might lead to different residue concentrations. The Meeting estimated a maximum residue level, STMR and HR for cauliflower at 0.1, 0.05 and 0.08 mg/kg respectively.

Cucumber

A total of nine supervised trials were carried out in France (5 in greenhouse), the Netherlands (1 in greenhouse), Portugal (1 in greenhouse) and Spain (2 in field). In the field trials 2 spray applications at 1.0 kg ai/ha were carried out, while in the greenhouse trials 1-3 spray applications at rates between 0.8 and 1.1 kg ai/ha were made.

Registered use patterns for cucumbers related to the supervised trials are as follows:

Country	Form.	Method	No.	Rate kg ai/ha	PHI
Belgium (F)	500 SC	Spraying	1	0.425	3
Greece (F/G)	50 WP	Spraying	2	1.5	15
Italy (F)	50 WP	Spraying	2*	1.0	21
Netherlands (F)	500 SC	Spraying of aerial parts	1-3	0.25-0.5	3
Spain (F/S)	50 WP	Spraying	3*	1.5	7

* Last application before flowering

Two field trials conducted in Spain were in accordance with Spanish GAP. Residues found were < 0.04 mg/kg (2).

Greenhouse trials conducted in France (1), the Netherlands (1) and in Portugal (1) used application rates of 1.0 and 1.1 kg ai/ha. These were regarded to be in accordance with Spanish GAP as the rates were within ±30% of the maximum rate specified in the Spanish GAP. Residues found were: 0.04, 0.10 and 0.21 mg/kg.

Other trials conducted in greenhouses in France were not in accordance with any reported GAP.

Residues in samples from the greenhouse trials were found to be significantly higher than those from field trials and therefore these results could not be combined. The Meeting concluded that there was insufficient data to estimate a maximum residue level in cucumber.

Melons

A total of eleven supervised trials were conducted on melons in France (4), Italy (1), Portugal (2 in greenhouses) and Spain (4). In these trials methiocarb was sprayed 1 to 3 times at application rates ranging from 0.75 to 1.1 kg ai/ha.

Registered use patterns for melons related to the supervised trials are as follows:

Country	Form.	Method	No.	Rate kg ai/ha	PHI
Italy (F)	50 WP	Spraying	2	1.0	21
Netherlands (G)	500 SC	Spraying of aerial parts	1-3	0.25–0.5	3
Portugal (F/G)	50 WP	Spraying	2	1.0	7

Two greenhouse trials conducted in Portugal were in accordance with Portuguese GAP and residues found in whole fruits were 0.25 and 0.48 mg/kg respectively.

Two field trials conducted in Spain in 1993 and two trials in France in 1996 were also in accordance with Portuguese GAP, with residues found in ranked order of: 0.07, 0.10, 0.12 and 0.16 mg/kg.

In one trial in Italy, two other trials in Spain and one other trial in France conducted in the field, samples (whole fruit) were taken at a PHI of 21 days (GAP in Italy) and did not contain any of the three components above the LOQ of 0.02 mg/kg.

Since the residues in whole fruits taken 7 and 21 days after treatment were significantly different, the Meeting decided that these values could not be combined. Residues in samples taken 7 days after treatment in greenhouses and those from field trials were also significantly different and therefore could not be combined. The Meeting estimated a maximum residue level for melons, except watermelon, at 0.2 mg/kg on the basis of four field trials conducted in Spain (2) and France (2).

In these trials residues in pulp were: < 0.02 mg/kg (4). The Meeting estimated an STMR and HR at 0.02 and 0.02 mg/kg.

Peppers

A total of nine supervised trials were conducted on sweet peppers: two in Portugal in greenhouses and seven in Spain in greenhouses (5) and field (2). The number of spray applications was either 2 or 3 with application rates ranging from 1.16 to 1.5 kg ai/ha.

Registered use patterns for peppers related to the supervised trials are as follows:

Country	Form.	Method	No.	Rate kg ai/ha	PHI
Greece (F/G)	50 WP	Spraying	2	1.5	7
Portugal (F/G)	50 WP	Spraying	2	1.0	14
Spain (F/G)	50 WP	Spraying	3	1.0	7

All seven greenhouse trials were in accordance with Spanish GAP. In two trials only the sum of the three components was reported with no information on the levels of individual components provided. Residues found in ranked order were: 0.22, 0.67, 0.84, 0.92, 1.2, 1.3 and 1.3 mg/kg.

One field trial conducted in Spain with the variety Lamuyo was in accordance with Spanish GAP. The residues found were 1.5 mg/kg.

Residues from valid trials in ranked order were: 0.22, 0.67, 0.84, 0.92, 1.2, 1.3, 1.3 and 1.5 mg/kg. The Meeting estimated a maximum residue level, STMR and HR for sweet peppers at 2, 1.06 and 1.5 mg/kg respectively.

Tomato

The Meeting received information on supervised residue trials on tomatoes in Germany (2 in greenhouses) France, Greece (1 in greenhouses), Portugal (1 in greenhouses) and Spain (7 in greenhouses and field). The spray application rate ranged from 1.0 to 1.5 kg ai/ha with either 2 or 3 applications made.

Registered use patterns for tomato related to the supervised trials are as follows:

Country	Form.	Method	No.	Rate kg ai/ha	PHI
Portugal (F/G)	50 WP	Spraying	2	1.0	14
Spain (F/G)	50 WP	Spraying	3	1.0	7

Two trials conducted in Germany and one in Greece in greenhouses were evaluated against Spanish GAP but samples were taken only up to 3 days post treatment and therefore could not be used for estimating a maximum residue level.

One greenhouse trial conducted in Portugal was in accordance with Spanish GAP with a residue concentration found of 0.80 mg/kg.

Two greenhouse trials conducted in Spain in 1993 used rates more than 30% above the maximum GAP rate. Residues found were 0.22 and 0.58 mg/kg.

Three field trials conducted in Spain in 1990 were in accordance with Spanish GAP with residues levels found of < 0.04 (2) and 0.11 mg/kg.

Two field trials conducted in Spain in 1988 were in accordance with Spanish GAP. However, only the sum of the three components was reported with no information on the levels of individual components provided. The residues found in these were 0.17 mg/kg (2).

The greenhouse trials conducted seemed to result in higher residues than the trials conducted in the field and the Meeting therefore decided these results could not be combined. Residues from field trials matching Spanish GAP in ranked order were: < 0.04 (2), 0.11, 0.17 and 0.17 mg/kg.

The Meeting concluded that five valid trials were insufficient to estimate a maximum residue level for tomato.

Lettuce

A total of eight supervised trials were conducted on lettuce in Germany (7) and the United Kingdom (1) with an application rate of 0.12 or 0.45 mg ai/ha using the RTU bait formulation. Residues were determined as methiocarb sulfone and calculated as methiocarb.

Registered use patterns for lettuce related to the supervised trials are as follows:

Country	Form.	Method	No.	Rate kg ai/ha	PHI
Germany	2 RB	Spreading	2	0.10	14
Ireland	3 RB	Spreading	1	0.12	14
Ireland	4 RB	Spreading	2	0.20	14
Italy	1 RB	Spreading	2	0.10	21
Netherlands	4 RB	Spreading	2	0.20	-
Poland	2 RB	Spreading	1	0.10	14
Spain	1 RB	Spreading	1	0.10	-
UK	2 RB	Spreading	1	0.10	14
UK	3 RB	Spreading	1	0.12	14

Seven trials conducted in Germany were in accordance with the maximum GAP in Germany. Residues levels found were: < 0.05 mg/kg (7).

One trial from the United Kingdom used approximately four times (4x) the GAP rate resulting in residues below the LOQ on day 15 after treatment.

The number of valid trials was seven, and together with the supporting information above, the Meeting estimated a maximum residue level, STMR and HR at 0.05*, 0.05 and 0.05 mg/kg respectively.

Peas

Eight supervised residue trials were performed in Germany on peas using the 500 FS seed treatment formulation according to German GAP. Residues were determined as methiocarb sulfone and calculated as methiocarb.

Registered use pattern for field peas related to the supervised trials is as follows:

Country	Form.	Method	No.	Rate kg 100 kg seed	PHI
Germany	500 FS	Seed treatment	1	0.50	N/A

Residues in peas with pod were: < 0.05 (6) and 0.07 mg/kg. Residues in dry peas were: < 0.05 (4) and 0.06 mg/kg.

The Meeting estimated a maximum residue level and STMR for both peas (pods and succulent=immature seeds) and pea (dry) at 0.1and 0.05 mg/kg respectively. An HR of 0.05 mg/kg was estimated for peas (pods and succulent=immature seeds).

Potato

Two supervised trials were performed in the United Kingdom with 3 applications of the ready-to-use bait formulation at 0.22 kg ai/ha. Potatoes were harvested after a PHI of 18-20 days. Eight other trials were performed in Germany, the Netherlands and the United Kingdom with a lower annual rate and frequency of treatment, i.e., 2 x 0.15 kg ai/ha with a shorter PHI of 7 days.

Registered use patterns for potatoes related to the supervised trials are as follows:

Country	Form.	Method	No.	Rate kg ai/ha	PHI
Ireland	3 RB	Spreading	3	0.15	18
Ireland	4 RB	Spreading	3	0.22	*
UK	2 RB	Spreading	3	0.15	18
UK	3 RB	Spreading	3	0.15	18

* Last application prior to desiccation of leaves

Two UK trials were in accordance with Irish GAP and no quantifiable residues were found in tubers harvested 18 or 20 days after treatment. Residues were: < 0.02 mg/kg (2).

Concerning the other eight trials, and taking into consideration the shorter PHI of 7 days and that the method of application was spreading, these trials could be regarded as appropriate for estimating a maximum residue level. There were no quantifiable residues found in samples taken : < 0.01 mg/kg (8).

The Meeting estimated a maximum residue level, STMR and HR for potato at 0.05*, 0.01 and 0.02 mg/kg respectively.

Sugar beet

Four supervised trials on sugar beet were conducted with 2 applications at 0.15 kg ai/ha of the ready-to-use formulation (2RB) (France, Germany and the United Kingdom) and 10 trials with 2 applications of 0.12 g ai/ha of the ready-to-use bait formulation (4RB) (France, Germany, Italy, Spain and the United Kingdom). The last treatment of soil was conducted at growth stages 9-14 (BBCH – scale).

Registered use patterns for sugar beet related to the supervised trials are as follows:

Country	Form.	Method	No.	Rate kg/100kg seed or kg ai/ha	PHI	GS
Netherlands	500 WP	Seed treatment	1	0.5	-	-
France	4 RB	Spreading	2	0.12	-	
Germany	2 RB	Spreading	2	0.10		15
Ireland	3 RB	Spreading	1	0.15	6 mo.	
Italy	1 RB	Spreading	-	0.10	-	
UK	2 RB	Spreading	1	0.15	6 mo	
UK	3 RB	Spreading	1	0.15	6 mo	

* Last application should be made before the specified BBCH growth stage.

All of the 14 trials were in accordance with the maximum GAP in France or Germany or within 30% of the maximum GAP in France. There were no quantifiable residues found in sugar beet roots (LOQ 0.01 mg/kg).

The Meeting estimated a maximum residue level, STMR and HR for sugar beet at 0.05*, 0.01 and 0.01 mg/kg respectively.

Artichoke, Globe

A total of four supervised trials were conducted on artichoke in France (1) and Italy (3). Methiocarb was applied as a ready-to-use bait twice at a rate of 0.1 or 0.12 kg ai/ha.

Registered use patterns for artichokes related to the supervised trials are as follows:

Country	Form.	Method	No.	Rate kg ai/ha	PHI
France	4 RB	Spreading	-	0.12	15
Italy	1 RB	Spreading	-	0.10	21

One trial in France and one trial in Italy in 2001 were in accordance with maximum GAP rate in France but no samples were analysed 15 days after application. Together with the two other trials from Italy, they were reviewed against Italian GAP although the formulations were not identical.

In all trials no quantifiable residues were found in samples taken either on day 14 (if available) or day 21 (LOQ 0.01 (2) or 0.005 (2) mg/kg).

The Meeting estimated a maximum residue level, STMR and HR for artichoke, globe at 0.05*, 0.005 and 0.01 mg/kg respectively.

Barley

A total of 12 residue trials were performed on barley in France, Germany, Greece and Italy using the RTU bait formulation. The trials were conducted with 2 applications at 0.12 kg ai/ha. In all trials the last application was conducted at growth stage 12. PHIs for ripe grains and straw ranged between 76 and 141 days.

Registered use patterns for barley related to the supervised trials are as follows:

Country	Form.	Method	No.	Rate kg ai/ha	PHI	GS*
France	4 RB	Spreading	-	0.12	15	
Germany	2 RB	Spreading	2	0.10		31
Ireland	3 RB	Spreading	2	0.15		31
Poland	2 RB	Spreading	2	0.10	14	
Poland	4 RB	Spreading	2	0.12	14	
UK	2 RB 3 RB	Spreading	2	0.15		31

* Last application should be made before the specified BBCH growth stage.

All twelve trials were in accordance with German GAP. No quantifiable residues were found in the harvested grain (LOQ 0.01 (9) or 0.05 (3) mg/kg).

The Meeting estimated a maximum residue level, STMR and highest residue for barley at 0.05*, 0 and 0 mg/kg respectively.

Wheat

A total of nine residue trials were conducted on wheat in France, Germany, Portugal and the United Kingdom in 1991, 2000 and 2001 using the ready-to-use bait formulation at a rate of 0.12 or 0.22 kg ai/ha applied twice. In these trials, the growth stage at last application ranged between 11 and 33.

Registered use patterns for wheat related to the supervised trials are as follows:

Country	Form.	Method	No.	Rate kg ai/ha	PHI	GS*
France	4 RB	Spreading		0.12	15	
Germany	2 RB	Spreading	2	0.10		31
Poland	2 RB	Spreading	2	0.10	14	
Poland	3 RB	Spreading	2	0.12	14	
UK	2 RB 3 RB	Spreading	2	0.15		31

* Last application should be made before the specified BBCH growth stage.

Seven trials conducted in France and Germany were in accordance with German GAP. No quantifiable residues were found in the harvested grains (LOQ 0.01 mg/kg).

In two UK trials, a 2× rate was used with the last application at growth stage 30 or 33. No quantifiable residues were found in harvested grains (LOQ 0.04 mg/kg).

The Meeting estimated a maximum residue level, STMR and highest residue for wheat at 0.05*, 0 and 0 mg/kg respectively.

Maize

A total of 23 supervised trials were conducted on maize using the 500 FS seed treatment formulation. The trials were carried out in Belgium, France, Germany, Greece, Italy and Spain. The application rate was 0.5 kg ai/100 kg seed.

An additional four trials were conducted with methiocarb granules applied twice at a rate of 0.12 kg ai/ha in Germany, Italy and Spain. The last application was conducted at growth stages 11-13.

Registered use patterns for maize related to the supervised trials are as follows:

Country	Form.	Method	No.	Rate kg/100kg seed or kg ai/ha	PHI	GS#
Austria	50 WP	Seed treatment	1	0.5		
Belgium	500 FS	Seed treatment	1	0.5		
France	500 FS	Seed treatment	1	0.5		
Germany	500 FS	Seed treatment	1	0.5		
Italy	50 WP	Seed treatment	1	0.5		
Poland	500 FS	Seed treatment	1	0.5		
France	4 RB	Spreading		0.12	15	
Ireland	2 RB	Spreading	2	0.10		31
Poland	2 RB	Spreading	2	0.10	14	
UK	2 RB 3 RB	Spreading	2	0.15		31

[#] Last application should be made before the specified BBCH growth stage.

Fifteen trials conducted in Belgium, France, Greece, Italy and Spain, using the 500 FS seed treatment formulation, were all done in accordance with the GAP of Belgium, France and Germany (identical GAP). At the time of harvest no quantifiable residues were found in the grain: < 0.01 mg/kg (15).

In the four trials conducted with the granular treatment, a bait formulation was applied to the ground and not incorporated into the soil and therefore was unlikely to lead to residues in the harvested maize grain: < 0.01 mg/kg (4).

Based on 15 trials using the FS seed treatment formulation, the Meeting estimated a maximum residue level, STMR and highest residue at 0.05*, 0 and 0 mg/kg for maize.

Hazelnut

Five trials were conducted in Turkey on hazelnuts in 1 year. Methiocarb was applied by dusting or spraying.

The registered use pattern for hazelnut available to the Meeting is as follows:

Country	Form.	Method	No.	Rate kg ai/ha	PHI
Turkey	50 WP	Spraying	1	0.75	90

All five Turkish trials were according to Turkish GAP with no quantifiable residues found in hazelnut kernels (LOQ 0.04 mg/kg).

The Meeting estimated a maximum residue level, STMR and HR for hazelnut at 0.05*, 0.04 and 0.04 mg/kg respectively.

Rape-seed

A total of 10 supervised trials were conducted on rape with methiocarb 500 FS used for seed dressing at a seed rate of 2.5 kg ai/100 kg of seed. Trials were carried out in France (5), Germany (4) and in

the UK (1). Thirteen other trials were conducted with a RTU bait formulation applied twice at a rate of 0.12 kg ai/ha in Belgium (2), France (3), Germany (5), Sweden (1) and the UK (2).

Registered use patterns for rape-seed related to the supervised trials are as follows:

Country	Form.	Method	No.	Rate kg/100kg seed or kg ai/ha	PHI	GS
France	50 WP	Seed dressing	1	2.5		
France	4 RB	Spreading	-	0.12	15	33
Germany	2 RB	Spreading	2	0.10		33
Ireland	3 RB	Spreading	2	0.15		
Poland	2 RB	Spreading	2	0.10	14	33
UK	2 RB	Spreading	2	0.15		33
UK	3 RB	Spreading	2	0.15		

* Last application should be made before the specified growth stage.

Ten supervised trials conducted using the 500FS seed treatment formulation were in accordance with French GAP. No quantifiable residues were found in the harvested seeds (LOQ 0.01 mg/kg (10)).

The thirteen granular treatment trials were conducted in accordance with Irish GAP. No quantifiable residues were found in the harvested seeds (LOQ 0.01 (10) or 0.05 (3) mg/kg).

The Meeting estimated a maximum residue level and STMR at 0.05* and 0 mg/kg respectively.

Sunflower seed

Four supervised trials were conducted in France (3) and Italy (1) using the ready-to-use bait formulations. The last application was performed at growth stage 31–51, which corresponded to a PHI of 80-86 days.

Registered use patterns for sunflower related to the supervised trials are as follows:

Country	Form.	Method	No.	Rate kg ai/ha	PHI	GS
France	4 RB	Spreading	-	0.12	15	
Ireland	3 RB	Spreading	2	0.15		33
Poland	2 RB	Spreading	2	0.10	14	
UK	2 RB 3 RB	Spreading	2	0.15		33

* Last application should be made before the specified BBCH growth stage.

Three of four trials were in accordance with the GAP in Ireland or the UK. In another trial the last application was carried out at growth stage 53.

There were no quantifiable residues in harvested seeds even with the last application at growth stage 53 (LOQ 0.01 mg/kg).

The Meeting estimated a maximum residue level and STMR for sunflower seed at 0.05* and 0 mg/kg respectively.

Animal feeds

Pea vines/hay

Residues in whole plant other than pods from trials matching GAP (see the section on peas) in rank order were: 0.04, < 0.05 (7) mg/kg.

No information was available for moisture content in pea vines. The Meeting estimated an STMR and highest residue for pea vines on a fresh weight basis at 0.05 and 0.05 mg/kg respectively for the purpose of calculating the animal dietary burden.

Residues in pea straw at the time of harvest were: < 0.05 (2), 0.08 and 0.38 mg/kg.

No information was available for moisture content in pea hay. The Meeting estimated an STMR and highest residue for pea hay on a fresh weight basis at 0.065 and 0.38 mg/kg respectively for the purpose of calculating the animal dietary burden. The Meeting also estimated a maximum residue level of 0.5 mg/kg (dry weight basis) for pea hay or pea fodder (dry) using the percentage of dry matter of 88% as listed in Appendix IX of the *FAO Manual* (FAO, 2002).

Sugar beet, Leaves or Tops

Residues in sugar beet leaves from trials matching GAP (see the section on sugar beet) were below the LOQ of 0.01 mg/kg (14). No information was available for moisture content in sugar beet leaves. The Meeting estimated an STMR and highest residue for sugar beet leaves on a fresh weight basis at 0.01 and 0.01 mg/kg respectively these values were used to calculate the animal dietary burden.

Barley forage/fodder

Residues in green material from all twelve trials which matched the German GAP (see the section on barley) were: < 0.01 (9) and < 0.05 (3) mg/kg. No information was available for moisture content in the barley forage. The Meeting estimated an STMR and highest residue for barley forage on a fresh weight basis at 0.01 and 0.05 mg/kg respectively for the purpose of calculating the animal dietary burden.

Residues in straw taken at the time of normal grain harvest from all twelve trials, which matched the German GAP were: < 0.05 (12) mg/kg. No information was available for moisture content in the barley fodder. The Meeting estimated an STMR and highest residue for barley fodder on a fresh weight basis at 0.05 and 0.05 mg/kg respectively for the purpose of calculating the animal dietary burden. The Meeting also estimated a maximum residue level of 0.05 mg/kg (dry weight basis) for barley straw and fodder, using the dry matter percentage of 89% as listed in Appendix IX of the *FAO Manual* (FAO, 2002).

Wheat forage/fodder

Residues in green plant material from seven trials matching German GAP (see the section on wheat) were: < 0.01 (7) mg/kg. In two UK trials, a 2x rate was used with the last application at growth stage 30 or 33. Residues in green plant material were below the LOQ of 0.1 mg/kg. No information was available for moisture content in wheat forage. The Meeting estimated an STMR and highest residue for wheat forage on a fresh weight basis at 0.01 and 0.01 mg/kg respectively for the purpose of calculating the animal dietary burden.

Residues in straw taken at the time of grain harvest from all seven trials, which matched German GAP were: < 0.05 (7) mg/kg. In two UK trials, a 2× rate was used with the last application at growth stage 30 or 33. Residues in straw were below the LOQ of 0.1 mg/kg. No information was available for moisture content in the wheat straw. The Meeting estimated an STMR and highest residue for wheat fodder on a fresh weight basis at 0.05 and 0.05 mg/kg respectively for the purpose

of calculating the animal dietary burden. The Meeting also estimated a maximum residue level of 0.05 mg/kg (dry weight basis) for wheat straw and fodder, dry, using the dry matter percentage of 89% as listed in Appendix IX of the *FAO Manual* (FAO, 2002).

Maize forage

In supervised trials, residues were also determined on a whole plant basis, without roots. Whole plant residues, without roots, found from samples taken on the day of the last harvest of corn-on-the-cob, from trials matching GAP (see the section on maize), were: < 0.01 mg/kg (16).

No information was available for moisture content in maize forage. The Meeting estimated an STMR and highest residue for maize forage on a fresh weight basis at 0.01 and 0.01 mg/kg respectively for the purpose of calculating the animal dietary burden.

Rape forage

Residues in green plant materials of rape, taken close to normal harvest, from trials matching GAP (see the Section on rape-seed) in ranked order were: < 0.01 (19), < 0.05 (3) and 0.05 mg/kg.

No information was available for moisture content in rape forage. The Meeting estimated an STMR and highest residue for rape forage on a fresh weight basis at 0.01 and 0.05 mg/kg respectively for the purpose of calculating the animal dietary burden.

Fate of residues during processing

Grapes

A wine processing study was conducted with table grapes to which methiocarb 50WP was sprayed twice at an application rate of 1.0 kg ai/ha with the last application occurring 42 days prior to harvest.

Residues of methiocarb, methiocarb sulfone, methiocarb sulfoxide and the total residues were determined in grape bunches, berries and in wine. The calculated total residues were 0.07 mg/kg for grape bunches, 0.06 mg/kg for berries and 0.03 mg/kg for wine. Processing factors are shown below.

Grape	Processing factor
Bunch	-
Berry	0.86
Wine	0.43

Farm animal dietary burden

The Meeting estimated the farm animal dietary burden of methiocarb residues, using the diets listed in Appendix IX of the *FAO Manual* (FAO, 2002).

In the tables below, farm animal dietary burden was calculated by summing the residue contribution of each feed (mg/kg).

Estimated maximum dietary burden of farm animals

Commodity	CC	Residue mg/kg	Basis	% DM	Residue dw mg/kg	*Diet Content (%)*			Residue contribution (mg/kg)		
						Beef cattle	*Dairy cows*	*Poul-try*	Beef cattle	Dairy cows	Poul-try
Barley	GC	0	highest residue	88	0						
Barley forage	AF	0.05	highest residue								
Barley fodder	AS	0.05	highest residue	89	0.056						
Maize	GC	0	highest residue	88	0						
Maize forage	AS	0.01	highest residue	40	0.025						
Pea vines	AL	0.05	highest residue	25	0.2						
Pea hay	AL	0.38	highest residue	88	0.43	*25*	*50*		0.11	0.22	
Rape forage	AM	0.05	highest residue	30	0.17	*30*			0.05		
Sugar beet tops	AV	0.01	highest residue	23	0.043						
Wheat	GC	0	highest residue	89	0						
Wheat forage	AF	0.05	highest residue	25	0.2	*25*	*50*		0.05	0.1	
Wheat fodder	AS	0.05	highest residue	88	0.057						
Total						*80*	*100*		0.21	0.32	0

Estimated STMR value for dietary burden of farm animals.

Commodity	CC	Residue mg/kg	Basis	% DM	Residue dw mg/kg	*Diet Content (%)*			Residue contribution, mg/kg		
						Beefcat tle	*Dairy cows*	*Poultry*	Beef cattle	Dairy cows	Poultry
Barley	GC	0	STMR	88	0						
Barley forage	AF	0.01	STMR								
Barley fodder	AS		STMR	89	0.056						
Maize	GC	0.01	STMR	88	0.011						
Maize fodder	AS	0.01	STMR	40	0.025						
Pea vines	AL	0.05	STMR	25	0.2						
Pea hay	AL	0.065	STMR	88	0.074	25	50		0.018	0.037	
Rape forage	AM	0.01	STMR	30	0.033	30			0.01		
Sugar beet tops	AV	0.01	STMR	23	0.043						
Wheat	GC	0	STMR	89	0						
Wheat forage	AF	0.01	STMR	25	0.04	25	50		0.01	0.02	
Wheat fodder	AS	0.01	STMR	88	0.057						
Total						80	100		0.04	0.06	0

The dietary burden of methiocarb, for estimates of animal commodity MRLs and STMRs are respectively: beef cattle, 0.21 and 0.04 ppm; dairy cattle, 0.32 and 0.06 ppm; and poultry, 0 and 0 ppm.

Farm animal feeding studies

The 1999 JMPR received and reviewed farm animal feeding studies.

In one feeding study, dairy cows were given feed containing methiocarb at the equivalent of 0, 10, 30 and 100 ppm methiocarb for 29 days. Maximum methiocarb residue in milk on day 29 was 0.007, 0.020 and 0.033 mg/kg at the 10, 30 and 100 ppm feeding levels, respectively. No residues (< 0.05 mg/kg total methiocarb) were found in any tissue at any feeding level, except 0.08-0.1 mg/kg methiocarb in liver at 30 and in kidney at 100 ppm.

At the estimated maximum animal dietary burden of 0.32 mg/kg, maximum residue levels were calculated to be far below the LOQ for enforcement at 0.005 mg/kg in milk and 0.05 mg in meat and edible offal of mammals. The Meeting estimated maximum residue levels in meat and edible offal of mammals at the practical LOQ at 0.05 * mg/kg and STMR at 0 mg/kg and in milk at 0.005 mg/kg and 0 mg/kg respectively. An HR of 0 mg/kg was estimated for meat and edible offal of mammals.

In one 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. The sum of methiocarb and methiocarb sulfoxide was below the LOQ of 0.02 mg/kg in muscle, skin and fat at all dose levels except 0.02 mg/kg in skin at the 360 ppm feeding level. In eggs (28 days) residues were 0.03 and 0.06 mg/kg at 120 and 360 ppm level respectively and in giblets (heart, gizzard and liver), 0.06, 0.13 and 0.13 mg/kg at 60, 120 and 360 ppm level respectively.

No residues were expected to occur in feed items for poultry, such as barley, maize and wheat grains. The Meeting therefore concluded that maximum residue levels for poultry tissues and eggs could be estimated at the practical LOQ of 0.05 * mg/kg, STMR at 0 mg/kg and HR at 0 mg/kg for poultry meat, edible offal and eggs.

The above maximum residue levels for animal commodities were, however, not recommended for use as maximum residue limits by Codex as the information on the storage stability in animal tissues had not been submitted.

Plant commodities and animal commodities

Definition of the residue for compliance with MRLs: the sum of methiocarb, methiocarb sulfoxide and methiocarb sulfone, expressed as methiocarb

Definition of the residue for estimation of dietary intake: the sum of methiocarb, methiocarb sulfoxide and methiocarb sulfone, expressed as methiocarb

DIETARY RISK ASSESSMENT

Long-term intake

The International Estimated Dietary Intakes (IEDIs) were calculated for the five GEMS/Food regional diets using STMR for vegetables, cereals, oil seeds and hazelnuts estimated by the current Meeting and the STMR for strawberry estimated by the 1999 JMPR (Annex 3). The maximum ADI is 0.02 mg/kg and the calculated IEDIs were 0–2% of the maximum ADI. The Meeting concluded that the intake of residues of methiocarb resulting from the uses considered by the current JMPR was unlikely to present a public health concern.

Short-term intake

The International Estimated Short-Term Intakes (IESTIs) of methiocarb by the general population and by children were calculated for commodities for which STMRs or STMR-Ps estimated by the current Meeting where information on consumption was available. An HR of 0.83 mg/kg was

estimated for strawberry on a basis of data submitted to and reviewed by the 1999 JMPR (Annex 4). The ARfD is 0.02 mg/kg and the calculated IESTIs for children up to 6 years range from 0 to 70% and those for general population from 0 to 50% of the ARfD. The Meeting concluded that the short-term intake of residues of methiocarb from uses considered by the current Meeting was unlikely to present a public health concern.

4.15 S-METHOPRENE (147)

RESIDUE AND ANALYTICAL ASPECTS

Methoprene, an insect growth regulator originally evaluated by the JMPR in 1984 and re-evaluated for residues several times up to 1989, is included in the CCPR periodic review programme. At the 30th session of the CCPR (ALINORM 99/24, Appendix VII), methoprene was originally scheduled for periodic residue review by the 2003 JMPR but this was postponed to 2005.

The manufacturer supplied information on identity; metabolism and environmental fate; residue analysis; use pattern; residues resulting from supervised trials on wheat, maize, rice, sorghum, barley, and oats; and the fate of residues on wheat, maize and rice during storage and in processing. GAP information and enforcement method were supplied by the manufacturer and the government of Australia. In addition, methoprene is also recommended by WHO for treatment of drinking water.

Animal metabolism

The Meeting received information on the fate of orally-dosed methoprene in steers, lactating cows and laying hens.

S-methoprene is the biologically active enantiomer in the racemic methoprene and constitutes 50% of methoprene. Investigations into the metabolism and fate of methoprene could be accepted as supporting metabolism and fate requirements of S-methoprene.

The metabolism of methoprene in laboratory animals (mice, rats, guinea pigs, rabbits and dogs) was evaluated by the WHO panel of the 2001 JMPR. It was concluded that, after administration of single oral doses of methoprene, the radiolabel was relatively rapidly absorbed and excreted in urine, faeces and expired air. In most species investigated, the bulk of the radiolabel was extensively metabolized by O-demethylation and hydrolysis to polar conjugates and excreted within 5 days or less, and the [5-^{14}C]-molecule underwent rapid α and β oxidation to produce CO_2 and acetate, which was incorporated into natural products.

[5-^{14}C]-methoprene was administered orally in gelatin capsules to a Hereford steer as a single dose of 2 g (corresponding to 7.2 mg/kg bw). The administered radiolabel was quantitatively excreted during a 2 week post-treatment period, exclusive of unquantified respiratory losses and other minor losses; 22% of the dose was excreted in the urine, 39% in faeces. In faeces, the major extractable radioactive compound was unchanged methoprene. Approximately 13% of the administered radiolabel remained in the animal tissues.

At sacrifice 2 weeks after treatment, the levels of radioactivity in edible tissues were: liver (5.0 mg/kg), kidney (4.4 mg/kg) and fat (3.2 mg/kg). All the principal meat tissues had less than 1 mg/kg wet tissue. No primary methoprene metabolites could be characterized, but the major identified radiolabeled compound in liver, muscle and fat was cholesterol (16% TRR, 28% TRR and 88% TRR, respectively. TRR = total radioactive residue).

[5-^{14}C]-methoprene was administered orally in gelatin capsules to a Jersey lactating cow as a single dose of 208 mg (corresponding to 0.61 mg/kg bw). After 7 days, 73% of the radiolabel had been eliminated, with 20% in urine, 30% in faeces, 15% in expired air and 8% in the milk. Only about 0.08% of the applied dose was excreted as methoprene and no detectable primary metabolites occurred in milk. About 27% of the administered radiolabel remained in the cows' tissues. The concentrations of radiolabel in expired air, urine, faeces and milk peaked about 24–48 h after treatment. By day 7 after treatment, the concentrations of radiolabel in edible tissues were: liver (0.49 mg/kg), kidney (0.37 mg/kg) and omental fat (0.25 mg/kg). Muscle tissues of the cow had less than 0.1 mg/kg of total radioactive equivalents.

In whole milk, peak radioactivity occurred at 30-h post-treatment. After 7 days, the amount present was only about 10% of the maximum value. The total recovery of radioactive material in the milk was 8% of the applied dose. [5-^{14}C]-methoprene was extensively metabolized by the lactating dairy cow to acetate. Radioactive acetate incorporated into milk fat was degraded to radiolabeled saturated, monoenoic, and dienoic fatty acids. Radioactive lactose (11% TRR), lactalbumin (3.8% TRR) and casein (2.5% TRR) were also isolated from milk.

[5-^{14}C]-methoprene was administered orally in gelatin capsules to colostomized or intact laying White Leghorn hens, as single oral doses of 0.6–77 mg/kg bw. The average percentage elimination of ^{14}C in the 0-48 hr period via respiration was 37% when chickens were given low doses of methoprene (0.6–3.4 mg/kg bw) and was 24% when chickens were given high doses (31-64 mg/kg bw).

Over 14 days after administration, up to 19% of the radiolabel was eliminated in eggs, mainly in the yolk. At doses of 0.6 to 77 mg/kg, methoprene contributed only 1-2% of the total ^{14}C in yolk and primary metabolites were only detectable (< 0.1 mg/kg) at the 77 mg/kg dose rate. For the range of doses tested, the majority of radiolabeled products in meat were natural triglycerides (20% TAR at a rate of 59 mg/kg, TAR = total applied radioactivity). Radiolabeled natural products were by far the main ^{14}C residues in tissues and eggs, particularly at the lower dose of 0.6 mg/kg where cholesterol and normal fatty acids (as triglyceride) contributed 8% and 71% of the total radiolabel in egg yolk. The high initial doses resulted in methoprene residues in muscle (0.01 mg/kg), fat (2.1 mg/kg) and egg yolk (8.0 mg/kg), which represented 39 and 2% of the total ^{14}C label in fat and egg yolk, respectively. After 48 h, chicken liver contained about 1% of the applied ^{14}C from methoprene.

The metabolism of methoprene in laboratory animals was qualitatively similar to that in farm animals.

Plant metabolism

The Meeting received plant metabolism studies for methoprene on wheat in storage, alfalfa and rice.

Individual wheat grains were exposed to the vapour of [5-^{14}C]-methoprene at 20°C for 1 day, or were topically treated with [5-^{14}C]-methoprene, using aqueous emulsions or solutions in cyclohexane. Two days after treatment or exposure, highest residue of intact methoprene was found in the aleurone layers, much less in the germ and virtually none in the endosperm or outer seed coats. There was no significant amount of ^{14}C-activity associated with the high molecular weight fraction after either 1 week or 3 weeks storage at 20 °C and 18% moisture content.

Forty 25 g lots of wheat samples were dosed in screw-capped jars with 10 mL of a solution of methoprene in hexane at a rate of 10 mg/kg. The jars were sealed and stored in the dark at 20 °C. The residual half-life of methoprene in freshly–harvested wheat of 19% moisture was 2-3 weeks. In the older wheat at 12% and 18% moisture contents, the respective half lives were 6-7 weeks and 3-4

weeks. The main metabolic change observed was ester cleavage. Detectable metabolism was almost entirely to the free acid and could account for only 20-40% of the degradation.

Leaves of potted alfalfa were painted with the diluted [5-^{14}C]-methoprene emulsifiable concentrate at a rate equivalent to 1.1 kg ai/ha. Parent methoprene disappeared in approximate first-order decay with a half-life of about 2 days for alfalfa. Volatility was a minor pathway for loss. The concentration of nonpolar metabolites maximized after 3 days in alfalfa. The primary nonpolar metabolites in alfalfa after 7 days constituted only approximately 1% of TAR. The aglycones in alfalfa after enzymic cleavage constituted approximately 10% of TAR as identifiable metabolites. A large amount (56%) of the radioactivity in chloroform extract fraction was associated with high molecular weight products (mol weight > 600). Further analysis of GPC fractions supported the incorporation of ^{14}C label into naturally occurring plant pigments and other higher molecular weight plant constituents. After 30 days in alfalfa, 1% of the applied methoprene was retrieved as methoprene.

Leaves of potted *rice* were painted with the diluted [5-^{14}C]-methoprene emulsifiable concentrate at a rate equivalent to 1.1 kg ai/ha. Parent methoprene disappeared in an approximate first-order decay with a half-life of about 0.5 day for rice. A total of 30% of the applied dose of methoprene on rice was isolated as condensed vapours after 1 week, which proved that volatility was a major path of elimination. The concentration of nonpolar metabolites maximized after 1 day in rice. The primary nonpolar metabolites in rice after 3 days constituted approximately 2% of TAR. The aglycones in rice after enzymic cleavage constituted approximately 1.5% of TAR. After 15 days in rice, 0.4% of the applied methoprene was retrieved as methoprene.

In both animals and plants, methoprene undergoes ester hydrolysis, O-demethylation, and oxidative scission of the 4-ene double bond. Further metabolism results in the corporation of methoprene-derived fragments into natural products.

Environmental fate in soil

The Meeting received information on aerobic degradation in soil.

The aerobic degradation of [5-^{14}C]-methoprene was studied in sandy loam and silt loam soils for 60 days at dose rates of 0.7, 1.0 and 10 kg ai/ha. The residual half-life of methoprene in sandy loam was about 10 days at a surface treatment rate of 1 kg ai/ha. By day 14 only 0.7% of TAR could be identified as known metabolites of methoprene.

Environmental fate in water/sediment systems

The Meeting received information on sterile aqueous hydrolysis, photolysis, thin film photolysis and metabolism in pond water.

Sterile aqueous solutions of methoprene (0.5 mg/L), buffered at various pH values (pH5, 7 and 9), were found to be extremely stable to hydrolysis over four weeks at 20°C in the dark. No degradation was seen for the duration of the experiment in sterile water buffered at pH 7 and 9, and similar stability was observed in pH 5 buffer for 21 days.

In the first study of photolysis, photodecomposition of [5-^{14}C]-methoprene was investigated in the autoclaved phosphate buffer (0.05 M, pH 7) at 0.01 mg/kg and 0.50 mg/kg. Methoprene was rapidly decomposed with both concentrations giving half-lives of apparently less than 1 day. In a second study of photolysis after 1 week, four photoproducts (24% yield overall) were characterized as metabolites of methoprene. Parent methoprene was not detectable and there were at least 46 other photoproducts but none represented more than 2% yield.

Photolysis on glass was investigated at a rate corresponding to 11 μg/cm^2 (1.1 kg ai/ha) and film thickness of 0.1 μm. Methoprene was rapidly degraded when a thin film on glass was exposed to sunlight through glass. The half-life for photochemical breakdown under these conditions was 6 h. The recovery of only 72% of TAR after 27 h suggested photolysis of methoprene to volatile products which were lost by vaporization. Collection of vapours above the photolysate resulted in recovery of 13% of TAR, of which only 0.2% was methoprene and 6%, $^{14}CO_2$. Resolution of the crude photolysate after exposure of methoprene to sunshine for 4 days gave methoprene (7%, equal mixture of 2E and 2Z) and at least 50 other metabolites and photoproducts, but none represented more than 6% of TAR.

In the first study, the degradation studies of methoprene labelled in the 10-^{3}H (purity > 99%) and the 5-^{14}C (purity 97.9%) were performed in the pond water. The half-lives of [10-^{3}H]methoprene at 0.001 mg/kg and at 0.01 mg/kg were approximately 30 h and 40 h, respectively.

Methods of analysis

The Meeting received information on several methods for the determination of parent methoprene and /or S-methoprene residues in cereal grains, related processed products, stored grain and corn, milk, eggs, poultry and cattle tissues using GC-FID and HPLC, and on a method for the detection of methoprene residues in wheat grain with ELISA.

Residues of methoprene are first extracted with solvents (acetonitrile, acetone/hexane, hexane, methanol, and iso-octane). Fatty extracts are subjected to cold-temperature precipitation and filtration to remove fat. Solvent partitioning and/or column chromatography (florisil, alumina and silica column) are used for clean-up. Methoprene was analysed by GC with FID or HPLC-UV. The identity of suspected residues was confirmed by alternative GC column, GC-MS, and [^{14}C]-methoprene. The lower limits of quantification (LOQs) are: soils, blood and urine, 0.001-0.01 mg/kg; forage grasses, forage legumes and rice foliage, 0.005 mg/kg; milk, eggs, stored grain and corn kernels, fish, shellfish, poultry and cattle tissues and faeces, 0.01 mg/kg; cereal grains and processed products 0.01-0.2 mg/kg. The LOQ's and recoveries were validated by analysis of laboratory and field samples fortified with [^{14}C]methoprene in some methods. Two methods (LOQ: 0.008 mg/kg and 0.05 mg/kg, respectively) are considered suitable for enforcement for grain and grain products.

A rapid enzyme immunoassay was used as a screening test for methoprene in animal feed grains, and sensitive enough to detect methoprene at 0.5 ppm in the grain. This assay can be used as a screening test, but cannot be used for quantitative detection of methoprene.

Stability of pesticide residues in stored analytical samples

The Meeting received information on the stability of methoprene in milk, and supplemental information on the stability of S-hydroprene in bologna, chicken, bread and hamburger.

Information on storage stability of methoprene in cereal grains was not submitted. However, field residue samples were stored at -20°C until needed for analysis (storage time not stated). Numerous lab studies and field trials have shown long-term stability of methoprene in stored grains, not only at -20°C but even at room temperature.

Stability of S-hydroprene was demonstrated in hamburger, chicken, bread, apples and lettuce at -15°C for 7 to 24 days. S-hydroprene is a compound with very similar structure and properties to S-methoprene. It is therefore likely that S-methoprene was also stable in animal commodities at -15°C

The Meeting concluded that methoprene would be stable in cereal grains and animal commodities when stored frozen.

Definition of the residue

Methoprene was rapidly and extensively metabolized by animals and plants. There was 8% of TRR in whole cow milk. 0.015 mg/kg of methoprene was detected, but primary metabolites were not detected (< 0.01 mg/kg). [5-^{14}C]-methoprene was extensively metabolized to acetate by the lactating dairy cow.

In steer tissues, no primary methoprene metabolites were found, and the major identified radioactivity (16–88%, depending on tissue) was [^{14}C]-cholesterol.

At doses of 0.6 to 77 mg/kg, methoprene contributed only 1–2% of the total ^{14}C in yolk and primary metabolites were only detectable (< 0.1 mg/kg) at the 77 mg/kg dose rate. Higher initial doses resulted in detectable residues of methoprene in muscle, fat and egg yolk. Radiolabeled natural triglycerides and cholesterol also contributed major portions of the total ^{14}C residue in fat.

In the animal metabolism studies, the concentration of residue was substantially higher in fat and egg yolk than that in muscle and egg white. The values of log P_{ow} (4 for methoprene, approximate 6 for S-methoprene) also indicate that methoprene is a fat-soluble compound. However, methoprene was metabolized quickly and extensively by animals, so its accumulation in fat was just temporary.

After the pre-harvest treatment of alfalfa and rice, five primary non-polar metabolites were found. Methoprene which remained in alfalfa and rice was a minor part of the residue. However, after post-harvest treatment of wheat grains, the residue consisted mainly of methoprene.

The primary metabolites were not toxicologically significant compounds, which were evaluated by the WHO panel of 2001 JMPR. The Meeting agreed that methoprene is suitable for enforcement in plant and animal commodities and is also the compound of interest for estimation of dietary risk.

Definition of residue (for compliance with the MRL and for estimation of dietary intake): methoprene.

The residue is fat-soluble.

Results of supervised trials on crops

The Meeting received information on supervised trials of post-harvest treatments of methoprene/S-methoprene in wheat grain, shelled corn, rice, sorghum grain, barley grain and oats grain in USA, Australia and Thailand. This data was generated from large-scale storage trials with the exception of four laboratory studies on S-methoprene in 2003; most of the trials were conducted in Australia and the USA.

Methoprene

Wheat

Thirty-one trials were conducted on wheat in Australia (GAP: 0.50~1.0 g ai/t) in 1982~89. In twenty-four trials conducted at the maximum GAP, the highest concentrations during sampling were 0.38, 0.50 (2), 0.59, 0.60, 0.63, 0.70 (3), 0.72, 0.74 (3), 0.78, 0.79, 0.80 (2), 0.85, 0.90, 1.0, 1.1, 1.2, 1.9 and 2.0 mg/kg.

Four trials on wheat were conducted in the USA (GAP: 5.0 g ai/t) in 1982~85. Two USA trials and two Australian trials were conducted against the maximum GAP (USA), and the highest concentrations during sampling were 2.1, 4.0, 5.1 and 8.0 mg/kg.

Maize

Seventeen trials were conducted on maize in the USA (GAP: 5.0 g ai/t) in 1982~85. In three trials conducted at the maximum GAP, the highest concentrations during sampling were 3.9, 4.2 and 4.6 mg/kg.

Rice

Eight trials on rice were conducted in the USA (GAP: 5.0 g ai/t) in 1984~1985, and in Thailand (no GAP; uses that of the USA) in 1984. In three trials conducted at the maximum GAP (USA), the highest concentrations were 2.9, 6.8, and 8.1 mg/kg.

Sorghum

Two trials were conducted on sorghum at GAP in Australia (GAP: 0.50~1.0 g ai/t) in 1984. The highest concentrations of methoprene residues found during storage were 0.93 and 0.98 mg/kg.

Two trials were conducted on sorghum at the maximum in the USA (GAP: 5.0 g ai/t) in 1985. The highest concentrations of methoprene residues found during storage were 7.5 and 7.8 mg/kg.

Barley

Four trials on barley were conducted on barley grain in Australia (GAP: 0.50~1.0 g ai/t) in 1985. In three trials conducted at the maximum GAP, the highest concentrations were 0.60, 0.63, 0.65 and 1.1 mg/kg.

Oats

Four trials were conducted on oats grain in Australia (GAP: 0.50–1.0 g ai/t) in 1985. The highest concentrations of methoprene residues found during storage were 0.77, 0.96 and 1.0 (2) mg/kg.

The Meeting considered the combined data sufficient for cereal grains. The data from Australia and the USA were considered to represent different populations. The Meeting decided to evaluate the USA trials and other trials against the critical GAP in USA (5.0 g ai/t). The concentrations of residues in trials conducted (4 trials on wheat, 3 trials on maize, 3 trials on rice and 2 trials on sorghum) were, in ranked order: 2.1, 2.9, 3.9, 4.0, 4.2, 4.6, 5.1, 6.8, 7.5, 7.8, 8.0 and 8.1 mg/kg. The Meeting estimated an STMR value of 4.85 mg/kg, a highest residue of 8.1 mg/kg and a maximum residue level of 10 mg/kg for cereal grains. The recommendation for a maximum residue level of 10 mg/kg for cereal grains replaces the previous recommendation of 5 mg/kg.

S-Methoprene

Wheat

Two trials were conducted on wheat grain at the maximum GAP in Australia (GAP: 0.60 g ai/t) in 1986. The highest concentrations of S-methoprene residues found during storage were 0.33 and 0.54 mg/kg.

One trial and four laboratory studies were conducted on wheat grain in the USA (GAP: 0.60–4.4 g ai/t) in 1985 and 2003, but none of trials were conducted at the maximum GAP.

As residues arising from S-methoprene were covered by those from methoprene, the Meeting agreed not to recommend a maximum residue level for S-methoprene in wheat after post-harvest treatment.

Fate of residues during processing

The Meeting received information on the fate of residue of methoprene and S-methoprene during simulated processing of stored wheat (milling), stored rice (husking and polishing) and stored maize (extraction and refinement of maize oil).

In processing

Wheat with various storage times after post-harvest treatment with methoprene, was milled. The parent compound was determined in processed products. Processing factors derived from stored wheat were comparable. Calculated processing factors were 0.13 - 0.56 for flour; 0.43 - 1.1 for wholemeal; 1.5 - 4.1 for bran; 1.7–7.0 for germ; 1.4 - 4.3 for pollard.

In the USA, a processing study was conducted in 1985 on milling products, generated from whole maize that was previously treated with 5.3 g ai/t methoprene. At 30 day intervals, grain composites were removed from the granary and were extracted for crude and refined oil. The parent compound was determined in processed products. Calculated processing factors were 0.81 - 1.4 for maize meal; 3.9 - 44 for crude oil; < 0.06 (3) and < 0.05 (3) for edible oil. The refining processes converting crude to refined oil evidently removed or destroyed all methoprene residues.

In the USA, a processing study was conducted in 1985 on rice that was previously treated with 5.3 g ai/t methoprene. At 30 day intervals, rice was removed from the granary and milled and polished. The parent compound was determined in processed products. Calculated processing factors were 0.12 - 0.26 for husked rice; 4.6 for hulls; < 0.01, < 0.02 (3), and < 0.03 (3) for polished rice. Polished rice produced by hulling followed by polishing of the exterior bran layers virtually removed all methoprene residues.

The processing factors for wheat, maize and rice commodities are summarized in Table 14. All processing data on maize crude oil were generated with samples coming from the same trial at various intervals. Because of the large variability in the same processing study, the use of the median processing factor for the calculation of highest residue-Ps and STMR-Ps for maize crude oil is more suitable than using the maximum processing factor. The Meeting decided to take the median processing factor for the calculation of highest residue-Ps and STMR-Ps.

Table 14. Processing factors for wheat, maize and rice commodities.

Commodity	Processing factor (range)	Processing factor (median)	STMR-P (mg/kg)	highest residue-P (mg/kg)
Wheat bran	1.5, 1.7 (2), 1.8, 2.4, 2.6 (2), 3.0 (2), 3.5, 3.9, 4.1(2), 4.1	2.8	13.6	22.7
Wheat flour	0.13, 0.20, 0.25, 0.29 (2), 0.33 (2), 0.38 (2), 0.41, 0.49, 0.51, 0.53, 0.56	0.355	1.72	
Wholemeal	0.43, 0.64, 0.82, 0.91, 0.93 (2), 0.96, 1.0, 1.1	0.93	4.51	
Wheat germ	1.7, 1.9, 4.6, 4.8 (2), 5.6 (2), 6.0, 7.0	4.8	23.3	38.9
Wheat pollard	1.4, 2.1, 2.5, 3.9, 4.0 (2), 4.3	3.9	18.9	31.6
Maize meal	0.81, 0.85, 0.91, 0.92, 1.0 (2), 1.4	0.92	4.46	
Maize crude oil	3.9, 11, 13, 18, 19, 38, 44	18	87.3	146
Maize refined oil	< 0.05 (4), < 0.06 (3)	< 0.05	0	
Husked rice	0.12, 0.15, 0.19, 0.22, 0.23, 0.25, 0.26	0.22	1.07	
Polished rice	< 0.01, < 0.02 (3), < 0.03 (3)	< 0.01	0.1	
Rice hulls	4.6	4.6	22.3	37.3

From the highest residue and STMR for cereal grains (8.1 mg/kg and 4.85 mg/kg respectively) and the processing factors for wheat bran (unprocessed), flour and wholemeal, the Meeting estimated STMR-P values of 13.6 mg/kg in bran (unprocessed), 1.72 mg/kg in flour, and 4.51 mg/kg in wholemeal, 18.9 mg/kg in pollard, 23.3 mg/kg in germ and a maximum residue level of 25 mg/kg in bran (unprocessed), which replace the previous estimate of 10 mg/kg in unprocessed bran. The Meeting also recommended withdrawal of the existing CXL for wheat flour of 2 mg/kg and for wheat wholemeal of 5 mg/kg because the processing factors are less than 1.

No residues of methoprene were found at levels above the LOQ of 0.2 mg/kg in refined oil prepared from maize in the processing studies. The Meeting recommended withdrawal of the existing CXL for edible oil of 0.2 mg/kg PoP and estimated STMR-P values of 87.3 mg/kg in crude oil, 0 mg/kg in edible oil, and a maximum residue level of 200 mg/kg in crude oil.

From the STMR for cereal grains (4.85 mg/kg) and the processing factors for husked rice, hulls and polished rice indicated above, the Meeting estimated STMR-Ps of 1.07 mg/kg in husked rice, and 22.3 mg/kg in hulls, and a maximum residue level of 40 mg/kg in hulls. No residues of methoprene were found at levels above the LOQ of 0.1 mg/kg in polished rice prepared from rice in the processing studies. The STMR-P for polished rice was estimated to be 0.1 mg/kg.

Farm animal dietary burden

The Meeting estimated the dietary burden of methoprene residues in farm animals from the diets listed in Appendix IX of the *FAO Manual* (FAO, 2002). Calculation from the highest residues and STMR-P values provided the concentrations in feed suitable for estimating MRLs for animal commodities, while calculation from the STMR values for feed was suitable for estimating STMR values for animal commodities.

Estimation of maximum farm animal dietary burdens.

Commodity	CC	Residue (mg/kg)	Basis	% Dry matter	Residue, dry wt (mg/kg)	*Diet content (%)*			Residue contribution (mg/kg)		
						Beef cattle	*Dairy cows*	*Poul-try*	Beef cattle	Dairy cows	Poul-try
Barley	GC	8.1	highest residue	88	9.20						
Corn	GC	8.1	highest residue	88	9.20						
Oats	GC	8.1	highest residue	89	9.10						
Rice	GC	8.1	highest residue	88	9.20						
Rice hulls	CM	22.3	STMR-P	90	24.8						
Sorghum	GC	8.1	highest residue	86	9.42						
Wheat	GC	8.1	highest residue	89	9.10						
Wheat milled by-products[1]	CF	13.6	STMR-P	88	15.45	*40*	*50*	*50*	6.18	7.73	7.73
Total						*40*	*50*	*50*	6.18	7.73	7.73

[1] Use of wheat bran.

Estimation of median farm animal dietary burdens.

Commodity	Codex code	Residue (mg/kg)	Basis	% Dry matter	Residue, dry wt (mg/kg)	Diet content (%)			Residue contribution (mg/kg)		
						Beef cattle	*Dairy cows*	*Poultry*	Beef cattle	Dairy cows	Poultry
Barley	GC	4.85	STMR	88	5.51						
Corn	GC	4.85	STMR	88	5.51						
Oats	GC	4.85	STMR	89	5.45						
Rice	GC	4.85	STMR	88	5.51						
Rice hulls	CM	22.3	STMR-P	90	24.8						
Sorghum	GC	4.85	STMR	86	5.64						
Wheat	GC	4.85	STMR	89	5.45						
Wheat milled by-products[1]	CF	13.6	STMR-P	88	15.45	40	50	50	6.18	7.73	7.73
Total						40	50	50	6.18	7.73	7.73

[1] Use of wheat bran.

Farm animal feeding studies

The Meeting received information on residues in the tissues of several steers and a cow, in the milk of lactating cows, and in the egg of laying hens orally administered with [5-^{14}C]methoprene through the feed.

Lactating dairy cows have been fed methoprene in their feed for 28 days at the levels of 0.1, 0.3 and 1.0 ppm. No residues were found in the muscle tissues at any of the three treatment levels at the limits of detection (0.01 mg/kg). The residues found in kidney, liver, fat (subcutaneous, renal and omental) ranging from < 0.01–0.096 mg/kg. No residues of methoprene were found in the milk at the limits of quantitation (0.01 mg/kg) 2 to 28 days after beginning the feeding. No residue data in cream were provided.

A lactating dairy cow was administered methoprene at a rate of 83 ppm daily in feed for 4 months. Residues were found in milk ranging from 0.29–0.72 mg/kg (mean 0.47 mg/kg).

A steer was administered methoprene at a rate of 33 ppm daily in feed for 14 days. Residues were found in fat, muscle and edible offal (liver, kidney, spleen and heart) (1.3–2.3 mg/kg in fat, 0.05–0.10 mg/kg in muscle, 0.01–0.06 mg/kg in edible offal).

Three groups of two steers were administered methoprene at rates of 16.7, 33.3 and 167 ppm in feed for 14 days. No residues were found in liver at any of the three treatment levels at the LOQ (0.01 mg/kg). The residues found in edible offal, muscle, fat ranging from <0.01–0.92 mg/kg, <0.01–0.39 mg/kg and 0.17 –7.9mg/kg, respectively.

Laying hens were fed methoprene at 25, 50 and 100 ppm in the diet for varying periods between 14 and 63 days. At these three administered rates, residues found in poultry meat ranged from < 0.01–0.032 mg/kg, < 0.01–0.074 mg/kg, and < 0.01–0.302 mg/kg, respectively. The residues found in egg ranging from < 0.01–0.045 mg/kg, < 0.01–0.054 mg/kg and < 0.01–0.201 mg/kg, respectively. In all of the studies, there was also a withdrawal period of varying duration. At all three treatment levels, residues in poultry meat and egg decreased rapidly as withdrawal periods increased.

Animal commodity maximum residue levels

The dietary burden for the dairy cow was 7.73 mg/kg, below the feeding level (83 ppm) and the dietary burden for the steers was 6.18 mg/kg, below the lowest level in the feeding study (16.7 ppm in the feed). Therefore the resulting residues in milk and steer tissues were calculated by applying the respective transfer factors (transfer factor = residue level in tissue or milk ÷ residue level in feed) to the estimated dietary burden. In the feeding study the highest residue levels in tissues were used to calculate the highest likely mammal commodity residue levels and mean residue levels in milk and tissues were used to estimate the mammal commodity STMRs (Table 15).

Table 15. Calculation of MRLs and STMRs for milk and animal tissues.

	Feeding level (mg/kg) actual[2]	Methoprene residues, mg/kg[1]									
		Milk		Muscle		Fat		Liver		Kidney	
		Highest[3]	Mean[4]	Highest	Mean	Highest	Mean	Highest	Mean	Highest	Mean
MRL steer	*6.18*			*(0.015)*		*(0.137)*		*(< 0.004)*		*(0.017)*	
	16.7			0.040		0.37		< 0.010		0.045	
MRL dairy cow	*7.73*	*(0.067)*									
	83	0.72									
STMR steer	*6.18*				*(0.007)*		*(0.092)*		*(< 0.004)*		*(0.014)*
	16.7				0.020		0.248		< 0.010		0.039
STMR dairy cow	*7.73*		*(0.044)*								
	83		0.47[5]								

[1] Residue values in parentheses in *italics* are extrapolated from residues found at the feeding level in the cattle metabolism study.
[2] Values in *italics* are the estimated dietary burdens. Values in normal font are feeding levels in the cattle metabolism study.
[3] Highest is the residue level calculated from that found in the feeding study and the estimated maximum dietary burden.
[4] Mean is the residue level calculated from that found in the feeding study and the estimated STMR dietary burden.
[5] Exclude 0 day residue value.

The dietary burden for laying hens was 7.73 mg/kg, below the lowest level in the feeding study (25 ppm in the feed) and therefore the resulting residues in eggs and hen meats (including edible offal) were calculated by applying the respective transfer factors (transfer factor = residue level in egg or tissue ÷ residue level in feed) to the estimated dietary burden. In the feeding study the highest residue levels in meat and egg were used to calculate the highest likely poultry commodity residue levels, and mean residue levels in meat and egg were used to estimate the poultry commodity STMRs (Table 16).

Table 16. Calculation of MRLs and STMRs for poultry meat and eggs.

	Feeding level (mg/kg) actual[2]	Methoprene residues, mg/kg[1]			
		Meats		Eggs	
		High[3]	Mean[4]	High	Mean
MRL poultry	*7.73*	*(0.010)*		*(0.014)*	
	25	0.032		0.045	
STMR poultry	*7.73*		*(0.007)*		*(0.006)*
	25		0.024		0.021

[1] Residue values in parentheses in italics are extrapolated from residues found at the feeding level in the hen metabolism study.
[2] Values in italics are the estimated dietary burdens. Values in normal font are feeding levels in the hen metabolism study.
[3] High is the residue level calculated from that found in the feeding study and the estimated maximum dietary burden.
[4] Mean is the residue level calculated from that found in the feeding study and the estimated STMR dietary burden.

The concentration of residues in milk when dairy cows were "fed through" with up to 1ppm showed no residues in milk which were lower than those calculated from dietary burden and animal feeding studies. The recommended MRLs were therefore based on the dietary burden of farm animals and animal feeding studies.

The Meeting estimated maximum residue levels of 0.2 mg/kg for methoprene in meat (fat) from mammals, other than marine mammals, 0.02 mg/kg in edible offal from mammals and 0.1 mg/kg for milk. The Meeting also recommended withdrawal of the existing CXL for cattle milk of 0.05 mg/kg F, for edible offal (mammalian) except cattle of 0.1 mg/kg; and for meat from mammals other than marine mammals and cattle of 0.2 mg/kg (fat). The Meeting could not estimate maximum residue levels for methoprene in milk fat without data submission on cream.

The Meeting estimated STMRs of 0.007 mg/kg for muscle, 0.092 mg/kg for fat, 0.014 mg/kg for edible offal and 0.044 mg/kg for milk.

The Meeting estimated a maximum residue level of 0.02 mg/kg and STMR of 0.007 mg/kg for methoprene in poultry meat and edible offal from poultry, a maximum residue level of 0.02 mg/kg and STMR of 0.006 mg/kg for methoprene in eggs.

DIETARY RISK ASSESSMENT

Long-term intake

The International Estimated Daily Intakes (IEDIs) of methoprene, based on the STMRs estimated for seven commodities, were 20–40% of the maximum ADI 0.09 mg/kg bw for the five GEMS/Food regional diets. The Meeting concluded that the long-term intake of residues of methoprene resulting from its uses that have been considered by JMPR is unlikely to present a public health concern.

Short-term intake

The 2001 JMPR decided that an ARfD is unnecessary. The Meeting therefore concluded that the short-term intake of methoprene residues is unlikely to present a public health concern.

4.16 NOVALURON (217)

TOXICOLOGY

Novaluron is the provisionally approved ISO common name for (±)-1-[3-chloro-4-(1,1,2-trifluoro-2-trifluoromethoxyethoxy) phenyl]-3-(2,6-difluorobenzoyl)urea, a racemic compound. Novaluron is an insecticide of the benzoylphenyl urea class that inhibits chitin synthesis, affecting the moulting stages of insect development. It acts by ingestion and contact, and causes abnormal endocuticular deposition and abortive moulting. Novaluron has not been evaluated previously by the JMPR.

For technical novaluron, the FAO specification was established by the FAO/WHO Joint Meeting on Pesticide Specifications (JMPS) and published as FAO Specification 672/TC (December 2004).

All pivotal studies with novaluron were certified to be compliant with GLP.

Biochemical aspects

After oral administration in rats, [chlorophenyl-^{14}C (U)]-novaluron was poorly absorbed (≤ 7%) after a single low dose (2 mg/kg bw) and about tenfold less after a single high dose (1000 mg/kg bw), with maximum plasma concentrations occurring at 5–8 h or 2–5 h, respectively. Novaluron was widely distributed. The tissue concentrations of radioactivity were highest in fat, liver and kidneys and were about three- to fivefold higher after 14 repeated daily doses than after a single dose, with a terminal half-life of 52–56 h in fat after the final dose. Excretion was rapid, primarily via the faeces (> 94%; via bile ≤ 1%) and to a lesser extent via urine (about 5%), with most of the administered dose being excreted within 48 h.

Absorbed novaluron was extensively metabolized, mainly by cleavage of the urea bridge between the chlorophenyl and difluorophenyl moieties. In urine and bile, up to 15 metabolites were detected, and individual metabolites accounted for ≤ 1% of a low dose of [chlorophenyl-^{14}C (U)]-novaluron. Most of the faecal radioactivity consisted of unchanged novaluron, which was also the major component present in fat, liver and kidneys. The aniline metabolite of novaluron, 3-TFA, (3-chloro-4-(1,1,2-trifluoro-2-trifluoromethoxyethoxy)aniline) was identified at low levels (≤ 0.7%) in the urine, bile, liver and kidneys.

Toxicological data

Novaluron had low acute toxicity in rats, causing no mortality at limit doses after oral (LD_{50} > 5000 mg/kg bw), dermal (LD_{50} > 2000 mg/kg bw) or inhalation (LC_{50} > 5.15 mg/L air) exposure. Novaluron was not irritating to the skin and eyes of rabbits and not sensitizing not sensitizing to guinea-pig skin.

In short-term and long-term studies of toxicity, the erythrocyte was identified as the primary target of toxicity attributable to novaluron, with secondary effects apparent in the spleen and less commonly in liver and kidneys. The spectrum of effects was essentially similar in mice, rats and dogs, and the underlying mechanism was considered to be the same. Although the mechanism of the effects on erythrocytes has not been elucidated, it was considered to be most likely that the aniline metabolite of novaluron, 3-TFA, caused oxidative damage to the mature erythrocyte, resulting in increased concentrations of methaemoglobin (caused by accelerated oxidation of haemoglobin from the ferrous to the ferric state) and increased numbers of erythrocytes containing Heinz bodies (which are formed when damaged haemoglobin precipitates onto the cell membrane). The presence of Heinz bodies led to early destruction of erythrocytes by the spleen, with the consequence of increased erythrocyte turnover, characterized by stimulated erythropoiesis in both normal sites (sternum, femur) and in functional reserve sites (spleen, liver) and increased deposition of the products of haemoglobin catabolism (haemosiderin) in the spleen, liver and kidneys. After cessation of treatment, the adverse effects regressed, although incompletely, over a 4-week period after treatment in rats and dogs, and completely within 8 weeks in mice.

In 28-day and 90-day studies of toxicity in mice treated orally, the overall NOAEL was 30 ppm (equal to 4.2 mg/kg bw per day) on the basis of haematological changes (decrease in erythrocyte volume fraction and erythrocyte counts, increase in Heinz bodies and sulfhaemoglobin) at dietary concentrations of 100 ppm (equal to 12.8 mg/kg bw per day) and above, while changes in the spleen (increased weight, increased haematopoiesis and haemosiderosis) were evident at 700 ppm (equal to 114.7 mg/kg bw per day) and above.

In 28-day and 90-day studies in rats treated orally, the overall NOAEL was 50 ppm (equal to 4.2 mg/kg bw per day) on the basis of haematological changes (decrease in haemoglobin, erythrocyte volume fraction and erythrocyte counts) and histopathological changes in the spleen and liver

(increased haemopoiesis and haemosiderosis) at dietary concentrations of 100 ppm (equal to 8.3 mg/kg bw per day) and above. By week 4 of the reversibility period there was full recovery for most changes, except for increased concentrations of methaemoglobin, spleen weights and splenic haemosiderosis at dietary concentrations of 20 000 ppm (equal to 1667 mg/kg bw per day).

In 90-day and 1-year studies in dogs treated orally, the overall NOAEL was 10 mg/kg bw per day on the basis of haematological changes (decrease in haemoglobin, erythrocyte volume fraction and erythrocyte counts; increase in reticulocytes, Heinz bodies and Howell-Jolly bodies), increased serum concentrations of bilirubin and changes in the spleen and liver (increased weight; increased red pulp congestion, increased haemosiderin in Kupffer cells) at doses of 100 mg/kg bw per day or greater, while increased concentrations of methaemoglobin were evident at doses of 300 mg/kg bw per day or greater. By week 4 of a reversibility period there was full recovery for most changes, except for increased liver weights in female dogs at 1000 mg/kg bw per day.

In a 28-day study in rats treated dermally, the NOAEL for systemic toxicity was 75 mg/kg bw per day on the basis of increased concentrations of methaemoglobin at doses of 400 mg/kg bw per day or greater.

Novaluron gave negative results in an adequate battery of studies of genotoxicity in vitro and in vivo.

The Meeting concluded that novaluron was unlikely to be genotoxic.

Long-term studies of toxicity and carcinogenicity were conducted in mice and rats. In the study of carcinogenicity in mice, the NOAEL was 30 ppm (equal to 3.6 mg/kg bw per day) on the basis of increased body-weight gain (in the first 4 or 26 weeks in males or females, respectively), haematological changes (decrease in haemoglobin concentration, erythrocyte volume fraction and erythrocyte counts; increase in reticulocytes, sulfhaemoglobin, and Heinz bodies) and changes in spleen (increased weight, increased incidence of extramedullary haemopoiesis, haemosiderosis and congestion) and kidneys (increase in cortical tubular pigment) at dietary concentrations of 450 ppm (equal to 53.4 mg/kg bw per day) and greater. There was no evidence of carcinogenicity in mice at dietary concentrations of up to 7000 ppm (equal to 800 mg/kg bw per day), the highest dose tested.

In the long-term study of toxicity and carcinogenicity in rats, the NOAEL was 25 ppm (equal to 1.1 mg/kg bw per day) on the basis of haematological changes (decreases in haemoglobin concentration, erythrocyte volume fraction and erythrocyte counts; increases in methaemoglobin formation and reticulocytes) and changes in the spleen (increase in weight, haemosiderosis) and kidneys (increase in cortical tubular pigment) at dietary concentrations of 700 ppm (equal to 30.6 mg/kg bw per day) and greater. There was no evidence of carcinogenicity in rats at dietary concentrations of up to 20 000 ppm (equal to 884.2 mg/kg bw per day), the highest dose tested.

In view of the absence of a carcinogenic potential in rodents and the lack of genotoxic potential in vitro and in vivo, the Meeting concluded that novaluron is unlikely to pose a carcinogenic risk to humans.

In a two-generation study of reproductive toxicity in rats, the NOAEL for effects on fertility was 12 000 ppm (equal to 894.9 mg/kg bw per day), the highest dose tested. The NOAEL for systemic toxicity in parental animals and offspring could not be identified since there were secondary changes in spleen and liver relating to increased erythrocyte damage at all doses tested. The LOAEL for systemic toxicity was 1000 ppm (equal to 74.2 mg/kg bw per day) on the basis of increased spleen weights in adults and increased spleen and liver weights in offspring.

In a study of prenatal developmental toxicity in rats, the NOAEL for maternal and for developmental toxicity was 1000 mg/kg bw per day, the highest dose tested. The increases in body-weight gain and food consumption in all treated groups were not considered to be adverse effects.

In a study of prenatal developmental toxicity in rabbits, the NOAEL for both maternal and developmental toxicity was 1000 mg/kg bw per day, the highest dose tested. In the absence of any other evidence for an effect on fetal development, the slight increase in incidence of incompletely ossified fifth sternebrae at 300 mg/kg bw per day and 1000 mg/kg bw per day was not considered to be adverse. The finding of absent implantation or high rates of pre-implantation loss in two dams at 1000 mg/kg bw per day was considered to be incidental and not related to treatment.

The Meeting concluded that novaluron is not a developmental toxicant.

In a study of acute neurotoxicity in rats, non-specific clinical signs (fast respiration, piloerection) of minor toxicological relevance were seen in all groups treated at doses of 200 mg/kg bw and greater. The NOAEL for neurotoxic effects was 2000 mg/kg bw, the highest dose tested.

The manufacturing impurity MCW RI 458 had low acute oral and dermal toxicity in rats (LD_{50} > 5000 and > 2000 mg/kg bw, respectively) and was not mutagenic in an assay for gene mutation in bacteria. The manufacturing intermediate MCW I was not mutagenic in an assay for gene mutation in bacteria.

The Meeting concluded that the existing database on novaluron was adequate to characterize the potential hazards to fetuses, infants and children.

Toxicological evaluation

The Meeting established an ADI of 0–0.01 mg/kg bw on the basis of the NOAEL of 1.1 mg/kg bw per day for erythrocyte damage and secondary splenic and liver changes in a 2-year dietary study in rats, and a safety factor of 100.

The Meeting concluded that it was not necessary to establish an ARfD for novaluron in view of its low acute toxicity, the absence of relevant developmental toxicity in rats and rabbits that could have occurred as a consequence of acute exposure, and the absence of any other toxicological effect that would be elicited by a single dose.

A toxicological monograph was prepared.

Levels relevant to risk assessment

Species	Study	Effect	NOAEL	LOAEL
Mouse	3-month study of toxicity[a]	Toxicity	30 ppm, equal to 4.2 mg/kg bw per day	100 ppm, equal to 12.8 mg/kg bw per day
	78-week study of carcinogenicity[a]	Toxicity	30 ppm, equal to 3.6 mg/kg bw per day	450 ppm, equal to 53.4 mg/kg bw per day
		Carcinogenicity	7000 ppm, equal to 800 mg/kg bw per day[d]	—
Rat	3-month study of toxicity[a]	Toxicity	50 ppm, equal to 4.2 mg/kg bw per day	100 ppm, equal to 8.3 mg/kg bw per day
	2-year study of toxicity and carcinogenicity[a]	Toxicity	25 ppm, equal to 1.1 mg/kg bw per day	700 ppm, equal to 30.6 mg/kg bw per day
		Carcinogenicity	20000 ppm, equal to 884.2 mg/kg bw per day[d]	—

Species	Study	Effect	NOAEL	LOAEL
	Multigeneration study of reproductive toxicity[a]	Reproduction/fertility	12000 ppm, equal to 894.9 mg/kg bw per day[d]	—
		Parental toxicity	—	1000 ppm, equal to 74.2 mg/kg bw per day[e]
		Offspring toxicity	—	1000 ppm, equal to 74.2 mg/kg bw per day[e]
	Developmental toxicity[b]	Maternal toxicity	1000 mg/kg bw per day[d]	—
		Embryo- and fetotoxicity	1000 mg/kg bw per day[d]	—
	Acute neurotoxicity[b]	Neurotoxicity	2000 mg/kg bw per day[d]	—
Rabbit	Developmental toxicity[b]	Maternal toxicity	1000 mg/kg bw per day[d]	—
		Embryo- and fetotoxicity	1000 mg/kg bw per day[d]	—
Dog	3-month study of toxicity[c]	Toxicity	10 mg/kg bw per day	100 mg/kg bw per day
	1-year study of toxicity[c]	Toxicity	10 mg/kg bw per day	100 mg/kg bw per day

[a] Dietary administration
[b] Gavage administration
[c] Capsules
[d] Highest dose tested
[e] Lowest dose tested

Estimate of acceptable daily intake for humans

0–0.01 mg/kg bw

Estimate of acute reference dose

Unnecessary

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

Results from epidemiological, occupational health and other such observational studies of human exposures

Critical end-points for setting guidance values for exposure to novaluron

Absorption, distribution, excretion and metabolism in mammals	
Rate and extent of oral absorption	Rapid; ≤ 7% at low dose
Distribution	Widely; highest concentrations in fat, liver, kidneys
Rate and extent of excretion	Largely complete within 48 h; primarily via faeces (> 94%) and to a lesser extent via urine (< 5%)
Potential for accumulation	Evidence of accumulation in fat after repeated doses
Metabolism in mammals	Extensive for absorbed material; cleavage of the urea bridge between the chlorophenyl and difluorophenyl moieties
Toxicologically significant compounds (animals, plants and the environment)	Parent compound and animal metabolite 3-chloro-4-(1,1,2-trifluoro-2-trifluoromethoxyethoxy) aniline
Acute toxicity	
Rat LD_{50} oral	> 5000 mg/kg bw
Rat LD_{50} dermal	> 2000 mg/kg bw
Rat LC_{50} inhalation	> 5.15 mg/L (4-h, nose-only exposure)
Rabbit, skin irritation	Non-irritant

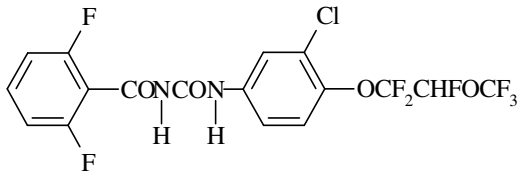
Rabbit, eye irritation	Non-irritant
Skin sensitization (test method)	Not sensitizing (Magnusson & Kligman test, Buehler test)
Short-term studies of toxicity	
Target/critical effect	Erythrocytes (haemoglobin oxidation, resulting in methaemoglobinaemia and haemolysis), secondary changes in spleen, liver and kidneys
Lowest relevant oral NOAEL	4.2 mg/kg bw per day (90-day studies in rats and mice)
Lowest relevant dermal NOAEL	75 mg/kg bw per day (28-day study in rats)
Lowest relevant inhalation NOAEC	No data
Genotoxicity	
	Not genotoxic in vitro or in vivo
Long-term studies of toxicity and carcinogenicity	
Target/critical effect	Erythrocytes (haemoglobin oxidation, resulting in methaemoglobinaemia and haemolysis), secondary changes in spleen, liver and kidneys
Lowest relevant NOAEL	1.1 mg/kg bw per day (2-year study in rats)
Carcinogenicity	Not carcinogenic in rats or mice
Reproductive toxicity	
Reproduction target/critical effect	No effect on fertility at highest dose tested; splenic and liver changes in offspring at parentally toxic doses
Lowest relevant reproductive NOAEL	895 mg/kg bw per day for effects on fertility (two-generation study in rats)
	< 74.2 mg/kg bw per day for systemic toxicity in offspring and parents
Developmental target/critical effect	No developmental effect at highest dose tested
Lowest relevant developmental NOAEL	1000 mg/kg bw per day (rats and rabbits)
Neurotoxicity/delayed neurotoxicity	
Acute neurotoxicity	No evidence for neurotoxicity at highest dose tested (2000 mg/kg bw)
Medical data	
	No data

Summary

	Value	Study	Safety factor
ADI	0–0.01 mg/kg bw	Rat, 2-year study	100
ARfD	Unnecessary	—	—

RESIDUE AND ANALYTICAL ASPECTS

Novaluron, or (±)-1-[3-chloro-4-(1,1,2-trifluoro-2-trifluoromethoxy ethoxy) phenyl]-3-(2,6-difluorobenzoyl)urea, is an insect growth regulator. Novaluron inhibits chitin synthesis, affecting the moulting stages of insect development. It acts by ingestion and contact and causes abnormal endocuticular deposition and abortive moulting. It is being evaluated for the first time by the 2005 JMPR.



Animal metabolism

The metabolism of novaluron uniformly radiolabeled in the difluorphenyl ring and separately in the chlorophenyl ring was studied in goats and chickens. *Lactating goats* were dosed with the radiolabled compounds at rates equivalent to 11–12 ppm in the feed for five consecutive days. Most of the radioactivity was eliminated in the faeces, 52% of the administered dose for the [difluorophenyl-^{14}C(U)]-novaluron and 72% for the [chlorophenyl-^{14}C(U)]- novaluron. The Total Radioactive Residue (TRR) did not reach a plateau in milk during the five days, with the final concentration being 0.23–0.24 mg/kg. TRR concentrations in the tissues resulting from administration of the two radiolabelled compounds were similar: peritoneal fat, 1.4–1.9 mg/kg; kidney, 0.14–0.16 mg/kg; liver, 0.34–0.43 mg/kg, muscle, 0.09–0.16 mg/kg. Methanol extraction released 80 100% of the TRR from the various tissues, and greater than 90% of the TRR was extracted from milk with hexane/methanol.

Novaluron was the only residue identified in milk (93-95% TRR), peritoneal fat (96- 100% TRR), and foreleg muscle (98% TRR). It was the major component in kidney (73-83% TRR) and liver (80-84% TRR). The metabolite 2,6-difluorobenzoic acid was found in kidney (5.1% TRR), and 1-[3-chloro-4-(1,1,2-trifluoro-2-trifluoro methoxyethoxy)phenyl]urea was identified in liver, at 7.3% TRR (0.025 mg/kg). In faeces, 3-chloro-4-(1,1,2-trifluoro-2-trifluoro methoxyethoxy)aniline was tentatively identified. Very little degradation of the parent novaluron occurred, and the metabolites found are consistent with cleavage at the benzoyl–urea linkage.

Even less metabolism/degradation of novaluron was observed in poultry. [Difluorophenyl] ^{14}C-Labelled novaluron was administered orally to five laying hens for fourteen consecutive days at a nominal rate of 10 ppm in the diet. The TRR concentrations were as follows: liver, 0.39 mg/kg; kidney, 0.39 mg/kg; muscle, 0.061–0.30 mg/kg; fat, 3.6 mg/kg; eggs (day 14), 0.50 mg/kg. Novaluron was the only TRR component detected and identified, accounting for 90–107% of the TRR.

The results of the ruminant metabolism studies compare favourably to those of a rat metabolism study. The ruminant metabolites 1-[3-chloro-4-(1,1,2-trifluoro-2-trifluoro-methoxyethoxy)phenyl] urea and 3-chloro-4-(1,1,2-trifluoro-2-trifluoro methoxyethoxy) aniline were also found in the rat. Additionally, 2,6-difluorobenzamide was found in rat kidney (7% TRR).

The Meeting concluded that novaluron undergoes only minor metabolism in goats and hens, and that the limited metabolism is consistent with a cleavage of the benzoyl urea bond.

Plant metabolism

The metabolism of difluorophenyl-^{14}C- or chlorophenyl-^{14}C-labelled novaluron in apples, cabbages, potatoes, and cotton following foliar application(s) was reported to the Meeting. Novaluron, radiolabelled in either the [chlorophenyl-^{14}C(U)] or [difluorophenyl-^{14}C(U)] ring was formulated as a 10% EC and sprayed onto trees growing in outdoor pots in a netted tunnel. Either 2 (4 trees per radiolabelled form) or 3 applications (2 trees per radiolabelled form) were made to trees at a rate of 2.5–2.7 mg/tree/application. The applications were made 110 days, 90 days, and 60 days (3 applications only) before harvest. Novaluron comprised >90% TRR in all fruit samples from all applications and sampling intervals. No metabolite (HPLC) comprised more than 1% (< 0. 01 mg/kg) of the TRR.

Novaluron, radiolabelled in either the [chlorophenyl-^{14}C(U)] or difluorophenyl-^{14}C(U)] ring was prepared as a 10% EC formulation and sprayed onto two groups of cabbage plants growing in outdoor pots. Two applications (either, 8 and 6 weeks before harvest or 5 and 2 weeks before harvest) were made to replicate a rate of 30–45 g ai/ha. Residues (TRR) were 0.23–0.35 for the 6 week PHI application and 0.32–0.45 mg/kg for the 2 week PHI application. An acetonitrile wash removed 81–90% of the TRR at final harvest. Acetonitrile/water extraction released an additional 9–15% TRR,

the majority of which was on the outer cabbage leaves. About 96–100% of the TRR on cabbage heads at final harvest (and at earlier harvest intervals) was identified as novaluron.

Novaluron, radiolabelled in either the [chlorophenyl-^{14}C(U)] or [difluorophenyl-^{14}C(U)] ring was prepared as a 10% EC formulation and sprayed onto potato plants growing in outdoor field plots. Two applications (43 and 29 days before harvest) were made to replicate plants at a rate of 91-100 g ai/ha. Whole plant samples were taken after each application and also at 22, 10 and 0 days before harvest. For both radiolabels, the TRR on tubers at all intervals was < 0.001 mg/kg. At harvest (29 days after the second application) the TRR on plants was 9.9 mg/kg for the [difluorophenyl-^{14}C(U)] and 5.9 mg/kg for the [chlorophenyl-^{14}C(U)]novaluron. An acetonitrile wash removed 82% of the TRR, and an acetonitrile/water extraction released an additional 17% TRR. Novaluron comprised 97% of the TRR for both labelled compounds. An unknown (1.3% TRR, 0.074 mg/kg) was found with the [chlorophenyl-^{14}C(U)]novaluron.

Cotton plants grown outdoors were treated with [chlorophenyl-^{14}C]novaluron or [difluorophenyl-^{14}C]novaluron at an application rate equivalent to 50 g ai/ha/treatment. Two treatment regimes were used; Regime 1 consisted of two applications, 14 days apart with a 90 day PHI and Regime 2 consisted of two applications 14 days apart with a 30 day PHI. Samples from plants treated according to Regime 1 were taken for analysis after each application and at 60 and 30 days before the normal harvest. The maximum TRR on undelinted seed (for both treatment regimes) was 0.005 mg/kg, and no isolation and characterization of the residue was attempted. The TRR on cotton gin trash at harvest ranged from 0.27 mg/kg (90 day PHI) to 0.85 mg/kg (30 day PHI). Acetonitrile extraction released 91–97% TRR from the various final harvest gin trashes. Novaluron constituted 88–95% TRR. Total unidentified components in the extracts were <4% TRR (< 0.012 mg/kg)

The Meeting concluded that novaluron is stable when used as a foliar spray on various food crop plants. There is no appreciable metabolism or degradation under typical GAP conditions.

Environmental fate

Novaluron is stable in water at pH 5 and pH 7. At pH 9 (25°C), however, novaluron degraded with a first-order DT_{50} of about 100 days. At 50 and 70 °C, first order DT_{50}s were 1.2 and 0.09 days, respectively (pH 9). Major metabolites exceeding 10% of applied radioactivity were identified as the chlorophenyl ring urea (1-[3-chloro-4-(1,1,2-trifluoro-2-trifluoromethoxyethoxy)phenyl]urea) and 2,6-difluorobenzoic acid. These degradates are also the metabolites observed in livestock metabolism.

In a confined rotational crop study, six containers of soil were treated with chlorophenyl-^{14}C(U)]novaluron at a rate of 100 g ai/ha (approximately 3.5 mg ai/container). Rotational crops of spinach, turnips, and spring wheat were planted into separate containers (one container per crop at each plantback interval of 30 and 120 days). Crop and soil samples were taken at times after sowing that was representative of immature harvest, early harvest, and final harvest. At the 30 day plantback interval, all crops contained only very low levels of TRR, 0.001–0.004 mg/kg. Soil samples were extracted and analysed. Novaluron declined from 98–99% of the TRR on the day of application to 32–49% TRR at final harvest (127–195 days after application). Degradates identified in soil at final harvest were 1-[3-chloro-4-(1,1,2-trifluoro-2-trifluoromethoxyethoxy)phenyl]urea (10–14% TRR) and 3-chloro-4-(1,1,2-trifluoro-2-trifluoromethoxyethoxy)aniline (21–30% TRR).

The Meeting concluded that the accumulation of novaluron, or its degradates, in rotational crops from use on primary crops, under typical GAP conditions, is unlikely.

Methods of analysis

The Meeting concluded that adequate analytical methods exist both for the monitoring/enforcement of MRLs and for data gathering in supervised field trials and processing studies. Two methods were developed and validated for the determination of novaluron in plant and animal commodities.

A gas chromatography (GC) method with electron capture detection (ECD) may be used for various plant commodities (apple, cabbage, potato, apple processed commodities, broccoli, tomato, orange processed commodities) and animal commodities (fat, kidney, liver, muscle, milk, egg). Homogenized samples are extracted into aqueous methanol and portioned with hexane. The hexane extract is purified with a solid phase extraction cartridge prior to GC determination. A variation of the method uses a mass selective detector (MSD; ions m/z 337 and m/z 335). The method and its variations have been validated at 0.01 or 0.05 mg/kg for plant commodities and at 0.01 mg/kg for animal commodities.

The GC method was radiovalidated for animal commodities (but not for plant commodities). Samples of liver, fat (mesenteric/abdominal), thigh muscle and eggs (final day sample only) from the nature of the residue in poultry study (see above) were extracted and analysed according to the GC method. To radiovalidate this method, samples of extracts were radioassayed by LSC and the final post-SPE samples were analysed by TLC with radiodetection. Both methods of analysis gave similar results, with the GC method giving 110–120% of the recovery and detection of the metabolism results.

A HPLC reverse phase with ultraviolet detection (UV, 252 nm or 264 nm) method may be used for various plant commodities (apple, pear, peach, maize forage, soya plant and seeds, undelinted cotton seed, cotton foliage, tomato, potato). The method was validated at 0.01 or 0.05 mg/kg. A macerated sample is extracted with acetone and methylene chloride, and the organic layer is exchanged to acetonitrile. A gel permeation step may be used for high oil/fat content samples (e.g., cotton seed). The acetonitrile is extracted with hexane, and the residual acetonitrile extract is purified sequentially on Florisil and silica/Rumsil.

A variation of the HPLC method with tandem mass spectrometer detection (MS/MS) may be used for plant and animal matrices. Matrices are extracted with methanol/water and cleaned-up with hexane extraction and SPE. Analysis is by LC-MS/MS in the negative electrospray ionization mode. Novaluron m/z 491 > 471 is monitored. The method was validated at 0.05 mg/kg for apples and at 0.01 mg/kg for potatoes. An independent laboratory validation showed adequate recoveries of novaluron from milk, muscle, and liver at 0.02, 0.02, and 0.05 mg/kg respectively. Recovery from fat in another study was acceptable at a 0.1 mg/kg fortification

Stability of pesticide residues in stored analytical samples

The stability of novaluron in plant commodities under frozen storage conditions (-18^{o}C) for periods of at least 3 to 12 months was demonstrated. The periods of stability adequately cover the storage intervals for all supervised field trials reported. The following minimum intervals of frozen storage stability were determined: apple, 12 months; pear fruit, 158 days; apple juice, 99 days; potato, 12 months; undelinted cotton seed, 160 days; broccoli, 6 months; tomato, 12 months; orange processed fractions, 8 months.

No storage stability data was presented for animal products. The information in the livestock feeding study indicates that all analyses were completed within 53 days of the first sacrifice. The metabolism studies in ruminants and poultry indicate very little metabolism or degradation of novaluron occurs. The Meeting concluded that the relatively short interval of frozen storage (< 53 days) of the animal feeding study commodities should not have resulted in loss of novaluron residues.

Definition of the residue

The results of the radiolabeled novaluron plant metabolism studies on apple, cabbage, cotton, and potato indicate that novaluron does not metabolize or degrade under typical foliar application conditions. Greater than 90% of the TRR is recovered as novaluron, and no significant metabolites/degradates are found.

In ruminants, orally administered radiolabled novaluron (equivalent to 11–12 ppm in the diet) undergoes limited metabolism to 2,6-difluorobenzoic acid and 1-[3-chloro-4-(1,1,2-trifluoro-2-trifluoro methoxyethoxy)phenyl]urea, each < 10% TRR. The major component of the TRR was novaluron, ≥ 93% TRR in milk, fat, and muscle and ≥ 73% TRR in liver and kidney. In poultry orally administered novaluron (equivalent to 10 ppm in the diet) for 14 days, virtually no metabolism/degradation of novaluron occurred.

The log of the octanol/water partition coefficient, 4.3, suggests a preferential solubility in fat. In both ruminants and poultry, novaluron accumulated preferentially in fat as opposed to muscle (12–16:1 for ruminant; 12:1 for poultry).

The analytical methods determine only novaluron.

The Meeting noted that the residue definition in Australia and in the United States for monitoring/enforcement and for risk assessment purposes is novaluron.

Given the results of the metabolism studies and the capability of the analytical methods, the Meeting concluded that the residue definition for both enforcement and dietary intake considerations for both plant and animal commodities is novaluron. The Meeting also decided that novaluron is fat-soluble.

Results of supervised trials on crops

Supervised trials were presented for the foliar treatment of a variety of crops worldwide.

Apple and Pear

Trials on apples were conducted in Chile (GAP of foliar applications using a 100 g/L EC formulation at a rate of 0.07 kg ai/hL and a PHI of 14 days), USA and Canada (GAP foliar applications, at a rate of 0.37 kg ai/ha using a 75 g/kg WG formulation and a PHI of 14 days). The number of applications was not specified. One trial was not within 30% of GAP (0.005 kg ai/hL and 11 day PHI) with a residue of 0.17 mg/kg.

The GAP for apples in the USA is foliar application of a 75 g/kg WG formulation at 0.37 kg ai/ha. No more than 4 applications may be made per season and no more than 1.1 kg ai/ha may be applied per season. The rate per hectare is maintained regardless of water volume or tree size with a maximum spray concentration of 0.05 kg ai/hL for trees over 3 metre in height and a maximum of 0.08 kg ai/hL for trees less than 3 metres in height. The PHI is 14 days.

Many of the USA trials and all of the Canadian trials were conducted with three early season trials (commencing at petal fall) each at 0.38 kg ai/ha plus three late season trials (commencing at about 30 days before harvest) each at 0.38 kg ai/ha, for a total of 2.2–2.4 kg ai/ha (2× concentration). The early season applications started at petal fall and continued at 7 day intervals. The time from the final early season application to harvest is 60–160 days. There were no apple residue decline studies upon which to estimate the residue attributable to the early season applications. However, several side-by-side trials were conducted in which 6 applications (3 early season plus 3 late season) and 3 applications (3 late season) were applied. It was found that the residues from 6 applications were comparable to those from 3 applications: Michigan: 0.81 mg/kg (2.2 kg ai/ha total) and 0.73 mg/kg

(1.1 mg/kg ai/ha total); New York, 0.55 and 0.77 mg/kg; Oregon, 0.37 and 0.50 mg/kg; Virginia, 0.65 and 0.67 mg/kg respectively. Therefore, the trials conducted with 6 applications were considered to be at the approximate maximum GAP. The residues from 27 trials at GAP in ranked order were: 0.23, 0.27, 0.35, 0.37, 0.44, 0.44, 0.49, 0.49, 0.50, 0.50, 0.54, 0.55, 0.60, 0.65, 0.67, 0.67, 0.68, 0.71, 0.71, 0.73, 0.75, 0.77, 0.81, 0.86, 0.93, 0.96, and 1.1 mg/kg.

The GAP for pears in the USA is identical to that for apples (above). In eight trials conducted in the USA and four trials conducted in Canada, 3 early season applications each at 0.38 kg ai/ha were followed by 3 late season applications each at 0.38 kg ai/ha, for a total seasonal application of about 2.2 kg ai/ha, or 2× the maximum GAP. However, side-by-side trials with apples (above) indicated that the early season use did not contribute to the final residue. Assuming a translation to pears, ten trials were conducted at the approximate maximum GAP, and the residues in ranked order are: 0.18, 0.42, 0.46, 0.47, 0.59, 0.91, 1.0, 1.3, 1.6, and 1.8 mg/kg.

The Meeting decided that the apple and pear residue data, resulting from identical application patterns, were from the same population and combined the data to give the following residues in ranked order: 0.18, 0.23, 0.27, 0.35, 0.37, 0.42, 0.44, 0.44, 0.46, 0.47, 0.49, 0.49, 0.50, 0.50, 0.54, 0.55, 0.59, 0.60, 0.65, 0.67, 0.67, 0.68, 0.71, 0.71, 0.73, 0.75, 0.77, 0.81, 0.86, 0.91, 0.93, 0.96, 1.0, 1.1, 1.3, 1.6, and 1.8 mg/kg. The Meeting estimated an STMR of 0.65 mg/kg and a maximum residue level of 3 mg/kg for pome fruit.

Fruiting vegetables, other than cucurbits

Tomatoes

Supervised field trials for the foliar application of novaluron to tomatoes were reported from Argentina and Brazil. The GAP for Argentina specifies foliar application of a 100 g/L EC foliar application at 0.005 kg ai/hL, 4 applications, and a 1 day PHI. Two trials were conducted in Argentina, but none were at GAP. Twelve trials were reported from Brazil, where the GAP is for the foliar application of a 100 g/L EC formulation at 0.002 kg ai/hL (0.02 kg ai/ha), with repeat applications as needed and a PHI of 7 days. The residues in ranked order are: < 0.01 (4) and < 0.02 (8). The Meeting estimated an STMR of 0.02 mg/kg and a maximum residue level of 0.02 (*) mg/kg.

Soya bean (immature seeds)

Field trials were reported for the foliar application of novaluron to soya beans (immature seeds) in Brazil. The GAP in Brazil specifies a foliar application of a 100 g ai/l EC formulation at a rate of 0.01 kg ai/ha with a PHI of 53 days. The number of applications is not specified. Eleven trials were conducted at the maximum GAP, and the residues on soya beans in ranked order were: < 0.01 (11) mg/kg. The Meeting estimated an STMR of 0.01 mg/kg and a maximum residue level of 0.01 (*) mg/kg.

Potato

Field trials were reported the EU, Mexico, and the USA for the foliar application of novaluron to potatoes. The GAP for use in Switzerland is a maximum of 2 applications (foliar) of a 100 g ai/L EC formulation at a single application rate of 0.02 kg ai/ha with a 21 day PHI. This GAP may be applied to trials conducted in Europe (Switzerland, Germany, France, Italy and Spain). Fourteen trials were at the GAP of Switzerland, and the residues in ranked order are: < 0.01 (14) mg/kg.

The GAP of Mexico specifies one foliar application of a 100 g/L EC formulation at a rate of 0.015 kg ai/ha with a PHI of 30 days. Two trials were conducted at 0.028 kg ai/ha (about 2×) and a PHI of 14 days, but may be considered as no quantifiable residues were found. The residues in ranked order were: < 0.01 (2) mg/kg.

The GAP of the USA specifies a maximum of 2 applications per season of a 100 g/L EC formulation at a rate of 0.087 kg ai/ha (0.17 kg ai/ha/season) with a PHI of 7 days. Two trials were reported from the USA, where two applications were made at a rate of 0.28 kg ai/ha each (3×). The trials may be considered as no quantifiable residues were found. The residues in ranked order were: < 0.05 (2) mg/kg. The analytical method (GC/ECD) was validated by concurrent fortified sample recoveries at 0.05 mg/kg. However, the same method was validated elsewhere at 0.01 mg/kg, including the method used for the European trials. The limit of quantitation was not adequately established for these USA trials.

The Meeting agreed to combine the non-quantifiable residues for the EU and Mexico, which in ranked order are: < 0.01 (16) mg/kg. The Meeting estimated an STMR of 0.01 mg/kg and a maximum residue level of 0.01 (*) mg/kg.

Oilseeds

Cotton seed

Supervised field trials for the foliar application of novaluron to cotton were conducted in Brazil, Mexico, South Africa, and the USA. The GAP of Brazil specifies foliar application of a 100 g/L EC formulation at a rate of 0.01 kg ai/ha (0.005 kg ai/hL) with a 93 day PHI. Four trials were conducted, three of which were at an exaggerated rate (2×) or a substantially shorter PHI. However, all residues on the cottonseed were below the limit of quantitation. The ranked order of residues found were: < 0.01 (4) mg/kg.

The GAP of Mexico specifies foliar application of a 100 g/L EC formulation at a rate of 0.015 kg ai/ha with a 30 day PHI. Only 1 application is allowed. Two trials were reported, but both were at an exaggerated rate (3×) with quantifiable residues.

The GAP of South Africa specifies the foliar application of a 100 g/L EC formulation at a rate of 0.035 kg ai/ha (0.007 kg ai/hL for ground equipment and 0.12 kg ai/hL for aerial equipment) with no specified PHI and a maximum of 3 applications per season. Two trials are reported, but the PHI is 71 days.

The GAP of the USA specifies the foliar application of a 100 g/L EC formulation at a rate of 0.1 kg ai/ha (0.53 kg ai/hL for aerial equipment and 0.21 kg ai/hL for ground equipment) with a PHI of 30 days. No more than 4 applications and a maximum application of 0.3 kg ai/ha are to be used per season. The re-treatment interval is a minimum of 7 days. The majority of the trials involved 5 applications with a total application of 0.42 kg ai/ha, or 140% of the maximum seasonal rate. The last three applications were made late in the season (3 × 0.1 kg ai/ha, 100% seasonal rate), with a 7 day retreatment interval and with 44–80 days between the first two and these three applications. The first two applications were made early season (3 to 4 weeks after crop emergence and 14 days later) at a nominal rate of 0.058 kg ai/ha/application. As the majority of the residue would result from the three late season applications, the trials may be considered to be at GAP.

The residues in ranked order for 16 trials at GAP are: < 0.05 (5), 0.060, 0.066, 0.067, 0.069, 0.10, 0.19, 0.21, 0.22, 0.25, 0.34, and 0.40 mg/kg. The trials from Brazil are considered not to be from the same population as the USA trials. The Meeting estimated an STMR of 0.068 mg/kg and a maximum residue level of 0.5 mg/kg.

Primary animal feed commodities of plant origin

Cotton gin trash

Eleven supervised field trials conducted in the USA were considered to be consistent with the GAP of the USA (see cotton above). The residues in ranked order are: 3.7, 4.0, 4.5, 5.4, 6.7, 7.3, 10, 11, 17, 20, and 27 mg/kg. The Meeting estimated a median of 7.3 mg/kg and a high residue of 27 mg/kg.

Fate of residues during processing

Commercial-type processing studies were reported for apple and cottonseed, and the processing factors and resulting STMR-P values are summarized as follows:

Raw Agricultural Commodity[1]				Processed Commodity				
Commodity	MRL (mg/kg)	STMR (mg/kg)	HR (mg/kg)	Commodity	Proces-sing factor	MRL (mg/kg)	STMR(P) (mg/kg)	HR(P) (mg/kg)
Apple	3	0.65	1.8	Juice	< 0.1	-	0.065	-
				Wet pomace[2]	7.2	13[3]	4.7[4]	-
Cotton seed (undelinted)	0.7	0.068	0.40	Meal	< 0.6	-	0.041	-
				Hulls	< 0.6	-	0.041	-
				Refined oil	< 0.6	-	0.041	-

[1] Only one processing study was available for each raw agricultural commodity.
[2] Water content (%) was not reported.
[3] 40 mg/kg for apple pomace dry based on a default dry matter content of 40%.
[4] 12 mg/kg for apple pomace dry based on a default dry matter content of 40%.

Farm animal dietary burden

The Meeting estimated the dietary burden of novaluron residues in farm animals on the basis of the diets listed in Appendix IX of the *FAO Manual*. Calculation from MRLs, highest residues (HR) and STMR-P values provides the levels in feed suitable for estimating MRLs for animal commodities, while calculation from STMR and STMR-P values for feed is suitable for estimating STMR values for animal commodities. The percentage of dry matter is taken as 100% when MRLs and STMR values are already expressed as dry weight.

Estimated maximum dietary burden of farm animals

Commodity	Group	Residue (mg/kg)	Basis of Residue	Dry matter (%)	*Diet content (%)*			Residue contribution (mg/kg)		
					Beef cattle	*Dairy cows*	*Poultry*	Beef cattle	Dairy cows	Poultry
Apple pomace	AB	4.7	STMR-P	40	*40*	*20*	-	4.7	2.4	
Cotton gin trash	AM	27	HR	90	*20*	*20*	-	6	6	
Cotton seed meal	-	0.041	STMR-P	89			*20*			0.01
Cotton seed hulls	AM	0.041	STMR-P	90			-			
Cotton seed	SO	0.40	HR	88	*25*	*25*	-	0.11	0.11	
TOTAL					***85***	***65***	***20***	**11**	**8.5**	**0.01**

The calculated maximum dietary burdens for beef cattle, dairy cows, and poultry are 11, 8.5, and 0.01 ppm, respectively.

Estimated STMR dietary burden of farm animals

Commodity	Group	Residue (mg/kg)	Basis of Residue	Dry matter (%)	*Diet content, (%)*			Residue contribution (mg/kg)		
					Beef cattle	*Dairy cows*	*Poultry*	Beef cattle	Dairy cows	Poultry
Apple pomace	AB	4.7	STMR-P	40	*40*	*20*	-	4.7	2.4	
Cotton gin trash	AM	7.3	STMR	90	*20*	*20*	-	1.6	1.6	
Cotton seed meal	-	0.041	STMR-P	89			*20*			0.01
Cotton seed hulls	AM	0.041	STMR-P	90			-			
Cotton seed	SO	0.068	STMR	88	*25*	*25*	-	0.019	0.019	
TOTAL					***85***	***65***	***20***	**6.3**	**4.0**	**0.01**

The STMR dietary burdens for beef cattle, diary cows, and poultry are 6.3, 4.0, and 0.01 mg/kg, respectively.

Farm animal feeding studies

A feeding study was conducted with Friesian cows in which groups received the equivalent of 0, 0.35, 2.6, 8.0, or 26 ppm in the feed for 42–44 consecutive days. Average novaluron residues in whole milk on day 42 at the 8 and 26 ppm feeding levels were 0.38 and 1.7 mg/kg; in cream, 6.6 and 14 mg/kg; and in skimmed milk, 0.03 and 0.12 mg/kg. The novaluron maximum residue levels in tissues at the 8 ppm feeding level were: muscle, 0.34 mg/kg; kidney, 0.35 mg/kg; liver, 0.41 mg/kg; subcutaneous fat, 4.4 mg/k; peritoneal fat, 6.8 mg/kg. The novaluron maximum residue levels in tissues at the 26 ppm feeding level were: muscle, 0.56 mg/kg; kidney, 1.2 mg/kg; liver, 1.4 mg/kg; subcutaneous fat, 8.2 mg/kg; peritoneal fat, 13 mg/kg.

Residues were quantifiable at the lowest feeding level (0.35 ppm): milk, 0.04 mg/kg; muscle, 0.05 mg/kg; kidney, 0.06 mg/kg; liver, 0.05 mg/kg; subcutaneous fat, 0.43 mg/kg; and peritoneal fat, 0.56 mg/kg.

Novaluron total residues, mg/kg

Dietary burden *(ppm)* Feeding level [ppm]	Cream mean	Milk mean	Muscle highest	Muscle mean	Liver highest	Liver mean	Kidney highest	Kidney mean	Fat Highest	Fat mean
MRL beef cattle										
(11)			*(0.47/ 0.24)*		*(0.56/ 0.59)*		*(0.48/ 0.51)*		*(9.4/ 5.5)*	
[8/26]			0.34/ 0.56		0.41/ 1.4		0.35/ 1.2		6.8/ 13	
MRL dairy cattle										
(8.5)	*(7.0)*	*(0.40)*								
[8]	6.6	0.38								
STMR beef cattle										
(6.3)				*(0.19)*		*(0.24)*		*(0.26)*		*(4.1)*
[8]				0.24		0.31		0.33		5.2
STMR dairy cattle										
(4.0)	*(4.3/3.3)*	*(0.20/0.19)*								
[2.6/8]	2.8/6.6	0.13/0.38								

A poultry feeding study was not provided. The nature of the residue in poultry was conducted for fourteen consecutive days at a rate equivalent to 10 ppm in the diet. Novaluron residues in eggs, fat, muscle, kidney, and liver were 0.45, 3.5, 0.31, 0.37 and 0.41 mg/kg, respectively. Residues would most likely be non-quantifiable at the calculated dietary burden level of 0.01 ppm (1/1000 ×).

Maximum residue levels

The Meeting estimated maximum residue levels of 10 mg/kg for meat (fat), 0.7 mg/kg for edible offal, 7 mg/kg for milk fat, and 0.4 mg/kg for milk. The Meeting also estimated the following STMR values: muscle 0.19 mg/kg, fat 4.1 mg/kg, edible offal 0.26 mg/kg, whole milk 0.20 mg/kg, and cream 4.3 mg/kg.

The Meeting estimated maximum residue levels of 0.01 (*) mg/kg for eggs, poultry meat, and poultry edible offal, based on the demonstrated limit of quantification for poultry commodities by the GC/ECD method. Also estimated were STMRs of 0 for eggs, meat, and edible offal and 0.005 mg/kg for poultry fat.

DIETARY RISK ASSESSMENT

Long-term intake

The International Estimated Daily Intakes of novaluron, based on the STMRs estimated for 17 commodities, for the five GEMS/Food regional diets were in the range of 7% to 40% of the ADI (Annex 3). The Meeting concluded that the long-term intake of residues of novaluron resulting from its uses that have been considered by JMPR is unlikely to present a public health concern.

Short-term intake

The 2005 JMPR decided that an ARfD is unnecessary. The Meeting therefore concluded that the short-term intake of novaluron residues is unlikely to present a public health concern.

4.17 PHORATE (112)

RESIDUE AND ANALYTICAL ASPECTS

Phorate is a systemic organophosphate contact insecticide and acaricide that inhibits acetyl cholinesterase activity. Residue and analytical aspects of phorate were evaluated by the JMPR in 1977, 1984, 1990, 1991, and 1992. The 30th Session of CCPR (1998) requested priority scheduling of a full review of the compound because of acute intake concerns. Phorate was listed in the Periodic Re-Evaluation Programme at the 36th Session of the CCPR for periodic review by 2005 JMPR. The JMPR toxicological review was conducted in 2004, which established an ADI of 0–0.0007 mg/kg bw and an ARfD of 0.003 mg/kg bw.

Information on the latest GAP, residue data, metabolism, analytical methods, storage stability and processing studies were provided by the manufacturer to enable the assessment of existing and proposed MRLs on a number of crops or crop groups, including beans, potatoes, sugar beet, sweet corn, maize, sorghum, cotton, and coffee.

In addition, GAP information and/or national MRLs were supplied by Australia and The Netherlands.

The following common names were used for the metabolites discussed below:

phorate sulfoxide	*O,O*-diethyl *S*-ethylsulfinylmethylphosphorodithioate
phorate sulfone	*O,O*-diethyl *S*-ethylsulfonylmethylphosphorodithioate
phoratoxon	*O,O*-diethyl *S*-ethylthiomethylphosphorothioate
phoratoxon sulfoxide	*O,O*-diethyl *S*-ethysulfinylmethylphosphorothioate
phoratoxon sulfone	*O,O*-diethyl *S*-ethylsulfonylmethylphosphorothioate

Animal metabolism

The Meeting received information on the fate of orally dosed phorate in lactating goats and laying hens. Phorate was ^{14}C labelled at the methylene position.

Studies on laboratory animal metabolism (rats) were evaluated by the WHO Core Assessment Group of the 2004 JMPR. It was reported that after oral administration of radiolabelled phorate to rats, 77% of the administered dose was recovered in the urine within 24 h after dosing. Faecal excretion accounted for approximately 12% of the administered dose. Over the total duration of the study (192 h), effectively the entire administered dose was eliminated by excretion. The bulk of the administered dose (94%) was biotransformed to nonphosphorylated metabolites. The metabolic pathway responsible for the formation of these metabolites resulted from the cleavage of the phosphorus-sulfur bond, methylation of the liberated thiol group and oxidation of the resulting divalent sulfur moiety to the sulfoxide and sulfone. Thus, these studies demonstrated that in rats phorate is rapidly absorbed and excreted and the accumulation of any toxicologically significant residue is not of concern.

In two consecutive studies, lactating goats were orally treated (balling gun) with ^{14}C-labelled phorate at dose rates of 1.35 and 5.40 ppm in the feed for either 3 or 7 days. At the highest dose, significant depression in plasma cholinesterase activity was observed. Recovery of total applied radioactivity (in excreta, tissues, milk) was not investigated. After 3 days of treatment, the highest concentration of radioactive residues was found in the liver (0.62 mg/kg eq). Kidney, milk, muscle and fat contained 0.41, 0.26, 0.19, < 0.05 mg/kg eq, respectively. After 7 days of treatment, concentration levels in liver, kidney, milk, muscle and fat were 0.90, 0.76, 0.50, 0.64, and 0.21 mg/kg eq, respectively (all results from highest dose level). Residue levels in milk increased steadily and no plateau was reached during both the dosing periods.

Approximately 95% to 99% total radiolabelled residue (TRR) in extracts of milk, liver, kidney, leg muscle, tenderloin muscle, and omental fat was composed of non-phosphorylated metabolites, which resulted from cleavage of the phosphorus-sulphur bond and the methylation of the resultant mercaptan. The major metabolite in all tissues and milk was, ethylsulfonyl methylsulfonyl methane accounting for 94% to 99% TRR in the tissues and milk. The remaining radioactivity was composed of the parent compound and its various oxidative products (< 0.01% to 2.2% TRR). In the 3 days experiment (highest dose level) the toxicologically significant compounds parent, phorate sulfone and phorate sulfoxide were found at very low levels: milk contained 0.052 µg/kg eq parent and 0.39 µg/kg eq phorate sulfoxide, liver contained 4.34 µg/kg eq parent, kidney 2.50 µg/kg eq phorate sulfoxide, muscle 0.019 µg/kg eq parent, 0.077 µg/kg eq phorate sulfone and 0.14 µg/kg eq phorate sulfoxide, and fat contained none of those at a detectable level.

Groups of laying hens were orally treated (gelatin capsules) for 5 days with ^{14}C-labelled phorate at dose rates of about 1 and 3 ppm in the feed. Recoveries of the administered doses averaged 64–66%: 62–64% of the total administered radioactivity in excreta, 0.7–1.5% in eggs, 0.5%-0.8% in organs and 1.2% in carcass. Fortification of control excreta with [^{14}C]phorate resulted in a recovery of 78% after 24 h at room temperature. These results suggest that the low but consistent overall recovery may be associated with the volatility of phorate and/or the low molecular weight of the metabolic products.

Liver and kidney were found to contain the highest level of radioactive material. At the highest dose level, the amounts were 0.31 and 0.24 mg/kg eq respectively. At this dose level total radioactive residues in breast muscle, skin/fat, egg white and egg yolk amounted to 0.031, 0.047, 0.048–0.10, and 0.017–0.20 mg/kg eq respectively. Residue levels in egg yolks and whites increased steadily and no plateau was reached during the dosing period.

Metabolites found in the tissues and eggs include ethylsulfonyl methylsulfonyl methane; (ethylsulfinyl)methyl methyl sulfone; ethyl (methylsulfinyl)methyl sulfone. One additional non-phosphorylated metabolite, ethylsulfinyl methylsulfinyl methane was also found in the egg white. Neither the parent compound phorate, nor any of the oxidative metabolites phorate sulfoxide, phorate sulfone, phoratoxon, phoratoxon sulfoxide or phoratoxon sulfone was found in tissues or in eggs. Significant fractions of the radioactive residues in tissues and eggs (47–59% TRR) were unextractable but were released by enzyme hydrolysis with protease. Since the released activity was highly polar, it was not any of the phorate oxidative metabolites.

In conclusion, the metabolism of phorate in farm animals was similar to that in laboratory animals. Goats and laying hens dosed with phorate quickly detoxify the compound through a set of oxidative, toxic, metabolites. Neither parent nor any of its oxidative metabolites accumulate in edible tissues, milk and eggs.

Plant metabolism

The Meeting received information on the translocation and metabolism of phorate in plants placed in a phorate emulsion, in cotton grown from seeds treated with phorate, and in various plants after soil or foliar application of phorate. Characterization of metabolites was limited to root and foliar parts of young or immature plants. Confined rotational crop studies gave information on the metabolite composition of mature crops (see environmental fate section). Experiments were carried out with ^{32}P labelled phorate or with phorate ^{14}C labelled at the methylene position.

The roots of red kidney bean seedlings were placed in an emulsion of ^{32}P-phorate for 1 day and transplanted afterwards. Leaves were analysed 1, 4 and 12 days after treatment. The bases of young cotton plants, lemon seedlings and alfalfa seedlings were treated with a topical application of ^{32}P-labelled phorate solution. At various intervals after application (up to 14–17 days) the upper leaves were removed. In all experiments, radioactive residues translocated to the leaves. In red kidney bean leaves analysed 1, 4 and 12 days after application the primary metabolites were phorate sulfoxide and/or phorate sulfone, which could not be separated on the columns used. Small amounts of phoratoxon sulfoxide and/or phoratoxon sulfone and unchanged phorate were also found. No phoratoxon was found. The hydrolysis products formed were phosphoric acid, the diethyl esters of phosphoric acid, phosphorothioic acid and phosphorodithioic acid. Parent and the same four metabolites were also identified in a chloroform extract of cotton, lemon and alfalfa leaves (day 1–17). For cotton leaves, parent was found up to 5 d and never exceeded 5% of the radioactivity. Phorate sulfoxide reached a maximum of 85% of the radioactivity at day 1 after application and thereafter decreased to 35% at day 14. Phorate sulfone, phoratoxon sulfoxide and phoratoxon sulfone increased with time at up to 35%, 15% and 10% radioactivity at day 14, respectively. Phoratoxon was not found at any time point.

A mixture of ^{32}P-phorate and charcoal was coated on cotton seeds wetted with 2% methylcellulose at a concentration of 160 kg ai/t or 320 kg ai/t. Treated seeds were planted and cotton plants were sampled at 3.9, 7.4, 10.7 or 16 weeks after planting. In addition, foliage from cotton plants grown for 2 weeks from treated seed was sampled for identification of metabolites. Total ^{32}P residues were less than 0.03 mg/kg eq in leaves and seeds maturing from plants grown from seed treated with 320 kg ai/t at 16 weeks after planting. The residues isolated from the foliage consisted of phorate sulfoxide and phorate sulfone (ratio 61:39) and phoratoxon sulfoxide and phoratoxon sulfone (ratio 70:30). The parent itself was not identified because of interference from plant pigments. Phoratoxon was not found.

Beans, beets, cabbage, carrots, lettuce and peas were treated with radiolabelled ^{32}P-phorate using both a foliar and a soil application. Applications were made with an EC formulation at a rate of 1.12 kg ai/ha. The vegetable foliage was sampled at 2 hrs and 1, 2, 4, 8, 17 and 32 DAT. In addition pea plants were soil treated and the foliage was sampled at 14 DAT for identification of metabolites. Average values of the distribution of ^{32}P radioactivity and anti-cholinesterase activity in pooled extracts from beans, beets, cabbage, carrots, lettuce and peas were determined. Anti-cholinesterase activity increased when P=S was replaced by P=O, and increased further upon successive oxidation to sulfoxide and sulfone. Anti-cholinesterase activity increased for about the first four days and then declined but the presence of anti-cholinesterase activity persisted for 20 to 30 days. Residues became more polar in time, showing detoxification of the oxidative metabolites. The residues isolated from the pea foliage consisted of phorate sulfoxide and phorate sulfone (ratio 80:20). Parent itself was not identified because of interference from plant pigments. Phoratoxon was not found.

The translocation and metabolism of ^{14}C-labelled phorate in maize seedlings, planted in treated test soil (sandy soil), was investigated. After 18 days, 77% of the applied radioactivity was recovered: 71% in soil, 4.0% in maize greens and 1.8% in maize roots. Phorate sulfoxide, phorate sulfone and phoratoxon sulfoxide were the only compounds found in extracts from maize greens; no phorate, phoratoxon or phoratoxon sulfone was found. In nine supervised field trials on maize and sweet corn where phorate was banded at planting and at cultivation, the main metabolites in forage and fodder again were phorate sulfone and phorate sulfoxide. Incidentally parent, phoratoxon, phoratoxon sulfoxide and phoratoxon sulfone were also found.

The translocation and metabolism of [^{14}C]phorate in oat seedlings, planted in either treated silt loam soil or sandy soil, were investigated. After 13 days, for the sandy soil system 59% of total applied radioactivity was recovered: 26% in soil, 3.5% in roots and 30% in oat greens. For the silt loam soil system 76% of total applied radioactivity was recovered: 68% in soil, 0.5% in roots and 7.4% in oat greens. Although these results do not correspond to those of the maize experiment described above, they seem to indicate that the translocation of [^{14}C]phorate to the oat seedlings depends on the soil type, where uptake and translocation is more efficient in sandy soils. Phorate sulfoxide and phorate sulfone were the major compounds present in oat greens and roots; the remainder was unknown compounds.

A great difference in the nature of ^{14}C residues was found between carrots and the other two root crops when extraction efficiency was tested for potatoes, carrots and radishes, which were soil treated with [^{14}C]phorate phorate. Plants were grown from seeds (or seed potatoes) in pots in a silt loam soil. When plants began to produce edible portions, an aqueous suspension of [^{14}C]phorate phorate was pipetted onto both the soil and the partly exposed roots/tubers at an application rate equivalent to 2.25–3.35 kg ai/ha. Roots/tubers were harvested 5, 10, and 15 days after treatment (DAT). Total recovered radiolabelled (^{14}C) residues in the roots/tubers ranged from 0.86 to 12.6 mg/kg eq. With carrots, more than 96% of the radioactivity was extractable with organic solvent, and the ratio of water soluble to organic solvent soluble ^{14}C residues did not increase with increasing incorporation time. With potatoes and radishes, the ratio of water soluble ^{14}C residues was much greater than with carrots and this ratio increased with time, while that of carrots remained constant. Phorate sulfoxide (20-75%) and phorate sulfone (15–70%) were the major compounds present in

dichloromethane extracts from potatoes and radishes; parent (10–25%), phorate sulfoxide (50–60%) and phorate sulfone (10–25%) were the major compounds present in the dichloromethane extracts from carrots (expressed as % ^{14}C in dichloromethane extracts). Phorate and phorate sulfoxide decreased with time, while phorate sulfone increased with time. Phoratoxon, phoratoxon sulfoxide and phoratoxon sulfone were found at trace levels (< 3.2% of ^{14}C in dichloromethane extract). The six phorate residues accounted for 99% of ^{14}C in dichloromethane extracts of all three crops.

Effects of light intensity and temperature on the translocation and metabolism, in *oat, pea,* and maize plants, of [^{14}C]phorate in soil treated were investigated. Higher temperatures caused in most cases an increase in the uptake of ^{14}C compounds from soil. Higher light intensity also affected the metabolism of translocated ^{14}C compounds but primarily at 28°C. The relative distribution of benzene-soluble, water-soluble and unextractable radiocarbon was quite similar in all plants under all experimental conditions. Phorate sulfoxide was the major compound present in plant tops and soil. Contrary to soils, parent was not found in plant tops. Further compounds found in plant tops and soils were phorate sulfone, phoratoxon sulfoxide and phoratoxon sulfone.

In conclusion, when phorate is applied to the soil, it and its' degradates are taken up by the plants and translocated. When absorbed by plants, phorate is first oxidized at the thioether sulfur to form the phorate sulfoxide and sulfone and is then oxidized at the thiono sulfur to form the phoratoxon sulfoxide and sulfone. These oxidation products have a similar anticholinesterase activity as the phorate precursor and persist in plants for relatively long periods of time.

Environmental fate in soil

The Meeting received information on laboratory soil degradation and field and confined rotational crop studies. Experiments were carried out with phorate ^{14}C labelled at the methylene position.

Aerobic soil degradation studies showed that in soil, phorate degrades to phorate sulfoxide which in turn converts to phorate sulfone. Phorate degrades rapidly, while phorate sulfoxide degrades more slowly and phorate sulfone is the most persistent of the three. The half-life of phorate in sandy loam was estimated to be 3 days, while that of phorate sulfoxide was 75 days. The half-life of phorate sulfone could not be determined due to experimental difficulties.

From three confined accumulation studies in which maize, beetroot, lettuce, spring wheat, radish, carrots, peas and barley were grown at several time intervals after treating the soil with phorate (^{14}C labelled at the methylene position) the following conclusions could be drawn. A decrease of residue levels in soil was seen over time. Most of the radioactivity remained in the top 7.5 cm of soil, indicating that phorate and its metabolites exhibited no appreciable leaching beyond a 15 cm depth of soil. Phorate was rapidly oxidized in the soil and was converted into phorate sulfone. Only 0.2% TRR parent was found in the soil extract one month after treatment. Other metabolites identified in soil were phorate sulfoxide, phoratoxon, phoratoxon sulfoxide, phoratoxon sulfone and ethylsulfonyl methylsulfonyl methane.

In a field rotational crop study, radishes and carrots were planted in either a sand or a muck soil. The soil was treated with phorate at a rate of 3.4 kg ai/ha. The crops were planted either immediately after or one year following treatment. Radishes and carrots were harvested 4 and 14 weeks after planting, respectively. Greater conversion of phorate to phorate sulfoxide and phorate sulfone occurred in the muck soil as compared to the sand. More than 99% and 98% of the applied phorate and its oxidation products disappeared from the sand and muck soil, respectively, within a year of treatment. Low amounts of phorate sulfoxide and phorate sulfone (0.04–0.18 mg/kg eq) were found in radishes grown on both soils in the first year. No residues were present in the second year. No residues were found in carrots grown on either soil in the first year.

Soil residues consisting of phorate sulfone and predominantly non-toxic polar components can be taken up by rotational crops. However phorate applied at a rate of 3.8 kg ai/ha did not lead to the accumulation of phorate and its phosphorylated metabolites in following crops at a plant-back interval of 4 months after treatment (MAT). The assimilated phorate-derived residues are extensively metabolized by plants via non-phosphorylated metabolites to single carbon units, which subsequently are incorporated into endogenous cell components.

Environmental fate in water-sediment systems

The hydrolysis of [^{14}C]phorate, [^{14}C]phorate sulfoxide, and [^{14}C]phorate sulfone in sterile buffer systems was investigated under laboratory conditions. The hydrolysis half-lives of phorate at 25°C were estimated to be 2.36, 2.47, and 2.08 days, for pH 5, 7, and 9 respectively. The major degradate (maximum 31–87% of the total administered radioactivity at termination) observed in all treatments was formaldehyde. Phorate sulfoxide (maximum 5.2–6.6% of the total administered radioactivity at day 1) was formed only at pH 5. The results show that phorate will degrade under abiotic conditions and is not expected to persist in aquatic systems.

Hydrolysis of phorate sulfoxide and phorate sulfone occurs more slowly. At 25°C, hydrolysis half-lives were estimated to be 185, 118, and 7.02 days for phorate sulfoxide and 77.1, 60.2, and 5.25 days for phorate sulfone at pH 5, 7, and 9 respectively. The degradation pathway of phorate sulfoxide and phorate sulfone was pH-dependent at elevated temperatures with de-esterification being the predominant reaction at pH 5-7.

Methods of analysis

The Meeting received descriptions and validation data on methods of residue analysis for enforcement and for residue methods used in the various study reports.

The Pesticide Analytical Manual (PAM) Volume II lists ten methods (1963-1973) for the enforcement of MRLs for phorate residues in/on plants and animal commodities. The description of method I, IA, IB was submitted to the present Meeting. Method I is based on the extraction of the parent and its oxygenated metabolites phorate sulfoxide, phorate sulfone, phoratoxon, phoratoxon sulfoxide and phoratoxon sulfone. The extracts are cleaned-up by liquid-liquid partitioning or alumina column chromatography. Phorate-related residues are oxidized to the common moiety metabolite, phoratoxon sulfone, using 3-chloroperoxybenzoic acid. The oxidized product is then analysed by GC with a phosphorus specific detector.

Method I was validated for animal commodities (milk, meat, fat, offal). Milk, meat and offal are extracted with chloroform, fat is extracted with acetonitrile. The oxidation of phorate to phoratoxon sulfone is about 70% complete. Because of this, parent recoveries are based on oxidized phorate, while phoratoxon sulfone recoveries are based on phoratoxon standards. Recoveries from milk samples resulted in 75–85% for the parent compound at 0.02 mg/kg eq and 95–103% for phoratoxon sulfone at 0.04 mg/kg eq. The reported LOQ was 0.01 mg/kg eq for milk and 0.02 mg/kg eq for meat tissues (cattle, goat, hogs, horses and sheep). *Method IA* was validated for cottonseed and safflower seed. Validation results are not available. *Method IB* was validated for sugar beets with a reported LOQ of 0.1 mg/kg eq. This method is considered an identification method in case a confirmatory analysis is required.

Phorate and its five metabolites (phorate, phorate sulfoxide, phorate sulfone, phoratoxon, phoratoxon sulfoxide, and phoratoxon sulfone) were taken through the USA FDA multiresidue method protocols described in PAM Volume I with some success. Protocols C and D gave satisfactory results.

Based on the information available it is unknown what LOQs are achievable for plant products in an enforcement situation. Based on existing CXLs and the available supervised residue trial data, it is assumed that an LOQ of 0.05 mg/kg is a practical value.

Residues in very early residue studies (1961–1963) were analysed by their cholinesterase inhibitive power in an electrometric cholinesterase assay. However, these assays are non-specific. Further, in one of those methods (method A) there is no correlation between total phorate-related residue concentration and cholinesterase activity. Residues with higher cholinesterase activity than oxidized phorate will give an erroneously high residue concentration, whereas compounds with lower cholinesterase activity than oxidized phorate will give an erroneously low residue concentration. This assay is therefore considered inaccurate for the purposes of undertaking residue analyses.

From 1971 on, analytical methods based upon gas chromatography with flame photometric detection (GC-FPD) for determination of total phorate-related residues (oxidizable to phoratoxon sulfone) have been developed for a wide range of substrates. The methods are based on the extraction of the parent and its oxygenated metabolites phorate sulfoxide, phorate sulfone, phoratoxon, phoratoxon sulfoxide and phoratoxon sulfone with either methanol-dichloromethane (10-90; plants) or acetonitrile (animal commodities). The extracts are cleaned-up and phorate-related residues are oxidized to the common moiety metabolite, phoratoxon sulfone, using 3-chloroperoxybenzoic acid in dichloromethane. The reaction mixture is cleaned-up by washing with sodium sulfite and bicarbonate solutions in water, precipitation of oily/fatty residues with aqueous ammonium chloride-phosphoric acid solution and water-dichloromethane partitioning. The dichloromethane is removed and the residue is redissolved in acetone, which is then analysed by GC-FPD in phosphorus mode. GC conditions: packed column 3% OV-210 on Supelcoport 80/100 mesh deactivated with Carbowax 20M at 155–200°C. Calibration is performed by running phorate standards through the oxidation procedure (analysed as phoratoxon sulfone). Oxidation efficiency is verified against a phoratoxon sulfone reference standard and should be at least 50% to start the analysis procedure.

The methods vary in the extraction solvent, in the clean-up procedures used before and after oxidation and in the GC-column conditions. The LOQ for most of the reported trials was 0.05 mg/kg eq. The methods have in general been validated on a wide range of substrates. However, most of the methods were validated with only a limited number of recovery samples per concentration level ($n < 5$), of compounds used for recovery checks (phorate and 5 oxidized metabolites), and/or of control samples analysed ($n < 2$). Alternatively calibration data was lacking.

Stability of pesticide residues in stored analytical samples

The Meeting received data on the stability of residues in dry beans, potatoes, sugar beets and maize stored frozen. In addition, the Meeting received data on the stability of residues in milk stored frozen.

Total phorate-related residues (oxidizable to phoratoxon sulfone) are stable for at least two years in dry bean, potato tuber, sugar beet roots and tops, maize grain, green maize plants, and maize straw samples when stored frozen at approximately -10°C to -20°C. In maize meal and maize refined oil stored at ≤ -23°C total phorate-related residues are stable for at least one year.

No storage data are available on green beans (seeds, seeds with pods). However, storage data for sugar beet tops or green maize forage/fodder (see below) may be extrapolated to green beans (seeds, seeds with pods). Storage data for cotton dry fodder were unavailable as well but the results for dry maize fodder may be extrapolated to cover this.

Storage stability data on cotton seed, coffee beans and on processed potato commodities were not available. The Meeting decided that given the results discussed above, it was highly unlikely that total phorate-related residues were unstable in these commodities.

Total phorate-related residues are stable in cows' milk for at least 4 days when stored in the refrigerator and at least 18 months when stored in the freezer at -20°C or lower. No storage data was submitted on tissues (poultry, ruminants) and eggs. Ruminant tissues from a cow feeding study were stored for less than one month and therefore storage data on these tissues are not needed. However, storage data on poultry tissues and eggs is lacking.

Definition of the residue

In animals, phorate is quickly detoxified and neither parent nor any of its oxidative metabolites accumulate in edible tissues, milk and eggs. The major metabolite in all tissues, milk and eggs was ethylsulfonyl methylsulfonyl methane. Nevertheless, phorate-related residues can be found at low levels.

When absorbed by plants, phorate is first oxidized at the thioether sulfur to form the phorate sulfoxide and sulfone and is then oxidized at the thiono sulfur to form the phoratoxon sulfoxide and sulfone. These oxidation products are all similar anticholinesterase agents to the phorate precursor and persist in plants for relatively long periods of time. In most cases, parent itself is present at low levels, but the ratio of the different metabolites changes from crop to crop.

The analytical methodology available relies on the oxidation of all phorate-related residues to the common moiety metabolite, phoratoxon sulfone. Supervised residue trials show that total phorate-related residues (oxidizable to phoratoxon sulfone) are not to be expected in edible crops, except in potatoes. The composition of the residue in potato tubers after application according to GAP is unknown.

Considering all of the above, the Meeting decided that the residue definition for phorate, both for enforcement and for risk assessment for animal and plant commodities, is:

Sum of parent, its oxygen analogue, and their sulfoxides and sulfones, expressed as phorate.

Although the parent compound has a log K_{ow} of 3.92, animal metabolism studies indicate that the total residue is not fat-soluble.

Results of supervised trials on crops

Supervised residue trials were available for fruiting vegetables (sweet corn), legume vegetables (green beans, green snap beans), pulses (dry beans, dry soya beans), root and tuber vegetables (potato, sugar beet), cereals (maize, sorghum), oilseeds (cotton), and coffee. Supervised trials on the remaining commodities that currently have a CXL were not provided. Therefore the Meeting decided to withdraw the current recommendations for fodder beet, peanut, peanut oil crude, peanut oil edible, and wheat.

In situations where residues from supervised trials at GAP show **nil** residues, the MRL was chosen to reflect a sensitivity that is compatible with enforcement activities. Where two different LOQs apply to the residue data, the lowest value was chosen only if the above was true. In this case the lower LOQ will be taken to represent the STMR. The HR value would then be recommended at the highest LOQ used in the studies unless a majority of the observations were derived from the more sensitive LOQ.

In situations where residues from supervised trials at GAP show **nil** residues even at exaggerated rates, then the MRL will still be chosen to reflect an LOQ that is compatible with enforcement activities. However, both the STMR and HR values will be set at zero.

Sweet corn (corn-on-the-cob)

Nine trials were reported on sweet corn from the USA. No trials were according to GAP of the USA (1.1–1.5 kg ai/ha, PHI 30 days). In the trials Phorate granular formulation was either applied as a single application in a band at planting or as a double application: one in a band at planting followed by a band at cultivation. Rates per application ranged from 1.46 to 7.29 kg ai/ha, with sampling occurring 37–74 days after treatment.

The Meeting decided that there was insufficient data to estimate a maximum residue level for sweet corn (corn-on–the-cob) and decided to withdraw the current recommendation of 0.05 mg/kg.

Legume vegetables

Eighteen trials were reported from the USA. Four trials on green bean seeds (without pods), four trials on green bean pods (with seeds) and ten trials on snap bean pods (with seeds) were reported. At planting, the phorate granular formulation was either drilled to the side of the seed or banded over the row using a granular applicator at application rates between 1.68–4.70 kg ai/ha. Two of the trials on green bean seeds were according to USA GAP (1.1–2.3 kg ai/ha, PHI 60 days) and total phorate-related residues were < 0.05 (2) mg/kg eq. However, these trials could not be used since residues were measured in the beans without pods. The ten snap bean pod trials were all within GAP, albeit with a shorter PHI (48–52 days). All residues were < 0.05 mg/kg eq.

Although the analytical method used in these trials (Method M-1718) was not ideal for green beans, because of low recoveries at 0.05-0.10 mg/kg eq (< 70%) and high relative standard deviation (RSD_r) at 0.01 mg/kg eq (> 20%), the Meeting decided to use the results as no actual residues were measured or expected.

The Meeting agreed to withdraw the previous maximum residue level recommendation for common bean (pods and/or immature seeds) (0.1 mg/kg), to be replaced by a recommendation of 0.05* mg/kg. The Meeting estimated an STMR of 0.05, and a HR of 0.05 mg/kg for phorate on common beans (green pods and/or immature seeds).

Pulses

Dry beans

Twenty-three trials on dry harvested beans were available from the USA. The phorate granular formulation was applied at a rate of 2.0 to 4.7 kg ai/ha in furrow, as a band over the row, or drilled to the side of the seed at planting. In all trials total phorate-related residues were < 0.05 mg/kg eq, except for trials PA-720-010 and PA-720-011, where the actual LOQ was 0.06 mg/kg eq because of matrix interference.

Four of the trials were according to USA GAP (1.1-2.3 kg ai/ha, PHI 60 days) and total phorate-related residues were < 0.05 mg/kg eq. In four other trials where a twofold exaggerated dose was applied (4.7 kg ai/ha) total residues were also < 0.05 mg/kg eq.

The Meeting estimated a maximum residue level of 0.05* mg/kg, and an STMR of 0.05 mg/kg for phorate on dry beans.

Soya bean (dry)

Twenty eight trials on soya beans were available from the USA. At planting, the phorate formulation was applied as a side band in furrow, in a band, or drilled to the side of the seed, at rates of 1.1 to 9.4 kg ai/ha.

None of the trials were according to GAP of the USA (1.7 kg ai/ha, PHI not specified). In four trials rates were below GAP while the remainder were in excess of GAP. However, even at a rate of 9.4 kg ai/ha, total phorate-related residues were < 0.05 mg/kg eq.

The Meeting estimated a maximum residue level of 0.05* mg/kg, and an STMR of 0 mg/kg for phorate on soya beans, dry.

Potatoes

Ware potatoes are normally harvested within 90–120 days after planting. Early maturing varieties can be harvested before 90 days, while late maturing ones (such as Russet Burbank or Maris Piper varieties) are usually harvested after 120 days. The PHI therefore depends on the crop variety. Although on many labels a PHI of 90 days is indicated, the residue measured at maturity was taken for evaluation, as treatment was made before or at planting, and the potatoes are harvested when they are ready. In trials in which the time of maturity of the potatoes was not indicated, the residue level measured at the shortest PHI was used for evaluation.

Trials were reported from the USA and Canada. Twenty-one trials on potatoes were conducted in the USA and twenty-five in Canada. A phorate granulate formulation was applied in-furrow or in a band at planting, at a rate of 2.19 to 266 kg ai/ha. For the post-emergence trials, application was as a band or side dressing at hilling, at the rate of 2.7 to 10 kg ai/ha.

Seven of the USA trials could be evaluated against USA GAP (1.9-4.0 kg ai/ha, PHI 90 days). Total phorate-related residues were < 0.05 (6), 0.08 mg/kg.

Twenty of the Canadian trials could be evaluated against Canadian GAP (2.3–4.3 kg ai/ha, PHI 90 days), yielding total phorate-related residues of < 0.05 (12), 0.07 (2), 0.10, 0.11, 0.12, 0.15, 0.16, 0.27 mg/kg.

The Meeting decided to combine the USA and Canadian trials, yielding the following data set: < 0.05 (18), 0.07 (2), 0.08, 0.10, 0.11, 0.12, 0.15, 0.16, 0.27 mg/kg.

The Meeting agreed to withdraw the previous maximum residue level recommendation for potato (0.2 mg/kg), to be replaced by a recommendation of 0.5 mg/kg. The Meeting estimated an STMR of 0.05, and a HR of 0.27 mg/kg for phorate on potato.

Sugar beet

A total of 16 trials on sugar beets were conducted in the USA in 1985. Ten of these trials, were carried out with a single at planting or post-emergence treatment. In the remaining trials two applications, one at planting and the other post-emergence, were made. Rates ranged from 1.68 to 3.36 kg ai/ha per application.

Two trials were according to GAP of the USA (1.1-1.7 kg ai/ha, PHI 30 days), yielding total phorate-related residues of < 0.05(2) mg/kg eq. In two trials which received double (2×) rates total residues found were of < 0.05, 0.06 mg/kg eq. Three trials in which a second application was made yielded total residues of < 0.05 (2) and 0.06 mg/kg eq. In three trials in which a 2× at planting application rate was combined with a second application, total residues found were < 0.05 (2), 0.06 mg/kg eq.

Based on the above, the Meeting decided to confirm the present recommendation of 0.05* mg/kg, and estimated an STMR and an HR of 0.05 mg/kg.

Cereal grains

Maize

Forty-five trials on maize (field corn) were reported from the USA. A phorate granular formulation was either applied as a single application in a band at planting or as a double application: one in a band at planting followed by either a side dress beside each row or a foliar treatment at cultivation. Rates per application ranged from 1.12 to 8.8 kg ai/ha.

None of the trials were according to the GAP of the USA (1.1-1.5 kg ai/ha, PHI 30 days). In the trials application rates were exaggerated (2× or 3×) and/or the PHI was unacceptably long. However, in 14 maize trials where phorate was applied twice, at an application rate at GAP or two times GAP and the residue was measured at a PHI of 29 or 30 days, the total phorate-related residue was < 0.01(2), < 0.02 (12) mg/kg. From the application of even more exaggerated rates, finite residues were detected.

Based on the above, the Meeting decided to confirm the present recommendation of 0.05* mg/kg, and estimated a STMR of 0.02 mg/kg for maize.

Sorghum

Eighteen trials on sorghum were reported from the USA. Treatments ranged from one application of a granulate phorate formulation at the rate of 1.22-1.46 kg ai/ha at cultivation or at planting, to 2 applications, one at planting and another at cultivation, at rates of 1.12 up to 7.3 kg ai/ha.

In all but four of the trials, total phorate-related residues (oxidizable to phoratoxon sulfone) were determined by GC-FPD, following Method M-1722. This method is considered inaccurate for sorghum grain because of high recoveries at 0.01 mg/kg eq (> 120%) and high RSD_r (> 20%) at concentrations between 0.1–1.0 mg/kg eq. However, as all results were < 0.05 mg/kg eq, the Meeting decided to include them.

None of the trials were according to GAP of the USA (1.1–1.5 kg ai/ha, PHI 30 days). In the trials application rates were exaggerated (2×) and/or the PHI was unacceptably long. However, in eight trials where the residue was measured at a PHI of 30 days, the total phorate-related residues found were < 0.05 mg/kg eq.

Based on the above, the Meeting decided to confirm the present recommendation of 0.05* mg/kg, and estimated an STMR of 0.05 mg/kg for sorghum grain.

Cotton seed

Fourteen trials on cotton were reported from the USA. The majority of trials were conducted using two application timings. Rates applied ranged from 0.84 to 7.17 kg ai/ha for the first application to 2.47 to 9.86 kg ai/ha for the second.

None of the trials were according to the GAP of the USA ((0.61-2.4 kg ai/ha, PHI 60 days). In the trials application rates were exaggerated (2×) and/or the PHI was unacceptably long. However, in nine trials where the residue was measured at a PHI of 61–65 days, the total phorate-related residue was < 0.05 mg/kg . Two of these trials were at highly exaggerated rates (first application 7.17 kg ai/ha, second application 9.86 kg ai/ha).

Based on the above, the Meeting decided to confirm the present recommendation of 0.05* mg/kg, and estimated an STMR of 0 mg/kg for cotton seed.

Seed for beverages and sweets

Coffee beans

A total of 19 trials on coffee were conducted, two in Colombia, 13 in Brazil, and four in Puerto Rico. Dry unroasted coffee beans were analysed. There was no Colombian or Puerto Rican GAP; Brazilian GAP was 3.0–3.8 g ai/plants for up to 1660 plants /ha, and 5.0–6.2 kg ai/ha for > 1660 plants/ha, with a PHI of 90 days. Trials were considered at GAP when either the application rate in g ai/plant or in kg ai/ha was observed.

Two Colombian trials and two Puerto Rican trials were according to Brazilian GAP, yielding total phorate-related residues of < 0.05 (4) mg/kg eq. All other trials had much higher PHIs and had treatment rates either below or above the GAP rates.

Based on the above and additional information from the remaining trials, the Meeting estimated a maximum residue level of 0.05* mg/kg, and an STMR of 0.05 mg/kg for coffee beans.

Straw, fodder and forage of cereal grains and grasses

Maize forage

For the purpose of estimating the animal dietary burden, the Meeting decided to review data on sweet corn forage coupled with data on maize forage. In all of the nine sweet corn trials and six of the forty-five maize trials residues were measured in green plant material (forage). Rates per application ranged from 1.2 to 8.8 kg ai/ha.

None of the trials were according to GAP of the USA (1.1–1.5 kg ai/ha, waiting period 30 days). In the maize trials residues were measured at PHIs ranging from 83–103 days. In the trials the sweet corn was treated twice at exaggerated rates and/or a PHI that was unacceptably long. Residues were detected at varying levels. The Meeting decided to use data from the trials where two applications were made at 1.46 kg ai/ha, with a PHI of 28–37 days. Total phorate-related residues found were < 0.06, 0.09, and 0.10 mg/kg (wet weight basis).

The Meeting estimated a highest residue of 0.10 mg/kg (wet weight basis) and a median residue of 0.09 mg/kg (wet weight basis) for maize forage.

The Meeting considered that maize forage is not a traded commodity and that the data was insufficient to estimate a maximum residue level. The Meeting decided to withdraw the current recommendation of 0.2 mg/kg.

Maize fodder

In twenty-four of the forty-five trials conducted on maize (field corn) from the USA, residues were measured in dry maize plants (fodder). Rates per application ranged from 1.12 to 8.8 kg ai/ha.

None of the trials were according to the USA GAP (1.1–1.5 kg ai/ha, grazing waiting period 30 days). In the trials the maize was treated twice at rates and above GAP and/or with extended waiting periods. Residues were detected at varying levels. The Meeting decided to use data from trials that were treated twice at rates of 1.12–1.46 kg ai/ha, with a PHI of 29 days. Total phorate-related residues were 0.09 (2), 0.16 and 0.22 mg/kg (wet weight basis).

For the purpose of estimating the animal dietary burden, the Meeting estimated a highest residue of 0.22 mg/kg (wet weight basis) and a median residue of 0.125 mg/kg (wet weight basis) for maize fodder.

The Meeting considered that the data was insufficient to estimate a maximum residue level and decided to withdraw the current recommendation of 0.2 mg/kg.

Sorghum forage (green)

In three of the eighteen reported sorghum trials previously reported, residues were measured in the sorghum forage.

None of the trials were according to USA GAP (1.1–1.5 kg ai/ha, PHI 30 days) as the PHI was too long (47–78 days). The Meeting therefore decided that there were insufficient data from which to derive a conclusion on residue levels in sorghum forage.

Sorghum straw and fodder, dry

In 12 of the 18 trials conducted on sorghum, residues were measured in dry sorghum fodder.

None of the trials were according to USA GAP (1.1-1.5 kg ai/ha, PHI 30 days). In the trials the crop was treated twice at rates above GAP and/or with unacceptably long PHIs. However, in eight trials where the residue was measured at a PHI of 30 days, the total phorate-related residue was < 0.05 mg/kg eq. In these trials, total phorate-related residues (oxidizable to phoratoxon sulfone) were determined by GC-FPD, following Method M-1722. This method is considered inaccurate for sorghum dry fodder because of low recoveries below 0.2 mg/kg eq (< 70%).

Based on the above, the Meeting decided not to estimate an MRL, a highest residue or a median residue for sorghum dry fodder.

Miscellaneous fodder and forage crops (group 052)

Cotton fodder, dry

In nine out of the fourteen trials conducted on cotton from the USA, residues were measured in cotton fodder, dry. Most trials consisted of two treatments at rates ranging from 0.84 to 7.17 kg ai/ha for the first application and 2.47 to 9.86 kg ai/ha for the second.

None of the trials were according to USA GAP (0.61–2.4 kg ai/ha, PHI 60 days). In the trials the crop was treated twice at rates above GAP and/or with unacceptably long PHIs. In two trials where the first application was made at a rate of 1.79 kg ai/ha and the second at 2.47 kg ai/ha, with the PHI of 64 or 65 days, residues found were < 0.05 and 0.16 mg/kg.

The Meeting considered that the data was insufficient to estimate a maximum residue level, a highest residue and a median residue for cotton fodder, dry.

Sugar beet tops

In all of the 16 trials on sugar beets conducted in the USA in 1985 residues were measured in sugar beet tops. Ten of these trials were carried out with one treatment either at planting or post-emergence. The rest of the trials consisted of two applications, one at planting and the other post-emergence. Rates ranged from 1.68 to 3.36 kg ai/ha per application.

Four of the trials (study reports PA-724-025 and PA-724-026) were considered not to be acceptable for evaluation because of unacceptably high matrix interferences for sugar beet tops (up to 0.09 mg/kg eq in PA-724-025 and up to 0.41 mg/kg eq in PA-724-026). Only one of the remaining trials was according to USA GAP (1.1–1.7 kg ai/ha, PHI 30 days), yielding total phorate-related residues of < 0.08 mg/kg eq.

The Meeting considered that the data was insufficient to estimate a maximum residue level for sugar beet leaves and tops and decided to withdraw the current recommendation of 1 mg/kg. A highest residue and a median residue also could not be estimated.

Fate of residues in storage and during processing

The Meeting received information on the fate of residues during storage of field treated potatoes at ambient temperatures. Residues declined rapidly, after 23 days in storage it was found that only 33% of the original residue level remained.

The Meeting also received information on the fate of incurred residues of phorate during the processing of potatoes, maize and coffee beans.

Five processing studies were undertaken in which field treated potatoes were either processed into flakes, chips and granules, or were washed, peeled, boiled, baked or fried. In two of those studies, processing factors for potato chips, flakes and granules could not be estimated because residues in the raw agricultural commodity were less than the LOQ. One study was disregarded because residues in the washed potatoes were higher than in the raw agricultural commodity.

Calculated processing factors were < 0.07, < 0.3 for chips, 1.6 for flakes, 1.2, 3.6 for granules, 0.32, 0.49 for washing, 0.25, 0.28 for peeling, 0.13 for boiled with peel, 0.11 for boiled without peel, 0.14 for boiled peel, 0.28 for baked with peel, 0.27 for baked without peel, 2.4 for baked peel, 0.38 for French fries, 0.52, 0.63, 0.73, 0.87 for raw peel, 2.2 for dry peel, 0.36 for microwaved with peel.

In two studies field treated maize was processed into flour and oil. One study was disregarded because residues in the raw agricultural commodity (0.036 mg/kg) were lower than the LOQ (0.05 mg/kg). Calculated processing factors were 12 for hulls, 2.3 for germ, < 0.81 for grits, 2.7 for meal, 2.3 for flour, 4.0 for crude oil, expeller, 1.0 for presscake, expeller, 4.7 for crude oil, solvent extracted, < 0.81 for presscake, solvent extracted, 5.8 for refined oil, < 0.81 for soapstock, and < 0.81 for deodorized oil.

Green coffee beans were sprayed with a phorate sulfone solution in acetone at a final concentration of 0.1 or 4.6 mg/kg. Beans were roasted at 260°C for 5 to 6 minutes in an oven, cooled and ground. Residues in the roasted beans were < 0.05 mg/kg. Because processing was not carried out with incurred residues, no processing factors were calculated.

Field treated green coffee beans were harvested from plots treated at an exaggerated rate. Harvested coffee beans were air dried for a period of 21 days. Green beans were roasted at 260°C for 5 to 6 minutes. The calculated processing factor for roasted beans was 0.067.

In the table below, relevant processing factors for potato, maize and coffee commodities are summarized. Using the HRs for potato, maize and coffee bean (0.27, 0.02 and 0.05mg/kg, respectively) the Meeting estimated HR-Ps for their processed commodities as listed below. Furthermore, using the STMRs for potato, maize and coffee bean (0.05, 0.02, and 0.05 mg/kg) the Meeting estimated STMR-Ps for these commodities.

Commodity	Processing factors	Processing factor (median or best estimate)	STMR-P	HR-P
Washed potatoes	0.32, 0.49	0.405	0.02025	0.10935
Peeled potatoes	0.25, 0.28	0.265	0.01325	0.07155
Potatoes boiled with peel	0.13		0.0065	0.0351
Potatoes boiled without peel	0.11		0.0055	0.0287

Commodity	Processing factors	Processing factor (median or best estimate)	STMR-P	HR-P
Boiled potato peels	0.14		0.007	0.0378
Potatoes baked with peel	0.28		0.014	0.0756
Potatoes baked without peel	0.27		0.0135	0.0729
Baked potato peels	2.4		0.12	0.648
French fries	0.38		0.019	0.1026
Raw potato peels	0.52, 0.63, 0.73, 0.87	0.68	0.034	0.1836
Dry potato peels	2.2		0.11	0.594
Potatoes microwaved with peel	0.36		0.018	0.0972
Maize flour	2.3		0.046	0.046
Maize crude oil, expeller	4.0		0.08	0.08
Maize crude oil, solvent extracted	4.7		0.094	0.094
Maize deodorized oil#	< 0.81		0.0162	0.0162
Roasted coffee beans	0.067		0.00335	0.00335

taken to be edible oil

Using the highest residue for maize (0.02 mg/kg) and the processing factors as indicated above, the Meeting estimated a maximum residue level of 0.05 mg/kg in maize flour, and 0.1 mg/kg in maize oil, crude, and 0.02 mg/kg in maize oil, edible. For the remaining commodities no maximum residue levels were estimated, either because the commodity is not in the Codex system or because the MRL would be lower than that of the raw agricultural commodity.

The Meeting considered the appropriate HR-P and STMR-P to be used in the dietary intake calculation for potatoes. It was recognized that raw potatoes are not consumed, but that potatoes are not always eaten peeled. The percentage of people who eat unpeeled potatoes however is unknown. Also the ratio of boiled/baked/microwaved/fried for potatoes is unknown. The Meeting therefore decided to use the HR-P and STMR-P on potatoes, microwaved with peel in the dietary intake calculations for potatoes since this represents the worst-case situation.

Farm animal dietary burden

The Meeting estimated the dietary burden of phorate residues in farm animals from the diets listed in Appendix IX of the *FAO Manual* (FAO, 2002). One feed commodity only from each Codex Commodity Group was used. Calculation from the HR values provides the concentrations in feed suitable for estimating MRLs for animal commodities, while calculation from the STMR values for feed is suitable for estimating STMR values for animal commodities. In the case of processed commodities, the STMR-P value is used for both intake calculations.

Estimated maximum dietary burden of farm animals

Commodity	Group	Residue mg/kg	Basis	% Dry matter	Residue, on dry wt mg/kg	*Diet content (%)*			Residue contribution (mg/kg)		
						Beef cattle	*Dairy cows*	*Poultry*	Beef cattle	Dairy cows	Poultry
Cottonseed	SO	0	highest residue	88%	0	*25%*	*10%*	*NU*[§]			
Maize grain	GC	0.02	highest residue	88%	0.023	*80%*	*40%*	*80%*			
Maize forage	AF	0.10	highest residue	40%	0.25	*40%*	***50%***	*NU*		0.125	
Maize fodder	AS	0.22	highest residue	83%	0.26	***25%***	*15%*	*NU*	0.065		
Potato culls	VR	0.27	HR	20%	1.35	***75%***	***40%***	*NU*	1.0125	0.54	

Commodity	Group	Residue mg/kg	Basis	% Dry matter	Residue, on dry wt mg/kg	*Diet content (%)*			Residue contribution (mg/kg)		
						Beef cattle	*Dairy cows*	*Poultry*	Beef cattle	Dairy cows	Poultry
Potato processed waste#	AB	0.1836	HR-P	15%	1.22	*5%*	*10%*	*NU*			
Sorghum grain	GC	0.05	highest residue	86%	0.058	*20%*	*40%* ***(10%)***	***80%***		0.0058	0.0464
Soybean seeds	VD	0	highest residue	89%	0	*15%*	*15%*	*20%*			
Maximum dietary burden									**1.08**	**0.67**	**0.05**

take data raw potato peel; § NU – Not Used

Estimated median dietary burden of farm animals

Commodity	Group	Residue mg/kg	Basis	% Dry matter	Residue, on dry wt mg/kg	*Diet content (%)*			Residue contribution, mg/kg		
						Beef cattle	*Dairy cows*	*Poultry*	Beef cattle	Dairy cows	Poultry
Cottonseed	SO	0	STMR	88%	0	*25%*	***10%***	*NU*§			
Maize grain	GC	0.02	STMR	88%	0.023	*80%*	*40%*	*80%*			
Maize forage	AF	0.09	median residue	40%	0.225	*40%*	***50%***	*NU*		0.1125	
Maize fodder	AS	0.125	Median residue	83%	0.151	***25%***	*15%*	*NU*	0.0378		
Potato culls	VR	0.05	STMR	20%	0.25	***75%***	***40%***	*NU*	0.1875	0.1	
Potato processed waste#	AB	0.034	STMR	15%	0.227	*5%*	*10%*	*NU*			
Sorghum grain	GC	0.05	STMR	86%	0.058	*20%*	*40%* ***(10%)***	***80%***		0.0058	0.0464
Soybean seeds	VD	0	STMR	89%	0	*15%*	*15%*	*20%*			
						Median dietary burden			**0.22**	**0.22**	**0.05**

take data raw potato peel; § NU – Not Used

Farm animal feeding studies

The Meeting received information on feeding studies for calves, lactating cows and laying hens.

Two groups of three Holstein calves were dosed at levels of 0 and 0.1 mg ai/kg bw for 14 consecutive days by gelatin capsules. The calves weighed 220-234 kg (average 227 kg). Dosage as ppm in the feed was not stated. Assuming a daily feed intake of 4% of the bodyweight, the dose would be 2.5 ppm. Total phorate-related residues (oxidizable to phoratoxon sulfone) in thigh muscle, fat, liver and kidney were all below the LOQ of 0.1 mg/kg. At a dose equivalent to 0.1 mg ai/kg bw, animals showed no significant differences in red blood cell cholinesterase activity as compared to controls. When levels were increased to 0.2 mg ai/kg bw, animals showed significant depression of red blood cell cholinesterase activity.

Three groups of three lactating Holstein cows were dosed twice daily via gelatin capsules at levels of 0, 0.05, and 0.1 mg ai/kg bw per day for 14 consecutive days. The cows weighed 485–505

kg (average 493 kg). Dosage as ppm in the feed was not stated. Assuming a daily feed intake of 4% of the bodyweight, the doses would be 1.25 and 2.5 ppm. Milk was sampled daily and a.m. and p.m. milkings were pooled. Tissues were not collected. Total phorate-related residues (oxidizable to phoratoxon sulfone) were determined by their cholinesterase inhibitive power in an electrometric cholinesterase assay, method B, which is an unspecific method. Total phorate-related residues (oxidizable to phoratoxon sulfone) in milk from the 0.05 mg ai/kg dose rate were all below the LOQ of 0.02 mg/kg eq. In samples from the 0.1 mg ai/kg bw dose group residues were found from day 7 onwards ranging from 0.03–0.06 mg/kg.

Fourteen non-pregnant lactating Holstein cows were divided into three treatment groups. Animals in groups A (4 cows), B (4 cows), and C (6 cows) were dosed orally once a day for 28 consecutive days with gelatin capsules using a balling gun. For two cows of group C, a withdrawal period of up to 14 days was included. Using an average actual daily feed intake of 20 kg dry matter/day, mean actual doses were calculated to be equivalent 0, 1.39 and 3.21 ppm. Milk samples were collected each day and p.m. and a.m. milkings were pooled. Animals were sacrificed within 20 hrs after the last dose and samples of loin muscle, omental fat, both kidneys and whole liver were collected. In cows from all dose groups total phorate-related residues (oxidizable to phoratoxon sulfone) were below the LOQ of < 0.005 mg/kg for whole milk (day 2 to day 28) or < 0.02 mg/kg for tissues.

In a preliminary dose-finding study, animals showed severe signs of organophosphate poisoning (diarrhoea, stiffness, muscular tremors) at doses equivalent to 14 ppm, and mild signs of organophosphate poisoning (depression, salivation, off feed consumption) at doses equivalent to 7 and 5 ppm. At doses equivalent to 1.39 and 3.21 ppm, as used in the final study, animals showed no signs of organophosphate poisoning.

Four groups of six laying hens were dosed at levels of 0, 0.1, 0.3 and 1.0 ppm as total phorate (1:1 phorate: phoratoxon sulfone) for 21 consecutive days. A composite egg sample from each group was collected only on the final day of treatment. The hens were sacrificed 2 to 3 h after final dosing with muscle, fat, liver and kidney samples collected. Total phorate-related residues (oxidizable to phoratoxon sulfone) in muscle, liver and kidney and eggs were all below the LOQ of 0.05 mg/kg and below the LOQ of 0.06 mg/kg in fat.

Residues in animal commodities

In the most recent feeding study where lactating cows were dosed at 1.39 and 3.21 mg ai/kg dry feed, no total phorate-related residues were detected in tissues and milk. Therefore no residues are to be expected at the maximum calculated dietary burden of 1.08 mg/kg feed for beef cattle and 0.67 mg/kg for dairy cattle.

In the feeding study where laying hens were dosed at 0.1, 0.3 and 1.0 mg/kg feed, no total phorate-related residues were detected in tissues and eggs. Therefore no residues are to be expected at the maximum calculated dietary burden of 0.05 mg/kg feed for poultry.

The Meeting estimated a maximum residue level of 0.02* mg/kg in mammalian meat and offal and HRs and STMRs of 0.02 mg/kg. For milk, the Meeting estimated a maximum residue level of 0.01* mg/kg and an STMR of 0.005 mg/kg.

The Meeting estimated a maximum residue level of 0.05* mg/kg in poultry meat and eggs and HRs and STMRs of 0 mg/kg.

DIETARY RISK ASSESSMENT

Long-term intake

The International Estimated Daily Intakes (IEDI) of phorate, based on the STMRs estimated for 18 commodities, for the five GEMS/Food regional diets, were in the range of 9 to 20% of the maximum ADI (0.0007 mg/kg bw), see Annex 3. The Meeting concluded that the long-term intake of residues of phorate resulting from its uses that have been considered by JMPR are unlikely to present a public health concern.

Short-term intake

The International Estimated Short Term Intake (IESTI) for phorate was calculated for 18 food commodities for which maximum residue levels were estimated and for which consumption data was available. The results are shown in Annex 4.

The IESTI represented 0–50% of the ARfD (0.003 mg/kg bw) for the general population and 0–120% of the ARfD for children. The value of 120% represents the IESTI for potato, microwaved with peel. The Meeting concluded that the short-term intake of residues of phorate, resulting from its uses other than on potato that have been considered by the JMPR, is unlikely to present a public health concern. The information provided to the Meeting precludes an estimate that the acute dietary intake from the consumption of potatoes by children aged 6 years and under would be below the ARfD.

4.18 PROPAMOCARB (148)

TOXICOLOGY

Propamocarb (propyl-3-(dimethylamino) propylcarbamate) is a carbamate fungicide that was developed for the control of phycomycetous fungi. A toxicological monograph was prepared by the JMPR in 1984 and a monograph addendum was prepared in 1986. In 1986, an ADI of 0–0.1 mg/kg bw was established based on a NOAEL of 200 ppm, equivalent to 10 mg/kg bw per day, on the basis of minimal non-specific toxicity (i.e. reductions in body weight and food consumption) observed in a 2-year feeding study in rats.

Propamocarb was re-evaluated by the present Meeting within the periodic review programme of the CCPR. The Meeting reviewed a substantial amount of new data on propamocarb that had not been considered previously, as well as relevant data from the previous evaluation.

All pivotal studies with propamocarb were certified as being compliant with GLP.

Biochemical aspects

The kinetics of propamocarb have been studied in rats. After oral administration, propamocarb is rapidly and nearly completely absorbed with peak concentrations being reached within 1 h. Propamocarb is widely distributed, but was predominantly found in organs involved in elimination, i.e. liver and kidney. Elimination from tissues is rapid, with half lives ranging from 11 h to 26 h. Urine is the main route of excretion (about 75–91% of the administered dose within 24 h). Up to 6% of the administered dose is excreted in the faeces. Propamocarb is extensively metabolized. Unchanged propamocarb was found only in small quantities in the urine. Metabolism involves aliphatic oxidation of the propyl chain (to form hydroxypropamocarb) and *N*-oxidation and *N*-

demethylation of the tertiary amine resulting in propamocarb *N*-oxide and mono demethyl propamocarb, respectively. No marked sex differences were observed in the absorption, distribution, excretion and metabolism of propamocarb.

Toxicological data

The acute toxicity of propamocarb is low. The oral LD_{50}s in the rat were ≥ 2000 mg/kg bw. The dermal LD_{50}s in the rat were > 2000 mg/kg bw. The inhalation LC_{50} in the rat was > 5.54 mg/L. In studies of acute oral toxicity, clinical signs of toxicity included hypokinesia, lethargy, hunched posture, body tremors, clonic convulsions, nasal haemorrhage, mouth haemorrhage, piloerection, staggering gait and ataxia within 24 h after dosing.

Propamocarb is not irritating to the eye or skin. It induced skin sensitization in a Magnusson & Kligman maximization test, but gave negative results in a Buehler test.

In many studies of short- and long-term toxicity in rats and dogs treated orally, histological examination revealed that propamocarb induces vacuolar alterations in cells. In the rat, propamocarb predominantly induces vacuolization of cells in the choroid plexus of the brain and in the lacrimal glands. In dogs, propamocarb-induced vacuolization was observed in a number of tissues (including the lacrimal glands), but not in the brain.

Short-term studies of oral toxicity were available for mice, rats and dogs. In two 3-month studies in mice, propamocarb did not induce any toxicologically relevant effects when tested at doses of up to 1952 mg/kg bw per day. Propamocarb was tested in two 4-week dose range-finding studies, and at doses of 3–1549 mg/kg bw per day in one 5-week, three 3-month and one 1-year dietary studies in rats. The main toxicological findings were reductions in body weight and vacuolization in the choroid plexus and the lacrimal glands. The lowest NOAEL for these effects, observed in a 1-year dietary study in rats, was 29 mg/kg bw per day, on the basis of vacuolization of the choroid plexus in females receiving a dose of 114 mg/kg bw per day. In a 3-month study with a 28-day recovery period, partial recovery of the choroid plexus lesion was observed after cessation of treatment. The Meeting noted that for one 13-week study in rats the JMPR in 1984 had concluded that, "The study showed the no-effect level to be at least 200 ppm". The JMPR in 1986 had established an ADI of 0–0.1 mg/kg bw per day based, in part, on this study. The present Meeting concluded, however, that the observed effects in the treatment groups in this 13-week study were marginal and not toxicologically significant.

Propamocarb was tested in two 3-month, one 1-year and one 2-year dietary studies in the dog at doses ranging from 2 mg/kg bw per day to 471 mg/kg bw per day. The main toxicological findings were vacuolization in various organs. In a 3-month dietary study in dogs, the NOAEL was 131 mg/kg bw per day on the basis of vacuolar alterations in various organs. In a 1-year dietary study in dogs, the NOAEL was 39 mg/kg bw per day on the basis of vacuolization in various organs. In a 2-year study in dogs, the NOAEL was 71 mg/kg bw per day on the basis of an increase in the severity of glomerulosclerosis and loss of colour and reflectability of the tapetum lucidum of the ocular fundus. Since humans do not have a tapetum lucidum, the Meeting considered that the ocular effects in the dog were not relevant for humans.

The effects of dermal exposure to propamocarb were assessed in rats. In a 3-week study, no treatment-related systemic effects were observed at doses of up to 720 mg/kg bw per day (the highest dose tested). In a 4-week study in rats treated dermally, the NOAEL for systemic effects was 300 mg/kg bw per day on the basis of vacuolization of the choroid plexus of the brain and on reductions in body-weight gain, blood cholesterol and albumin concentrations and liver and thymus weight.

Long-term dietary studies have been performed in mice and rats. No carcinogenic effect of propamocarb was observed in any of these studies. In mice, no toxicologically relevant effects were observed in an 18-month study with doses of up to 883 mg/kg bw per day, and in a 2-year study with doses of up to 54 mg/kg bw per day. In another 18-month study in mice, the NOAEL was 106 mg/kg bw per day on the basis of reductions in body weight and body-weight gain.

In a 2-year study of toxicity and carcinogenicity in rats, minor decreases in food consumption (< 7%) and body weight (< 5%) were observed at a dose of 37 mg/kg bw per day (the highest dose tested). The present Meeting concluded that the small effects on food consumption and body weight were not toxicologically relevant. Since this study had several flaws, it was considered to be of limited value. In a second 2-year study of toxicity and carcinogenicity in rats, the NOAEL was 84 mg/kg bw per day on the basis of a decrease in body weight and body-weight gain and an increased incidence of vacuolization of the ependymal cells of the choroid plexus of the brain. In a third 2-year study of toxicity and carcinogenicity in rats, the LOAEL was 150 mg/kg bw per day (the lowest dose tested) on the basis of an increased incidence of vacuolization of the choroid plexus and the lacrimal gland ducts.

The Meeting concluded that propamocarb is not carcinogenic in rodents.

Propamocarb gave negative results in an adequate range of tests for genotoxicity in vitro and in vivo. The Meeting concluded that propamocarb is unlikely to be genotoxic.

In view of the lack of genotoxicity and the absence of carcinogenicity in mice and rats, the Meeting concluded that propamocarb is unlikely to pose a carcinogenic risk to humans.

In a two-generation dietary study of reproductive toxicity in rats, the NOAEL for parental toxicity was 1250 ppm (equal to 58 mg/kg bw per day for males) on the basis of reductions in body weight and body-weight gain. On the basis of a reduction in body-weight gain in the pups, the NOAEL for offspring toxicity was 1250 ppm (equal to 90 mg/kg bw per day based on the propamocarb intake in females). The NOAEL for reproductive effects was 8000 ppm (the highest dose tested, equal to 336 mg/kg bw per day). In a two-generation study of reproductive toxicity in rats treated by gavage, the NOAEL for parental toxicity was 50 mg/kg bw per day on the basis of clinical signs of toxicity and vacuolar changes in the epithelial cells of the choroid plexus and epididymis. The NOAEL for offspring toxicity was 200 mg/kg bw per day on the basis of decreased pup viability. The NOAEL for reproductive effects was 50 mg/kg bw per day on the basis of a reduced copulation index in females.

The effect of propamocarb on prenatal development was investigated in rats and rabbits. In none of the studies was propamocarb teratogenic. In a study in rats treated by gavage, the NOAEL for maternal toxicity was 680 mg/kg bw per day on the basis of clinical signs of toxicity, reduced body weight and increased mortality. The NOAEL for embryo- and fetotoxicity in this study was 204 mg/kg bw per day on the basis of a slightly increased incidence of number of dead fetuses and a delayed ossification. In a dietary study of developmental toxicity in rats, the NOAEL for maternal toxicity was 123 mg/kg bw per day on the basis of reduced body weight, body-weight gain and food consumption. The NOAEL for embryo- and fetotoxicity was also 123 mg/kg bw per day on the basis of reduced fetal weight and slightly delayed ossification of the cranial bones, cervical and caudal vertebrae, humerus, fore- and hind limb phalanges and metatarsals. The overall NOAEL for developmental toxicity in rats was 204 mg/kg bw per day. In a study in rabbits treated by gavage, the NOAEL for maternal toxicity was 278 mg/kg bw per day, on the basis of reduced body-weight gain. The NOAEL for embryo- and fetotoxicity was 278 mg/kg bw per day on the basis of increased postimplantation loss and increased incidence of a thirteenth rib. In a dietary study of developmental toxicity in rabbits, the NOAEL for maternal toxicity was 76 mg/kg bw per day on the basis of reduced body weight, body-weight gain and food consumption. The NOAEL for embryo- and fetotoxicity in this study was 269 mg/kg bw per day, the highest dose tested).

Studies of acute toxicity and short-term studies of oral toxicity in rats and dogs revealed no effect of propamocarb on cholinesterase activity in blood, plasma or brain, although when tested in vitro an inhibition of cholinesterase activity in rat and dog plasma was observed. In a single-exposure study of neurotoxicity, in which rats received propamocarb by gavage, the NOAEL was 200 mg/kg bw on the basis of reduced motor activity in females and increased incidence of soiled coats in both sexes. In a second single-dose study in rats treated by gavage, the NOAEL was 200 mg/kg bw per day on the basis of decreased activity 1 h after dosing in both sexes. In this study there was no evidence of treatment-related neuropathological effects 14 days after treatment with propamocarb at doses of up to 2000 mg/kg bw. In a 3-month dietary study of neurotoxicity in rats, the NOAEL was 142 mg/kg bw per day on the basis of a reduction in body-weight gain. In a study of neurotoxicity, in which rats received diets containing propamocarb for 101–104 days, the NOAEL was 100 mg/kg bw per day on the basis of intraepithelial vacuolization of the choroid plexus in both sexes and a reduction in body weight and food consumption in females.

The acute toxicity and genotoxicity of four impurities of formulations of propamocarb were tested. In studies of acute toxicity with the impurities *N*,*N*'-bis-(3-dimethylaminopropyl)urea dihydrochloride, *N*,*N*-bis-3-dimethylaminopropandiamine dihydrochloride, propyl-*N*-methyl-*N*-[3-(propoxycarbonylamino)propyl]carbamate and dipropylcarbonate in rats, the LD_{50}s were > 5000, > 3300, > 1045 and > 5000 mg/kg bw respectively. All four impurities gave negative results in tests for reverse mutation in bacteria.

In medical surveillance of manufacturing plant personnel and surveys of data banks of clinical cases and poisoning, no reports on adverse effects on human health were found.

The Meeting concluded that the existing database on propamocarb was adequate to characterize the potential hazards to fetuses, infants and children.

Toxicological evaluation

The Meeting established an ADI of 0–0.4 mg/kg bw based on a NOAEL of 39 mg/kg bw per day, on the basis of vacuolization observed in a range of organs in a 52-week study in dogs, and using a safety factor of 100.

The Meeting established an ARfD of 2 mg/kg bw based on a NOAEL of 200 mg/kg bw, on the basis of a decreased in activity in rats 1 h after dosing and using a safety factor of 100. This ARfD is adequately protective for effects observed in studies of developmental toxicity.

A toxicological monograph was prepared.

Levels relevant for risk assessment

Species	Study	Effect	NOAEL	LOAEL
Mouse	18-month study of toxicity[a]	Toxicity	840 ppm, equal to 106 mg/kg bw per day	6000 ppm, equal to 790 mg/kg bw per day
Rat	52-week study of toxicity[a]	Toxicity	375 ppm, equal to 29 mg/kg bw per day	1500 ppm, equal to 114 mg/kg bw per day
	2-year study of toxicity and carcinogenicity[a]	Toxicity	2800 ppm, equal to 84 mg/kg bw per day	22400 ppm, equal to 680 mg/kg bw per day
		Carcinogenicity	22400 ppm, equal to 680 mg/kg bw per day[c]	—
	Developmental toxicity[b]	Maternal toxicity	680 mg/kg bw per day	2040 mg/kg bw per day
		Fetotoxicity	204 mg/kg bw per day	680 mg/kg bw per day

Species	Study	Effect	NOAEL	LOAEL
	Acute neurotoxicity [b]	Neurotoxicity	200 mg/kg bw	2000 mg/kg bw
	101–104-day study of neurotoxicity [a]	Neurotoxicity	1500 ppm, equal to 100 mg/kg bw per day	6000 ppm, equal to 385 mg/kg bw per day
Dog	1-year study of toxicity [a]	Toxicity	1000 ppm, equal to 39 mg/kg bw per day	2500 ppm, equal to 97 mg/kg bw per day

[a] Dietary administration
[b] Gavage administration
[c] Highest dose tested
[d] Lowest dose tested

Estimate of acceptable daily intake for humans

0–0.4 mg/kg bw

Estimate of acute reference dose

2 mg/kg bw

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

Results from epidemiological, occupational health and other such observational studies of human exposures

Critical end-points for setting guidance values for exposure to propamocarb

Absorption, distribution, excretion and metabolism in mammals	
Rate and extent of absorption	Rapid and extensive (rats)
Distribution	Highest levels in liver, kidney, adrenals, spleen (rats)
Potential for accumulation	Low
Rate and extent of excretion	Rapid (75–91% in urine within 24 h in rats)
Metabolism in animals	Major metabolites: carbonyl propamocarb, hydroxy propamocarb, propamocarb-*N*-oxide, mono-*N*-demethyl propamocarb (rats)
Toxicologically significant compounds (animals, plants and environment)	Propamocarb
Acute toxicity	
Rat LD_{50} oral	≥ 2000 mg/kg bw
Mouse rat LD_{50} dermal	> 2000 mg/kg bw
Rat LC_{50} inhalation	> 5.5 mg/L
Rabbit, skin irritation	Not an irritant
Rabbit, eye irritation	Not an irritant
Skin sensitization (test method used)	Sensitizing in guinea-pigs (Magnusson & Kligman) Not sensitizing in guinea-pigs (Buehler)
Short-term studies of toxicity	
Target/critical effect	Vacuolar changes in various tissues, reduction of body weight (rat, dog)
Lowest relevant oral NOAEL	1000 ppm, equal to 39 mg/kg bw per day (dogs)
Lowest relevant dermal NOAEL	300 mg/kg bw per day (rats)
Lowest relevant inhalatory NOAEL	No data

Long-term studies of toxicity and carcinogenicity	
Target/critical effect	Vacuolar changes in choroid plexus and lacrimal glands, reduction of body weight (rats)
Lowest relevant NOAEL	2800 ppm, equal to 84 mg/kg bw per day (rats)
Carcinogenicity	Not carcinogenic (mice, rats)
Genotoxicity	
	Not genotoxic in vitro or in vivo
Reproductive toxicity	
Reproduction target/critical effect	Reduced copulation index in females (rats)
Lowest relevant reproductive NOAEL	50 mg/kg bw per day (rats)
Developmental target	Reduced body weight and delayed ossification (rats); increased postimplantation loss (rabbits)
Lowest relevant developmental NOAEL	204 mg/kg bw per day (rats)
Neurotoxicity/delayed neurotoxicity	
Neurotoxicity	Decreased activity 1 h after a single dose administered by gavage (rats)
	Vacuolization of the choroid plexus in the brain after repeated dosing (rats)
Lowest relevant oral NOAEL	200 mg/kg bw (single dose by gavage)
	52 mg/kg bw per day (repeated dietary dosing)
Other toxicological studies	
	No data
Medical data	
	No adverse effects reported in humans

Summary			
	Value	Study	Safety factor
ADI	0–0.4 mg/kg bw	Dog, 1-year study of toxicity	100
ARfD	2 mg/kg bw	Rat, acute neurotoxicity	100

4.19 PYRETHRINS (063)

RESIDUE AND ANALYTICAL ASPECTS

Pyrethrins were evaluated for residues in the Periodic Review Programme of the 2000 JMPR, which concluded that the existing CXL of 1 mg/kg Po for tree nuts should be withdrawn because no information was submitted. The 34th Session of the CCPR decided to maintain the CXL for tree nuts for 4 years, as the Government of Australia had indicated its intention to submit new residue data to the JMPR.

The 2005 JMPR received reports of studies on analytical methods and supervised residue trials and information on GAP for tree nuts. Reports were supplied by the government of Australia. The formulation used for trials contains not only pyrethrins but piperonyl butoxide. There is no residue information for piperonyl butoxide and a CXL for piperonyl butoxide in tree nuts has not been established.

Method of analysis

The sample was extracted with acetone and water. Extracts were assessed by HPLC with a fluorescence detector at 223nm. The limit of quantification (LOQ) was 0.2mg/kg for almond and 0.5mg/kg for macadamia nuts. This method was considered acceptable for supervised trials.

Definition of the residue

The Meeting agreed that the residue definition for enforcement purposes for plant commodities and for consideration of dietary intake should be total pyrethrins, calculated as the sum of pyrethrin 1, pyrethrin 2, cinerin 1, cinerin 2, jasmolin 1 and jasmolin 2, determined after calibration with World Standard pyrethrum extract. The Meeting agreed that the residues are fat-soluble.

Definition of the residue for compliance with MRLs and estimation of dietary intake: total pyrethrins, calculated as the sum of pyrethrin 1, pyrethrin 2, cinerin 1, cinerin 2, jasmolin 1 and jasmolin 2, determined after calibration with World Standard pyrethrum extract.

Results of supervised trials on crops

Tree nuts

The current Australian label indicates that a gas formulation of pyrethrins may be applied to stored tree nuts in food storage area. The application rate of pyrethrins for tree nuts is either 0.067 g ai/100m^3 (for flying insects) or 0.2 g ai/100m^3 (for crawling insects). However the frequency of applications is not described on the label. It is determined by the situation in which the products are being applied. Three supervised trials each were conducted for stored almond and macadamia nuts according to the maximum application rate based on the Australia GAP (0.2 g ai/100m^3). The number of applications to almond or macadamia nuts was 3 or 4 respectively. The residues of pyrethrins were below the respective LOQ's, < 0.2 mg/kg in almond and < 0.5 mg/kg in macadamia nuts.

The Meeting estimated a maximum residue level of 0.5 * mg/kg, an STMR of 0.2 mg/kg and an HR of 0.5 mg/kg for post-harvest use of pyrethrins on tree nuts and recommended withdrawal of the existing CXL for tree nuts of 1 mg/kg Po.

DIETARY RISK ASSESSMENT

Long-term intake

The International Estimated Daily Intakes (IEDI) of pyrethrins, based on the STMRs estimated by the 2000, 2003 and 2005 JMPR for 12 commodities, for the five GEMS/Food regional diets was 1% of the maximum ADI of 0.04 mg/kg bw (Annex 3). The Meeting concluded that the long-term intake of residues of pyrethrins, resulting from the uses considered by the JMPR, is unlikely to present a public health concern.

Short-term intake

The International Estimated Short Term Intake (IESTI) for pyrethrins was calculated for tree nuts for which the maximum residue level was estimated by the current JMPR (Annex 4).

The IESTI represented 1% of the ARfD (0.2 mg/kg bw) for the general population and 0% of the ARfD for children. The Meeting concluded that the short-term intake of residues of pyrethrins, resulting from the uses considered by the JMPR, is unlikely to present a public health concern.

4.20 SULFURYL FLUORIDE (218)

TOXICOLOGY

Sulfuryl fluoride (O_2SF_2) is a gas used as a fumigant for the control of a range of insect pests. It has been used for structural fumigation since the early 1960s. In the USA it is approved for "food uses" (grain, dried fruit and tree nuts), while in the United Kingdom, Germany and Italy the structures being fumigated must be emptied of food items. Sulfuryl fluoride is thought to inhibit the glycolysis and fatty acid cycles via the release of fluoride ions, thereby depriving the insect of energy necessary for survival.

Sulfuryl fluoride has not been evaluated previously by the JMPR.

All the critical studies contained statements of compliance with GLP.

Biochemical aspects

In rats exposed to [^{35}S]-labelled sulfuryl fluoride at 30 or 300 ppm by inhalation, the radiolabel was rapidly absorbed, achieving maximum concentrations in both plasma and erythrocytes near the end of the 4-h exposure period. Once absorbed, the radiolabel was rapidly excreted, primarily via the urine. The radiolabel was rapidly cleared from the plasma and erythrocytes with initial half-lives of approximately 2.5 h after exposure at 30 ppm and 1–2.5 h after exposure at 300 ppm, but the terminal half-life of radioactivity was approximately 2.5-fold longer in erythrocytes than in plasma. The identification of fluorosulfate and sulfate in blood and urine suggests that sulfuryl fluoride is rapidly hydrolysed to fluorosulfate, with the release of fluoride, followed by further hydrolysis to sulfate and release of the remaining fluoride. This is supported by the observation of increases in fluoride in blood and urine after exposure of rats to sulfuryl fluoride. Seven days after exposure, radioactivity was widely distributed with significant concentrations remaining in tissues at the site of first exposure to the gas.

Toxicological data

The primary concern of the Meeting was the risk assessment for dietary exposures to sulfuryl fluoride. Sulfuryl fluoride is a gas and routine tests for toxicity via the oral and dermal routes are difficult to perform. All the critical studies involved exposures by inhalation (for about 6 h/day, 5 days/week) and it was necessary to convert these to systemic doses in order to derive health-based guidance values. To convert from concentrations in air to a systemic dose in mg/kg bw per day, account was taken of the respiratory rates and volumes of the animals[11], the duration of exposure

[11] Twenty-four-hour respiratory volumes for test species: rats, 0.96 m^3/kg bw; rabbits, 0.54 m^3/kg bw; mice, 1.8 m^3/kg bw; and dogs, 0.39 m^3/kg bw.

(h/day and days/week) and the proportion (10%) of the inspired dose that was absorbed based on a toxicokinetic study.

In assessing the effects of sulfuryl fluoride, the Meeting focused on effects related to systemic exposures rather than local effects linked with sulfuryl fluoride gas. In foodstuffs exposed to sulfuryl fluoride the predominant residue is fluoride ion, although some residues of sulfuryl fluoride have been detected in certain fumigated products. The data indicated that some toxic effects observed after exposure to sulfuryl fluoride (e.g. renal toxicity) were consistent with the toxicity of fluoride. The Meeting concluded that the "slight" dental fluorosis seen in some studies was not an adverse finding. Although no studies on fluoride were submitted the Meeting was aware of a number of recent expert evaluations of exposure to and toxicity attributable to fluoride.

Sulfuryl fluoride was found to be moderately acutely toxic when administered by the oral route (LD_{50} of approximately 100 mg/kg bw; sulfuryl fluoride bubbled into corn oil), but the Meeting noted that the results of this study were difficult to interpret owing to the very high volume of corn oil administered (40 mL/kg bw). A standard study of dermal toxicity could not be performed, but whole-body (excluding head) exposure did not indicate any significant toxicity after exposure via the dermal route. Sulfuryl fluoride gas administered via inhalation has been extensively investigated in several studies of acute toxicity in rats and mice and was found to have low to moderate toxicity. All studies in rats and one of two studies in mice reported 4-h LC_{50} values of > 2 mg/L (about 500 ppm). Exposure of humans to sulfuryl fluoride gas at high concentrations within enclosed structural fumigation areas has resulted in death. No tests for skin and eye irritation or studies of skin sensitization have been conducted. However, whole-body exposures and experience in humans over a period of 40 years of use indicate that sulfuryl fluoride is not a significant irritant, nor a skin sensitizer. Mechanistic studies on "time to acute incapacitation" have revealed an approximately linear relationship between concentration and duration of exposure.

In a 1959 study in which rats were fed for 66 days with diets previously exposed to sulfuryl fluoride, the NOAEL was 2.5 mg of total fluoride/kg bw per day on the basis of reduced body-weight gain and evidence of fluorosis, but the details reported were limited and relatively few end-points were investigated. Sulfuryl fluoride has been studied in short-term studies of toxicity in rats, dogs, mice and rabbits exposed by inhalation; in most experiments, the exposure period was 6 h/day, 5 days/week. In 14-day studies of exposure by inhalation, the lowest NOAEC was 30 ppm (approximately equivalent to systemic exposure at 4.1 mg/kg bw per day) in mice on the basis of brain vacuolation, while the NOAEC in dogs was 100 ppm (approximately equivalent to systemic exposure at 2.9 mg/kg bw per day) on the basis of tremors and tetany, but no evidence of brain lesions. The NOAEC was also 30 ppm in 90-day studies in mice (approximately equivalent to systemic exposure at 4.1 mg/kg bw per day), and in rabbits (approximately equivalent to systemic exposure at 1.4 mg/kg bw per day). In these studies the LOAEC was 100 ppm on the basis of vacuolation in the brain. Local effects on the respiratory tract were seen in many of the studies of administration via inhalation, but the Meeting considered that these were not relevant to dietary intakes. In a 1-year study in dogs exposed by inhalation, the NOAEC was 80 ppm (approximately equivalent to systemic exposure at 2.3 mg/kg bw per day) on the basis of deaths and general toxicity (including brain vacuolation) at 150 ppm. A higher concentration of 200 ppm was not tolerated by the dogs beyond approximately 9 months, when primarily respiratory effects were associated with a terminal decline in health status. Slight dental fluorosis was the most sensitive effect in the 13-week study in rats and the 1-year study in dogs, but the Meeting concluded that this was not an adverse finding. Although no specific investigations were performed on other end-points associated with excess exposure to fluoride, e.g. bone density, the Meeting concluded that the NOAELs used for risk assessment provided adequate protection for the bone effects of fluoride, as such effects are considered to be at least threefold less sensitive than dental fluorosis, on the basis of human observations.

In rats, the principal effects of long-term exposure by inhalation were reduced survival, brain vacuolation, chronic progressive glomerular nephrosis and associated lesions such as fibrous osteodystrophy in both sexes exposed at 80 ppm (approximately equivalent to 5.6 mg/kg bw per day). These latter findings are consistent with toxicity attributable to fluoride ions. In mice, the principal effects were reduced survival and slight vacuolation in the cerebrum. In rats, the NOAEC was 20 ppm (approximately equivalent to 1.4 mg/kg bw per day). In mice, the NOAEC was 20 ppm (approximately equivalent to 3.0 mg/kg bw per day). Sulfuryl fluoride was not tumourigenic or carcinogenic in rats or mice at concentrations of up to 80 ppm, the highest concentration tested (approximately equivalent to 5.6 and 12 mg/kg bw per day, respectively).

Sulfuryl fluoride showed no genotoxic potential in tests in vitro for bacterial cell mutation or unscheduled DNA synthesis in mammalian cells. The results of tests for mutagenicity and clastogenicity in mammalian cells in vitro (mouse lymphoma $Tk^{+/-}$ and rat lymphocytes) were positive, consistent with the database on genotoxicity of the fluoride ion. A test for micronucleus formation in vivo gave negative results. The Meeting noted that sulfuryl fluoride is a highly reactive compound and dietary exposures would be predominantly to fluoride ion. It is generally recognized that fluoride does not represent a genotoxic risk to humans in vivo.

The Meeting concluded that consumption of foodstuffs treated with sulfuryl fluoride would not present a genotoxic risk to humans.

In view of the negative results obtained in studies of genotoxicity in vivo and the absence of carcinogenicity in mice and rats, the Meeting concluded that sulfuryl fluoride is unlikely to pose a carcinogenic risk to humans.

In a two-generation study of reproduction, no effect on reproductive parameters was observed in rats exposed by inhalation to sulfuryl fluoride at concentrations of up to 150 ppm, the highest concentration tested (approximately equivalent to 11 mg/kg bw per day). At 150 ppm, parental toxicity comprised reduced body weights and brain vacuolation; the NOAEC was 20 ppm. Reduced body-weight gain in F_1 and F_2 pups during the lactation period was noted at 150 ppm and was the only effect in offspring. The NOAEC in offspring was 20 ppm (approximately equivalent to 1.4 mg/kg bw per day). Sulfuryl fluoride has been tested for developmental effects in both rats and rabbits and found not to be teratogenic in either species. Pregnant rabbits were somewhat more sensitive to sulfuryl fluoride than were pregnant rats. In rats, there were no adverse effects on dams or offspring exposed to sulfuryl fluoride at concentrations of up to 225 ppm, the highest concentration tested (approximately equivalent to 16 mg/kg bw per day). In rabbits, however, there was slight toxicity to dams and offspring at 225 ppm, which was manifested as reduced body weights and lower fetal weights. The lowest relevant NOAEC for developmental toxicity was 75 ppm (approximately equivalent to 4.3 mg/kg bw per day) in rabbits.

Three studies specifically investigated the neurotoxicity of sulfuryl fluoride: a study of acute toxicity in rats exposed via inhalation, a 13-week study in rats exposed via inhalation and a 1-year in rats exposed via inhalation (a satellite group of the long-term/carcinogenicity study). The 13-week study was conducted first and comprised comprehensive electrophysiological tests, a functional observational battery (FOB) and histological examination of the peripheral and central nervous system. It demonstrated that the most sensitive indicator of effects on the nervous system after 13 weeks was a change in evoked potentials (visual, auditory and somatosensory). At a dietary concentration of 100 ppm and greater, visual and somatosensory evoked potentials were significantly slower in exposed female rats and auditory brainstem responses were possibly slower in exposed males relative to controls. Only at 300 ppm were histological effects evident, in the form of mild vacuolation in the brain (specifically, white fibre tracts of the caudate putamen). The NOAEC in the 13-week study was 30 ppm (approximately equivalent to 2.2 mg/kg bw per day) on the basis of alterations in evoked potentials at 100 ppm in females.

On the basis of the findings in the 13-week study of neurotoxicity, a study of acute neurotoxicity (two 6 h exposures in 30 h) in female rats was performed. This included extensive neurophysiological and behavioural investigations, including evoked potentials, but there were no investigations of brain histopathology. The Meeting considered that the absence of investigations of brain histopathology was not crucial as the brain lesions did not appear to be an acute effect, being absent in dogs or rats after 2 weeks, but were present at lower exposures in the 13-week studies. No adverse effects were produced at 300 ppm (approximately equivalent to 31 mg/kg bw per day), the highest concentration tested. The 1-year study of neurotoxicity in male and female F344 rats included a FOB, motor activity tests, fore- and hindlimb grip strength, hindlimb landing foot splay and neurohistopathology with perfusion fixation. These animals were a satellite group of the long-term/carcinogenicity study and no general histopathological examinations were performed as these were covered by other segments of the study. There were no effects on the nervous system at 80 ppm (approximately equivalent to 5.6 mg/kg bw per day), the highest concentration tested.

Sulfuryl fluoride has been used as a structural fumigant for more than 40 years. Health surveillance examinations in manufacturing plants have revealed no significant sulfuryl fluoride-related health problems among employees. Thirteen deaths have been reported in humans who gained access to buildings during fumigation, but the lethal concentration has not been determined. More than 300 incidents of non-lethal adverse effects associated with exposure to sulfuryl fluoride have been reported in the USA. Symptoms included irritation of eyes and respiratory tract, headache, nausea, fever and diarrhoea; some of these might be attributable to exposure to chloropicrin used as a sensory marker. Two epidemiological investigations of sulfuryl fluoride and methyl bromide fumigators have reported a small number of findings in the cohorts exposed to sulfuryl fluoride. Some of these findings appear to be related to physical activities associated with the fumigation process. Others present no clear pattern that can be attributed to the use of sulfuryl fluoride. In neither study was there any biomonitoring to assess exposure.

The Meeting concluded that the existing database on sulfuryl fluoride was adequate to characterize the potential hazards to fetuses, infants and children.

Toxicological evaluation

The Meeting established an ADI for sulfuryl fluoride of 0–0.01 mg/kg bw based on a NOAEC of 20 ppm (approximately equivalent to systemic exposure at 1.4 mg/kg bw per day) in both a 24-month study in rats exposed to sulfuryl fluoride by inhalation, on the basis of effects on the kidney, brain, bone and survival at 80 ppm, and the two-generation study of reproductive toxicity in rats exposed to sulfuryl fluoride by inhalation, on the basis of effects on the brain and body weight at 150 ppm, with a 100-fold safety factor**.** The Meeting noted that some of the end-points in the long-term study in rats, such as kidney toxicity, were consistent with the data on fluoride toxicity. The Meeting considered that the slight dental fluorosis seen at the toxicological NOAEC was not an adverse effect.

The Meeting noted that the residue resulting from sulfuryl fluoride fumigation of foodstuffs was primarily fluoride. The critical studies of toxicity with sulfuryl fluoride used inhalation exposures and while this would result in a significant systemic dose of fluoride, it was impossible to separate reliably the effects attributable to systemic exposure to fluoride with those attributable to gaseous sulfuryl fluoride. The Meeting did not receive any studies on fluoride that would enable it to derive reference values for fluoride. The Meeting concluded that the dietary intake of fluoride associated with the use of sulfuryl fluoride as a fumigant should be included in an overall assessment of fluoride from all sources. Upper levels for fluoride intakes have been proposed by a number of organizations[12].

[12] For example: www.efsa.eu.int/science/nda/nda_opinions/851_en.html or www.nap.edu/books/0309063507/html/288.html

The Meeting established an ARfD of 0.3 mg/kg bw for sulfuryl fluoride based on a NOAEC of 300 ppm (approximately equivalent systemic exposure at 31 mg/kg bw per day) the highest concentration tested in a study of acute neurotoxicity in rats exposed to sulfuryl fluoride by inhalation, and a 100-fold safety factor. The Meeting noted that there was no clear evidence for acute systemic toxicity associated with sulfuryl fluoride. However, as the acute oral LD_{50} was reported to be about 100 mg/kg bw, the Meeting agreed on the need to derive an ARfD. The Meeting concluded that the only appropriate study for deriving the ARfD was the study of acute neurotoxicity, although this was likely to result in a conservative assessment and was probably not relevant to intakes of fluoride ion as such from sulfuryl fluoride-treated commodities. The Meeting considered that the critical end-point of brain vacuolation, which had not been evaluated in this study, was not an acute effect based on its absence in the 2-week studies in dogs and rats.

A toxicological monograph was prepared.

Levels relevant to risk assessment

Species	Study	Effect	NOAEL	LOAEL
Mouse	18 month (6 h/day 5 days/week); whole-body exposure	Toxicity	20 ppm (3.0 mg/kg bw per day)	80 ppm (12 mg/kg bw per day)
		Carcinogenicity	80 ppm[a] (12 mg/kg bw per day)	—
Rat	Study of acute neurotoxicity (2 × 6 h in 30 h); whole-body exposure	Toxicity	300 ppm[a] (31 mg/kg bw per day)	—
	2 year (6 h/day, 5 days/week); whole-body exposure	Toxicity	20 ppm (1.4 mg/kg bw per day)	80 ppm (5.6 mg/kg bw per day)
		Carcinogenicity	80 ppm[a] (5.6 mg/kg bw per day)	—
	Two-generation study of reproductive toxicity (6 h/day, 5 days/week); whole-body exposure	Reproduction	150 ppm[a] (11 mg/kg bw per day)	—
		Offspring	20 ppm (1.4 mg/kg bw per day)	80 ppm (5.6 mg/kg bw per day)
		Parental	20 ppm (1.4 mg/kg bw per day)	80 ppm (5.6 mg/kg bw per day)
	Developmental toxicity (6 h/day, 5 day/week) whole-body exposure	Maternal	225 ppm[a] (16 mg/kg bw per day)	—
		Developmental	225 ppm[a] (16 mg/kg bw per day)	—
Rabbit	90-day (6 h/day, 5 days/week); whole-body exposure	Toxicity	30 ppm (1.4 mg/kg bw per day)	100 ppm (4.1 mg/kg bw per day)
	Study of developmental toxicity (6 h/day, 5 days/week); whole-body exposure	Maternal	75 ppm (4.3 mg/kg bw per day)	225 ppm (13 mg/kg bw per day)
		Developmental	75 ppm (4.3 mg/kg bw per day)	225 ppm (13 mg/kg bw per day)
Dog	1-year (6 h/day, 5 days/week); whole-body exposure	Toxicity and mortality	80 ppm (2.3 mg/kg bw per day)	200 ppm (5.8 mg/kg bw per day)

[a] Highest concentration tested

Estimate of acceptable daily intake for humans

0–0.01 mg/kg bw

Estimate of acute reference dose

0.3 mg/kg bw

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

Studies with sulfuryl fluoride administered orally

Results from epidemiological, occupational health and other such observational studies of human exposures

Critical end-points for setting guidance values for exposure to sulfuryl fluoride

Absorption, distribution, excretion and metabolism in mammals (studies with ^{35}S-labelled sulfuryl fluoride; fluoride was not investigated specifically)	
Rate and extent of absorption	Rapidly absorbed after exposure via inhalation (nose only); maximum concentrations attained near the end of 4-h exposure). Absorbed dose (radioactivity in urine, faeces and tissues) estimated to be 14% at 30 ppm and 11% of the dose entering lungs at 300 ppm.
Distribution	Seven days after exposure, ^{35}S was widely distributed among the tissues. Significant concentrations of radioactivity remained in tissues at the site of first exposure to the gas. Increased concentrations of fluoride were detected in blood and tissues.
Potential for accumulation	Increased intake of fluoride may lead to fluorosis (i.e. accumulation of fluoride in bones and teeth).
Rate and extent of excretion	Rapidly excreted, primarily via the urine. Radioactivity (^{35}S) was rapidly cleared from plasma and erythrocytes with initial half-lives of approximately 2.5 h after exposure at 30 ppm and 1–2.5 h after exposure at 300 ppm. The terminal half-life of radioactivity was about 2.5-fold longer in erythrocytes than in plasma.
Metabolism in animals	Initially hydrolysed to fluorosulfate, with release of fluoride, followed by further hydrolysis to sulfate and release of the remaining fluoride.
Toxicologically significant compounds (animals, plants and environment)	Sulfuryl fluoride and fluoride ion
Acute toxicity	
Rat LD_{50} oral	Approximately 100 mg/kg bw (bubbled into corn oil, dosed at 40 mL/kg bw)
Rat LD_{50} dermal	No adverse effects at 40.3 mg/L (4 h exposure, whole body except head)
Rat LC_{50} inhalation	4.7–5.8 mg/L (4 h exposure) (1000–1122 ppm)
Skin sensitization (test method used)	No data submitted, but repeated whole-body exposures and experience of use by humans have identified no indications of sensitization.
Short-term studies of toxicity	
Target/critical effects after inhalation	Local effect on respiratory tract (after inhalation): inflammation (rats, dogs, rabbits) and alveolar histiocytosis (rats), aggregates of macrophages in alveoli (dogs) Brain: vacuolation (rats/dogs/mice/rabbits) Kidney: mild hyperplasia, tubular degeneration (rats) Overt dental fluorosis (rats)
Target/critical effects after oral administration	Reduced body-weight gain, overt dental fluorosis, renal lesions
Lowest relevant oral NOAEL	Total fluoride, 2.5 mg/kg bw per day
Lowest relevant dermal NOAEL	None (no data)

Lowest relevant inhalation NOAEC	100 ppm (rats, 7.0 mg/kg bw per day) 80 ppm (dogs, 2.3 mg/kg bw per day) 30 ppm (mice, 4.1 mg/kg bw per day; rabbits, 1.4 mg/kg bw per day)
Genotoxicity	
	Some positive results in vitro, negative results in vivo. No genotoxic risk to humans from dietary exposure.
Long-term studies of toxicity and carcinogenicity	
Target/critical effect	Kidney: renal failure (rats). Reduced survival (mice, rats)
	Brain: minimal vacuolation of cerebrum (mice, rats)
Lowest relevant NOAEC/NOAEL	20 ppm (mice, 3.0 mg/kg bw per day) 20 ppm (rats, 1.4 mg/kg bw per day)
Carcinogenicity	Not carcinogenic in rats or mice
Reproductive toxicity	
Reproduction target/critical effect ‡	Reproduction: none Parental toxicity: reduced body weight and brain vacuolation Offspring: reduced body weight during lactation
Lowest relevant reproductive NOAEC	Reproduction: 150 ppm (11 mg/kg bw per day)[a] Parental: 20 ppm (1.4 mg/kg bw per day) Offspring: 20 ppm (1.4 mg/kg bw per day)
Developmental target/critical effect	Rabbit: reduced fetal weights. Not teratogenic.
Lowest relevant developmental NOAEC	Maternal: 75 ppm (rabbits, 4.3 mg/kg bw per day) Developmental : 75 ppm (rabbit, 4.3 mg/kg bw per day) Teratogenicity: 225 ppm (rats and rabbits)[a]
Neurotoxicity/delayed neurotoxicity	
2-day (two 6-h exposures in 30 h) study of acute neurotoxicity in female F344 rats	No effects at 300 ppm (31 mg/kg bw), the highest concentration tested
13-week (6-h exposures, 5 days/week) study of neurotoxicity in F344 rats	Mild vacuolation of the brain, slowing of visual auditory and somatosensory evoked potentials at 300 ppm. Evoked potentials slower in female rats and auditory brainstem responses possibly slower in males at 100 ppm. The NOAEC was 30 ppm (2.2 mg/kg bw per day). Recovery within 2 months.
12-month (6-h exposures, 5 days/week) neurotoxicity study in F344 rats	No effects on the nervous system at the highest concentration tested, NOAEC was 80 ppm (5.8 mg/kg bw per day).
Other toxicological studies	
	None submitted.
Medical data	
	In the USA, 335 reports of alleged human health effects associated with sulfuryl fluoride have been made since 1993. Thirteen human deaths, primarily from unauthorized entry into the tented fumigated structures. 60% of non-fatal incidents involved symptoms of irritation possibly related to residual chloropicrin (a sensory marker). The next most common (9%) complaint was flu-like symptoms of nausea, diarrhoea, fever, and headache; about 6% complained of shortness of breath or respiratory distress.
	No findings in production plant workers. Epidemiology studies of fumigators inconclusive.

Summary

	Value	Study	Safety factor
ADI	0–0.01 mg/kg bw	Rat, 24-month study of toxicity and carcinogenicity after inhalation; reproductive toxicity after inhalation.	100
ARfD	0.3 mg/kg bw	Rat, acute neurotoxicity after inhalation	100

[a] Highest concentration tested

RESIDUE AND ANALYTICAL ASPECTS

Sulfuryl fluoride is a post-harvest and structural fumigant for controlling a wide range of insect pests. Sulfuryl fluoride penetrates the insect's body through inhalation in actively respiring life stages or diffusion into the egg. It is a non-specific target poison acting by disrupting the glycolysis and citric acid cycles, thereby depriving the insect of the necessary energy for survival. Upon sulfuryl fluoride entering a target organism it is broken down to the insecticidally active fluoride anion which then inhibits the insect's metabolism. It is being evaluated for the first time by the 2005 JMPR.

Animal metabolism

No adequate animal metabolism study for sulfuryl fluoride was available.

Degradation in stored products

The metabolism/degradation of ^{35}S-labelled sulfuryl fluoride was studied after fumigation of a variety of food items.

Wheat flour was fumigated with ^{35}S- sulfuryl fluoride at 32 mg/L in a fumigation chamber under reduced pressure for 92 h at room temperature. The insoluble flour residue remaining after 80% ethanol extraction retained 24% of the radioactivity. Radiolabeled residues were characterized as anionic, and some of the radiolabeled residue was characterized as amino acids or soluble polypeptides. Sulfate is formed as a result of conventional hydrolysis of sulfuryl fluoride. This reaction proceeds stepwise, first to fluorosulfonic acid and then to the sulfate anion. An additional product of the breakdown of sulfuryl fluoride is inorganic fluoride.

Seven food items contained in open cups were fumigated with sulfuryl fluoride at 36 and 360 mg/L for 20 h in a chamber of 4.2 m^3 volume. The food items included unbleached enriched wheat flour, dry dog food, non-fat dry milk, vegetable cooking oil, dried beef, Red Delicious Washington apples and snack cakes. Fluoride and sulfate residue levels were analysed at 1, 8, and 15 days after the treatment for both fumigation concentrations.

After the exposure to sulfuryl fluoride at 36 mg/L, fluoride residues found on the seven commodities ranged from approximately nil (for vegetable oil) to 170 mg/kg (for dried beef) at day one; 215 mg/kg (for dried beef) at day eight; and 216 (for dried beef) at day fifteen. Sulfate residues found on the seven commodities were up to 106 mg/kg at day one, 160 mg/kg at day eight and 189 mg/kg at day fifteen.

After exposure to sulfuryl fluoride at 360 mg/L, fluoride residues found on the seven commodities were up to 1300 mg/kg in dried beef at day one, 1200 mg/kg at day eight and 1200 mg/kg at day fifteen.

Any unreacted sulfuryl fluoride present in the matrix degrades to fluoride and sulfate as the terminal residues.

Environmental fate

Sulfuryl fluoride is a structural fumigant used only for post-harvest treatment. Since there are no uses on agriculture crops, an environmental fate study is not applicable.

Methods of analysis

The Meeting received separate methods for the analysis of sulfuryl fluoride and fluoride anion. It was concluded that adequate analytical methods exist both for the monitoring/enforcement of MRLs and for data gathering in fumigation facilities.

Gas chromatography with electron capture detection is suitable for the determination of sulfuryl fluoride residues in dried fruits, tree nuts, maize, wheat and rice commodities. A limit of quantification (LOQ) of 0.008 mg/kg was typically achieved.

The method for the analysis of fluoride anion uses aqueous extraction followed by use of a fluoride selective electrode. This method is suitable for the determination of fluoride in cereal grains, dried fruits and tree nuts. An LOQ of 0.2–2.4 mg/kg was typically achieved for fluoride ion.

No analytical methods were developed for animal tissue matrices.

Stability of pesticide residues in stored analytical samples

Residues of fluoride in maize, wheat grain, raisin, walnut, and maize meal are considered to be stable when stored at room temperature for at least 35 days, and when stored frozen at approximately –20 °C for at least 138 days. The exception is for wheat flour, which is stable for at least 104 days. No data on storage stability for sulfuryl fluoride was provided.

Definition of the residue

The degradation of sulfuryl fluoride results in the formation of sulfate and inorganic fluoride. Sulfate residues resulting from the degradation of sulfuryl fluoride are insignificant in comparison to naturally occurring levels.

Residue data revealed that sulfuryl fluoride could be present in a commodity following the 24 h aeration period. The measured levels of sulfuryl fluoride in small grains, grain process fractions, and in dried fruit were extremely low, except for maize oil. The sulfuryl fluoride retained on tree nuts was higher, but declined rapidly with time. With the possible presence of sulfuryl fluoride on a commodity following the 24 h aeration, sulfuryl fluoride was considered as suitable for monitoring purposes. Fluoride is ubiquitous in the environment and is not suitable as a residue for enforcement purposes.

Adequate analytical methods exist for the determination of fluoride and sulfuryl fluoride.

The Meeting concluded that the residue definition for monitoring/enforcement is “sulfuryl fluoride”, and for dietary intake considerations “sulfuryl fluoride and fluoride ion” measured separately.

Results of the supervised trials on crops

Fumigation treatments in the supervised trials for cereals, dried fruits and tree nuts summarized in the following paragraphs represent a wide range of treatment rates, calculated as the product of fumigant Concentration (C) x Exposure Time (T) or CTP with either single or multiple applications, and residues determined at different PFIs (Post-Fumigation Intervals). Based on the maximum cumulative CTP of 1500 (or 1500 gram-hours per cubic metre given as g·h/m^3 or mg·h/L), and the consideration of allowing a ± 25% GAP variation, residues generated from a single application at ± 25 GAP (1125–1875 CTP, or 1,125-1,875 mg·h/L or g·h/ m^3) will be used for MRL estimation and dietary risk assessment. Since sulfuryl fluoride (SF) residues are rapidly degraded to F^- (fluoride ion) after 24 h

and the latter is stable in treated commodities, the Meeting decided that SF residues collected from 1 day PFI, and F^- residues collected at all PFIs would be used for MRL, STMR and HR estimations.

Cereals

The USA GAP specifies that for stored product pests a particular plant will be fumigated on a schedule from three times per year to once every few years at the maximum cumulative CTP of 1500 g h/m^3, and the maximum cumulative CTP for vacuum fumigation of 200 g h/m^3. In practice, stored cereal grains are likely to receive only one fumigation treatment. Sulfuryl fluoride residues reported in the following paragraphs were all from 1-day PFI, and were analysed immediately; fluoride residues were the highest residues from each sample irrespective of the PFI.

Barley

In trials matching USA GAP conducted in the USA, England, Germany, and Italy the sulfuryl fluoride (SF) residues were < 0.008 (4) mg/kg. Fluoride ion (F^-) residues in ranked order were: 2.8, 2.8, 3.1, 6.5, 7.1, 8.0, 10, 12, 18, 18, and 21 mg/kg.

Maize

In trials matching USA GAP conducted in the USA the SF residues were: < 0.008 (7), 0.02(2), and 0.03 mg/kg. F^- residues in ranked order were: 0.8, 0.9, 1.0, 1.2, 1.3, 1.4(4), 1.5, 1.6, 1.7, 1.9 and 2.3(3) mg/kg.

Oat

In seven trials matching USA GAP conducted in the USA, SF residues were < 0.008 (4) mg/kg. F^- residues in ranked order were: 7.0, 7.4, 7.5, 8.3, 9.2, 12, and 14 mg/kg.

Rice

In 19 trials matching USA GAP conducted in the USA, England, Italy, and Germany SF residues were < 0.008 (8) mg/kg. F^- residues were: 1.8, 2.0, 2.0, 2.0, 2.2, 2.2, 2.2, 2.4, 2.8, 3.6, 5.5, 6.2, 7.0, 7.3, 7.6, 7.9, 8.4, 11, and 15 mg/kg.

Wheat

In 52 trials matching USA GAP conducted in the USA, England, Italy, and Germany, SF residues in ranked order, were: < 0.008 (13), 0.01(3) and 0.03(2) mg/kg. F^- residues in ranked order were: 1.5, 1.8, 1.9(2), 2.0(3), 2.1(2), 2.2(2), 2.4, 2.6, 2.7, 2.9(2), 3.3, 3.4, 3.8, 3.9(2), 4.2, 4.5, 4.7, 4.8(3), 4.9, 5.0, 5.7, 5.8, 5.9, 6.1, 6.2, 9.2(2), 12 and 14(2) mg/kg.

The Meeting noted that maize, rice, and wheat along with barley and oats represent major commercial cereal grain commodities. Since residues of sulfuryl fluoride and fluoride ion among the five cereal commodities are comparable (< 0.008–0.03 mg/kg for sulfuryl fluoride, and 0.8–21 mg/kg for fluoride ion), a group MRL and STMR may be estimated for cereal grains. Overall, a total of 44 SF residues in ranked order, were: < 0.008 (36), 0.01(3), 0.02(2) and 0.03(3) mg/kg. A total of 92 F^- residues in ranked order were: 0.8, 0.9, 1.0, 1.2, 1.3, 1.4(4), 1.5(2), 1.6, 1.7, 1.8(2), 1.9(3), 2.0(6), 2.1(2), 2.2(5), 2.3(3), 2.4(2), 2.6, 2.7, 2.8(3), 2.9(2), 3.1, 3.3, 3.4, 3.6, 3.8, 3.9(2), 4.2, 4.5, 4.7, 4.8(2), 4.8, 4.9, 5.0, 5.5, 5.7, 5.8, 5.9, 6.1, 6.2(2), 6.5, 7.0(2), 7.1, 7.3, 7.4, 7.5, 7.6, 7.9, 8.0, 8.3, 8.4, 9.2(3), 10, 11, 12(3), 14(3), 15, 18(2) and 21 mg/kg.

The Meeting estimated a maximum residue level of 0.05 mg/kg, an HR of 0.03 mg/kg, and an STMR of 0.008 mg/kg for sulfuryl fluoride; and estimated an HR of 21 mg/kg and an STMR of 3.5 mg/kg for fluoride ion for cereal grains.

Cereal grain milling fractions and milled cereal products

Maize flour

In trials matching USA GAP conducted in the USA, England, Germany, and Italy the SF residues were < 0.008 (2) mg/kg. F^- residues in ranked order were: 14, 19(2), 24, 37, 56 and 70 mg/kg.

Maize meal

Two trials were conducted in the USA at higher than USA GAP rate. SF residues were < 0.008 mg/kg; F^- residues were 5.6 and 6.3 mg/kg.

Rice bran

Two trials were conducted in the USA at higher than USA GAP rate. SF residues were < 0.008 mg/kg; F^- residues were 24.2 and 28.5 mg/kg.

Rice polished

Two trials were conducted in the USA at higher than USA GAP rate. SF residues were < 0.008 mg/kg; F^- residues were 1.5 and 1.6 mg/kg.

Wheat bran

In four trials matching USA GAP conducted in the USA the SF residues were < 0.008 mg/kg (4). F^- residues in ranked order were 34, 36 and 37(2) mg/kg.

Wheat flour

In 32 trials matching USA GAP conducted in the USA, England, Germany, and Italy, SF residues in ranked order were all < 0.008 (10) mg/kg. F^- residues in ranked order were: 15, 16, 19, 21, 22, 26, 26, 28, 29, 33, 34(2), 35, 37(2), 38(2), 40, 41, 43(2), 45, 51 and 55 mg/kg.

Wheat germ

In 20 trials matching USA GAP conducted in the USA, SF residues were all < 0.008 (10) mg/kg. F^- residues were: 17, 19, 42, 44, 54, 55, 59(3), 66, 72, 73, 82, 83, 84 (2) 88, 90 and 104 mg/kg.

Residue data was insufficient for estimating maximum residue levels and STMRs for rice bran, rice polished, maize starch, maize meal, maize grits, and rice bran individually. However, group MRLs and STMRs may be estimated for the members of the Codex commodity group's cereal grain milling fractions and milled cereal products, utilizing the data from rice bran and rice polished trials for milled cereal products; and maize flour, maize meal, wheat bran, wheat flour and wheat germ trials for cereal grain milling fractions.

Overall, a total of 30 SF residues in ranked order, were: < 0.008 (29) and 0.06 mg/kg. A total of 58 F^- residues in ranked order were: 3.9, 5.4, 5.6, 14, 15, 16, 17, 19(4), 21, 22, 24(2), 26(2), 28, 29, 33, 34(3), 35, 36, 37(5), 38(2), 40, 41, 42, 43(2), 44, 45, 51, 54, 55(2), 56, 59(3), 66, 70, 72, 73, 82, 83, 84(2), 88, 90.3 and 104 mg/kg. The Meeting estimated maximum residue levels of 0.1 mg/kg, HRs of 0.06 mg/kg, and STMRs of 0.008 mg/kg for sulfuryl fluoride in cereal grain milling fractions and milled cereal products; and estimated an HR of 104 mg/kg and a STMR of 37 mg/kg for fluoride in both cereal grain milling fractions and milled cereal products.

Dried Fruits

For fumigation of stored dried fruits and tree nuts commodities the US EPA specifies that the maximum cumulative CTP is 1500 g h/m^3 and the maximum cumulative CTP for vacuum fumigation is 200 g h/m^3. In practice, stored dried fruits can be treated as many as four times with fumigation at a

maximum cumulative CTP of 1500 g h/m^3. Sulfuryl fluoride residues reported in the following paragraphs were all from a 1 day PFI, analysed immediately after sample collection; F^- residues were the highest residues from each sample.

Dates

In two trials matching USA GAP conducted in the USA, SF residues were 0.007(2) mg/kg. F^- residues were not detected (< 2.4 mg/kg).

Figs

In two trials matching USA GAP conducted in the USA, SF residues were 0.03 and 0.04 mg/kg. F^- residues were < 2.4(2) mg/kg.

Dried plum

In two trials matching USA GAP conducted in the USA, SF residues were not detected (< 0.0042 mg/kg). F^- residues were also not detected (< 2.4 mg/kg LOQ).

Raisin

Eight post-harvest fumigation trials conducted in the USA were all at above GAP rates. SF residues were not detected (< 0.0042 mg/kg) (4) mg/kg. F^- residues were below the LOQ: < 2.2 mg/kg (2) and < 2.4(2) mg/kg.

Data was insufficient to estimate maximum residue levels or STMRs on each commodity individually; however, since residues of sulfuryl fluoride and fluoride ion on each commodity from limited fumigation trials are comparable and consistent (< 0.0042–0.04 mg/kg for sulfuryl fluoride, and < 2.2–< 2.4 mg/kg for fluoride ion), a crop group MRL and STMR may be estimated. SF residues from the four dried fruits were < 0.004 (6), 0.007(2), 0.03 and 0.04 mg/kg. F^- residues were: < 2.2(2) and < 2.4 (8) mg/kg. The Meeting estimated an MRL of 0.06 mg/kg, an HR of 0.04 mg/kg, and an STMR of 0.004 mg/kg for sulfuryl fluoride; and estimated an HR of 2.4 mg/kg and an STMR of 2.4 mg/kg for fluoride ion in dried fruits.

Tree Nuts

For fumigation of stored dried fruits and tree nuts commodities the US EPA specifies that the maximum cumulative CTP is 1500 g h/m^3 and the maximum cumulative CTP for vacuum fumigation is 200 g h/m^3. In practical terms, stored tree nuts can receive as many as four fumigation treatments at a maximum cumulative CTP of 1500 g h/m^3. Sulfuryl fluoride residues reported in the following paragraphs were all from a 1 day PFI, analysed immediately after sample collection; fluoride ion residues were the highest residues from each sample.

Almonds

In four trials matching USA GAP conducted in the USA, SF residues were 0.01, 0.02, 0.03, 0.04 mg/kg. F^- residues were: < 2.4(2), 4.3 and 5.0 mg/kg.

Pecans

In four trials matching USA GAP conducted in the USA, SF residues were: 1.1, 1.2, 2.3 and 2.5 mg/kg. F^- residues were < 2.4(2), 8.0 and 9.1 mg/kg.

Pistachios

In four trials matching USA GAP conducted in the USA, SF residues were: 0.01, 0.02, 0.27, 0.29 mg/kg. F^- residues were < 2.4(2) and 4.1(2) mg/kg.

Walnuts

In two trials at above USA GAP conducted in the USA, SF residues were 0.58 and 0.63 mg/kg. F^- residues were < 2.4(2) mg/kg.

Since residues of sulfuryl fluoride and fluoride ion on the four commodities tested are comparable (0.01–2.5 mg/kg for sulfuryl fluoride, and < 2.4–9.1 mg/kg for fluoride ion), a crop group MRL and STMR may be estimated. Overall, SF residues from the four tree nuts commodities, in ranked order, were 0.01(2), 0.02(2), 0.03, 0.04, 0.27, 0.29, 0.58, 0.63, 1.1, 1.2, 2.3 and 2.5 mg/kg. F^- residues from the four tree nuts commodities, in ranked order, were: < 2.4 (8), 4.1)2), 4.3, 5.0, 8.0 and 9.1 mg/kg. The Meeting estimated a maximum residue level of 3.0 mg/kg, an HR of 2.5 mg/kg and an STMR of 0.28 mg/kg for sulfuryl fluoride; and estimated an HR of 9.1 mg/kg and an STMR of 2.4 mg/kg for fluoride for tree nuts except coconuts.

Fate of residues in storage and processing

In storage

Sulfuryl fluoride rapidly degrades to fluoride under typical GAP conditions. No significant decline in the residue of fluoride was observed for the maize grain and wheat grain for 138 days, raisin and walnut for 141 days, and maize meal for 140 days of storage after treatment with sulfuryl fluoride. At present, sulfuryl fluoride is only registered for use on stored (i.e. post-harvest) food commodities. Sulfuryl fluoride is unstable and readily desorbs from the commodity or degrades under storage conditions, yielding fluoride and sulfate as the terminal residues.

In processing

Post-harvest fumigation on whole grain wheat and kernel maize was conducted to determine the fate of incurred residues of sulfuryl fluoride during the processing of the grain. Whole grain wheat and kernel maize were fumigated at 1787 mg·h/L and 1565 mg·h/L, respectively. The fumigated grain samples were then processed, and the control and treated processed samples, wheat flour, shorts, bran, middlings, impurities and germ, and maize flour, meal, grits, oil impurities, oil wet and starch (wet) were analysed. The LOQs were 0.6 mg/kg (fluoride) for whole wheat grain and maize grain; 0.3 mg/kg for wheat flour, shorts, middlings and impurities, maize meal, grits and oil; and 0.8 mg/kg for wheat germ and bran, and maize impurities; 0.4 mg/kg for maize starch; and 0.5 mg/kg for maize flour.

The processing of sulfuryl fluoride-fumigated whole grain wheat, containing fluoride ion at a concentration of 1.19 mg/kg, yielded flour, shorts, bran, middlings, impurities and germ containing fluoride at concentrations of 0.45, 1.50, 3.05, 0.72, 1.07, and 5.74 mg/kg, respectively. The elevated fluoride ion levels in wheat germ and wheat bran indicate that fluoride ion selectively accumulates in those grain fractions. The processing of fumigated whole grain maize, containing fluoride ion at a concentration of 1.76 mg/kg, produced flour, meal, grits and impurities containing fluoride ion at concentrations of 1.29, 1.37, 0.83, and 9.67 mg/kg, respectively. Thus, the maize impurities were the only fraction where it appears that fluoride ion concentrates.

Supervised fumigation trials conducted in food storage facilities on processed cereal grain commodities resulted in higher fluoride residues than those from processing studies, where the whole grains were fumigated and then processed. As a consequence, the higher residues values (HR) are derived from direct treatment rather than from the processing of the raw agricultural products, viz grains.

Farm animal feeding studies

No animal feeding studies were submitted.

Farm animal dietary burden

The Meeting considered the dietary burden for fluoride resulting from feeding treated commodities to dairy cattle and poultry. No animal dietary burden for sulfuryl fluoride could be estimated since no data was submitted.

Estimated maximum dietary burden of farm animals

Commodity	Group	HR (mg/kg)	Basis of residue	% Dry matter	Residue dw mg/kg	*Diet content (%)*			Residue contribution (mg/kg)		
						Beef cattle	*Dairy cows*	*Poultry*	Beef cattle	Dairy cows	Poultry
Barley-grain	GC	21	HR	88	23.9	*50*	*40*	*75*	12.0	9.6	17.9
Maize – whole kernel	GC	2.3	HR	88	2.6						
Oats	GC	14	HR	89	15.7						
Rice	GC	14.6	HR	88	16.6						
Wheat – whole grain	GC	14.3	HR	89	16.1						
Wheat-bran	CF	37.1	HR	88	42.2	*40*	*50*	*25*	16.9	21.1	10.6
TOTAL						*90*	*90*	*100*	28.9	30.7	28.5

Estimated median dietary burden of farm animals

Commodity	Group	Residue (mg/kg)	Basis of residue	% Dry matter	Residue, dw mg/kg	*Diet content (%)*			Residue contribution (mg/kg)		
						Beef cattle	*Dairy cows*	*Poultry*	Beef cattle	Dairy cows	Poultry
Barley-grain	GC	8.0	STMR	88	9.1						
Maize – whole kernel	GC	1.4	STMR	88	1.6						
Oats	GC	8.3	STMR	89	9.3	*50*	*40*	*80*	4.7	3.7	7.4
Rice	GC	3.6	STMR	88	4.1						
Wheat – whole grain	GC	3.9	STMR	89	4.4						
Wheat-bran	CF	36.1	STMR	88	41.0	*40*	*50*	*20*	16.4	20.5	8.2
TOTAL						*90*	*90*	*100*	21.1	24.2	15.6

The calculated dietary burden for estimation of maximum residue level was 28.9 ppm for beef cattle, 30.7 ppm for dairy cattle and 28.5 ppm for poultry. The calculated dietary burden of fluoride for estimation of STMR level was 21.1 ppm for beef cattle, 24.2 ppm for dairy cattle and 15.6 ppm for poultry. No recommendation for maximum residues level in animals could be made since adequate feeding studies were not submitted.

DIETARY RISK ASSESSMENT

Long-term intake

The evaluation of sulfuryl fluoride resulted in recommendations for MRLs and STMR values for raw and processed commodities. Data on consumption were available for 18 food commodities and were used to calculate dietary intake. The results are shown in Annex 3.

The IEDIs in the five GEMS/Food regional diets, based on estimated STMRs were 1% of the maximum ADI of 0.01 mg/kg bw. The Meeting concluded that the long-term intake of residues of sulfuryl fluoride from uses that have been considered by the JMPR is unlikely to present a public health concern.

The Meeting concluded that the dietary intake of fluoride associated with the use of sulfuryl fluoride as a fumigant (range of 7–15 mg/person/day across the five GEMS/Food regional diets) should be included in an overall assessment of fluoride from all sources. Upper levels for fluoride intakes have been proposed by a number of organizations. The dietary risk assessment for fluoride from fumigant use needs to be considered in light of the overall exposure to fluoride from other sources and FAO and WHO are requested to further investigate how this issue can be addressed at an international level.

Short-term intake

The IESTI of sulfuryl fluoride calculated on the basis of the recommendations made by the JMPR represented 0–3% of the ARfD (0.3 mg/kg bw) for children and 0–5% for the general population. The Meeting concluded that the short-term intake of residues of sulfuryl fluoride on commodities that have been considered by the JMPR is unlikely to present a public health concern.

4.21 TERBUFOS (167)

RESIDUE AND ANALYTICAL ASPECTS

Terbufos, a systemic nematicide and soil insecticide, was evaluated for the first time by JMPR in 1989. A further residue review was undertaken in 1990. At the 36th Session of the CCPR the compound was scheduled for a residue evaluation within the periodic review programme for 2005. The toxicological review was conducted in 2003, which established an ADI of 0.0006 mg/kg bw/day and an ARfD of 0.002 mg/kg bw/day.

The Meeting received information on identity; metabolism and environmental fate; analytical methods; relevant storage stability studies; use pattern; residues resulting from supervised trials on a number of crops including bananas, coffee beans, sugar beets, maize, sorghum, and sweet corn; residues in food in commerce and at consumption and national maximum residue limits.

List of terbufos and related metabolites:

Terbufos	*S-tert*-butylthiomethyl *O,O*-diethyl phosphorodithioate
Terbufos sulfoxide	*S-tert*-butylsulfinylmethyl *O,O*-diethyl phosphorodithioate
Terbufos sulfone	*S-ter*t -butylsulfonylmethyl *O,O*-diethyl phosphorodithioate

Terbufoxon	*S-tert*-butylthiomethyl, *O,O*-diethyl phosphorodithioate
Terbufoxon sulfoxide	*S-tert* -butylsufinylmethyl, *O,O*-diethyl phosphorodithioate
Terbufoxon sulfone	*S-tert*-butylsulfonylmethyl, *O,O*-diethyl phosphorodithioate

Animal metabolism

The Meeting received information on the fate of [methylene-^{14}C]terbufos in rats, lactating goats and laying hens dosed orally.

Studies on metabolism in *rats* were evaluated by the WHO Expert Group of the 2003 JMPR, which concluded that absorption of single doses of ^{14}C-labelled terbufos was rapid and fairly complete. Most of the radiolabel was excreted within 24–48 h. Excretion was primarily by the urinary route (about 70–80% of the administered dose). Terbufos was extensively metabolized and little radioactivity was found in the tissues. Sulfoxidation and desulfuration of terbufos is followed by hydrolysis of the thiolophosphorus bond, enzymatic *S*-methylation and then additional *S*-oxidation. On the basis of a 14-day study of repeated doses, terbufos showed little potential for accumulation.

[Methyllene-^{14}C]terbufos at doses equivalent to 0.281 and 2.53 mg/kg body weight, were administered via capsule to two *lactating goats* separately, i.e., one dose regime per goat. Each goat was dosed once daily for seven consecutive days. The major route of excretion was via the urine, which accounted for 96.0 and 86.9% of the administered radioactivity respectively. The main metabolic pathway in lactating goats and rats is qualitatively similar, thus suggesting a common metabolic pathway. Neither terbufos nor any of the phosphorylated oxidative metabolites – sulfoxide, sulfone, oxygen analog and its sulfoxide and sulfone – were observed in milk. None of the phosphorylated oxidative metabolites were detected in tissues. However, terbufos (parent) was observed at low concentrations in liver (< 0.01 mg/kg eq) and in kidney (< 0.01 mg/kg eq).

The total radioactive residue (TRR) in daily milk samples were < 0.01 mg/kg eq (low dose, 0.28 mg/kg eq in diet, day 7) and 0.02-0.03 mg/kg eq (high dose, 2.53 mg/kg eq in diet, day 7). Residues in the liver, kidney, muscle and fat of the low dose animal were all < 0.01 mg/kg eq. In the high dose animal, residues were 0.08, 0.04, < 0.01 and < 0.01 mg/kg eq, respectively.

Two groups of *laying hens* were dosed via capsules with [methyllene-^{14}C]terbufos for five consecutive days with the feed equivalent of 0.35 ppm for one group (Group B) and an exaggerated level of 1.05 ppm equivalent for the second group (Group C). Recovery of [^{14}C] residues in excreta over the 5-day treatment period averaged 91.4% of the total administered dose for the 1st group, and 88.9% for the 2nd group. For both dose levels, residues in eggs (days 1 through 5, both white and yolk), skin with adhering fat, muscle, liver or kidney tissues were all less than the LOQ of the radioassay (< 0.05 mg/kg eq).

The results of the hen study showed that terbufos when orally ingested at highly-exaggerated levels does not give rise to residues in the eggs or edible tissues of the laying hen.

Plant metabolism

The Meeting received information on the metabolic fate of [^{14}C]terbufos in soybeans, sugar beet, sweet corn, cabbage and rape seed.

Soybean plants were grown under field conditions from seed treated in the furrow at a rate of 1.1 kg ai/ha with [methylene-^{14}C]terbufos. The TRR levels found in the plant, expressed as terbufos

equivalent, were 13.3 and 1.5 mg/kg in plants at one and two months after treatment, respectively. At harvest, residue levels were 1.8 mg/kg in fodder, 1.6 mg/kg in hulls and 1.3 mg/kg in the seed.

At the one-month sampling, 43% of the total extractable residue was identified as the phosphorylated metabolites: sulfoxide, sulfone, oxygen analog sulfone, and oxygen analog sulfoxide. The non-phosphorylated metabolites accounted for 11% of the residue. The remaining residue was comprised of five unknown metabolites (4%) and origin-bound compounds (17%). At harvest only non-phosphorylated metabolites were identifiable at low (< 10%) levels in all three commodities, i.e., hulls, fodder and seed. The remaining residue was shown to be very polar extractable materials or to have the ^{14}C incorporated into the cellulose and lignin of the hulls, fodder and protein and oil of the seed.

In conclusion, soybean seedlings can readily take up terbufos applied to the soil. The absorbed compound is then translocated and metabolized by oxidation, hydrolysis, methylation and subsequent oxidation to eventually yield principally non-phosphorylated, non-toxic metabolites.

In *sugar beet* metabolism studies, plants were grown from seed in soil treated with [methyllene-^{14}C]terbufos at a rate of 6.8 kg ai/ha. The levels of radioactivity in both foliage and roots were determined at 4.5, 8, l6, and 32 weeks after treatment. The TRR levels found in the various samples declined with time from 6.27 to 1.07 mg/kg eq in foliage and from 7.44 to 0.284 mg/kg eq in roots. The levels of ^{14}C recovered in all plants represented a total of only 2.3% of the applied dose. The data showed that metabolism of terbufos occurred at a faster rate in the roots. Chromatographic data obtained at different stages of plant growth indicated that terbufos is degraded mainly by way of oxidation, hydrolysis and methylation followed by subsequent oxidation to yield principally non-phosphorylated, non-toxic metabolites.

There is also evidence of incorporation of terbufos-derived radioactivity into the sucrose fraction of sugar beets.

In *sweet corn* metabolism studies, corn was grown in metal cylinders contained in greenhouses and treated with [methylene-^{14}C]terbufos at 1.1 kg ai/ha. Sweet corn contained 0.34, 2.64, 4.70 and 6.85% of the applied dose at 2, 4, 7 and 10 weeks of growth. The identified phosphate esters found as metabolites in sweet corn accounted for about 89% of the radioactivity. Levels of ^{14}C extracted from plants were separated into at least 19 radioactive metabolites using thin layer chromatography (TLC). The expected oxidation products of terbufos, i.e., the sulfoxide, the sulfone, the oxygen analog of sulfoxide and sulfone, were confirmed to be present as residues in the corn plants. In the corn plants sampled at 10 weeks the phosphorylated metabolites, terbufos sulfoxide (8.1 mg/kg eq), terbufos sulfone (2.8 mg/kg eq), terbufoxon (0.3 mg/kg eq), terbufoxon sulfoxide (16.9 mg/kg eq) and terbufoxon sulfone (5.6 mg/kg eq) accounted for 34% of the chloroform-soluble extractable radioactivity. A significant amount of the total hydrophilic radioactivity could be in the form of natural products.

In the *cabbage* metabolism study, plants were grown in a greenhouse and externally from seed in soil treated with [methyllene-^{14}C]terbufos at a rate of 2.2 kg ai/ha, using both a 15-G granular formulation and a liquid concentrate. The levels of radioactivity found in the cabbage plants, expressed as mg/kg equivalent of terbufos, declined with time (4 to 16 weeks) from 3.93 to 0.09 mg/kg eq for external granular treatment, from 1.48 to 0.04 mg/kg eq for the external liquid treatment and from 1.71 to 0.07 mg/kg eq for the greenhouse liquid treatment. The absolute amounts of radioactivity (in μCi) recovered in plants did not vary much with time. The recovered radioactivity represents a maximum of 1.5% of the total applied dose. At the end of 12 weeks, 92% (0.07 to 0.22 mg/kg eq) of the total radioactivity consisted of unidentified water-soluble metabolites and the total amount of phosphate compounds were less than 0.01 mg/kg eq. There was no apparent metabolic difference between granular (15-G) or liquid-treated soil in developing cabbage. The metabolism of terbufos in cabbage is similar to that reported for sugar beet.

In a *rape* metabolism study, rape seed was grown in soil treated with [methylene^{14}C]terbufos in the furrow at 0.28 kg ai/ha. The total residual radioactivity in rape plants expressed as parent was 0.63 and 0.68 mg/kg eq for 1 and 2 month post-treatment samples respectively. Residues were 0.42 mg/kg eq in the 2 month hulls sample. At harvest (3-months post treatment), the residue levels in fodder, hull and seed were 3.21, 3.63 and 1.11 mg/kg eq, respectively. The extractable radioactivity from the 1-month old rape plant was 90%, of which 48% was organosoluble and 42% was aqueous soluble. By two-dimensional TLC analysis, about 16.3% of the radioactive organosolubles migrated away from the plate origin and the remaining 31.7% of the radioactivity stayed at the origin. Among the migrating radiocomponents, non-phosphorylated compounds predominated with 4.9%, terbufoxon sulfoxide accounted for 4.0% and non-phosphorylated compounds and terbufos sulfoxide contributed to 1.7 and 1.3% of the resolved organoextractables respectively. The remaining 4.4% of the migrating radioactivity was made up of at least 6 minor components.

Rape plants can readily take up terbufos and closely related metabolites from the soil. The absorbed compounds are then initially metabolized in plant tissues by way of oxidation to phosphorylated metabolites such as terbufos sulfoxide and terbufoxon sulfoxide. These oxidized products degrade further through hydrolysis, methylation and subsequent oxidation thus leading to the formation of certain non-phosphorylated metabolites. In rape seeds, the hexane fraction comprised of 22% of the radioactivity which was probably associated with fatty acids or lipid-type compounds. The acetonitrile fraction, accounting for about 12%, mainly consisted of oil-related compounds and a non-phosphorylated compound along with trace amounts of several other minor components., The hydrolysis study indicated that incorporation of [^{14}C]formaldehyde or $^{14}CO_2$, derived from [^{14}C]terbufos, into natural products of various rape tissues accounts for a very large fraction of the radioactivity present in the plants or seeds.

In conclusion, the metabolic pathway for the formation of observed metabolites arises from sulfoxidation and desulfuration of terbufos, hydrolysis of the thiol-phosphorous bond (S=P), enzymatic *S*-methylation and finally *S*-oxidation. The studies evaluated show that the same oxidative phosphorylated metabolites of terbufos occur in plants and in animals. In addition, terbufos has been shown to be taken up by the roots, with the residues and metabolites translocated to all parts of the plants examined.

Environmental fate

The Meeting received information on aerobic degradation in soil, hydrolysis rates and products and a confined rotational crop study.

Degradation in soil (aerobic)

The metabolic fate of terbufos in soil was investigated in silt loam soil under aerobic conditions using [methylene-^{14}C]terbufos. The half-life of terbufos was approximately 5 days and of the total terbufos related residues was approximately 100 days. Major degradation products were carbon dioxide and the oxidative metabolites terbufos sulfoxide and terbufos sulfone. The concentration of terbufos sulfoxide in soil increased rapidly to a maximum of 2.6 mg/kg eq (52% of the applied dose) after 30 days and then declined to 0.3 mg/kg eq (6% of dose) after one year. Terbufos sulfone residues increased slowly to a maximum level of 1.0 mg/kg eq (20% of applied dose) at 60-days and then decreased to 0.1 mg/kg eq (2.3% of dose) after one year.

Hydrolysis rate and products

Terbufos hydrolyses rapidly under abiotic conditions at environmentally relevant temperatures and would not be expected to persist in aquatic systems. Hydrolysis of terbufos sulfoxide and terbufos sulfone occurs more slowly, but the des-ethyl derivatives that formed are not expected to be of toxicological concern.

Confined rotational crop study

Residues of terbufos and related compounds were determined in soil and rotational crops (cabbage, red beets, and wheat) from a treated corn field. In the study in Wisconsin, corn was planted in a silt loam soil and treated at planting with 2.24 kg ai/ha. Residues of terbufos and related compounds were less than the LOQ of the method (0.05 mg/kg) in all cabbage, red beet and wheat grain samples. Wheat straw contained residues of 0.1 mg/kg. The soil half-life of terbufos and related compounds was calculated to be 30 days.

In another study conducted in Nebraska, corn planted in silt loam soil was treated at planting by soil incorporation with terbufos at the rate of 2.24 kg ai/ha. Residues of terbufos and related compounds were less than the LOQ of the method (0.05 mg/kg) in all cabbage, sugar beet and wheat grain samples. Spring wheat forage contained residues of 0.15 mg/kg. No residues were detected in winter wheat straw and grain. The soil half-life of terbufos and related compounds was calculated to be 17 days in beet plots, 16 days in cabbage plots, and 10 days in wheat plots.

Methods of analysis

The Meeting received information on validated methods of analysis of terbufos in plant matrices, animal matrices and environmental samples that were used in supervised trials, rotational crops studies and storage stability studies. Enforcement methods and multiresidue methods of analysis were also submitted to the Meeting.

Several analytical methods have been developed for the determination of terbufos in plant commodities and animal tissues, suitable for data collection and enforcement. All analytical methods for terbufos residues are designed to extract parent terbufos and its oxygenated metabolites: terbufos sulfoxide, terbufos sulfone, terbufoxon and terbufoxon sulfoxide. Terbufos and its metabolites are oxidized to the common moiety terbufoxon sulfone using m-chlorobenzoic acid, which is then analysed by gas chromatograph equipped with a phosphorus-selective detector. The methods vary slightly, usually in the extraction solvent used.

In plant samples, the LOQ for most of the reported trials was 0.05 mg/kg, but limits for some methods/substrates were 0.01 or 0.005 mg/kg. Recoveries of terbufos and its related metabolites were tested over the concentration range of 0.01–1.0 mg/kg on samples from all plant commodities reported in the trials.

In animal tissue samples, the LOQ for the milk is 0.005 or 0.01 mg/kg, for the tissue, 0.05 mg/kg, and for eggs, 0.01 mg/kg. Recoveries of terbufos and its related metabolites were tested on the samples over the concentration range of 0.005–1.0 mg/kg.

An adequate method is available for enforcement of terbufos MRLs in or on plant commodities. The GC method for determining terbufos and its phosphorylated metabolites is described in the Pesticide Analytical Manual (PAM), Vol.II as Method I modified by Method M-1754 substituting acetone for benzene and dichloromethane for chloroform.

Terbufos and its metabolites were taken through the US FDA Multiresidue Method with limited success.

Stability of pesticide residues in stored analytical samples

The stability of terbufos residues has been determined in freezer storage stability studies (from < 0 to -10ºC or -17ºC) in the representative plant commodities of corn (grain, plants and straw); sugar beet (tops and roots); and banana (unpeeled and pulp). Terbufos residues fortified in representative crop samples (root, grain, watery and oily commodities) were shown to be stable in frozen storage for approximately 18 months.

The stability of terbufos residues in milk (1.7–3.3ºC) has been determined and 79% of the residues were recovered after 14 days.

No stability studies were submitted to the Meeting on other animal matrices.

Definition of the residue

Metabolic studies on animals and plants have demonstrated that terbufos is metabolized in much the same way in all the biological systems studied. The decrease in the parent compound is accompanied by a short-term build-up of the sulfoxide and sulfone metabolites. The corresponding oxygen analogues are also formed, but at a much slower rate. Cleavage of the P=S bond yields, after methylation of the resulting thiol, a series of methylated metabolites differing in the oxidation state of the sulfur atoms.

Terbufos and all oxidation products are considered potent anticholinesterase agents.

Terbufos is readily metabolized in both plant and animal tissues by way of oxidation, hydrolysis and methylation which is then followed by further oxidation to principally non-toxic metabolites.

All analytical methods used to determine terbufos residues are designed to extract parent terbufos, and its oxygenated metabolites terbufos sulfoxide, terbufos sulfone, terbufoxon, and terbufoxon sulfoxide.

The Meeting confirmed the previous (JMPR 1989) residue definition for terbufos, both for enforcement and for risk assessment and for both animal and plant commodities as follows:

The sum of terbufos, its oxygen analogue and their sulfoxides and sulfones expressed as terbufos.

Although terbufos has a log k_{ow} of 4.71 based on the parent terbufos, the total residue of terbufos and related metabolites are not considered fat soluble.

Results of supervised trials on crops

Supervised residue trials were available for bananas, sugar beets, sweet corn, cereal grains (maize and sorghum); coffee beans, fodder and forage of cereal grains (maize and sorghum); and miscellaneous forage and fodder crops (sugar beet tops). A large number of trials were submitted from the 1970s based on analytical methods with an LOQ of 0.05 mg/kg. More recent trials were provided which had an improved LOQ of 0.01 and were used in estimating residues and establishing MRLs. In cases of finite residues, then relevant data from trials with an LOQ of 0.05 were considered acceptable to include in the data set. Supervised trials on the remaining commodities that currently have CXLs were not provided. The Meeting decided to withdraw the current recommendations for broccoli, cabbages (head), mustard seed, onion (bulb), peanut, peanut fodder, peanut forage (green), popcorn, rape seed, rapeseed oil (crude), soy beans (dry); straw and fodder of cereal grains, sugar beet fodder and wheat.

In situations where residues from supervised trials from GAP show nil residues, the MRL was chosen to reflect a level of sensitivity that is compatible with enforcement activities. Where analytical methods applied had different LOQs, the lowest value was chosen only if the nil residue could be expected. In this case, the High Residue value would be recommended at the highest LOQ used in the study unless a majority of the observations were derived from the more sensitive LOQ.

In situations where supervised trials from GAP showed nil residues, even at exaggerated rates, the MRL was chosen to reflect an LOQ that is compatible with enforcement activities. However, both the STMR and high residue values were recommended at zero.

Banana

Thirty six field trials were submitted to the Meeting from banana producing areas of the world including Australia, Costa Rica, Ecuador, Honduras, Panama, Philippines and Mexico. In the trials 100 g ai/kg (10G) or 150 g ai/kg (15G) granule (G) terbufos was applied to the soil at the base of daughter banana plants at 1-9 g ai/plant/application. Application rates varied with a maximum rate of application per plant per year at of 41 g ai. GAP application rates ranged from 2-4 g ai/plant with a maximum of 12 g ai/year in Australia and Central America, 2 g ai/plant with a maximum of 8 g ai/year in Philippines and 3 g ai/plant to the maximum of 9 g ai/year in Mexico. No PHI was specified in the various national GAPs.

Residue levels ranged from <LOQ (< 0.01 or < 0.002) to 0.03 mg/kg for those trials where substantially exaggerated rates (2-3 times GAP) were applied. However, the majority of the trials did not conform to GAP. The residues from trials that were conducted according to GAP were $\underline{< 0.01}$(6) and 0.02(2) mg/kg.

The Meeting estimated a maximum residue level for bananas of 0.05 mg/kg, and STMR of 0.01 mg/kg and a HR of 0.02 mg/kg.

Sugar beets (roots)

Field trials involving at-planting and post-emergence treatments with terbufos were made available to the Meeting from the USA. The trials were conducted during the 1986, 1989 and 1994 growing seasons. In 1986, terbufos (15G) was applied at planting (banded, knifed-in, or in-furrow) at 2.2 kg ai/ha. In the trials conducted in 1989, terbufos (15G) was knifed in as a band at planting at 4.9 kg ai/ha, in excess of the current USA GAP. Residues reflecting GAP were < 0.01(6) and 0.01(2) mg/kg where the PHI was considered equivalent to GAP, i.e., from 91-141 days.

In more recent field trials (1994), terbufos (15G) was applied as a band over the row to sugar beets at 2.2 to 2.4 or 4.4-4.9 kg ai/ha. The lower rate reflects the maximum GAP rate. Again, residues reflecting GAP were < 0.01(5) mg/kg. The PHI was considered equivalent to GAP at 90 days.

For knifed-in applications data was available at only 2 times the GAP rate where low finite residues could be found in some cases (< 0.01, 0.01, 0.02 and 0.03). Another knifed-in application trial had residues at < 0.01. The PHI for these trials ranged from 139-180 days (GAP is 150 days).

For all trials conducted according to GAP, total terbufos-related residues were: < 0.01(11) and 0.01(2) mg/kg.

The Meeting withdrew its previous recommendation of 0.1 mg/kg and estimated a maximum residue level for sugar beets of 0.02 mg/kg, an STMR of 0.01 mg/kg and a highest residue of 0. 01 mg/kg.

Sweet corn kernels and corn-on-the-cob

Field trials involving at-planting and post-emergence treatments with terbufos were made available to the Meeting from the USA. In trials from 1972–1974, terbufos granules were applied in the furrow or in a band at the time of planting at rates of 1.1 to 9.0 kg ai/ha. In 1986 terbufos granules were applied to the soil at planting (in furrow or in a band), at post-emergence or at cultivation at a combined rate of about 6.0 kg ai/ha. GAP in the USA for 15G or 20G (200 g ai/kg) terbufos formulations is at a maximum rate of 1.5 kg ai/ha applied once at planting, post-emergent, or at cultivation. For post-emergent applications, the PHI is 30 days for forage, and 60 days for corn-on-the cob.

For post-emergent use, samples were analysed only where the PHI was less than that for GAP. Residue values from the majority of trials (7) were lower than the LOQ (0.01 mg/kg). For two trials, where the equivalent of three times the GAP rate was applied in two applications, residues found were 0.01 mg/kg (2).

The Meeting withdrew its previous recommendation of 0.01 (*) mg/kg and estimated a maximum residue level for sweet corn of 0.01(*) mg/kg, an STMR of 0.01 mg/kg and a HR of 0.01 mg/kg.

Cereal grains

Maize grain

Field trials involving at-planting and post-emergence treatments with terbufos were made available to the Meeting from the USA. GAP in the USA for terbufos 15G or 20G formulations is at the maximum rate of 1.5 kg ai/ha applied once at planting, post-emergent, or at cultivation. A PHI of 30 days is required for forage if applied post-emergent. In trials conducted from 1981 to 1986, terbufos granules were applied to the soil at planting, either in furrow or as a band, at the rate of 1.1 to 1.8 kg ai/ha. In some trials, additional plots were treated with terbufos at rates up to five times the recommended label rates. In trials conducted from 1990 to 1996 terbufos granules were applied post-emergent at the recommended rate of 1.5 kg ai/ha as well as at higher rates up to five times the recommended application rates.

In all the trials conducted on maize grain according to GAP, total terbufos-related residues were below the LOQ of the analytical method: < 0.01 mg/kg (13). In trials where higher rates of application or more than one application was made, the residue levels were also below the LOQ. Since there were finite residues found in the trials for sweet corn at exaggerated rates, the use pattern for maize grain is not considered a nil residue situation and relevant values for STMR and HR have been proposed.

The Meeting confirmed its previous recommendation for a maximum residue level of 0.01(*) mg/kg and estimated an STMR of 0.01 mg/kg and a highest residue of 0.01 mg/kg for maize.

Sorghum grain

Field trials involving at-planting and post-emergence treatments with terbufos were made available to the Meeting from the USA. GAP in the USA for terbufos 15G or 20G formulation consists of a maximum rate of 2.0 kg ai/ha applied once with a PHI of 50 days for forage, and 100 days for grain and fodder.

Results of all trials conducted according to the GAP for sorghum grain, including post emergent applications, showed total terbufos-related residues below the LOQ: < 0.01 mg/kg (5). Residues were at non-detectable levels even in trials where higher rates of application or shorter PHI 58-76 days (6 trials) were used.

The Meeting estimated a maximum residue level for sorghum grain of 0.01(*) mg/kg, an STMR of 0.

Coffee beans

Residue trials were conducted during 1982–1988 in Costa Rica, Guatemala, and El Salvador.

In field trials in Costa Rica conducted in 1982–1983, a 10G granular formulation of terbufos was applied to the soil at the base of established coffee plants at the rate of 0.75–7.5 g ai/plant. Berries were collected from treated plants at various intervals, field dried according to common practice, and the outer shell removed from the dried beans.

In the trials in El Salvador and Guatemala (1988), terbufos (10G) was band applied to plants after flowering but before bean formation, at the rate of 1 or 5 g ai/plant. From treated plants field dried berries, with outer shell removed, were collected at 38–56 days in El Salvador and at 163-197 days in Guatemala.

GAP in coffee bean plantations permits the application of terbufos at a maximum rate of 1.1g ai/plant for up to 2 applications with a PHI of 60 days. No trials were conducted at the maximum GAP. However, residue levels were below the LOQ (< 0.05 mg/kg) in all coffee bean samples (10) collected 58–120 days after treatment with terbufos at 0.75–7.75 g ai/plant rate. At one site, where coffee beans had been treated with 3.75 and 7.5 g ai/plant and shorter than GAP PHI of 60 days (47 or 35 days after treatment), maximum residues of 0.12 and 0.17 mg/kg respectively, were found. Residues declined to < 0.05 mg/kg at the next sampling interval, 124 or 53 days post-treatment.

The Meeting confirmed its previous recommendation for a maximum residue level of 0.05 (*) mg/kg and estimated an STMR of 0.05 mg/kg for coffee beans.

Animal feed commodities

Fodder and forage of cereal grains

As maize forage, sorghum forage and sugar beet tops are not moving in international trade the Meeting made no recommendations regarding maximum residue levels for these commodities.

Maize forage and fodder

The GAP for terbufos 15G or 20G formulation in the USA allows for a maximum application rate of 1.5 kg ai/ha applied once either at-planting, early post-emergence, or at cultivation. A PHI of 30 days is required for forage when applied post-emergent. The same GAP applies to both maize and sweet corn. Trials on maize and sweet corn for residues in fodder and forage were conducted in the USA during 1972–1990. Terbufos granules were applied to the soil either in-furrow or in a band during planting at the rate of 1.1–5.8 kg ai/ha. In a few trials, tests were performed where two applications were made to maize one at planting and a second treatment 5–6 weeks after planting.

The residues deriving from trials conducted in sweet corn and maize were found to represent similar populations which could be combined (Mann-Whitney U-test). Residues, on a fresh weight basis, from trials conducted according to GAP were, with median underlined, <u>< 0.05</u> (11), 0.07(2), 0.14, 0.16, 0.17, 0.23, 0.32 and 0.96 mg/kg. The highest residue value (HR) was 0.96 mg/kg from trials in Colorado, USA from forage samples taken 90 days after treatment at planting at a rate of 1.5 kg ai/ha. Applying the default percent dry matter content (average between %DM of sweet corn forage and field corn forage, as listed in the *FAO Manual* (FAO, 2002) for maize forage (44%)), the highest residue on dry weight basis is estimated as 2.2 mg/kg.

The Meeting withdrew its previous recommendation of 1 mg/kg and estimated an STMR of 0.10 mg/kg and a highest residue of 2.2 mg/kg for maize forage.

Residue levels from trials according to GAP for maize fodder were: < LOQ i.e., < 0.05(38) and 0.08 mg/kg (from one trial in Colorado, USA, sampled at harvest after treatment at the rate of 1.5 k ai/ha at planting). Applying the default percent dry matter value of 83% for corn fodder, as listed in the *FAO Manual* (FAO, 2002), the highest residue on dry weight basis was calculated as 0.10 mg/kg.

The Meeting withdrew its previous recommendation of 0.1 mg/kg and estimated, on a dry weight basis, a maximum residue level of 0.2 mg/kg, an STMR of 0.06 mg/kg and a highest residue of 0.10 mg/kg for maize fodder.

Sorghum forage and fodder

Supervised trials on sorghum were conducted during 1978–1996. In the 1996 trials, terbufos granules were applied post-emergent, at the rate of 2.1 or 2.2 kg ai/ha. Forage samples were harvested 48 to 72 days after treatment while fodder samples were taken at normal grain harvest time, 88 to 90 days after treatment. In the rest of the trials (1978–1991), terbufos granules were applied at planting, at the GAP rate (2 kg ai/ha) and at twice that rate (4–4.3 kg ai/ka).

All trials according to the GAP resulted in residues below the LOQ for sorghum forage (≤ 0.05 mg/kg), except one trial (Louisiana, USA) where a level of 0.07 mg/kg was recorded. This highest residue value was from forage samples taken 50 days after treatment with terbufos at a rate of 2.0 kg ai/ha at the vegetative stage. The moisture content of samples was only determined from some trials with the results showing wide variations. The Meeting therefore decided to use the default percent dry matter for sorghum forage (35%), as listed in the *FAO Manual* (FAO, 2002) to estimate the highest residue value.

The Meeting estimated an STMR for sorghum forage, on a dry weight basis, of 0.14 mg/kg and a highest residue of 0.20 mg/kg.

Residue levels in sorghum fodder ranged from < 0.05 to 0.19 mg/kg. Residues from trials conducted according to GAP were < 0.05 (12), 0.12 and 0.19 mg/kg. The highest residue value was 0.19 mg/kg from trials where fodder samples were taken 88 days after a post-emergent treatment at a rate of 2.2 kg ai/ha. Applying the default percent dry matter for sorghum fodder/stover of 88%, as listed in the *FAO Manual* (FAO, 2002), the highest residue on dry weight basis was estimated as 0.22 mg/kg.

The Meeting estimated, on a dry weight basis, a maximum residue level of 0.3 mg/kg, an STMR of 0.057mg/kg and a highest residue of 0.22 mg/kg for sorghum fodder.

Sugar beet tops

Field trials were conducted in the USA and Canada during 1971–1975 in which terbufos (15G) was either applied in-furrow or banded at 1.0 to 2.5 kg ai/ha or at exaggerated rates of 4.0–12.3 kg ai/ha. Several trials were also conducted which consisted of sequential at-planting and post emergence banded applications, typically utilizing exaggerated rates.

Several trials were also conducted in the USA during the 1989 growing season in which terbufos (15G) was knifed in at-planting at 4.9 kg ai/ha. Samples were harvested by hand at maturity, 150–180 days after treatment. Residues found in all control samples of tops were < 0.05 mg/kg.

In US field trials in 1994, terbufos (15G) was applied as a band over the row to sugar beets at the maximum GAP rate of 2.2 to 2.4 kg ai/ha and at 2× GAP rates of 4.4 to 4.9 kg ai/ha. Residue levels ranged from < LOQ (0.01 or < 0.05) to 0.82 mg/kg for sugar beet tops samples. Residues found from trials conducted according to GAP were < 0.01(3), 0.01, 0.04, ≤ 0.05 (18), 0.12, 0.15 and 0.82 mg/kg. The highest residue value (HR) found was 0.82 mg/kg, from samples taken 91 days following an at-planting treatment of 1.8 kg ai/ha Applying the default percent dry matter for sugar beet tops (23%), as listed in the *FAO Manual* (FAO, 2002), the highest residue on dry weight basis was estimated as 3.57 mg/kg.

The Meeting withdrew its previous recommendation for a maximum residue level of 1 mg/kg for fodder beet leaves or tops and estimated, on a dry weight basis, an STMR of 0.22 mg/kg for sugar beet tops and a highest residue of 3.6 mg/kg.

Dietary burden in farm animals

The Meeting estimated the dietary burden of terbufos residues in farm animals on the basis of the diets listed in Appendix IX of the *FAO Manual* (FAO, 2002). One feed commodity from each Codex Commodity Group was used. Calculation from the HR values provides the concentrations in feed suitable for estimating MRLs for animal commodities, while calculation based on STMR values for feed is suitable for estimating the STMR values for animal commodities.

Estimated maximum dietary burden of farm animals

Commodity	CC	Residue (mg/kg)	Basis	DM (%)	Residue, dry wt. (mg/kg)	*Diet content (%)*			Residue Contribution (mg/kg)		
						Beef cattle	*Dairy cows*	*Poultry*	Beef cattle	Dairy cows	Poultry
Maize forage	AF	0.96	highest residue	44%	2.2	*40%*	*50%*	*NU*	0.88	1.1	
Maize fodder	AS	0.08	highest residue	83%	0.10			*NU*			
Maize grain	GC	0.01	highest residue	88%	0.011	*40%*	*40%*	*80%*	0.004	0.004	0.009
Sorghum	GC	0.0	highest residue	86%	0			*20%*			0
Sorghum forage	AF	0.07	highest residue	35%	0.20			*NU*			
Sorghum fodder	AS	0.19	highest residue	88%	0.22			*NU*			
Sugar beet tops	AV	0.82	highest residue	23%	3.60	*20%*	*10%*	*NU*	0.72	0.36	
TOTAL						*100%*	*100%*	*100%*	1.60	1.47	0.009

Estimated median dietary burden of farm animals

Commodity	Codex group	Residue (mg/kg)	Basis	DM (%)	Residue, dry wt. (mg/kg)	Diet content (%)			Residue Contribution (mg/kg)		
						Beef cattle	Dairy cows	Poultry	Beef cattle	Dairy cows	Poultry
Maize forage	AF	0.05	STMR	44%	0.10	40%	50%	NU	0.04	0.05	
Maize fodder	AS	0.05	STMR	83%	0.06			NU			
Maize grain	GC	0.01	STMR	88%	0.011	40%	40%	80%	0.004	0.004	0.009
Sorghum	GC	0.0	STMR	86%	0.0			20%			0
Sorghum forage	AF	0.05	STMR	35%	0.14			NU			
Sorghum fodder	AS	0.05	STMR	88%	0.057			NU			
Sugar beet tops	AV	0.05	STMR	23%	0.22	20%	10%	NU	0.044	0.022	
TOTAL						100%	100%	100%	0.088	0.076	0.009

The highest residues or STMR values for feed commodities were used in calculating the worst-case dietary burden for dairy cows, beef cattle and poultry while the STMR values were used in the estimation of the median dietary burdens. The respective dietary burdens were then compared with the results of the feeding studies at various dose levels (mg/kg in diet) to estimate the maximum residue levels and STMR in animal commodities.

The dietary burdens of terbufos for estimates of STMR and highest residue level values in animal commodities (residue levels in animal feeds expressed as dry weight) are 0.088 mg/kg and 1.60 mg/kg for beef cattle, 0.076 mg/kg and 1.47 mg/kg for dairy cows and 0.009 mg/kg and 0.009 mg/kg for poultry.

Farm animal feeding studies

Feeding studies indicated that at a dose (2ppm for 21 days) approximately equivalent to the calculated animal diets, no residues (< 0.05 mg/kg) of terbufos or its metabolites were detectable in cattle tissues and milk. In another study, done at an exaggerated rate (50 ppm), only one milk sample had a finite residue (0.011 mg/kg) while one sample had residue at the LOQ (0.005 mg/kg) and the rest were below the LOQ.

The Meeting received a feeding study in poultry. Hens were fed at 2 ppm terbufos for 21 days and residues were determined in poultry tissues and eggs. The LOQ was 0.05 and 0.01 mg/kg for tissues and eggs, respectively. All tissues and eggs samples contained residues below the LOQ value.

Maximum residue levels

The estimated maximum dietary burdens for beef cattle (1.60 mg/kg) and for dairy cows (1.47 mg/kg) matched the feeding level from the respective cattle feeding studies (2 mg/kg). As a result the Meeting decided to use the residue levels from the feeding studies as estimates of the maximum residue levels for cattle tissues and milk. Residues in cattle tissues and milk in the feeding studies were all below the LOQ (< 0.05 mg/kg for cattle fat, muscle, liver, and kidney, and < 0.01 mg/kg for milk). The calculated median dietary burdens were lower than the actual feeding level in both transfer studies, 0.088 mg/kg for beef cattle and 0.076 mg/kg in dairy cattle therefore the calculated median residues would also be expected to be lower.

The actual feeding level of laying hens was (2 ppm for 21 days), the calculated maximum and median dietary burdens (0.009 ppm) were lower than the residue levels in both tissue and eggs. Consequently, no detectable residues are expected in both tissues and eggs. Therefore, residues are expected to be well below the LOQ for the method used (< 0.05 mg/kg for poultry tissues and < 0.01 mg/kg for eggs).

The calculations confirmed the findings of the animal metabolism studies as well as the results of the feeding studies, that showed no residues of terbufos or its metabolites were detectable in cattle tissues, poultry tissues, milk, and eggs. The MRL and STMR for residues of terbufos in animal commodities are proposed at the limit of quantification of the analytical method.

The Meeting withdrew its previous recommendation of 0.05 (*) mg/kg for cattle meat, cattle edible offal, chicken meat and chicken edible offal and 0.01 (*) mg/kg for cattle milk. The Meeting confirmed its previous recommendation of 0.01 (*) mg/kg for eggs and estimated a maximum residue level of 0.05 (*) mg/kg for meat from mammals other than marine mammals and mammalian edible offal, and 0.01(*) mg/kg for milks. The Meeting recommended an STMR of 0.05 mg/kg for mammalian meat and edible offal and poultry tissues and 0.01 mg/kg for milk and eggs. The estimated high residues are 0.05 mg/kg for mammalian meat, edible mammalian offal, chicken meat and edible chicken offal and 0.01 mg/kg for milks and eggs.

DIETARY RISK ASSESSMENT

Long-term intake

The International Estimated Dietary Intakes (IEDIs) were calculated for the five GEMS/Food regional diets using the STMR for banana, coffee beans, edible offal (mammalian), eggs, maize (fresh, flour), meat from mammals other than marine mammals, milks, poultry meat, poultry edible offal, sorghum, sugar beet and sweet corn (corn on the cob) estimated by the current Meeting (Annex 3). The ADI is 0–0.0006 mg/kg and the calculated IEDIs were 9–40% of the maximum ADI. The

Meeting concluded that the intake of residues of terbufos resulting from the uses considered by the current JMPR were unlikely to present a public health concern.

Short-term intake

The International Estimated Short-Term Intakes (IESTIs) of terbufos by the general population and by children were calculated for commodities by the current Meeting. This was based on HRs estimated by the Meeting from available information on consumption. The ARfD is 0.002mg/kg and the calculated IESTIs for children up to 6 years range from 0–60% and those for general population from 0–30% of the ARfD. The Meeting concluded that the short-term intake of residues of terbufos resulting from the uses considered by the current Meeting were unlikely to present a public health concern.

5. RECOMMENDATIONS

5.1 Work sharing

The Meeting emphasized that it is critical that JMPR continues to perform an independent evaluation and expert review of the evaluation that ensures consistency, and results in an international consensus evaluation. In this context, the JMPR monographs can be described in three parts:

(1) the description of the actual studies;

(2) the interpretation and evaluation of the studies; and

(3) the final evaluation/appraisal of the compound

Part 1 is most practicable for work sharing, provided there is sufficient harmonization between monograph formats used by different authorities. By using study descriptions and data tables from existing evaluations, the JMPR expert may be able to save time in the preparation of the JMPR monograph. Part 2 could be taken directly or modified or rewritten from existing national/regional evaluations after a review by the JMPR experts. Part 3 should represent an independent JMPR evaluation and review.

The main criterion for a new pesticide to be evaluated via work sharing (toxicological and residue evaluations) is that it has been reviewed by at least three national/regional agencies. If the findings are similar, relevant parts of national/regional reviews should be used in the preparation of JMPR documents. An independent appraisal that represents international consensus should be prepared and approved by JMPR.

5.2 Joint FAO/WHO Meeting on Pesticide Specifications (JMPS)

The Meeting considered that it is important to coordinate the activities of the JMPR and the JMPS as far as possible. The conclusions of the 1999 Meeting were reiterated that new and existing pesticide specifications for the technical material should be developed before a pesticide is evaluated within the periodic review programme of the CCPR and that this should not delay evaluation of pesticides by the JMPR.

The Meeting suggested there should be clear indication whether the sections “Hazard summary” and “Appraisal”, (which include toxicological information and an appraisal of the hazard potential of the compound), are based on existing national/regional or international evaluations.

The Meeting recommended that if JMPR evaluations exist for a particular pesticide, toxicological information from the summary tables and toxicological evaluations of the JMPR report should be used as the only entry in the relevant parts of the specifications.

The 2005 JMPR agreed to refer to available JMPS specifications in the JMPR report. However, this reference is not an endorsement of the toxicological information therein (except for JMPR hazard assessments).

5.3 Crop classification systems

The Meeting encourages the collaboration initiatives being made by the two workgroups to bring the strength of the two systems the Codex Crop Classification and the US Crop Grouping Scheme together in a harmonized classification system. This would facilitate the work of JMPR and CCPR, and would benefit participating countries in residue research, risk assessment, and MRL setting.

5.4. Processing factors

The Meeting agreed that in the evaluation of processing studies, the median would generally provide the best estimate for the processing factor, and decided to use it instead of the average value.

5.5. Fat solubility

The Meeting recommended that in determining "fat solubility" for a residue, the following factors should be considered:

- When available, it is the partitioning of the residue (as defined) in muscle versus fat in the metabolism studies and livestock feeding studies that determines whether a residue is designated "fat soluble".

- In the absence of useful information on the distribution of residues in muscle and fat, residues with log $P_{ow} > 3$ are likely to be "fat soluble".

The Meeting noted that in the design of animal feeding studies, account should be taken of the likely fat solubility of residues with log $P_{ow} > 3$

The Meeting also recommended that the *FAO Manual* be amended accordingly (see section 2.10 of this Report).

5.6 Animal forage

In the past, JMPR has recommended MRLs for forage crops and has used information on their residue status in estimating farm animal dietary burden. Codex MRLs are used as standards for commodities in international trade. The Meeting was of the opinion that forage was not an item of international trade requiring Codex MRLs and decided not to recommend further forage MRLs. Fodder MRLs would continue to be evaluated and recommended as before. Forage residue data would continue to be evaluated and used in the estimation of farm animal dietary burden.

5.7 Acute dietary exposure

The Meeting recommended that GEMS/Food and Codex Members put more effort into refinement of the short-term consumption database currently used by JMPR, since anomalies and missing data often cause problems for the IESTI calculations.

5.8 Variability factor for the use for calculation of short-term intake

The JMPR agreed to continue using the default variability factor of 3 for calculation of IESTI, which will be expressed with one significant figure corresponding to its uncertainty.

It is emphasized that the deterministic IESTI calculation used by JMPR should only be applied for residue data derived from supervised trials and from single lots. It is not applicable for mixed lots.

6. FUTURE WORK

The items listed below should be considered by the Meeting in 2006 and 2007. The compounds listed include those recommended as priorities by the CCPR at its 36th and earlier sessions and compounds scheduled for re-evaluation within the CCPR periodic review programme.

2007 JMPR

Toxicological evaluations	Residue evaluations
New compounds	***New compounds***
Dimethomorph	Dimethomorph
Pyrimethanil	Pyrimethanil
Zoxamide	Zoxamide
Difenoconazole	Difenoconazole
Periodic re-evaluations	***Periodic re-evaluations***
Azinphos-methyl (002)	Benalaxyl (155)
λ-Cyhalothrin	Clofentezine (156)
Flusilazole (165)	Cyfluthrin and β-cyfluthrin (157)
Procymidone (136)	Cyromazine (169)
Profenofos (171)	Flusilazole (165)
Vinclozolin (159)	Permethrin (120)
	Profenofos (171)
	Propiconazole (160)
Evaluations	***Evaluations***
Fenitrothion – review of acute and chronic toxicity	Tebuconazole
Carbaryl – review of basis for ARfD setting	Carbaryl - review of alternate GAP

2008 JMPR

Toxicological evaluations	Residue evaluations
New compounds	***New compounds***
Periodic re-evaluations	***Periodic re-evaluations***
Bioresmethrin (93)	Azinphos-methyl (002)
Buprofezin (173)	λ-Cyhalothrin
Chlorpyrifos-methyl (090)	Procymidone (136)
Hexythiazox (176)	

ANNEX 1

Acceptable daily intakes, short-term dietary intakes, acute references doses, recommended maximum residue levels and supervised trials median residue values recorded by the 2005 Meeting

The following extracts of the results of the annual Joint FAO/WHO Meeting on Pesticide Residues (JMPR) are provided to make them accessible to interested parties at an early date.

The Meeting evaluated 21 pesticides, of which five were new compounds, and eight were re-evaluated within the periodic review programme of the Codex Committee on Pesticide Residues (CCPR). The Meeting established acceptable daily intakes (ADIs) and acute reference doses (ARfDs).

The Meeting estimated maximum residue levels, which it recommended for use as maximum residue limits (MRLs) by the CCPR. It also estimated supervised trials median residue (STMR) and highest residue (HR) levels as a basis for estimation of the dietary intake of residues of the pesticides reviewed. Application of HR levels is explained in the report of the 1999 Meeting (section 2.4). The allocations and estimates are shown in the table.

Pesticides for which the estimated dietary intakes might, on the basis of the available information, exceed their ADIs are marked with footnotes, as explained in detail in the report of the 1999 Meeting (section 2.2). Footnotes are also applied to specific commodities when the available information indicated that the ARfD of a pesticide might be exceeded when the commodity was consumed. It should be noted that these distinctions apply only to new compounds and those re-evaluated within the CCPR periodic review programme.

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 Alimentarius Commission. Both compounds and commodities are listed in alphabetical order.

Apart from the abbreviations indicated above, the following qualifications are used in the Table.

* (following name of pesticide)	New compound
** (following name of pesticide)	Compound reviewed within CCPR periodic review programme
* (following recommended MRL)	At or about the limit of quantification
HR-P	Highest residue in a processed commodity, in mg/kg, calculated by multiplying the HR in the raw commodity by the processing factor
Po	The recommendation accommodates post-harvest treatment of the commodity.
PoP (following recommendation for processed foods (classes D and E in the Codex classification)	The recommendation accommodates post-harvest treatment of the primary food commodity.
STMR-P	An STMR for a processed commodity calculated by applying the concentration or reduction factor for the process to the STMR calculated for the raw agricultural commodity.
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.

Allocated ADI and ARfD values and recommended MRL, STMR and HR values

Pesticide (Codex reference number)	**CCN**	**Commodity**	**Recommended MRL mg/kg**		**STMR or STMR-P, mg/kg**	**HR or HR-P mg/kg**
			New	Previous		
Acephate (95) ADI: 0–0.03 mg/kg bw ARfD: 0.1 mg/kg bw						
Benalaxyl (155)** ADI: 0–0.07 mg/kg bw ARfD: 0.1 mg/kg bw for women of child-bearing age and unnecessary for the rest of the population						
Azocyclotin (129) / **Cyhexatin** (67) **	FP 0226	Apple	0.2	2[2]	0.025	0.16
Group ADI: 0–0.003 mg/kg bw	JF 226	Apple juice			0.002	
Group ARfD: 0. 02 mg/kg bw for women of child-bearing age and unnecessary for the rest of the population	FP 0230	Pear	0.2	2[2]	0.025	0.16
	FC0001	Citrus fruits	W	2		
	JC0001	Orange	0.2	2[1]	0.035	0.049
	JF 04	Orange juice			0.002	
	FB0269	Grapes	0.3	0.2[1]	0.085	0.19
	DF 0269	Grapes, dried (= currants, raisins and sultanas)			0.076	
	JF 269	Grape juice			0.068	
	FB 1236	Wine grape			0.060	
	FB 21	Currants, red, black, white	0.1		0.05	
	MM 0095	Meat (from mammals other than marine mammals)[3]	W	0.2[1]		
	AO3 0001	Milk products[3]	W	0.05*[1]		
	ML 0106	Milks[3]	W	0.05*[1]		

Residue for compliance with MRLs and estimation of dietary intake in plant and animal commodities: cyhexatin

[1] Azocyclotin and cyhexatin

[2] Cyhexatin

[3] The MRL accommodates external animal treatment

Carbendazim (72)
ARfD: 0.1 mg/kg bw for women of child-bearing age
ARfD: 0.5 mg/kg bw for the general population

Chlorpropham (201)
ADI: 0–0.05 mg/kg bw
ARfD: 0.5 mg/kg bw

Pesticide (Codex reference number)	CCN	Commodity	Recommended MRL mg/kg		STMR or STMR-P, mg/kg	HR or HR-P mg/kg
			New	Previous		
Clofentezine (156) **						
ADI: 0–0.02 mg/kg bw						
ARfD: unnecessary						
Dimethenamid-P (214) *	AL 061	Bean fodder	0.01*			
ADI: 0–0.07 mg/kg bw	VD 071	Beans, dry	0.01*		0	
ARfD: 0.5 mg/kg bw	VR 574	Beetroot	0.01*		0	0
	PE 112	Eggs	0.01*		0	0
	AM 1051	Fodder beet	0.01*			
	VA 381	Garlic	0.01*		0	0
	GC 647	Maize	0.01*		0	
	AS 645	Maize fodder	0.01*			
	MM 095	Meat (from mammals other than marine mammals)	0.01*		0 muscle 0 fat	0 muscle 0 fat
	ML 106	Milks	0.01*		0	0
	VA 385	Onion, Bulb	0.01*		0	0
	SO 697	Peanut	0.01*		0	
	AL 697	Peanut fodder	0.01*			
	VR 589	Potato	0.01*		0	0
	PM 110	Poultry meat	0.01*		0 muscle 0 fat	0 muscle 0 fat
	PO 111	Poultry, Edible offal of	0.01*		0	0
	VA 388	Shallot	0.01*		0	0
	GC 651	Sorghum	0.01*		0	
	AS 651	Sorghum straw and fodder, Dry	0.01*			
	VD 541	Soya bean, dry	0.01*		0	
	VR 596	Sugar beet	0.01*		0	
	VO 447	Sweet corn (corn-on-the-cob)	0.01*		0	0
	VR 508	Sweet potato	0.01*		0	0

Residue for compliance with MRLs and for estimation of dietary intake: dimethenamid-P and its enantiomer.

This definition applies to both plant and animal commodities. The residue definition could apply to residues arising from the use of either dimethenamid-P or dimethenamid.

Note: The ADI and the ARfD apply to dimethenamid-P and the racemic dimethenamid.

Ethoxyquin (108)

ADI: 0–0.005 mg/kg bw

ARfD: 0.5 mg/kg bw

Note: The ADI and the ARfD are applicable to ethoxyquin and its metabolites/degradation products methylethoxyquin (MEQ), dihydroethoxyquin (DHEQ), dehydromethylethoxyquin (DHMEQ)

Fenhexamid (215) *	TN 0660	Almonds	0.02*	0.02
ADI: 0–0.2 mg/kg bw	AM 0660	Almond hulls[1]	2	
ARfD: unnecessary	FS 0240	Apricot	10	3.85
	FB 0261	Bilberry	5	1.65
	FB 0264	Blackberries	15	2.0

Pesticide (Codex reference number)	**CCN**	**Commodity**	**Recommended MRL mg/kg**		**STMR or STMR-P, mg/kg**	**HR or HR-P mg/kg**
			New	Previous		
	FB 0020	Blueberries	5		1.65	
	FS 0013	Cherries	7		1.35	
		Cherry juice			0.03	
		Cherry preserve			0.31	
	FB 0021	Currants, Black, Red, White	5		1.65	
	VC 0424	Cucumber	1		0.185	
	FB 0266	Dewberries	15		2.0	
	DF 0269	Dried grapes (Currants, Raisins and Sultanas)	25		8.0	
	MO 0105	Edible offal (Mammalian)	0.05*		0	
	VO 0440	Egg plant	2		0.71	
	FB 0267	Elderberries	5		1.65	
	VC 0425	Gherkin	1		0.185	
	FB 0268	Gooseberries	5		1.65	
	FB 0269	Grapes	15		4.3	
	JF 0269	Grape juice			2.2	
		Grape must			1.8	
		Grape wine			1.2	
	FB 0270	Juneberries	5		1.65	
	FI 0341	Kiwifruit	15		6.3	
	VL 0482	Lettuce, Head	30		11.5	
	VL 0483	Lettuce, Leaf	30		11.5	
	FS 0247	Peach	10		3.85	
	VO 0051	Peppers	2		0.71	
	FS 0014	Plums (including Prunes)	1		0.31	
	MM 0095	Meat (from mammals other than marine mammals)	0.05* (fat)		0	
	ML 0106	Milks	0.01* F		0	
	FS 0245	Nectarine	10		3.85	
	FB 0272	Raspberries, Red, Black	15		2.0	
	FB 0275	Strawberry	10		3.3	
		Strawberry jam			0.96	
	VC 4249	Squash, Summer	1		0.185	
	VO 0448	Tomato	2		0.395	
	JF 0448	Tomato juice			0.13	
		Tomato paste			2.05	
		Tomato puree			0.12	

Residue for compliance with MRLs and for estimation of dietary intake in plant and animal commodities: *fenhexamid.*

The residue is fat-soluble.

[1] Expressed on dry weight basis

Glyphosate (158) **	AL 1020	Alfalfa fodder	500		
ADI: 0–1 mg/kg bw	AL 1021	Alfalfa forage	W		
ARfD: unnecessary	FI 0327	Banana	0.05*		0.05
	GC 0640	Barley	W	20	7.65

Pesticide (Codex reference number)	**CCN**	**Commodity**	**Recommended MRL mg/kg**		**STMR or STMR-P, mg/kg**	**HR or HR-P mg/kg**
			New	Previous		
	AS 0640	Barley straw and fodder, dry	400			
	VD 0071	Beans (dry)	2	2	0.17	
	Al 0061	Bean fodder	200			
	MM 0812	Cattle meat	W	0.1*		
	ML 0812	Cattle milk	W	0.1*		
	MO 0812	Cattle, Edible offal of	W	2		
	GC 0080	Cereal grains [except maize and rice]	30		3.7	
	SO 0691	Cotton seed	40	10	5.2	
	OC 0691	Cotton seed oil, Crude	W	0.05*		
	OR 0691	Cotton seed oil, Edible	W	0.05*		
	MO 0105	Edible offal (mammalian) (except pigs)	5		2.9	
	PE 0112	Eggs	0.05*	0.1*	0	
	AS 0162	Hay or fodder (dry) of grasses	500	50		
	FI 0341	Kiwifruit	W	0.1*		
	GC 0645	Maize	5		0.12	
	AF 0645	Maize forage	W	1		
	AS 0645	Maize fodder	150			
	MM 0095	Meat (from mammals other than marine mammals)	0.05*		0.05	
	ML 0106	Milks	0.05*		0	
	GC 0647	Oats	W	20	4.15	
	AS 0647	Oat straw and fodder, dry	100			
	VD 0072	Peas (dry)	5	5	0.5	
	AL 0072	Pea hay or pea fodder (dry)	500			
	MM 0818	Pig meat	W	0.1*	0	
	MO 0818	Pig, Edible offal of	0.5	1	0.12	
	PM 0110	Poultry meat	0.05*	0.1*	0	
	PO 0111	Poultry, Edible offal of	0.5		0.05 liver 0.088 kidney	
	SO 0495	Rape seed	20	10	0.93	
	GC 0649	Rice	W	0.1*		
	GC 0651	Sorghum	W	20	4.8	
	AS 0651	Sorghum straw and fodder, dry	50			
	VD 0541	Soya bean (dry)	20	20	5.0	
	VP 0541	Soya bean (immature seed)	W	0.2		
	AL 0541	Soya bean fodder	W	200		
	AL 1265	Soya bean forage (green)	W	5		
	AS 0081	Straw and fodder (dry) of cereal grains	W	100		
	GS 0659	Sugar cane	2		0.27	
	DM 0659	Sugar cane molasses	10		2.3	
	SO 0702	Sunflower seed	7		0.395	
	VO 0447	Sweet corn (corn-on-the-cob)	W	0.1*		
	GC 0654	Wheat	W	5	1.05	

Pesticide (Codex reference number)	**CCN**	**Commodity**	**Recommended MRL mg/kg**		**STMR or STMR-P, mg/kg**	**HR or HR-P mg/kg**
			New	Previous		
	CM 0654	Wheat bran, Unprocessed	20	20	1.8	
	CF 1211	Wheat flour	W	0.5		
	AS 0654	Wheat straw and fodder, dry	300			
	CF 1212	Wheat wholemeal	W	5		
Residue for compliance with MRLs in plant and animal commodities: *glyphosate*						
Residue for estimation of dietary intake: *sum of glyphosate and AMPA expressed as glyphosate*						
Imazalil (110)						
ARfD: 0.05 mg/kg bw						
Indoxacarb (216) *	AL 1020	Alfalfa fodder	60			
ADI: 0–0.01 mg/kg bw	FP 0226	Apple	0.5		0.21	0.30
ARfD: 0.1 mg/kg bw	VB 0400	Broccoli	0.2		0.055	0.14
	VB 0041	Cabbages, Head [1]	3		0.435	2.7
	FM 0812	Cattle milk fat	2		1.0	
	VB 0404	Cauliflower	0.2		0.02	0.14
	VD 0524	Chick-pea (dry)	0.2		0.02	
	AM 691	Cotton fodder, dry	20			
	SO 0691	Cotton seed	1		0.36	0.92
	VC 0424	Cucumber	0.2		0.02	0.10
	DF 0269	Dried grapes (= Currants, Raisins, Sultanas)	5		0.81	4.1
	MO 0105	Edible offal (Mammalian)	0.05		0.016	0.027
	VO 0440	Egg plant	0.5		0.11	0.30
	PE 0112	Eggs	0.01*		0	0
	FB 0269	Grapes	2		0.30	1.5
	VL 0482	Lettuce, Head	7		2.8	4.3
	VL 0483	Lettuce, Leaf	15		6.6	8.4
	AS 0645	Maize fodder	25		7.8	15
	MM 0095	Meat (from mammals other than marine mammals)	1 (fat)		0.01 muscle 0.44 fat	0.03 muscle 0.91 fat
	VC 0046	Melons, except Watermelon	0.1		0.02	0.02
	ML 0106	Milks	0.1 [2]		0.048	
	VD 0536	Mung bean (dry)	0.2		0.02	
	FS 0247	Peach	0.3		0.11	0.18
	AL 0697	Peanut fodder	50			
	SO 0697	Peanuts	0.02*		0.01	0.01
	FP 0230	Pear	0.2		0.051	0.11
	VO 0051	Peppers	0.3		0.038	0.21
	VR 0589	Potato	0.02		0.01	0.01
	PM 0110	Poultry meat	0.01* (fat)		0 muscle 0 fat	0 muscle 0 fat
	PO 0111	Poultry, Edible offal of	0.01*		0	0
	VD 0541	Soya bean (dry)	0.5		0.027	
	VO 0447	Sweet corn (corn-on-the-cob)	0.02		0.01	0.012

Pesticide (Codex reference number)	**CCN**	**Commodity**	**Recommended MRL mg/kg**		**STMR or STMR-P, mg/kg**	**HR or HR-P mg/kg**
			New	Previous		
	VO 0448	Tomato	0.5		0.11	0.30
		Apple juice			0.011	
		Apple pomace, wet			0.55	
		Cotton seed refined oil			0.013	
		Grape juice			0.002	
		Peach juice			0.009	
		Peaches, canned			0.009	
		Peanut oil			0.003	
		Soybean refined oil			0.018	
		Tomato juice			0.022	
		Tomato paste			0.21	
		Wine			0.018	

Definition of the residue (for compliance with the MRL for all commodities and for estimation of dietary intake for plant commodities): *sum of indoxacarb and its R enantiomer*.

The residue is fat soluble.

Definition of the residue (for estimation of dietary intake for animal commodities): *sum of indoxacarb, its R enantiomer and methyl 7-chloro-2,5-dihydro-2-[[[4-(trifluoromethoxy)phenyl]amino]carbonyl]indeno[1,2-e][1,3,4]oxadiazine-4a(3H)-carboxylate, expressed as indoxacarb.*

***Note*:** the ADI and ARfD applies to indoxacarb (S-enantiomer) and it's R-enantiomer.

[1] The information provided precluded an estimate that the dietary intake would be below the ARfD for children aged ≤ 6 years.

[2] Indoxacarb is a fat-soluble compound. Previously, the milk MRL would have been marked with an "F" to indicate a procedure for calculating "MRLs" for processed dairy products. Currently, indoxacarb MRLs for milk and milk fat are available to support "MRLs" for processed dairy products.

Methiocarb (132)	VS 0620	Artichoke, Globe	0.05*	W	0.005	0.01
ADI: 0–0.02 mg/kg bw	GC 0640	Barley	0.05*		0	
ARfD: 0.02 mg/kg bw	AS 0640	Barley straw and fodder, dry	0.05			
	VB 0402	Brussels sprout	0.05*	W	0.01	0.01
	VB 0041	Cabbages, head	0.1	W	0.05	0.08
	VB 0404	Cauliflower	0.1	W	0.05	0.08
	TN 0666	Hazelnuts	0.05*	W	0.04	0.04
	VA 0384	Leek	0.5		0.15	0.33
	VL 0482	Lettuce, head	0.05*	W	0.05	0.05
	GC 0645	Maize	0.05*		0	
	VC 0046	Melons, except watermelon	0.2		0.02	0.02
	VA 0385	Onion, bulb	0.5		0.025	0.35
	AL 0072	Pea hay or pea fodder (dry)	0.5			
	VP 0063	Peas (pods and succulent=immature seeds)	0.1		0.05	0.05
	VP 0072	Peas (dry)	0.1		0.05	
	VO 0445	Peppers, sweet	2		1.06	1.5
	VR 0589	Potato	0.05*		0.01	0.02
	SO 0495	Rape seed	0.05*	W	0	
	VR 0596	Sugar beet	0.05*	W	0.01	0.01
	SO 0702	Sunflower seed	0.05*		0	
	GC 0654	Wheat	0.05*		0	
	AS 0654	Wheat straw and fodder, dry	0.05			

Pesticide (Codex reference number)	**CCN**	**Commodity**	**Recommended MRL mg/kg**		**STMR or STMR-P, mg/kg**	**HR or HR-P mg/kg**
			New	Previous		
Residue for compliance with MRLs and for estimation of dietary intake in plant commodities: *the sum of methiocarb, methiocarb sulfoxide and methiocarb sulfone, expressed as methiocarb*						
Methoprene (147) **	ML 0812	Cattle milk	W	0.05 F		
ADI: 0-0.09 mg/kg bw for the R,S racemate; 0-0.05 mg/kg bw for S-methoprene	GC 0080	Cereal grains	10 Po	5 Po	4.85	
	MO 0105	Edible offal (mammalian) [except cattle]	W	0.1		
ARfD: Unnecessary	MO 0105	Edible offal (mammalian)	0.02		0.014	
	PE 0112	Eggs	0.02	0.05	0.006	
	OC 0645	Maize oil, crude	200		87.3	
	OR 0645	Maize oil, edible	W	0.2* PoP	0	
	MM 0095	Meat from mammals other than marine mammals [except cattle]	W	0.2 (fat)		
	MM 0095	Meat from mammals other than marine mammals	0.2 (fat)		0.007 muscle	
					0.092 fat	
	ML 0106	Milks	0.1 F		0.044	
	PM 0110	Poultry meat [except fat]	0.02		0.007 muscle	
	PO 0111	Poultry, edible offal of	0.02		0.007	
	CM 0654	Wheat bran, unprocessed	25 PoP	10 PoP	13.6	
	CF 1211	Wheat flour	W	2 PoP	1.72	
	CF 1212	Wheat wholemeal	W	5 PoP	4.51	
	-	Rice hulls	40 PoP		22.3	
Residue for compliance with MRLs and for estimation of dietary intake in plant and animal commodities: methoprene The residue is fat soluble.						
Novaluron (217) *	JF 0226	Apple juice			0.065	
ADI: 0–0.01 mg/kg bw	AB 0226	Apple pomace, dry	40		12	
ARfD: unnecessary	FM0812	Cattle milk fat	7		4.3	
	SO 691	Cotton seed	0.5		0.068	
	OR 691	Cotton seed oil, edible			0.041	
	MO 105	Edible offal (mammalian)	0.7		0.26	
	PE 0112	Eggs	0.01*		0	
	MM 0095	Meat (from mammals other than marine mammals)	10 (fat)		0.19 muscle	
					4.1 fat	
	ML0106	Milks	0.4		0.20	
	FP 0009	Pome fruits	3		0.65	
	PM 0110	Poultry meat	0.01* (fat)		0 muscle	
					0.005 fat	
	PO 0111	Poultry, Edible offal of	0.01*		0	
	VR 0589	Potato	0.01*		0.01	
	VP 541	Soya bean (immature seeds)	0.01*		0.01	
	VO0448	Tomato	0.02*		0.02	
Residue for compliance with MRLs and for estimation of dietary intake in plant and animal commodities: novaluron						

Pesticide (Codex reference number)	**CCN**	**Commodity**	**Recommended MRL mg/kg**		**STMR or STMR-P, mg/kg**	**HR or HR-P mg/kg**
			New	Previous		
The residue is fat soluble						
Phorate (112) **	VD 0071	Beans (dry)	0.05*		0.05	-
ADI: 0–0.0007 mg/kg bw	SB 0716	Coffee beans	0.05*		0.05	-
ARfD: 0.003 mg/kg bw	VP 0526	Common bean (pods and/or immature seeds)	0.05*	0.1	0.05	0.05
	SO 0691	Cotton seed	0.05*	0.05	0	-
	MO 0105	Edible offal (mammalian)	0.02*		0.02 liver	0.02 liver
					0.02 kidney	0.02 kidney
	PE 0112	Eggs	0.05*	0.05*	0	0
	AM 1051	Fodder beet	W	0.05		
	GC 0645	Maize	0.05*	0.05	0.02	-
	CF 1255	Maize flour	0.05		0.046	-
	AS 0645	Maize fodder	W	0.2 fresh wt		
	AF 0645	Maize forage	W	0.2 fresh wt		
	OC 0645	Maize oil, crude	0.1		0.069	-
	OR 0645	Maize oil, edible	0.02		0.0162	-
	MM 0095	Meat (from mammals other than marine mammals)	0.02*	0.05*	0.02 muscle	0.02 muscle
					0.02 fat	0.02 fat
	ML 0106	Milks	0.01*	0.05*	0.005	
	SO 0697	Peanut	W	0.1		
	OC 0697	Peanut oil, Crude	W	0.05*		
	OR 0697	Peanut oil, Edible	W	0.05*		
	VR 0589	Potato [1]	0.5	0.2	0.05	0.27
		Potatoes, microwaved with peel			0.018	0.0972
	PM 0110	Poultry meat	0.05*		0 muscle	0 muscle
					0 fat	0 fat
	GC 0651	Sorghum	0.05*	0.05	0.05	-
	VD 0541	Soya bean (dry)	0.05*	0.05	0	-
	VR 0596	Sugar beet	0.05*	0.05	0.05	0.05
	AV 0596	Sugar beet leaves or tops	W	1		
	VO 0447	Sweet corn (corn-on-the-cob)	W	0.05		
	GC 0654	Wheat	W	0.05		

Residue for compliance with MRLs and for estimation of dietary intake in plant and animal commodities: *sum of parent, it's oxygen analogue, and their sulfoxides and sulfones, expressed as phorate*

[1] The information provided precluded an estimate that the dietary intake would be below the ARfD for children aged ≤ 6 years.

Propamocarb (148) **

ADI: 0–0.4 mg/kg bw

ARfD: 2 mg/kg bw

Pyrethrins (063)	TN 0085	Tree nuts	0.5* Po	1 Po	0.2	0.5

Pesticide (Codex reference number)	**CCN**	**Commodity**	**Recommended MRL mg/kg**		**STMR or STMR-P, mg/kg**	**HR or HR-P mg/kg**
			New	Previous		
ADI: 0–0.04 mg/kg bw						
ARfD: 0.2 mg/kg bw						
Residue for compliance with MRLs and for estimation of dietary intake in plant and animal commodities: *total pyrethrins, calculated as the sum of pyrethrin 1, pyrethrin 2, cinerin 1, cinerin 2, jasmolin 1 and jasmolin 2, determined after calibration with World Standard pyrethrum extract*						
Sulfuryl fluoride (218) *	GC 0080	Cereal grains	0.05 Po		0.008	0.03
ADI: 0–0.01 mg/kg bw	CF 0081	Cereal brans, processed	0.1 Po		0.008	0.06
ARfD: 0.3 mg/kg bw	CF 1255	Maize flour	0.1 Po		0.008	0.06
	CF 0645	Maize meal	0.1 Po		0.008	0.06
	CF 1250	Rye flour	0.1 Po		0.008	0.06
	CF 1251	Rye wholemeal	0.1 Po		0.008	0.06
	CF 1210	Wheat germ	0.1 Po		0.008	0.06
	CF 1211	Wheat flour	0.1 Po		0.008	0.06
	CF 1212	Wheat wholemeal	0.1 Po		0.008	0.06
	CM 0081	Bran, unprocessed of cereal grain (except buckwheat, cañihua and quinoa)	0.1 Po		0.008	0.06
	CM 0649	Rice, husked	0.1 Po		0.008	0.06
	CM 1205	Rice, polished	0.1 Po		0.008	0.06
	DF 0167	Dried fruits	0.06 Po		0.004	0.04
	TN 0085	Tree nuts	3 Po		0.28	2.5
Fluoride	GC 0080	Cereal grains			3.5	21
	CF 0081	Cereal brans, processed			37	104
	CF 1255	Maize flour			24	70
	CF 0645	Maize meal			37	104
	CF 1250	Rye flour			37	104
	CF 1251	Rye wholemeal			37	104
	CF 1210	Wheat germ /			66	104
	CF 1211	Wheat flour			35	55
	CF 1212	Wheat wholemeal			37	104
	CM 0081	Bran, unprocessed of cereal grain (except buckwheat, cañihua and quinoa)			37	104
	CM 0649	Rice, husked			37	104
	CM 1205	Rice, polished			37	104
	DF 0167	Dried fruits			2.4	2.4
	TN 0085	Tree nuts			0.28	9.1
Residue for compliance with MRLs in plant commodities: sulfuryl fluoride						
Residue for the estimation of dietary intake from plant commodities: sulfuryl fluoride and fluoride ion, measured separately.						
Note: Residues resulting from sulfuryl fluoride fumigation of foodstuffs are primarily fluoride. The dietary risk assessment for fluoride from fumigant use needs to be considered in light of the overall exposure to fluoride from other sources.						
Terbufos (167) **	FI 0327	Banana	0.05	0.05	0.01	0.02
ADI: 0–0.0006 mg/kg bw	VB 0400	Broccoli	W	0.05*		
ARfD: 0.002 mg/kg bw	VB 0041	Cabbages, head	W	0.05*		

Pesticide (Codex reference number)	**CCN**	**Commodity**	**Recommended MRL mg/kg**		**STMR or STMR-P, mg/kg**	**HR or HR-P mg/kg**
			New	Previous		
	MM 0812	Cattle meat	W	0.05*		
	ML 0812	Cattle milk	W	0.01*		
	MO 0812	Cattle, Edible offal	W	0.05*		
	PM 0840	Chicken meat	W	0.05*		
	PO 0840	Chicken, Edible offal	W	0.05*		
	SB 0716	Coffee beans	0.05*	0.05*	0.05	
	PE 0112	Eggs	0.01*	0.01 *	0.01	0.01
	AV 1051	Fodder beet leaves or tops	W	1		
	GC 0645	Maize	0.01*	0.01*	0.01	
	AF 0645	Maize forage,	W	1		
	AS 0645	Maize fodder, (dry)	0.2.3	0.1		
	MO 0105	Edible offal (mammalian)	0.05*	0.05*	0.05	0.05
	MM 0095	Meat (from mammals other marine mammals)	0.05*	0.05 *	0.05	0.05
	ML 0106	Milks	0.01*	0.01 *	0.01	
	SO 0485	Mustard seed	W	0.05*		
	VA 385	Onion, bulb	W	0.05*		
	SO 0697	Peanut	W	0.05*		
	AL 0697	Peanut fodder	W	1		
	AL 1270	Peanut forage (green)	W	1		
	GC 0656	Popcorn	W	0.01		
	PM 0110	Poultry meat	0.05*		0.05	0.05
	PO 0111	Poultry edible offal of	0.05*		0.05	0.05
	GC0656	Popcorn	W	0.01*		
	SO 0495	Rape seed	W	0.05*		
	OC0459	Rape seed oil, Crude	W	0.05*		
	VD 0541	Soybeans (dry)	W	0.05*		
	GC 0651	Sorghum	0.01*		0	
	AS 0651	Sorghum straw and fodder,(dry)[1]	0.3			
	AS 0081	Straw and fodder of cereal grains	W	1		
	VR 0596	Sugar beet	0.02	0.1	0.01	0.01
	VO 0447	Sweet corn (corn-on-the-cob)	0.01	0.01*	0.01	0.01
	GC 0654	Wheat	W	0.01*		

Residue for compliance with MRLs and for estimation of dietary intake in plant and animal commodities: *sum of terbufos, its oxygen analogue, and their sulfoxides and sulfones, expressed as terbufos*

[1] Expressed on a dry weight basis

ANNEX 2: INDEX OF REPORTS AND EVALUATIONS OF PESTICIDES BY THE JMPR

Numbers in parentheses after the names of pesticides are Codex classification numbers. The abbreviations used are:

T, evaluation of toxicology

R, evaluation of residue and analytical aspects

E, evaluation of effects on the environment

Abamectin (177)	1992 (T,R), 1994 (T,R), 1995 (T), 1997 (T,R), 2000 (R)
Acephate (095)	1976 (T,R), 1979 (R), 1981 (R), 1982 (T), 1984 (T,R), 1987 (T), 1988 (T), 1990 (T,R), 1991 (corr. to 1990 R evaluation), 1994 (R), 1996 (R), 2002 (T), 2003 (R), 2004 (corr. to 2003 report), 2005 (T)
Acrylonitrile	1965 (T,R)
Aldicarb (117)	1979 (T,R), 1982 (T,R), 1985 (R), 1988 (R), 1990 (R), 1991 (corr. to 1990 evaluation), 1992 (T), 1993 (R), 1994 (R), 1996 (R), 2001 (R), 2002 (R)
Aldrin (001)	1965 (T), 1966 (T,R), 1967 (R), 1974 (R), 1975 (R), 1977 (T), 1990 (R), 1992 (R)
Allethrin	1965 (T,R)
Aminocarb (134)	1978 (T,R), 1979 (T,R)
Aminomethylphosphonic acid (AMPA, 198)	1997 (T,R)
Amitraz (122)	1980 (T,R), 1983 (R), 1984 (T,R), 1985 (R), 1986 (R), 1989 (R), 1990 (T,R), 1991 (R & corr. to 1990 R evaluation), 1998 (T)
Amitrole (079)	1974 (T,R), 1977 (T), 1993 (T,R), 1997 (T), 1998 (R)
Anilazine (163)	1989 (T,R), 1992 (R)
Azinphos-ethyl (068)	1973 (T,R), 1983 (R)
Azinphos-methyl (002)	1965 (T), 1968 (T,R), 1972 (R), 1973 (T), 1974 (R), 1991 (T,R), 1992 (corr. to 1991 report), 1993 (R), 1995 (R)
Azocyclotin (129)	1979 (R), 1981 (T), 1982 (R),1983 (R), 1985 (R), 1989 (T,R), 1991 (R), 1994 (T), 2005 (T,R)
Benalaxyl (155)	1986 (R), 1987 (T), 1988 (R), 1992 (R), 1993 (R), 2005 (T)
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 report, Annex I),

	1994 (R), 1995 (R), 1998 (T,R), 1999 (corr. to 1998 report), 2004(T)
BHC (technical-grade)	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), 2002 (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 report.), 1999 (R)
sec-Butylamine (089)	1975 (T,R), 1977 (R), 1978 (T,R), 1979 (R), 1980 (R), 1981 (T), 1984 (T,R: withdrawal of temporary ADI, but no evaluation)
Cadusafos (174)	1991 (T,R), 1992 (R), 1992 (R)
Campheclor (071)	1968 (T,R), 1973 (T,R)
Captafol (006)	1969 (T,R), 1973 (T,R), 1974 (R), 1976 (R), 1977 (T,R), 1982 (T), 1985 (T,R), 1986 (corr. to 1985 report), 1990 (R), 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 R evaluation), 1990 (T,R), 1991 (corr. to 1990 R evaluation), 1994 (R), 1995 (T), 1997 (R), 2000 (R), 2004 (T)
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), 2001 (T), 2002 (R)
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), 2003 (R), 2005 (T)
Carbofuran (096)	1976 (T,R), 1979 (T,R), 1980 (T), 1982 (T), 1991 (R), 1993 (R), 1996 (T), 1997 (R), 1999 (corr. to 1997 report), 2002 (T, R), 2003 (R) (See also carbosulfan), 2004 (R)
Carbon disulfide (009)	1965 (T,R), 1967 (R), 1968 (R), 1971 (R), 1985 (R)

Carbon tetrachloride (010)	1965 (T,R), 1967 (R), 1968 (T,R), 1971 (R), 1979 (R), 1985 (R)
Carbophenothion (011)	1972 (T,R), 1976 (T,R), 1977 (T,R), 1979 (T,R), 1980 (T,R), 1983 (R)
Carbosulfan (145)	1984 (T,R), 1986 (T), 1991 (R), 1992 (corr. to 1991 report), 1993 (R), 1997 (R), 1999 (R), 2002 (R), 2003 (T, R), 2004 (R, corr. to 2003 report)
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), 2000 (R)
Chlorobenzilate (016)	1965 (T), 1968 (T,R), 1972 (R), 1975 (R), 1977 (R), 1980 (T)
Chloropicrin	1965 (T,R)
Chloropropylate	1968 (T,R), 1972 (R)
Chlorothalonil (081)	1974 (T,R), 1977 (T,R), 1978 (R), 1979 (T,R), 1981 (T,R), 1983 (T,R), 1984 (corr. to 1983 report and T evaluation), 1985 (T,R), 1987 (T), 1988 (R), 1990 (T,R), 1991 (corr. to 1990 evaluation), 1992 (T), 1993 (R), 1997 (R)
Chlorpropham (201)	1965 (T), 2000 (T), 2001 (R). 2005 (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), 2000 (R), 2004 (R)
Chlorpyrifos-methyl (090)	1975 (T,R), 1976 (R, Annex I only), 1979 (R), 1990, (R), 1991 (T,R), 1992 (T and corr. to 1991 report), 1993 (R), 1994 (R), 2001 (T)
Chlorthion	1965 (T)
Clethodim (187)	1994 (T,R), 1997 (R), 1999 (R), 2002 (R)
Clofentezine (156)	1986 (T,R), 1987 (R), 1989 (R), 1990 (R), 1992 (R), 2005 (T)
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)
Cyanophenfos (091)	1975 (T,R), 1978 (T: ADI extended, but no evaluation), 1980, (T), 1982 (R), 1983 (T)

Cycloxydim (179)	1992 (T,R), 1993 (R)
Cyfluthrin (157)	1986 (R), 1987 (T and corr. to 1986 report), 1989 (R), 1990 (R), 1992 (R)
Cyhalothrin (146)	1984 (T,R), 1986 (R), 1988 (R)
Cyhexatin (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), 2005 (T,R)
Cypermethrin (118)	1979 (T,R), 1981 (T,R), 1982 (R), 1983 (R), 1984 (R), 1985 (R), 1986 (R), 1987 (corr. to 1986 evaluation), 1988 (R), 1990 (R)
Cyprodinil (207)	2003 (T,R), 2004 (corr. to 2003 report)
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 report, Annex I), 1996 (T), 1997 (E), 1998 (R), 2001 (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), 2000 (T), 2002 (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), 2001 (T)
1,2-Dibromoethane (023)	1965 (T,R), 1966 (T,R), 1967 (R), 1968 (R), 1971 (R), 1979 (R), 1985 (R)
Dicloran (083)	2003 (R)
Dichlorfluanid (082)	1969 (T,R), 1974 (T,R), 1977 (T,R), 1979 (T,R), 1981 (R),1982 (R), 1983 (T,R), 1985 (R)
1,2-Dichloroethane (024)	1965 (T,R), 1967 (R), 1971 (R), 1979 (R), 1985 (R)
Dichlorvos (025)	1965 (T,R), 1966 (T,R), 1967 (T,R), 1969 (R), 1970 (T,R), 1974 (R), 1977 (T), 1993 (T,R)
Dicloran (083)	1974 (T,R), 1977 (T,R), 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), 2001 (T), 2002 (R)
Dimethenamid- P (214)	2005 (T,R)
Dimethipin (151)	1985 (T,R), 1987 (T,R), 1988 (T,R), 1999 (T), 2001 (R), 2004 (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), 2003 (T,R), 2004 (corr. to 2003 report)
Dimethrin	1965 (T)
Dinocap (087)	1969 (T,R), 1974 (T,R), 1989 (T,R), 1992 (R), 1998 (R), 1999 (R), 2000 (T), 2001 (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), 2001 (R), 2003 (R)
Diquat (031)	1970 (T,R), 1972 (T,R), 1976 (R), 1977 (T,R), 1978 (R), 1994 (R)
Disulfoton (074)	1973 (T,R), 1975 (T,R), 1979 (R), 1981 (R), 1984 (R), 1991 (T,R), 1992 (corr. to 1991 report, Annex I), 1994 (R), 1996 (T), 1998 (R)
Dithianon (180)	1992 (T,R), 1995 (R), 1996 (corr. to 1995 report)
Dithiocarbamates (105)	1965 (T), 1967 (T,R), 1970 (T,R), 1983 (R propineb, thiram), 1984 (R propineb), 1985 (R), 1987 (T thiram), 1988 (R thiram), 1990 (R), 1991 (corr. to 1990 evaluation), 1992 (T thiram), 1993 (T,R), 1995 (R), 1996 (T,R ferbam, ziram;, R thiram), 2004 (R)
4,6-Dinitro-*ortho*-cresol (DNOC)	1965 (T)
Dodine (084)	1974 (T,R), 1976 (T,R), 1977 (R), 2000 (T), 2003 (R) 2004 (corr. to 2003 report)
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)
Esfenvalerate (204)	2002 (T, R)
Ethephon (106)	1977 (T,R), 1978 (T,R), 1983 (R), 1985 (R), 1993 (T), 1994 (R), 1995 (T), 1997 (T), 2002 (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 (T), 2004 (R)
Ethoxyquin (035)	1969 (T,R), 1998 (T), 1999 (R). 2005 (T)
Ethylene dibromide	See 1,2-Dibromoethane
Ethylene dichloride	See 1,2-Dichloroethane
Ethylene oxide	1965 (T,R), 1968 (T,R), 1971 (R)
Ethylenethiourea (ETU) (108)	1974 (R), 1977 (T,R), 1986 (T,R), 1987 (R), 1988 (T,R), 1990 (R), 1993 (T,R)
Etofenprox (184)	1993 (T,R)
Etrimfos (123)	1980 (T,R), 1982 (T,R[1]), 1986 (T,R), 1987 (R), 1988 (R), 1989 (R), 1990 (R)
Famoxadone (208)	2003 (T,R)
Fenamiphos (085)	1974 (T,R), 1977 (R), 1978 (R), 1980 (R), 1985 (T), 1987 (T), 1997 (T), 1999 (R), 2002 (T)
Fenarimol (192)	1995 (T, R, E), 1996 (R and corr. to 1995 report)
Fenbuconazole (197)	1997 (T,R)
Fenbutatin oxide (109)	1977 (T,R), 1979 (R), 1992 (T), 1993 (R)
Fenchlorfos (036)	1968 (T,R), 1972 (R), 1983 (R)
Fenhexamid (215)	2005 (T,R)
Fenitrothion (037)	1969 (T,R), 1974 (T,R), 1976 (R), 1977 (T,R), 1979 (R), 1982, (T) 1983 (R), 1984 (T,R), 1986 (T,R), 1987 (R and corr. to 1986 R evaluation), 1988 (T), 1989 (R), 2000 (T), 2003 (R), 2004 (R, corr. to 2003 report)
Fenpropathrin (185)	1993 (T,R)
Fenpropimorph (188)	1994 (T), 1995 (R), 1999 (R), 2001 (T), 2004 (T)
Fenpyroximate (193)	1995 (T,R), 1996 (corr. to 1995 report.), 1999 (R), 2004 (T)
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 report), 1997 (T), 2000 (R)
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 report), 1988 (R), 1990 (R), 1991 (corr. to 1990 R evaluation)
Ferbam	See Dithiocarbamates, 1965 (T), 1967 (T,R), 1996 (T,R)
Fipronil	1997 (T), 2000 (T), 2001 (R)
Fipronil-desulfinyl	1997 (T)
Flucythrinate (152)	1985 (T,R), 1987 (R), 1988 (R), 1989 (R), 1990 (R), 1993 (R)
Fludioxinil ( )	2004 (T,R)
Flumethrin (195)	1996 (T,R)

Flusilazole (165)	1989 (T,R), 1990 (R), 1991 (R), 1993 (R), 1995 (T)
Flutolanil (205)	2002 (T, R)
Folpet (041)	1969 (T,R), 1973 (T), 1974 (R), 1982 (T), 1984 (T,R), 1986 (T), 1987 (R), 1990 (T,R), 1991 (corr. to 1990 R evaluation), 1993 (T,R), 1994 (R), 1995 (T), 1997 (R), 1998 (R), 1999(R) , 2002 (T), 2004 (T)
Formothion (042)	1969 (T,R), 1972 (R), 1973 (T,R), 1978 (R), 1998 (R)
Glufosinate-ammonium (175)	1991 (T,R), 1992 (corr. to 1991 report, Annex I), 1994 (R), 1998 (R), 1999 (T,R)
Glyphosate (158)	1986 (T,R), 1987 (R and corr. to 1986 report), 1988 (R), 1994 (R), 1997 (T,R), 2004 (T), 2005 (R)
Guazatine (114)	1978 (T.R), 1980 (R), 1997 (T,R)
Haloxyfop (194)	1995 (T,R), 1996 (R and corr. to 1995 report), 2001 (R)
Heptachlor (043)	1965 (T), 1966 (T,R), 1967 (R), 1968 (R), 1969 (R), 1970 (T,R), 1974 (R), 1975 (R), 1977 (R), 1987 (R), 1991 (T,R), 1992 (corr. to 1991 report, Annex I), 1993 (R), 1994 (R)
Hexachlorobenzene (044)	1969 (T,R), 1973 (T,R), 1974 (T,R), 1978(T), 1985 (R)
Hexaconazole (170)	1990 (T,R), 1991 (R and corr. to 1990 R evaluation), 1993 (R)
Hexythiazox (176)	1991 (T,R), 1994 (R), 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), 2000 (T), 2001 (T), 2005 (T)
Imidacloprid	2001 (T), 2002 (R)
Indoxacarb (216)	2005 (T,R)
Iprodione (111)	1977 (T,R), 1980 (R), 1992 (T), 1994 (R), 1995 (T), 2001 (R)
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), 2001 (R)
Lead arsenate	1965 (T), 1968 (T,R)
Leptophos (088)	1974 (T,R), 1975 (T,R), 1978 (T,R)
Lindane (048)	1965 (T), 1966 (T,R), 1967 (R), 1968 (R), 1969 (R), 1970 (T,R, published as Annex VI to 1971 evaluations), 1973 (T,R), 1974 (R), 1975 (R), 1977 (T,R), 1978 (R), 1979 (R), 1989 (T,R), 1997 (T), 2002 (T), 2003 (R), 2004 (corr. to 2003 report)
Malathion (049)	1965 (T), 1966 (T,R), 1967 (corr. to 1966 R evaluation), 1968 (R), 1969 (R), 1970 (R), 1973 (R),

	1975 (R), 1977 (R), 1984 (R), 1997 (T), 1999 (R), 2000 (R), 2003 (T), 2004 (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)
Metalaxyl –M (212)	2002 (T), 2004 (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), 1984 (R), 1985 (T), 1989 (R), 1990 (T,R), 1994 (R), 1996 (R), 1997 (R), 2002 (T), 2003 (R), 2004 (R, corr. to 2003 report)
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), 2005 (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), 2001 (T,R), 2004 (R)
Methoprene (147)	1984 (T,R), 1986 (R), 1987 (T and corr. to 1986 report), 1988 (R), 1989 (R), 2001 (T), 2005 (R)
Methoxychlor	1965 (T), 1977 (T)
Methoxyfenozide (209)	2003 (T, R), 2004 (corr. to 2003 report)
Methyl bromide (052)	See Bromomethane
Metiram (186)	1993 (T), 1995 (R)
Mevinphos (053)	1965 (T), 1972 (T,R), 1996 (T), 1997 (E,R), 2000 (R)
MGK 264	1967 (T,R)
Monocrotophos (054)	1972 (T,R), 1975 (T,R), 1991 (T,R), 1993 (T), 1994 (R)
Myclobutanil (181)	1992 (T,R), 1997 (R), 1998 (R)
Nabam	See Dithiocarbamates, 1965 (T), 1976 (T,R)
Nitrofen (140)	1983 (T,R)
Novaluron (217)	2005 (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), 2002 (T,R)
Oxydemeton-methyl (166)	1965 (T, as demeton-*S*-methyl sulfoxide), 1967 (T), 1968 (R), 1973 (T,R), 1982 (T), 1984 (T,R), 1989 (T,R), 1992 (R), 1998 (R), 1999 (corr. to 1992 report), 2002 (T), 2004 (R)
Oxythioquinox	See Chinomethionat
Paclobutrazol (161)	1988 (T,R), 1989 (R)
Paraquat (057)	1970 (T,R), 1972 (T,R), 1976 (T,R), 1978 (R), 1981 (R), 1982 (T), 1985 (T), 1986 (T), 2003 (T), 2004 (R)
Parathion (058)	1965 (T), 1967 (T,R), 1969 (R), 1970 (R), 1984 (R), 1991 (R), 1995 (T,R), 1997 (R), 2000 (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), 2000 (R), 2003 (R)
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 report), 1999 (T)
2-Phenylphenol (056)	1969 (T,R), 1975 (R), 1983 (T), 1985 (T,R), 1989 (T), 1990 (T,R), 1999 (T,R), 2002 (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), 2004 (T), 2005 (R)
Phosalone (060)	1972 (T,R), 1975 (R), 1976 (R), 1993 (T), 1994 (R), 1997 (T), 1999 (R), 2001 (T)
Phosmet (103)	1976 (R), 1977 (corr. to 1976 R evaluation), 1978 (T,R), 1979 (T,R), 1981 (R), 1984 (R), 1985 (R), 1986 (R), 1987 (R and corr. to 1986 R evaluation), 1988 (R), 1994 (T), 1997 (R), 1998 (T), 2002 (R), 2003(R)
Phosphine	See Hydrogen phosphide
Phosphamidon (061)	1965 (T), 1966 (T), 1968 (T,R), 1969 (R), 1972 (R), 1974 (R), 1982 (T), 1985 (T), 1986 (T)
Phoxim (141)	1982 (T), 1983 (R), 1984 (T,R), 1986 (R), 1987 (R), 1988 (R)
Piperonyl butoxide (062)	1965 (T,R), 1966 (T,R), 1967 (R), 1969 (R), 1972 (T,R), 1992 (T,R), 1995 (T), 2001 (R), 2002 (R)
Pirimicarb (101)	1976 (T,R), 1978 (T,R), 1979 (R), 1981 (T,R), 1982 (T), 1985 (R), 2004 (T)
Pirimiphos-methyl (086)	1974 (T,R), 1976 (T,R), 1977 (R), 1979 (R), 1983 (R), 1985 (R), 1992 (T), 1994 (R), 2003 (R), 2004

	(R, corr. to 2003 report)
Prochloraz (142)	1983 (T,R), 1985 (R), 1987 (R), 1988 (R), 1989 (R), 1990 (R), 1991 (corr. to 1990 report, Annex I, and R evaluation), 1992 (R), 2001 (T), 2004 (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), 2005 (T)
Propargite (113)	1977 (T,R), 1978 (R), 1979 (R), 1980 (T,R), 1982 (T,R), 1999 (T), 2002 (R)
Propham (183)	1965 (T), 1992 (T,R)
Propiconazole (160)	1987 (T,R), 1991 (R), 1994 (R), 2004 (T)
Propineb	1977 (T,R), 1980 (T), 1983 (T), 1984 (R), 1985 (T,R), 1993 (T,R), 2004 (R)
Propoxur (075)	1973 (T,R), 1977 (R), 1981 (R), 1983 (R), 1989 (T), 1991 (R), 1996 (R)
Propylenethiourea (PTU, 150)	1993 (T,R), 1994 (R), 1999 (T)
Pyraclostrobin (210)	2003 (T), 2004 (R)
Pyrazophos (153)	1985 (T,R), 1987 (R), 1992 (T,R), 1993 (R)
Pyrethrins (063)	1965 (T), 1966 (T,R), 1967 (R), 1968 (R), 1969 (R), 1970 (T), 1972 (T,R), 1974 (R), 1999 (T), 2000 (R), 2003 (T,R), 2005 (R)
Pyriproxyfen (200)	1999 (R,T), 2000 (R), 2001 (T)
Quintozene (064)	1969 (T,R) 1973 (T,R), 1974 (R), 1975 (T,R), 1976 (Annex I, corr. to 1975 R evaluation), 1977 (T,R), 1995 (T,R), 1998 (R)
Spinosad (203)	2001 (T,R, 2004 (R)
Sulfuryl fluoride (218)	2005 (T,R)
2,4,5-T (121)	1970 (T,R), 1979 (T,R), 1981 (T)
Tebuconazole (189)	1994 (T,R), 1996 (corr. to Annex II of 1995 report), 1997 (R)
Tebufenozide (196)	1996 (T,R), 1997 (R), 1999 (R), 2001 (T,R), 2003(T)
Tecnazine (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), 2003 (T), 2005 (R)
Thiabendazole (065)	1970 (T,R), 1971 (R), 1972 (R), 1975 (R), 1977 (T,R), 1979 (R), 1981 (R), 1997 (R), 2000 (R)
Thiodicarb (154)	1985 (T,R), 1986 (T), 1987 (R), 1988 (R), 2000 (T), 2001 (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), 2002 (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 report)
Tolylfluanid (162)	1988 (T,R), 1990 (R), 1991 (corr. to 1990 report), 2002 (T,R), 2003 (R)
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 R evaluation), 1988 (R), 1989 (R), 1992 (R), 1995 (R), 2004 (T)
Triadimenol (168)	1989 (T,R), 1992 (R), 1995 (R), 2004 (T)
Triazolylalanine	1989 (T,R)
Triazophos (143)	1982 (T), 1983 (R), 1984 (corr. to 1983 report, Annex I), 1986 (T,R), 1990 (R), 1991 (T and corr. to 1990 R evaluation), 1992 (R), 1993 (T,R), 2002 (T)
Trichlorfon (066)	1971 (T,R), 1975 (T,R), 1978 (T,R), 1987 (R)
Trichloronat	1971 (T,R)
Trichloroethylene	1968 (R)
Tricyclohexyltin hydroxide	See Cyhexatin
Trifloxystrobin (213)	2004 (T, R)
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 report 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 3: INTERNATIONAL ESTIMATED DAILY INTAKES OF PESTICIDE RESIDUES

The following tables give details of the international estimated daily intakes of the pesticides evaluated by the Meeting for the five GEMS/ Food diets and show the ratios of the estimated intakes to the corresponding ADIs.
(*) at or about the LOQ
The ranges of the ratios of intake: ADI for all the compounds evaluated are tabulated in Section 3.
Diet: g/person per day; intake: daily intake: µg/person.

ACEPHATE (95) International Estimated Daily Intake (IEDI) ADI = 0-0.03 mg/kg bw

Codex Code	Commodity	STMR or STMR-P mg/kg	Diets: g/person/day									
			Mid-East		Far-East		African		Latin American		European	
			diet	intake	diet	intake	diet	intake	diet	intake	diet	intake
FP 0226	Apple	0.81	7.5	6.1	4.7	3.8	0.3	0.2	5.5	4.5	40.0	32.4
JF 0226	Apple juice	0.81	4.5	3.6	0	0.0	0	0.0	0.3	0.2	3.8	3.1
VS 0620	Artichoke globe	1.55	2.3	3.6	0.0	0.0	0.0	0.0	0.0	0.0	5.5	8.5
VP 0061	Beans except broad bean & soya bean (green pods & immature seeds)	1.35	3.9	5.3	0.9	1.2	0.0	0.0	4.4	5.9	13.2	17.8
VB 0400	Broccoli	0.16	0.5	0.1	1.0	0.2	0.0	0.0	1.1	0.2	2.7	0.4
VB 0401	Broccoli, Chinese	0.16	ND	-	ND	-	ND	-	ND	-	ND	-
VB 0404	Cauliflower	0.16	1.3	0.2	1.5	0.2	0	0.0	0.3	0.0	13	2.1
MO 0105	Edible offal (mammalian)	0.022	4.2	0.1	1.4	0.0	2.8	0.1	6.1	0.1	12.4	0.3
PE 0112	Eggs	0	14.6	0.0	13.1	0.0	3.7	0.0	11.9	0.0	37.6	0.0
FC 0003	Mandarins (incl. Mandarin-like hybrids)	1.15	8.8	10.1	0.2	0.2	0.0	0.0	6.3	7.2	6.0	6.9
MM 0095	Meat from mammals other than marine mammals: 20% as fat	0.022	7.4	0.2	6.6	0.1	4.8	0.1	9.4	0.2	31.1	0.7
MM 0095	Meat from mammals other than marine mammals: 80% as muscle	0.022	29.6	0.7	26.2	0.6	19.0	0.4	37.6	0.8	124.4	2.7
ML 0106	Milks	0.011	116.9	1.3	32.1	0.4	41.8	0.5	160.1	1.8	289.3	3.2
	Peaches & nectarines	1.35	2.5	3.4	0.5	0.7	0.0	0.0	0.8	1.1	12.5	16.9
FP 0230	Pear	0.81	3.3	2.7	2.8	2.3	0.0	0.0	1.0	0.8	11.3	9.2
VO 0051	Peppers	1.9	3.4	6.5	2.1	4.0	5.4	10.3	2.4	4.6	10.4	19.8
PM 0110	Poultry meat: 10% as fat	0	3.1	0.0	1.3	0.0	0.6	0.0	2.5	0.0	5.3	0.0
PM 0110	Poultry meat: 90% as muscle	0	27.9	0.0	11.9	0.0	5.0	0.0	22.8	0.0	47.7	0.0

VD 0541	Soya bean (dry)	0.055	4.5	0.2	2.0	0.1	0.5	0.0	0.0	0.0	0.0	0.0
OR 0541	Soya bean oil, refined	0.023	1.3	0.0	1.7	0.0	3.0	0.1	14.5	0.3	4.3	0.1
	Total intake (µg/person)=			44.0		13.9		11.7		27.9		124.1
	Bodyweight per region (kg bw) =			60		55		60		60		60
	ADI (µg/person)=			1800		1650		1800		1800		1800
	%ADI=			2.4%		0.8%		0.7%		1.6%		6.9%
	Rounded %ADI=			2%		1%		1%		2%		7%

AZOCYCLOTIN/ (67)/ CYHEXATIN (129) International Estimated Daily Intake (IEDI) ADI = 0 - 0.003 mg/kg bw

			Diets: g/person/day									
Codex		STMR or	Mid-East		Far-East		African		Latin American		European	
Code	Commodity	STMR-P mg/kg	diet	intake	diet	intake	diet	intake	diet	intake	diet	intake
FC 0004	Oranges, sweet, sour (incl. Orange-like hybrids)	0.035	31.5	1.1	4.0	0.1	4.8	0.2	31.0	1.1	29.8	1.0
FP 0226	Apple	0.025	7.5	0.2	4.7	0.1	0.3	0.0	5.5	0.1	40.0	1.0
JF 0226	Apple juice	0.002	4.5	0.0	0	0.0	0	0.0	0.3	0.0	3.8	0.0
FI 0327	Banana	0.01	8.3	0.1	26.2	0.3	21.0	0.2	102.3	1.0	22.8	0.2
FB 021	Currants, red, black, white	0.05	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.3	0.0
FB 269	Grapes (fresh, wine, excluding dried grapes)	0.085	15.8	1.3	1.0	0.1	0.0	0.0	1.3	0.1	13.8	1.2
DF 269	Grapes, dried (= currants, raisins and sultanas)	0.076	0.3	0.0	0.0	0.0	0.0	0.0	0.3	0.0	2.3	0.2
JF 0004	Orange juice	0.002	7.3	0.0	0.0	0.0	0.0	0.0	0.3	0.0	4.5	0.0
FP 0230	Pear	0.025	3.3	0.1	2.8	0.1	0.0	0.0	1.0	0.0	11.3	0.2
VR 596	Sugar beet	0.05	0.5	0.0	0.0	0.0	0.0	0.0	0.3	0.0	2.0	0.1
	Wine only	0.06	0.5	0.0	0.0	0.0	0.8	0.0	19.8	1.2	97.8	5.9
	Total intake (µg/person)=			2.9		0.6		0.4		3.6		9.9
	Bodyweight per region (kg bw) =			60		55		60		60		60
	ADI (µg/person)=			180		165		180		180		180
	%ADI=			1.6%		0.4%		0.2%		2.0%		5.5%
	Rounded %ADI=			2		0		0		2		5

CHLORPROPHAM (201) International Estimated Daily Intake (IEDI) ADI = 0-0.05 mg/kg bw

Codex Code	Commodity	STMR or STMR-P mg/kg	Diets: g/person/day									
			Mid-East		Far-East		African		Latin American		European	
			diet	intake	diet	intake	diet	intake	diet	intake	diet	intake
VR 0589	Potato	3.60	59.0	212.4	19.2	69.1	20.6	74.2	40.8	40.8	240.8	866.9
MM 0812	Cattle meat: 20% as fat	0.004	2.9	0.0	0.5	0.0	2.1	0.0	6.0	0.0	12.7	0.1
MM 0812	Cattle meat: 80% as muscle	0.004	11.7	0.0	2.2	0.0	8.3	0.0	24.0	0.1	50.6	0.2
ML 0812	Cattle milk	0.0003	79.5	0.0	23.2	0.0	35.8	0.0	159.3	0.0	287.0	0.1
	Total intake (µg/person)=			212.5		69.1		74.2		147.0		867.2
	Bodyweight per region (kg bw) =			60		55		60		60		60
	ADI (µg/person)=			3000		2750		3000		3000		3000
	%ADI=			7.1		2.5		2.5		4.9		28.9
	Rounded %ADI=			7		3		2		5		30

FENHEXAMID (215) International Estimated Daily Intake (IEDI) ADI= 0-0.2 mg/kg bw

Codex Code	Commodity	STMR or STMR-P mg/kg	Diets: g/person/day									
			Mid-East		Far-East		African		Latin American		European	
			diet	intake	diet	intake	diet	intake	diet	intake	diet	intake
TN 0660	Almonds	0.02	0.5	0.0	0.0	0.0	0.0	0.0	0.1	0.0	1.8	0.0
FS 0240	Apricot	3.85	3.0	11.6	0.0	0.0	0.0	0.0	0.0	0.0	3.5	13.5
FB 0264	Blackberries	2	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
FB 0020	Blueberries	1.65	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.5	0.8
FS 0013	Cherries	1.35	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	3.0	4.1
VC 0424	Cucumber	0.185	2.4	0.4	2.3	0.4	0.0	0.0	4.2	0.8	4.5	0.8
FB 0021	Currants, red, black, white	1.65	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.3	0.5
FB 0266	Dewberries, incl boysen- & loganberry	2	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
MO 0105	Edible offal (mammalian)	0	4.2	0.0	1.4	0.0	2.8	0.0	6.1	0.0	12.4	0.0
VO 0440	Egg plant	0.71	6.3	4.5	3.0	2.1	0.7	0.5	6.0	4.3	2.3	1.6
FB 0267	Elderberries	1.65	ND	-	ND	-	ND	-	ND	-	ND	-
VC 0425	Gherkin	0.185	2.4	0.4	2.3	0.4	0.0	0.0	4.2	0.8	4.5	0.8
FB 0268	Gooseberry	1.65	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.5	0.8
FB 0269	Grapes (fresh, wine, excluding dried grapes)	4.3	15.8	67.9	1.0	4.3	0.0	0.0	1.3	5.6	13.8	59.3

FENHEXAMID (215) International Estimated Daily Intake (IEDI) ADI= 0-0.2 mg/kg bw

Codex Code	Commodity	STMR or STMR-P mg/kg	Diets: g/person/day									
			Mid-East		Far-East		African		Latin American		European	
			diet	intake	diet	intake	diet	intake	diet	intake	diet	intake
DF 0269	Grapes, dried (= currants, raisins and sultanas)	8	0.3	2.4	0.0	0.0	0.0	0.0	0.3	2.4	2.3	18.4
FI 0341	Kiwi fruit	6.3	0.0	0.0	0.0	0.0	1.9	12.0	0.1	0.6	1.5	9.5
VL 0482	Lettuce, head	11.5	2.3	26.5	0.0	0.0	0.0	0.0	5.8	66.7	22.5	258.8
VL 0483	Lettuce, leaf	11.5	2.3	26.5	0.0	0.0	0.0	0.0	5.8	66.7	22.5	258.8
MM 0095	Meat from mammals other than marine mammals	0	37.0	0.0	32.8	0.0	23.8	0.0	47.0	0.0	155.5	0.0
ML 0106	Milks	0	116.9	0.0	32.1	0.0	41.8	0.0	160.1	0.0	289.3	0.0
FS 0245	Nectarine	3.85	1.3	4.8	0.3	1.0	0.0	0.0	0.4	1.5	6.3	24.1
FS 0247	Peach	3.85	1.3	4.8	0.3	1.0	0.0	0.0	0.4	1.5	6.3	24.1
VO 0051	Peppers	0.71	3.4	2.4	2.1	1.5	5.4	3.8	2.4	1.7	10.4	7.4
FS 0014	Plums (fresh, prunes)	0.31	1.8	0.6	0.5	0.2	0.0	0.0	0.0	0.0	4.3	1.3
FB 0272	Raspberries, red, black	2	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.5	1.0
VC 0431	Squash, summer	0.185	10.5	1.9	2.2	0.4	0.0	0.0	14.0	2.6	3.5	0.6
FB 0275	Strawberry	3.3	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	5.3	17.5
VO 0448	Tomato (fresh)	0.395	44.1	17.4	5.7	2.3	14.6	5.8	25.5	10.1	34.9	13.8
JF 0448	Tomato juice	0.13	0.3	0.0	0.0	0.0	0.0	0.0	0.0	0.0	2.0	0.3
	Tomato paste	2.05	5.8	11.9	0.2	0.4	0.3	0.6	0.0	0.0	4.0	8.2
	Total intake (µg/person)=			184.0		13.9		22.7		165.3		725.9
	Bodyweight per region (kg bw)=			60		55		60		60		60
	ADI (µg/person)=			12000		11000		12000		12000		12000
	%ADI=			1.5		0.1		0.2		1.4		6.0
	Rounded %ADI=			2		0		0		1		6

FLUORIDE International Estimated Daily Intake (IEDI)

Codex Code	Commodity	STMR or STMR-P mg/kg	Diets: g/person/day									
			Mid-East		Far-East		African		Latin American		European	
			diet	intake	diet	intake	diet	intake	diet	intake	diet	intake
TN 0085	Tree nuts	0.28	1.1	0.3	13.5	3.8	4.5	1.3	17.8	5.0	4.6	1.3
DF 0226	Apple, dried	2.4	ND	-	ND	-	ND	-	ND	-	ND	-
DF 0240	Apricot, dried	2.4	ND	-	ND	-	ND	-	ND	-	ND	-
CM 0081	Bran, unprocessed of cereal grain (except buckwheat, cañihua, quinoa)	37	ND	-	ND	-	ND	-	ND	-	ND	-
GC 0080	Cereal grains	3.5	26.2		24.2		80.3		13.5		22.4	78.4
DF 0295	Dates, dried or dried and candied	2.4	ND	-	ND	-	ND	-	ND	-	ND	-
DF 0167	Dried fruits	2.4	ND	-	ND	-	ND	-	ND	-	ND	-
DF 0297	Fig, dried or dried and candied	2.4	0.5	1.2	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
DF 0269	Grapes, dried (= currants, raisins and sultanas)	2.4	0.3	0.7	0.0	0.0	0.0	0.0	0.3	0.7	2.3	5.5
CF 1255	Maize flour	24	31.8	763.2	31.2	748.8	106.2	2548.8	40.3	967.2	8.8	211.2
DF 0014	Prunes	2.4	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.5	1.2
CM 0649	Rice, husked	37	0.0	0.0	1.8	66.6	34.7	1283.9	21.0	777.0	2.5	92.5
CM 1205	Rice, polished	37	48.8	1805.6	277.5	10267.5	68.8	2545.6	65.5	2423.5	9.3	344.1
CF 1250	Rye flour	37	0.0	0.0	1.0	37.0	0.0	0.0	0.0	0.0	1.5	55.5
CF 1251	Rye wholemeal	37	0.0	0.0	1.0	37.0	0.0	0.0	0.0	0.0	1.5	55.5
CF 1211	Wheat flour	35	323.0	11305.0	114.0	3990.0	28.3	990.5	112.0	3920.0	175.8	6153.0
CF 1210	Wheat germ	66	0.1	6.6	0.1	6.6	0.0	0.0	0.1	6.6	0.1	6.6
CF 1212	Wheat wholemeal	37	ND	-	ND	-	ND	-	ND	-	ND	-
	Total intake (µg/person)=			13882.6		15157.3		7370.1		8100.0		7004.8

GLYPHOSATE (158) International Estimated Daily Intake (IEDI) ADI = 0-1 mg/kg

Codex Code	Commodity	STMR or STMR-P mg/kg	Diets: g/person/day									
			Mid-East		Far-East		African		Latin American		European	
			diet	intake	diet	intake	diet	intake	diet	intake	diet	intake
FI 0327	Banana	0.05	8.3	0.4	26.2	1.3	21.0	1.1	102.3	5.1	22.8	1.1
GC 0640	Barley (fresh) /1	7.65	1.0	7.7	3.5	26.8	1.8	13.8	6.5	49.7	19.8	151.5
VD 0071	Beans (dry)	0.17	2.3	0.4	4.8	0.8	0.0	0.0	13.0	2.2	3.5	0.6
GC 0641	Buckwheat /1	3.7	0.0	0.0	1.0	3.7	0.0	0.0	0.0	0.0	0.0	0.0

Annex 3

	GLYPHOSATE (158)	International Estimated Daily Intake (IEDI)									ADI = 0-1 mg/kg
		STMR or	Diets: g/person/day									
Codex	Commodity	STMR-P	Mid-East		Far-East		African		Latin American		European	
Code		mg/kg	diet	intake	diet	intake	diet	intake	diet	intake	diet	intake
OR 0691	Cotton seed oil, edible	0.04	3.8	0.2	0.5	0.0	0.5	0.0	0.5	0.0	0.0	0.0
MO 0105	Edible offal (mammalian) /2	2.9	4.2	12.2	1.4	4.1	2.8	8.1	6.1	17.7	12.4	36.0
PE 0112	Eggs	0	14.6	0.0	13.1	0.0	3.7	0.0	11.9	0.0	37.6	0.0
CF 1255	Maize flour	0.13	31.8	4.1	31.2	4.1	106.2	13.8	40.3	5.2	8.8	1.1
GC 0645	Maize (fresh)	0.12	16.5	2.0	0.0	0.0	0.0	0.0	1.5	0.2	0.0	0.0
OR 0645	Maize oil, edible	0.04	1.8	0.1	0.0	0.0	0.3	0.0	0.5	0.0	1.3	0.1
MM 0095	Meat from mammals other than marine mammals /2	0.05	37.0	1.9	32.8	1.6	23.8	1.2	47.0	2.4	155.5	7.8
ML 0106	Milks	0	116.9	0.0	32.1	0.0	41.8	0.0	160.1	0.0	289.3	0.0
GC 0646	Millet /1	3.7	2.5	9.3	9.3	34.4	51.8	191.7	0.0	0.0	0.0	0.0
GC 0647	Oats /1	4.15	0.0	0.0	0.0	0.0	0.2	0.8	0.8	3.3	2.0	8.3
VD 0072	Peas (dry)	0.5	0.5	0.3	1.7	0.9	5.1	2.6	1.3	0.7	1.8	0.9
PM 0110	Poultry meat	0	31.0	0.0	13.2	0.0	5.5	0.0	25.3	0.0	53.0	0.0
PO 0111	Poultry, edible offal of	0.088	0.1	0.0	0.1	0.0	0.1	0.0	0.4	0.0	0.4	0.0
SO 0495	Rape seed	0.93	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
OR 0495	Rape seed oil, edible	0.1	4.5	0.5	2.7	0.3	0.0	0.0	0.3	0.0	7.3	0.7
GC 0650	Rye /1	3.7	0.0	0.0	1.0	3.7	0.0	0.0	0.0	0.0	1.5	5.6
GC 0651	Sorghum /1	4.8	2.0	9.6	9.7	46.6	26.6	127.7	0.0	0.0	0.0	0.0
VD 0541	Soya bean (dry)	5	4.5	22.5	2.0	10.0	0.5	2.5	0.0	0.0	0.0	0.0
OC 0541	Soya bean oil, crude	0.1	1.3	0.1	1.7	0.2	3.0	0.3	14.5	1.5	4.3	0.4
GS 0659	Sugar cane	0.27	18.5	5.0	7.3	2.0	15.9	4.3	3.5	0.9	0.0	0.0
DM 0659	Sugar cane molasses	2	ND	-	ND	-	ND	-	ND	-	ND	-
SO 0702	Sunflower seed, consumed fresh	0.395	1.0	0.4	0.0	0.0	0.6	0.2	0.0	0.0	0.0	0.0
GC 0653	Triticale /1	3.7	0.0	0.0	1.0	3.7	0.0	0.0	0.0	0.0	0.0	0.0
CM 0654	Wheat bran, unprocessed /3	1.8	ND	-	ND	-	ND	-	ND	-	ND	-
	Wheat bulgur wholemeal /3	1.05	0.3	0.3	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
CF 1211	Wheat flour /3	0.11	323.0	35.5	114.0	12.5	28.3	3.1	112.0	12.3	175.8	19.3
	Wheat macaroni /3	1.05	1.0	1.1	0.3	0.3	0.0	0.0	2.8	2.9	1.3	1.4
	Wheat pastry /3	1.05	3.0	3.2	0.5	0.5	0.0	0.0	2.0	2.1	1.0	1.1
	Total intake (µg/person)=			116.4		157.4		371.1		106.3		235.8
	Bodyweight per region (kg bw) =			60		55		60		60		60
	ADI (µg/person)=			60000		55000		60000		60000		60000
	%ADI=			0.2		0.3		0.6		0.2		0.4
	Rounded %ADI=			0		0		1		0		0

	INDOXACARB (216)	International Estimated Daily Intake (IEDI)									ADI = 0 - 0.01 mg/kg bw
Codex Code	Commodity	STMR or STMR-P mg/kg	Diets: g/person/day									
			Mid-East		Far-East		African		Latin American		European	
			diet	intake	diet	intake	diet	intake	diet	intake	diet	intake
FP 0226	Apple	0.21	7.5	1.6	4.7	1.0	0.3	0.1	5.5	1.2	40.0	8.4
JF 0226	Apple juice	0.011	4.5	0.0	0	0.0	0	0.0	0.3	0.0	3.8	0.0
VB 0400	Broccoli	0.055	0.5	0.0	1.0	0.1	0.0	0.0	1.1	0.1	2.7	0.1
	Cabbages (head & leafy brassicas, kohlrabi)	0.435	5.0	2.2	9.7	4.2	0.0	0.0	10.5	4.6	26.8	11.7
VB 0404	Cauliflower	0.02	1.3	0.0	1.5	0.0	0	0.0	0.3	0.0	13	0.3
VD 0524	Chick-pea (dry)	0.02	3.3	0.1	2.5	0.1	0.0	0.0	0.0	0.0	1.0	0.0
SO 0691	Cotton seed	0.36	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
OR 0691	Cotton seed oil, edible	0.013	3.8	0.0	0.5	0.0	0.5	0.0	0.5	0.0	0.0	0.0
	Cucumbers & gherkins	0.02	4.8	0.1	4.5	0.1	0.0	0.0	8.3	0.2	9.0	0.2
MO 0105	Edible offal (mammalian)	0.016	4.2	0.1	1.4	0.0	2.8	0.0	6.1	0.1	12.4	0.2
VO 0440	Egg plant	0.11	6.3	0.7	3.0	0.3	0.7	0.1	6.0	0.7	2.3	0.3
PE 0112	Eggs	0	14.6	0.0	13.1	0.0	3.7	0.0	11.9	0.0	37.6	0.0
FB 0269	Grapes (fresh, wine, excluding dried grapes)	0.3	15.8	4.7	1.0	0.3	0.0	0.0	1.3	0.4	13.8	4.1
DF 0269	Grapes, dried (= currants, raisins and sultanas)	0.81	0.3	0.2	0.0	0.0	0.0	0.0	0.3	0.2	2.3	1.9
VL 0482	Lettuce, head	2.8	2.3	6.4	0.0	0.0	0.0	0.0	5.8	16.2	22.5	63.0
VL 0483	Lettuce, leaf	6.6	2.3	15.2	0.0	0.0	0.0	0.0	5.8	38.3	22.5	148.5
MM 0095	Meat from mammals other than marine mammals: 20% as fat	0.44	7.4	3.3	6.6	2.9	4.8	2.1	9.4	4.1	31.1	13.7
MM 0095	Meat from mammals other than marine mammals: 80% as muscle	0.01	29.6	0.3	26.2	0.3	19.0	0.2	37.6	0.4	124.4	1.2
VC 0046	Melons, except watermelon	0.02	16.0	0.3	2.0	0.0	0.0	0.0	2.8	0.1	18.3	0.4
ML 0106	Milks	0.048	116.9	5.6	32.1	1.5	41.8	2.0	160.1	7.7	289.3	13.9
VD 0536	Mung bean (dry)	0.02	ND	-	ND	-	ND	-	ND	-	ND	-
FS 0247	Peach	0.11	1.3	0.1	0.3	0.0	0.0	0.0	0.4	0.0	6.3	0.7
SO 0697	Peanut	0.01	0.3	0.0	0.2	0.0	2.3	0.0	0.3	0.0	3.0	0.0
OR 0697	Peanut oil, edible	0.003	0.0	0.0	1.8	0.0	3.5	0.0	0.5	0.0	1.8	0.0
FP 0230	Pear	0.051	3.3	0.2	2.8	0.1	0.0	0.0	1.0	0.1	11.3	0.6
VO 0051	Peppers	0.038	3.4	0.1	2.1	0.1	5.4	0.2	2.4	0.1	10.4	0.4
VR 0589	Potato	0.01	59.0	0.6	19.2	0.2	20.6	0.2	40.8	0.4	240.8	2.4
PM 0110	Poultry meat: 10% as fat	0	3.1	0.0	1.3	0.0	0.6	0.0	2.5	0.0	5.3	0.0
PM 0110	Poultry meat: 90% as muscle	0	27.9	0.0	11.9	0.0	5.0	0.0	22.8	0.0	47.7	0.0
PO 0111	Poultry, edible offal of	0	0.1	0.0	0.1	0.0	0.1	0.0	0.4	0.0	0.4	0.0
VD 0541	Soya bean (dry)	0.027	4.5	0.1	2.0	0.1	0.5	0.0	0.0	0.0	0.0	0.0
OR 0541	Soya bean oil, refined	0.018	1.3	0.0	1.7	0.0	3.0	0.1	14.5	0.3	4.3	0.1
VO 0447	Sweet corn (corn-on-the-cob)	0.01	0.0	0.0	0.0	0.0	4.4	0.0	0.0	0.0	8.3	0.1

	INDOXACARB (216)	International Estimated Daily Intake (IEDI)										ADI = 0 - 0.01 mg/kg bw
Codex Code	Commodity	STMR or STMR-P mg/kg	Diets: g/person/day									
			Mid-East		Far-East		African		Latin American		European	
			diet	intake	diet	intake	diet	intake	diet	intake	diet	intake
VO 0448	Tomato (fresh)	0.11	44.1	4.9	5.7	0.6	14.6	1.6	25.5	2.8	34.9	3.8
JF 0448	Tomato juice	0.022	0.3	0.0	0.0	0.0	0.0	0.0	0.0	0.0	2.0	0.0
	Tomato paste	0.21	5.8	1.2	0.2	0.0	0.3	0.1	0.0	0.0	4.0	0.8
	Wine only	0.018	0.5	0.0	0.0	0.0	0.8	0.0	19.8	0.4	97.8	1.8
	Total intake (µg/person)=			48.2		12.0		6.7		78.1		278.6
	Bodyweight per region (kg bw) =			60		55		60		60		60
	ADI (µg/person)=			600		550		600		600		600
	%ADI=			8.0		2.2		1.1		13.0		46.4
	Rounded %ADI=			8		2		1		10		50

	METHIOCARB (132)	International Estimated Daily Intake (IEDI)										ADI = 0 - 0.02 mg/kg bw
Codex Code	Commodity	STMR or STMR-P mg/kg	Diets: g/person/day									
			Mid-East		Far-East		African		Latin American		European	
			diet	intake	diet	intake	diet	intake	diet	intake	diet	intake
VS 0620	Artichoke globe	0.005	2.3	0.0	0.0	0.0	0.0	0.0	0.0	0.0	5.5	0.0
GC 0640	Barley (fresh)	0	1.0	0.0	3.5	0.0	1.8	0.0	6.5	0.0	19.8	0.0
VB 0402	Brussels sprouts	0.01	0.5	0.0	1.0	0.0	0.0	0.0	1.1	0.0	2.7	0.0
	Cabbages (head & leafy brassicas, kohlrabi)	0.05	5.0	0.3	9.7	0.5	0.0	0.0	10.5	0.5	26.8	1.3
VB 0404	Cauliflower	0.05	1.3	0.1	1.5	0.1	0	0.0	0.3	0.0	13	0.7
TN 0666	Hazelnuts	0.04	0.0	0.0	0.0	0.0	0.0	0.0	0.1	0.0	0.3	0.0
VA 0384	Leek	0.15	0.5	0.1	0.0	0.0	0.0	0.0	0.3	0.0	2.0	0.3
VL 0482	Lettuce, head	0.05	2.3	0.1	0.0	0.0	0.0	0.0	5.8	0.3	22.5	1.1
GC 0645	Maize (fresh, flour)	0	48.3	0.0	31.2	0.0	106.2	0.0	41.8	0.0	8.8	0.0
VC 0046	Melons, except watermelon	0.02	16.0	0.3	2.0	0.0	0.0	0.0	2.8	0.1	18.3	0.4
VA 0385	Onion, bulb	0.025	23.0	0.6	11.5	0.3	7.3	0.2	13.8	0.3	27.8	0.7
VD 0072	Peas (dry)	0.05	0.5	0.0	1.7	0.1	5.1	0.3	1.3	0.1	1.8	0.1
VP 0063	Peas (green pods & immature seeds)	0.05	5.5	0.3	2.0	0.1	0.0	0.0	0.8	0.0	14.0	0.7
VO 0445	Peppers, sweet (incl. pimiento)	1.06	3.3	3.5	2.0	2.1	5.3	5.6	2.3	2.4	10.3	10.9
VR 0589	Potato	0.01	59.0	0.6	19.2	0.2	20.6	0.2	40.8	0.4	240.8	2.4
SO 0495	Rape seed	0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0

Annex 3

	METHIOCARB (132)	International Estimated Daily Intake (IEDI)									ADI = 0 - 0.02 mg/kg bw
			Diets: g/person/day									
Codex Code	Commodity	STMR or STMR-P mg/kg	Mid-East		Far-East		African		Latin American		European	
			diet	intake	diet	intake	diet	intake	diet	intake	diet	intake
FB 0275	Strawberry	0.44	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	5.3	2.3
VR 0596	Sugar beet	0.01	0.5	0.0	0.0	0.0	0.0	0.0	0.3	0.0	2.0	0.0
SO 0702	Sunflower seed, consumed fresh	0	1.0	0.0	0.0	0.0	0.6	0.0	0.0	0.0	0.0	0.0
GC 0654	Wheat	0	327.3	0.0	114.8	0.0	28.3	0.0	116.8	0.0	178.0	0.0
	Total intake (µg/person)=			5.8		3.4		6.3		4.2		21.0
	Bodyweight per region (kg bw) =			60		55		60		60		60
	ADI (µg/person)=			1200		1100		1200		1200		1200
	%ADI=			0.5		0.3		0.5		0.6		1.8
	Rounded %ADI=			0		0		1		1		2

	METHOPRENE (147)	International Estimated Daily Intake (IEDI)									ADI = 0 - 0.09 mg/kg bw
			Diets: g/person/day									
Codex Code	Commodity	STMR or STMR-P mg/kg	Mid-East		Far-East		African		Latin American		European	
			diet	intake	diet	intake	diet	intake	diet	intake	diet	intake
GC 0080	Cereal grains	4.85	429.9	2085.0	450.8	2186.4	318.3	1543.8	252.4	1224.1	221.9	1076.2
MM 0095	Meat from mammals other than marine mammals: 20% as fat	0.092	7.4	0.7	6.6	0.6	4.8	0.4	9.4	0.9	31.1	2.9
MM 0095	Meat from mammals other than marine mammals: 80% as muscle	0.007	29.6	0.2	26.2	0.2	19.0	0.1	37.6	0.3	124.4	0.9
MO 0105	Edible offal (mammalian)	0.014	4.2	0.1	1.4	0.0	2.8	0.0	6.1	0.1	12.4	0.2
PM 0110	Poultry meat: 10% as fat*	-	3.1	-	1.3	-	0.6	-	2.5	-	5.3	-
PM 0110	Poultry meat: 90% as muscle	0.007	27.9	0.2	11.9	0.1	5.0	0.0	22.8	0.2	47.7	0.3
PO 0111	Poultry, edible offal of	0.007	0.1	0.0	0.1	0.0	0.1	0.0	0.4	0.0	0.4	0.0
ML 0106	Milks	0.044	116.9	5.1	32.1	1.4	41.8	1.8	160.1	7.0	289.3	12.7
PE 0112	Eggs	0.006	14.6	0.1	13.1	0.1	3.7	0.0	11.9	0.1	37.6	0.2
	Total intake (µg/person)=			2091.4		2188.8		1546.3		1232.6		1093.4
	Bodyweight per region (kg bw) =			60		55		60		60		60
	ADI (µg/person)=			5400		4950		5400		5400		5400
	%ADI=			38.7		44.2		28.6		22.8		20.2
	Rounded %ADI=			40		40		30		20		20

NOVALURON (217)		International Estimated Daily Intake (IEDI)								ADI = 0 - 0.01 mg/kg bw	
		STMR or STMR-P	Diets: g/person/day								
Codex			Mid-East		Far-East		African		Latin American		European	
Code	Commodity	mg/kg	diet	intake	diet	intake	diet	intake	diet	intake	diet	intake
FP 0009	Pome fruits	0.65	10.8	7.0	7.5	4.9	0.3	0.2	6.5	4.2	51.3	33.3
JF 0226	Apple juice	0.065	4.5	0.3	0	0.0	0	0.0	0.3	0.0	3.8	0.2
OR 0691	Cotton seed oil, edible	0.041	3.8	0.2	0.5	0.0	0.5	0.0	0.5	0.0	0.0	0.0
MO 0105	Edible offal (mammalian)	0.26	4.2	1.1	1.4	0.4	2.8	0.7	6.1	1.6	12.4	3.2
PE 0112	Eggs	0	14.6	0.0	13.1	0.0	3.7	0.0	11.9	0.0	37.6	0.0
MM 0095	Meat from mammals other than marine mammals: 20% as fat	4.1	7.4	30.3	6.6	26.9	4.8	19.5	9.4	38.5	31.1	127.5
MM 0095	Meat from mammals other than marine mammals: 80% as muscle	0.19	29.6	5.6	26.2	5.0	19.0	3.6	37.6	7.1	124.4	23.6
ML 0106	Milks	0.2	116.9	23.4	32.1	6.4	41.8	8.4	160.1	32.0	289.3	57.9
VR 0589	Potato	0.01	59.0	0.6	19.2	0.2	20.6	0.2	40.8	0.4	240.8	2.4
PM 0110	Poultry meat: 10% as fat	0.005	3.1	0.0	1.3	0.0	0.6	0.0	2.5	0.0	5.3	0.0
PM 0110	Poultry meat: 90% as muscle	0	27.9	0.0	11.9	0.0	5.0	0.0	22.8	0.0	47.7	0.0
PO 0111	Poultry, edible offal of	0	0.1	0.0	0.1	0.0	0.1	0.0	0.4	0.0	0.4	0.0
VP 0541	Soya bean (immature seeds)	0.01	0.1	0.0	0.1	0.0	0.1	0.0	0.0	0.0	0.0	0.0
VO 0448	Tomato (fresh, juice, paste, peeled)	0.02	81.5	1.6	7.0	0.1	16.5	0.3	25.5	0.5	66.6	1.3
	Total intake (µg/person)=			70.1		43.9		33.0		84.5		249.6
	Bodyweight per region (kg bw) =			60		55		60		60		60
	ADI (µg/person)=			660		605		660		660		660
	%ADI=			10.6		7.3		5.0		12.8		37.8
	Rounded %ADI=			10		7		5		10		40

PHORATE (112)		International Estimated Daily Intake (IEDI)								ADI = 0 - 0.0007 mg/kg bw/day	
		STMR or STMR-P	Diets: g/person/day								
Codex			Mid-East		Far-East		African		Latin American		European	
Code	Commodity	mg/kg	diet	intake	diet	intake	diet	intake	diet	intake	diet	intake
VD 0071	Beans (dry)	0.05	2.3	0.1	4.8	0.2	0.0	0.0	13.0	0.7	3.5	0.2

SM 0716	Coffee beans, roasted	0.00335	0.5	0.0	0.2	0.0	0.0	0.0	0.8	0.0	5.8	0.0
VP 0526	Common bean (green pods and/or immature seeds)	0.05	3.5	0.2	0.8	0.0	0.0	0.0	4.0	0.2	12.0	0.6
SO 0691	Cotton seed	0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
MO 0105	Edible offal (mammalian)	0.02	4.2	0.1	1.4	0.0	2.8	0.1	6.1	0.1	12.4	0.2
PE 0112	Eggs	0	14.6	0.0	13.1	0.0	3.7	0.0	11.9	0.0	37.6	0.0
CF 1255	Maize flour	0.046	31.8	1.5	31.2	1.4	106.2	4.9	40.3	1.9	8.8	0.4
GC 0645	Maize (fresh)	0.02	16.5	0.3	0.0	0.0	0.0	0.0	1.5	0.0	0.0	0.0
OR 0645	Maize oil, edible*	0.0162	1.8	0.0	0.0	0.0	0.3	0.0	0.5	0.0	1.3	0.0
MM 095	Meat from mammals other than marine mammals: 20% as fat	0.02	7.4	0.1	6.6	0.1	4.8	0.1	9.4	0.2	31.1	0.6
MM 095	Meat from mammals other than marine mammals: 80% as muscle	0.02	29.6	0.6	26.2	0.5	19.0	0.4	37.6	0.8	124.4	2.5
ML 0106	Milks	0.005	116.9	0.6	32.1	0.2	41.8	0.2	160.1	0.8	289.3	1.4
VR 0589	Potato**	0.018	59.0	1.1	19.2	0.3	20.6	0.4	40.8	0.7	240.8	4.3
PM 0110	Poultry meat: 10% as fat	0	3.1	0.0	1.3	0.0	0.6	0.0	2.5	0.0	5.3	0.0
PM 0110	Poultry meat: 90% as muscle	0	27.9	0.0	11.9	0.0	5.0	0.0	22.8	0.0	47.7	0.0
GC 0651	Sorghum	0.05	2.0	0.1	9.7	0.5	26.6	1.3	0.0	0.0	0.0	0.0
VD 0541	Soya bean (dry)	0	4.5	0.0	2.0	0.0	0.5	0.0	0.0	0.0	0.0	0.0
VR 0596	Sugar beet	0.05	0.5	0.0	0.0	0.0	0.0	0.0	0.3	0.0	2.0	0.1
	Total intake (µg/person)=			4.7		3.4		7.4		5.4		10.5
	Bodyweight per region (kg bw) =			60		55		60		60		60
	ADI (µg/person)=			42		38.5		42		42		42
	%ADI=			11.2		8.8		17.5		12.8		24.9
	Rounded %ADI=			10		9		20		10		20

	PYRETHRINS (063)	International Estimated Daily Intake (IEDI)										ADI = 0 - 0.04 mg/kg bw
		STMR or	Diets: g/person/day									
Codex	Commodity	STMR-P	Mid-East		Far-East		African		Latin American		European	
Code		mg/kg	diet	intake	diet	intake	diet	intake	Diet	Intake	diet	Intake
GC 0080	Cereal grains	0.05	429.9	21.5	450.8	22.5	318.3	15.9	252.4	12.6	221.9	11.1
FC 0001	Citrus fruits	0.04	47.1	1.9	6.3	0.3	5.1	0.2	54.6	2.2	44.6	1.8
DF 0167	Dried fruit	0.05	0.3	0.0	0.2	0.0	0.3	0.0	0.3	0.0	0.0	0.0
VC 0045	Fruiting vegetables, Cucurbits	0.04	80.5	3.2	18.2	0.7	0.0	0.0	30.5	1.2	38.5	1.5
SO 0697	Peanut	0.05	0.3	0.0	0.2	0.0	2.3	0.1	0.3	0.0	3.0	0.2
VO 0051	Peppers	0.04	3.4	0.1	2.1	0.1	5.4	0.2	2.4	0.1	10.4	0.4
VD 0070	Pulses	0.05	18.9	0.9	14.5	0.7	17.5	0.9	20.3	1.0	9.4	0.5
VR 0075	Root and tuber vegetables	0	61.8	0.0	108.5	0.0	321.3	0.0	159.3	0.0	242.0	0.0
VO 0448	Tomato	0.04	81.5	3.3	7.0	0.3	16.5	0.7	25.5	1.0	66.6	2.7
JF 0448	Tomato juice	0.018	0.3	0.0	0.0	0.0	0.0	0.0	0.0	0.0	2.0	0.0
	Tomato paste	0.018	5.8	0.0	0.2	0.0	0.3	0.0	0.0	0.0	4.0	0.0
TN 0085	Tree nuts	0.2	1.1	0.2	13.5	2.7	4.5	0.9	17.8	3.6	4.6	0.9
	Total intake (µg/person)=			31.3		27.3		18.9		21.7		19.1
	Bodyweight per region (kg bw) =			60		55		60		60		60
	ADI (µg/person)=			2400		2200		2400		2400		2400
	%ADI=			1.3		1.2		0.8		0.9		0.8
	Rounded %ADI=			1		1		1		1		1

	SULFURYL FLUORIDE (218)	International Estimated Daily Intake (IEDI)						ADI=0-0.01			
		STMR or	Diets: g/person/day								
Codex	Commodity	STMR-P	Mid-East		Far-East		African		Latin American		European	
Code		mg/kg	diet	intake	diet	intake	diet	intake	diet	intake	diet	intake
TN 0085	Tree nuts	0.28	1.1	0.3	13.5	3.8	4.5	1.3	17.8	5.0	4.6	1.3
DF 0226	Apple, dried	0.004	ND	-	ND	-	ND	-	ND	-	ND	-
DF 0240	Apricot, dried	0.004	ND	-	ND	-	ND	-	ND	-	ND	-
CM 0081	Bran, unprocessed of cereal grain (except buckwheat, cañihua, quinoa)	0.008	ND	-	ND	-	ND	-	ND	-	ND	-
GC 0080	Cereal grains	0.008	26.2		24.2		80.3		13.5		22.4	0.2
DF 0295	Dates, dried or dried and candied	0.004	ND	-	ND	-	ND	-	ND	-	ND	-
DF 0167	Dried fruits	0.004	ND	-	ND	-	ND	-	ND	-	ND	-
DF 0297	Fig, dried or dried and candied	0.004	0.5	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
DF 0269	Grapes, dried (= currants, raisins and sultanas)	0.004	0.3	0.0	0.0	0.0	0.0	0.0	0.3	0.0	2.3	0.0
CF 1255	Maize flour	0.008	31.8	0.3	31.2	0.2	106.2	0.8	40.3	0.3	8.8	0.1
DF 0014	Prunes	0.004	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.5	0.0
CM 0649	Rice, husked	0.008	0.0	0.0	1.8	0.0	34.7	0.3	21.0	0.2	2.5	0.0
CM 1205	Rice, polished	0.008	48.8	0.4	277.5	2.2	68.8	0.6	65.5	0.5	9.3	0.1
CF 1250	Rye flour	0.008	0.0	0.0	1.0	0.0	0.0	0.0	0.0	0.0	1.5	0.0
CF 1251	Rye wholemeal	0.008	0.0	0.0	1.0	0.0	0.0	0.0	0.0	0.0	1.5	0.0
CF 1211	Wheat flour	0.008	323.0	2.6	114.0	0.9	28.3	0.2	112.0	0.9	175.8	1.4
CF 1210	Wheat germ	0.008	0.1	0.0	0.1	0.0	0.0	0.0	0.1	0.0	0.1	0.0
CF 1212	Wheat wholemeal	0.008	ND	-	ND	-	ND	-	ND	-	ND	-
	Total intake (µg/person)=			3.5		7.2		3.2		6.9		3.1
	Bodyweight per region (kg bw) =			60		55		60		60		60
	ADI (µg/person)=			600		550		600		600		600
	%ADI=			0.6		1.3		0.5		1.1		0.5
	Rounded %ADI=			1		1		1		1		1

	TERBUFOS (167)	International Estimated Daily Intake (IEDI)									ADI = 0 - 0.0006 mg/kg bw
		STMR	Diets: g/person/day								
Codex Code	Commodity	or STMR-P mg/kg	Mid-East diet	Mid-East intake	Far-East diet	Far-East intake	African diet	African intake	Latin American diet	Latin American intake	European diet	European intake
FI 0327	Banana	0.01	8.3	0.1	26.2	0.3	21.0	0.2	102.3	1.0	22.8	0.2
SB 0716	Coffee beans	0.05	5.3	0.3	0.4	0.0	0.0	0.0	3.6	0.2	7.9	0.4
MO 0105	Edible offal (mammalian)	0.05	4.2	0.2	1.4	0.1	2.8	0.1	6.1	0.3	12.4	0.6
PE 0112	Eggs	0.01	14.6	0.1	13.1	0.1	3.7	0.0	11.9	0.1	37.6	0.4
GC 0645	Maize (fresh, flour)	0.01	48.3	0.48	31.2	0.31	106.2	1.06	41.8	0.42	8.8	0.09
MF 0100	Mammalian fats (except milk fats)	0.05	0.6	0.0	1.6	0.1	0.6	0.0	4.3	0.2	7.6	0.4
MM 0095	Meat from mammals other than marine mammals	0.05	37.0	1.9	32.8	1.6	23.8	1.2	47.0	2.4	155.5	7.8
ML 0106	Milks	0.01	116.9	1.2	32.1	0.3	41.8	0.4	160.1	1.6	289.3	2.9
PM 0110	Poultry meat	0.05	31.0	1.6	13.2	0.7	5.5	0.3	25.3	1.3	53.0	2.7
PO 0113	Poultry skin	0.05	0.1	0.0	0.1	0.0	0.1	0.0	0.1	0.0	0.1	0.0
PO 0111	Poultry, edible offal of	0.05	0.1	0.0	0.1	0.0	0.1	0.0	0.4	0.0	0.4	0.0
PF 0111	Poultry, fats	0.05	3.1	0.2	1.3	0.1	0.6	0.0	2.5	0.1	5.3	0.3
GC 0651	Sorghum	0	2.0	0.0	9.7	0.1	26.6	0.3	0.0	0.0	0.0	0.0
VR 0596	Sugar beet	0.05	0.5	0.0	0.0	0.0	0.0	0.0	0.3	0.0	2.0	0.1
VO 0447	Sweet corn (corn-on-the-cob)	0.05	0.0	0.0	0.0	0.0	4.4	0.2	0.0	0.0	8.3	0.4
VO 1275	Sweet corn (kernels)	0.05	0.0	0.0	0.0	0.0	3.3	0.2	0.0	0.0	6.2	0.3
	Total intake (µg/person)=			6.1		3.7		3.8		7.6		16.2
	Bodyweight per region (kg bw) =			60		55		60		60		60
	ADI (µg/person)=			36		33		36		36		36
										21.17		44.98
	%ADI=			16.91%		11.25%		10.57%		%		%
	Rounded %ADI=			20%		10%		10%		20%		40%

ANNEX 4: INTERNATIONAL ESTIMATES OF SHORT-TERM DIETARY INTAKES OF PESTICIDE RESIDUES

ACEPHATE (95) International estimate of short term intake (IESTI) for **GENERAL POPULATION** ARfD = 0.1 mg/kg bw Maximum % of ARfD: 170%

Codex Code	Commodity	STMR or STMR-P mg/kg	HR or HR-P mg/kg	Large portion diet			Unit weight			Variability factor	Case	IESTI µg/kg bw/day	%ARfD rounded
				Country	Body weight (kg)	Large portion, g/person	Unit weight (g)	Country	Unit weight, edible portion (g)				
FP 0226	Apple	-	6.6	USA	65.0	1348	110	FRA	100	3	2a	157.21	160
JF 0226	Apple juice	1.31	-	-	-	ND	-	-	ND	ND	ND	ND	-
VS 0620	Artichoke globe	-	2.8	FRA	62.3	534	230	FRA	99	3	2a	32.89	30
VP 0061	Beans except broad bean & soya bean (green pods & immature seeds)	-	8.3	FRA	62.3	312	-	-	ND	ND	1	28.00	30
VB 0400	Broccoli	-	4.5	USA	65.0	376	608	USA	474	3	2b	78.17	80
VB 0404	Cauliflower (head)	-	4.5	UNK	70.1	579	1733	UNK	780	3	2b	111.51	110
MO 0105	Edible offal (mammalian)	-	0.022	FRA	62.3	277	-	-	ND	ND	1	0.10	0
PE 0112	Eggs	-	0.01	-	-	ND	-	-	ND	ND	1	ND	-
FP 0228	Loquat	-	6.6	AUS	67.0	64	-	-	ND	ND	ND	ND	-
FC 0206	Mandarin	-	5.2	JPN	52.6	409	70	JPN	70	3	2a	54.24	50
MM 0095	Meat from mammals other than marine mammals: 20% as fat	-	0.022	AUS	67.0	104	-	-	ND	ND	1	0.03	0
MM 0095	Meat from mammals other than marine mammals: 80% as muscle	-	0.022	AUS	67.0	417	-	-	ND	ND	1	0.14	0
ML 0106	Milks	0.011	-	USA	65.0	2466	-	-	ND	ND	3	0.42	0
FS 0245	Nectarine	-	4.9	USA	65.0	590	110	FRA	99	3	2a	59.42	60
FS 0247	Peach	-	4.9	SAF	55.7	685	110	FRA	99	3	2a	77.69	80
FP 0230	Pear	-	6.6	USA	65.0	693	100	FRA	89	3	2a	88.43	90
VO 0444	Peppers, chili	-	19.7	USA	65.0	90	45	USA	43	3	2a	53.57	50
VO 0445	Peppers, sweet (incl. pim(i)ento)	-	19.7	FRA	62.3	207	172	UNK	160	3	2a	166.76	170
PM 0110	Poultry meat: 10% as fat	-	0.01	AUS	67.0	43	-	-	ND	ND	1	0.01	0
PM 0110	Poultry meat: 90% as muscle	-	0.01	AUS	67.0	388	-	-	ND	ND	1	0.06	0
PO 0111	Poultry, edible offal of	-	0.01	USA	65.0	248	-	-	ND	ND	1	0.04	0
FP 0231	Quince	-	6.6	AUS	67.0	175	92	USA	56	3	2a	28.28	30
VD 0541	Soya bean (dry)	0.105	-	JPN	52.6	159	-	-	ND	ND	3	0.32	0
OR 0541	Soya bean oil, refined	0.045	-	USA	65.0	98	-	-	ND	ND	3	0.07	0

Annex 4

ACEPHATE (95) International estimate of short term intake (IESTI) for ARfD = 0.1 mg/kg bw

CHILDREN UP TO 6 YEARS Maximum % of ARfD: 390%

Codex Code	Commodity	STMR or STMR-P mg/kg	HR or HR-P mg/kg	Large portion diet			Unit weight			Variability factor	Case	IESTI µg/kg bw/day	%ARfD rounded
				Country	Body weight (kg)	Large portion, g/person	Unit weight (g)	Country	Unit weight, edible portion (g)				
FP 0226	Apple	-	6.6	USA	15.0	679	110	FRA	100	3	2a	386.74	390
JF 0226	Apple juice	1.31	-	-	-	ND	-	-	ND	ND	ND	ND	-
VS 0620	Artichoke globe	-	2.8	FRA	17.8	89	230	FRA	99	3	2b	42.00	40
VP 0061	Beans except broad bean & soya bean (green pods & immature seeds)	-	8.3	FRA	17.8	203	-	-	ND	ND	1	63.78	60
VB 0400	Broccoli	-	4.5	USA	15.0	164	608	USA	474	3	2b	147.83	150
VB 0404	Cauliflower (head)	-	4.5	NLD	17.0	209	1733	UNK	780	3	2b	166.19	170
MO 0105	Edible offal (mammalian)	-	0.022	FRA	17.8	203	-	-	ND	ND	1	0.25	0
PE 0112	Eggs	-	0.01	-	-	ND	-	-	ND	ND	1	ND	-
FP 0228	Loquat	-	6.6	-	-	ND	-	-	ND	ND	ND	ND	-
FC 0206	Mandarin	-	5.2	JPN	15.9	353	70	JPN	70	3	2a	161.33	160
MM 0095	Meat from mammals other than marine mammals: 20% as fat	-	0.022	AUS	19.0	52	-	-	ND	ND	1	0.06	0
MM 0095	Meat from mammals other than marine mammals: 80% as muscle	-	0.022	AUS	19.0	208	-	-	ND	ND	1	0.24	0
ML 0106	Milks	0.011	-	USA	15.0	1286	-	-	ND	ND	3	0.94	1
FS 0245	Nectarine	-	4.9	AUS	19.0	302	110	FRA	99	3	2a	128.97	130
FS 0247	Peach	-	4.9	AUS	19.0	315	110	FRA	99	3	2a	132.43	130
FP 0230	Pear	-	6.6	UNK	14.5	279	100	FRA	89	3	2a	208.00	210
VO 0444	Peppers, chili	-	19.7	AUS	19.0	31	45	USA	43	3	2b	94.87	90
VO 0445	Peppers, sweet (incl. pim(i)ento)	-	19.7	AUS	19.0	60	172	UNK	160	3	2b	186.76	190
PM 0110	Poultry meat: 10% as fat	-	0.01	AUS	19.0	22	-	-	ND	ND	1	0.01	0
PM 0110	Poultry meat: 90% as muscle	-	0.01	AUS	19.0	201	-	-	ND	ND	1	0.11	0
PO 0111	Poultry, edible offal of	-	0.01	USA	15.0	37	-	-	ND	ND	1	0.02	0
FP 0231	Quince	-	6.6	NLD	17.0	1	92	USA	56	3	2b	1.19	1
VD 0541	Soya bean (dry)	0.105	-	JPN	15.9	88	-	-	ND	ND	3	0.58	1
OR 0541	Soya bean oil, refined	0.045	-	USA	15.0	35	-	-	ND	ND	3	0.11	0

AZOCYCLOTIN (67) CYHEXATIN (129) International estimate of short term intake (IESTI) for ARfD= 0.02 mg/kg bw

WOMEN OF CHILDBEARING AGE

Maximum % of ARfD: 10%

Codex Code	Commodity	STMR or STMR-P mg/kg	HR or HR-P mg/kg	Large portion diet			Unit weight			Variability factor	Case	IESTI µg/kg bw/day	% ARfD rounded
				Country	Body weight (kg)	Large portion, g/person	Unit weight, (g)	Country	Unit weight, edible portion (g)				
FC 0004	Oranges, sweet, sour (incl. Orange-like hybrids)	-	0.049	USA	65.0	564	251	SWE	178	3	2a	0.69	3
FP 0226	Apple	-	0.11	USA	65.0	1348	162	SWE	149	3	2a	2.79	10
JF 0226	Apple juice	0.002	-	-	-	ND	-	-	ND	ND	ND	ND	-
FB 0021	Currants, red, black, white	0.05	-	FRA	62.3	153	-	-	ND	ND	ND	ND	-
FB 0269	Grapes (fresh, dried, excluding wine)	-	0.19	AUS	67.0	513	125	FRA	118	3	2a	2.12	10
DF 0269	Grapes, dried (= currants, raisins and sultanas)	0.076	-	FRA	62.3	135	-	-	ND	ND	1	ND	-
JF 0004	Orange juice	0.002	-	-	-	ND	-	-	ND	ND	3	ND	-
FP 0230	Pear	-	0.11	USA	65.0	693	187	UNK	170	3	2a	1.75	9
	Wine only	0.06	-	AUS	67.0	1131	-	-	ND	ND	3	1.01	5

CARBENDAZIM (072) : International estimate of short term intake (IESTI) for ARfD: 0.5 mg/kg bw

GENERAL POPULATION

Maximum % of ARfD: 10%

Codex Code	Commodity	STMR or STMR-P mg/kg	HR or HR-P mg/kg	Large portion diet			Unit weight			Variability factor	Case	IESTI µg/kg bw/day	% acute RfD rounded
				Country	Body weight (kg)	Large portion, g/person	Unit weight (g)	Country	Unit weight, edible portion (g)				
VS 0621	Asparagus	-	0.09	NLD	63	398	25	FRA	13	3	2a	0.6	0
FI 0327	Banana	-	0.44	SAF	55.7	613	708	USA	481	3	2a	12.45	2
GC 0640	Barley (fresh, flour, beer)	0.05	-	NLD	63	378	-	-	-	-	3	0.3	0
VD 0071	Beans (dry)	0.165	-	FRA	62.3	255	-	-	-	-	3	0.68	0
VB 0402	Brussels sprouts	-	0.27	NLD	63	394	14	UNK	10	-	1	1.69	0
VR 0577	Carrot	-	0.14	NLD	63	335	61	USA	50	3	2a	0.97	0
FS 0013	Cherries	-	9.1	FRA	62.3	375	5	FRA	4	-	1	54.78	10
PE 0112	Eggs (Chicken eggs 1/)	-	0	FRA	62.3	219	-	-	-	-	1	0	0

CARBENDAZIM (072) : International estimate of short term intake (IESTI) for **GENERAL POPULATION**

ARfD: 0.5 mg/kg bw

Maximum % of ARfD: 10%

Codex Code	Commodity	STMR or STMR-P mg/kg	HR or HR-P mg/kg	Large portion diet			Unit weight			Variability factor	Case	IESTI µg/kg bw/day	% acute RfD rounded
				Country	Body weight (kg)	Large portion, g/person	Unit weight (g)	Country	Unit weight, edible portion (g)				
VP 0526	Common bean (green pods and/or immature seeds)	-	0.45	NLD	63	431	-	-	-	-	1	3.08	1
VC 0424	Cucumber	-	0.05	NLD	63	313	400	FRA	360	3	2b	0.75	0
MO 0105	Edible offal (mammalian)	-	0	FRA	62.3	277	-	-	-	-	1	0	0
VP 0529	Garden pea, shelled (immature seeds)	-	0.01	NLD	63	301	-	-	-	-	1	0.05	0
VC 0425	Gherkin	-	0.05	NLD	63	96	15	FRA	15	-	1	0.08	0
FB 0269	Grapes (fresh, dried, excluding wine)	-	1.9	AUS	67	513	125	FRA	118	3	2a	21.21	4
FI 0345	Mango	-	1.7	FRA	62.3	567	207	USA	139	3	2a	23.04	5
ML 0106	Milks	0	-	USA	65	2466	-	-	-	-	3	0	0
FC 0004	Oranges, sweet, sour (incl. Orange-like hybrids) 2/	-	0.63	USA	65	564	131	USA	96	3	2a	7.32	1
FS 0247	Peach	-	1	SAF	55.7	685	98	USA	85	3	2a	15.36	3
SO 0697	Peanut	0.08	-	FRA	62.3	161	-	-	-	-	3	0.21	0
FP 0009	Pome fruits (Pear 1/)	-	2.4	USA	65	693	166	USA	151	3	2a	36.74	7
VO 0444	Peppers, chili	-	0.98	USA	65	90	45	USA	43	3	2a	2.66	1
FI 0353	Pineapple (fresh, canned, juice, dried)	-	0.03	JPN	52.6	371	472	USA	245	3	2a	0.49	0
FS 0014	Plums (fresh, prunes)	-	0.34	USA	65	413	66	USA	62	3	2a	2.81	1
PM 0110	Poultry meat	-	0	AUS	67	431	-	-	-	-	1	0	0
SO 0495	Rape seed	0	-	-	-	-	-	-	-	-	3	-	
CM 0649	Rice, husked	0.05	-	JPN	52.6	319	-	-	-	-	3	0.3	0
VD 0541	Soya bean (dry)	0.08	-	JPN	52.6	159	-	-	-	-	3	0.24	0
VC 0431	Squash, summer		0.32	FRA	62.3	343	196	USA	186	3	2a	3.67	1
VR 0596	Sugar beet	-	0.08	-	-	-	-	-	-	-	-	-	
VO 0448	Tomato (fresh, juice, paste, peeled)	-	0.22	USA	65	391	105	FRA	102	3	2a	2.01	0
GC 0080	Cereal grains (Wheat 1/)	0.03	-	USA	65	383	-	-	-	-	3	0.18	0

1/ Highest consumed commodity represents group when consumption is not available

Annex 4

CARBENDAZIM (072) : International estimate of short term intake (IESTI) for **GENERAL POPULATION** ARfD: 0.5 mg/kg bw

Maximum % of ARfD: 10%

Codex Code	Commodity	STMR or STMR-P mg/kg	HR or HR-P mg/kg	Large portion diet: Country	Large portion diet: Body weight (kg)	Large portion diet: Large portion, g/person	Unit weight: Unit weight (g)	Unit weight: Country	Unit weight: Unit weight, edible portion (g)	Variability factor	Case	IESTI µg/kg bw/day	% acute RfD rounded

2/ HR for whole orange fruit, no residue data for edible portion available

CARBENDAZIM (072) International estimate of short term intake (IESTI) for **CHILDREN UP TO 6 YEARS** ARfD: 0.5 mg/kg bw

Maximum % of ARfD: 30%

Codex Code	Commodity	STMR or STMR-P mg/kg	HR or HR-P mg/kg	Large portion diet: Country	Large portion diet: Body weight (kg)	Large portion diet: Large portion, g/person	Unit weight: Unit weight (g)	Unit weight: Country	Unit weight: Unit weight, edible portion (g)	Variability factor	Case	IESTI µg/kg bw/day	% acute RfD rounded
VS 0621	Asparagus	-	0.09	USA	15	178	25	FRA	13	3	2a	1.22	0
FI 0327	Banana	-	0.44	JPN	15.9	312	708	USA	481	3	2b	25.89	5
GC 0640	Barley (fresh, flour, beer)	0.05	-	AUS	19	14	-	-	-	-	3	0.04	0
VD 0071	Beans (dry)	0.165	-	FRA	17.8	209	-	-	-	-	3	1.94	0
VB 0402	Brussels sprouts	-	0.27	NLD	17	213	14	UNK	10	-	1	3.38	1
VR 0577	Carrot	-	0.14	FRA	17.8	205	61	USA	50	3	2a	2.4	0
FS 0013	Cherries	-	9.1	FRA	17.8	297	5	FRA	4	-	1	151.7	30
PE 0112	Eggs (Chicken eggs 1/)	-	0	FRA	17.8	134	-	-	-	-	1	0	0
VP 0526	Common bean (green pods and/or immature seeds)	-	0.45	NLD	17	184	-	-	-	-	1	4.87	1
VC 0424	Cucumber	-	0.05	NLD	17	162	400	FRA	360	3	2b	1.43	0
MO 0105	Edible offal (mammalian)	-	0	FRA	17.8	203	-	-	-	-	1	0	0
VP 0529	Garden pea, shelled (immature seeds)	-	0.01	NLD	17	146	-	-	-	-	1	0.09	0
VC 0425	Gherkin	-	0.05	NLD	17	56	15	FRA	15	-	1	0.16	0
FB 0269	Grapes (fresh, dried, excluding wine)	-	1.9	AUS	19	342	125	FRA	118	3	2a	57.7	10
FI 0345	Mango	-	1.7	AUS	19	207	207	USA	139	3	2a	43.35	9
ML 0106	Milks	0	-	USA	15	1286	-	-	-	-	3	0	0
FC 0004	Oranges, sweet, sour (incl. Orange-like hybrids 2/)	-	0.63	UNK	14.5	495	131	USA	96	3	2a	29.82	6

Annex 4

CARBENDAZIM (072) International estimate of short term intake (IESTI) for ARfD: 0.5 mg/kg bw

CHILDREN UP TO 6 YEARS

Maximum % of ARfD: 30%

Codex Code	Commodity	STMR or STMR-P mg/kg	HR or HR-P mg/kg	Large portion diet			Unit weight			Varia-bility factor	Case	IESTI µg/kg bw/day	% acute RfD rounded
				Country	Body weight (kg)	Large portion, g/person	Unit weight (g)	Country	Unit weight, edible portion (g)				
FS 0247	Peach	-	1	AUS	19	315	98	USA	85	3	2a	25.58	5
SO 0697	Peanut	0.08	-	USA	15	78	-	-	-	-	3	0.41	0
FP 0009	Pome fruits (Pear 1/)	-	2.4	UNK	14.5	279	166	USA	151	3	2a	96.18	20
VO 0444	Peppers, chili	-	0.98	AUS	19	31	45	USA	43	3	2b	4.72	1
FI 0353	Pineapple (fresh, canned, juice, dried)	-	0.03	JPN	15.9	216	472	USA	245	3	2b	1.22	0
FS 0014	Plums (fresh, prunes)	-	0.34	FRA	17.8	254	66	USA	62	3	2a	7.23	1
PM 0110	Poultry meat	-	0	AUS	19	224	-	-	-	-	1	0	0
SO 0495	Rape seed	0	-	-	-	-	-	-	-	-	3	-	-
CM 0649	Rice, husked	0.05	-	FRA	17.8	223	-	-	-	-	3	0.63	0
VD 0541	Soya bean (dry)	0.08	-	JPN	15.9	88	-	-	-	-	3	0.44	0
VC 0431	Squash, summer		0.32	AUS	19	219	196	USA	186	3	2a	9.96	2
VR 0596	Sugar beet	-	0.08	-	-	-	-	-	-	-	-	-	-
VO 0448	Tomato (fresh, juice, paste, peeled)	-	0.22	USA	15	159	105	FRA	102	3	2a	5.32	1
GC 0080	Cereal grains (Wheat 1/)	0.03	-	USA	15	151	-	-	-	-	3	0.3	0

1/ Highest consumed commodity represents group when consumption is not available

2/ HR for whole orange fruit, no residue data for edible portion available

CARBENDAZIM (072) : International estimate of short term intake (IESTI) for ARfD: 0.1 mg/kg bw

WOMEN OF CHILDBEARING AGE

Maximum %ARfD: 50%

Codex Code	Commodity	STMR or STMR-P mg/kg	HR or HR-P mg/kg	Large portion diet			Unit weight			Varia-bility factor	Case	IESTI µg/kg bw/day	% acute RfD rounded
				Country	Body weight (kg)	Large portion, g/person	Unit weight (g)	Country	Unit weight, edible portion (g)				
VS 0621	Asparagus	-	0.09	NLD	63	398	25	FRA	13	3	2a	0.6	1
FI 0327	Banana	-	0.44	SAF	55.7	613	708	USA	481	3	2a	12.45	10
GC 0640	Barley (fresh, flour, beer)	0.05	-	NLD	63	378	-	-	-	-	3	0.3	0

Annex 4

CARBENDAZIM (072) : International estimate of short term intake (IESTI) for **WOMEN OF CHILDBEARING AGE**

ARfD: 0.1 mg/kg bw

Maximum %ARfD: 50%

Codex Code	Commodity	STMR or STMR-P mg/kg	HR or HR-P mg/kg	Large portion diet: Country	Large portion diet: Body weight (kg)	Large portion diet: Large portion, g/person	Unit weight: Unit weight (g)	Unit weight: Country	Unit weight: Unit weight, edible portion (g)	Variability factor	Case	IESTI µg/kg bw/day	% acute RfD rounded
VD 0071	Beans (dry)	0.165	-	FRA	62.3	255	-	-	-	-	3	0.68	1
VB 0402	Brussels sprouts	-	0.27	NLD	63	394	14	UNK	10	-	1	1.69	2
VR 0577	Carrot	-	0.14	NLD	63	335	61	USA	50	3	2a	0.97	1
FS 0013	Cherries	-	9.1	FRA	62.3	375	5	FRA	4	-	1	54.78	50
PE 0112	Eggs (Chicken eggs 1/)	-	0	FRA	62.3	219	-	-	-	-	1	0	0
VP 0526	Common bean (green pods and/or immature seeds)	-	0.45	NLD	63	431	-	-	-	-	1	3.08	3
VC 0424	Cucumber	-	0.05	NLD	63	313	400	FRA	360	3	2b	0.75	1
MO 0105	Edible offal (mammalian)	-	0	FRA	62.3	277	-	-	-	-	1	0	0
VP 0529	Garden pea, shelled (immature seeds)	-	0.01	NLD	63	301	-	-	-	-	1	0.05	0
VC 0425	Gherkin	-	0.05	NLD	63	96	15	FRA	15	-	1	0.08	0
FB 0269	Grapes (fresh, dried, excluding wine)	-	1.9	AUS	67	513	125	FRA	118	3	2a	21.21	20
FI 0345	Mango	-	1.7	FRA	62.3	567	207	USA	139	3	2a	23.04	20
ML 0106	Milks	0	-	USA	65	2466	-	-	-	-	3	0	0
FC 0004	Oranges, sweet, sour (incl. Orange-like hybrids) 2/	-	0.63	USA	65	564	131	USA	96	3	2a	7.32	7
FS 0247	Peach	-	1	SAF	55.7	685	98	USA	85	3	2a	15.36	20
SO 0697	Peanut	0.08	-	FRA	62.3	161	-	-	-	-	3	0.21	0
FP 0009	Pome fruits (Pear 1/)	-	2.4	USA	65	693	166	USA	151	3	2a	36.74	40
VO 0444	Peppers, chili	-	0.98	USA	65	90	45	USA	43	3	2a	2.66	3
FI 0353	Pineapple (fresh, canned, juice, dried)	-	0.03	JPN	52.6	371	472	USA	245	3	2a	0.49	0
FS 0014	Plums (fresh, prunes)	-	0.34	USA	65	413	66	USA	62	3	2a	2.81	3
PM 0110	Poultry meat	-	0	AUS	67	431	-	-	-	-	1	0	0
SO 0495	Rape seed	0	-	-	-	-	-	-	-	-	3	-	-
CM 0649	Rice, husked	0.05	-	JPN	52.6	319	-	-	-	-	3	0.3	0
VD 0541	Soya bean (dry)	0.08	-	JPN	52.6	159	-	-	-	-	3	0.24	0
VC 0431	Squash, summer		0.32	FRA	62.3	343	196	USA	186	3	2a	3.67	4
VR 0596	Sugar beet	-	0.08	-	-	-	-	-	-	-	-	-	-
VO 0448	Tomato (fresh, juice, paste, peeled)	-	0.22	USA	65	391	105	FRA	102	3	2a	2.01	2

CARBENDAZIM (072) : International estimate of short term intake (IESTI) for ARfD: 0.1 mg/kg bw

WOMEN OF CHILDBEARING AGE

Maximum %ARfD: 50%

Codex Code	Commodity	STMR or STMR-P mg/kg	HR or HR-P mg/kg	Large portion diet: Country	Large portion diet: Body weight (kg)	Large portion diet: Large portion, g/person	Unit weight: Unit weight (g)	Unit weight: Country	Unit weight: Unit weight, edible portion (g)	Variability factor	Case	IESTI µg/kg bw/day	% acute RfD rounded
GC 0080	Cereal grains (Wheat 1/)	0.03	-	USA	65	383	-	-	-	-	3	0.18	0

1/ Highest consumed commodity represents group when consumption is not available
2/ HR for whole orange fruit, no residue data for edible portion available

CHLORPROPHAM (201) International estimate of short term intake (IESTI) for ARfD = 0.5 mg/kg bw

GENERAL POPULATION

Maximum % of ARfD: 20%

Codex Code	Commodity	STMR or STMR-P mg/kg	HR or HR-P mg/kg	Large portion diet: Country	Large portion diet: Body weight (kg)	Large portion diet: Large portion, g/person	Unit weight: Unit weight, (g)	Unit weight: Country	Unit weight: Unit weight, edible portion (g)	Variability factor	Case	IESTI µg/kg bw/day	% ARfD rounded
MM 0812	Cattle meat: 20% as fat	-	0.004	AUS	67.0	93	-	-	ND	ND	1	0.01	0
MM 0812	Cattle meat: 80% as muscle	-	0.004	AUS	67.0	374	-	-	ND	ND	1	0.02	0
ML 0812	Cattle milk	0.0005	-	NLD	63.0	2515	-	-	ND	ND	3	0.02	0
MO 0812	Cattle, edible offal of	-	0.007	SAF	55.7	524	-	-	ND	ND	1	0.07	0
VR 0589	Potato, cooked	-	7.6	NLD	63.0	687	122	USA	122	3	2a	112.27	20
VR 0589	Potato, peeled and cooked	-	0.2	NLD	63.0	687	122	USA	99	3	2a	2.81	1

CHLORPROPHAM (201) International estimate of short term intake (IESTI) for ARfD = 0.5 mg/kg bw

CHILDREN UP TO 6 YEARS Maximum % of ARfD: 60%

Codex Code	Commodity	STMR or STMR-P mg/kg	HR or HR-P mg/kg	Large portion diet			Unit weight			Variability factor	Case	IESTI µg/kg bw/day	% ARfD rounded
				Country	Body weight (kg)	Large portion, g/person	Unit weight, (g)	Country	Unit weight, edible portion (g)				
MM 0812	Cattle meat: 20% as fat	-	0.004	AUS	19.0	48	-	-	ND	ND	1	0.01	0
MM 0812	Cattle meat: 80% as muscle	-	0.004	AUS	19.0	190	-	-	ND	ND	1	0.04	0
ML 0812	Cattle milk	0.0005	-	AUS	19.0	1450	-	-	ND	ND	3	0.04	0
MO 0812	Cattle, edible offal of	-	0.007	FRA	17.8	203	-	-	ND	ND	1	0.08	0
VR 0589	Potato, cooked	-	7.6	SAF	14.2	300	122	USA	122	3	2a	290.95	60
VR 0589	Potato, peeled and cooked	-	0.2	SAF	14.2	300	122	USA	99	3	2a	7.00	1

INDOXACARB (216) International estimate of short term intake (IESTI) for ARfD= 0.1 mg/kg bw

GENERAL POPULATION Maximum % of ARfD: 50%

Codex Code	Commodity	STMR or STMR-P mg/kg	HR or HR-P mg/kg	Large portion diet			Unit weight			Variability factor	Case	IESTI µg/kg bw/day	% ARfD rounded
				Country	Body weight (kg)	Large portion, g/person	Unit weight (g)	Country	Unit weight, edible portion (g)				
FP 0226	Apple	-	0.3	USA	65.0	1348	138	USA	127	3	2a	7.39	7
JF 0226	Apple juice	0.011	-	-	-	ND	-	-	ND	ND	ND	ND	-
VB 0400	Broccoli	-	0.14	USA	65.0	376	608	USA	474	3	2b	2.43	2
VB 0041	Cabbages, head	-	2.7	SAF	55.7	362	908	USA	717	3	2b	52.65	50
FM 0812	Cattle milk fat	1	-	NLD	63.0	79	-	-	ND	ND	3	1.26	1
VB 0404	Cauliflower (head)	-	0.14	UNK	70.1	579	1733	UNK	780	3	2b	3.47	3
PE 0840	Chicken eggs	-	0	FRA	62.3	219	-	-	ND	ND	1	0.00	0
VD 0524	Chick-pea (dry)	0.02	-	FRA	62.3	203	-	-	ND	ND	3	0.07	0
SO 0691	Cotton seed	0.36	-	USA	65.0	3	-	-	ND	ND	3	0.02	0
OR 0691	Cotton seed oil, edible	0.013	-	USA	65.0	9	-	-	ND	ND	3	0.00	0
VC 0424	Cucumber	-	0.1	NLD	63.0	313	400	FRA	360	3	2b	1.49	1
MO 0105	Edible offal (mammalian)	-	0.027	FRA	62.3	277	-	-	ND	ND	1	0.12	0
VO 0440	Egg plant	-	0.3	AUS	67.0	487	548	USA	444	3	2a	6.16	6

INDOXACARB (216) International estimate of short term intake (IESTI) for ARfD= 0.1 mg/kg bw

GENERAL POPULATION Maximum % of ARfD: 50%

Codex Code	Commodity	STMR or STMR-P mg/kg	HR or HR-P mg/kg	Large portion diet			Unit weight			Variability factor	Case	IESTI µg/kg bw/day	% ARfD rounded
				Country	Body weight (kg)	Large portion, g/person	Unit weight (g)	Country	Unit weight, edible portion (g)				
FB 0269	Grapes (fresh, wine, dried)	-	1.5	AUS	67.0	1004	125	FRA	118	3	2a	27.75	30
VL 0482	Lettuce, head	-	4.3	USA	65.0	213	539	USA	512	3	2b	42.18	40
VL 0483	Lettuce, leaf	-	8.4	NLD	63.0	152		USA	0	1	1	20.24	20
MM 0095	Meat from mammals other than marine mammals: 20% as fat	-	0.91	AUS	67.0	104	-	-	ND	ND	1	1.42	1
MM 0095	Meat from mammals other than marine mammals: 80% as muscle	-	0.03	AUS	67.0	417	-	-	ND	ND	1	0.19	0
VC 0046	Melons, except watermelon	-	0.02	USA	65.0	655	700	FRA	420	3	2a	0.46	0
ML 0106	Milks	0.048	-	USA	65.0	2466	-	-	ND	ND	3	1.82	2
VD 0536	Mung bean (dry)	0.015	-	AUS	67.0	78	-	-	ND	ND	3	0.02	0
FS 0247	Peach	-	0.18	SAF	55.7	685	110	FRA	99	3	2a	2.85	3
SO 0697	Peanut	0.01	-	FRA	62.3	161	-	-	ND	ND	3	0.03	0
OR 0697	Peanut oil, edible	0.003	-	FRA	62.3	57	-	-	ND	ND	3	0.00	0
FP 0230	Pear	-	0.11	USA	65.0	693	166	USA	151	3	2a	1.68	2
VO 0445	Peppers, sweet (incl. pim(i)ento)	-	0.21	FRA	62.3	207	172	UNK	160	3	2a	1.78	2
VO 0445	Peppers, sweet (incl. pim(i)ento)	-	0.21	FRA	62.3	207	119	USA	98	3	2a	1.36	1
VR 0589	Potato	-	0.01	NLD	63.0	687	122	USA	99	3	2a	0.14	0
PM 0110	Poultry meat: 10% as fat	-	0	AUS	67.0	43	-	-	ND	ND	1	0.00	0
PM 0110	Poultry meat: 90% as muscle	-	0	AUS	67.0	388	-	-	ND	ND	1	0.00	0
PO 0111	Poultry, edible offal of	-	0	USA	65.0	248	-	-	ND	ND	1	0.00	0
VD 0541	Soya bean (dry)	0.027	-	JPN	52.6	159	-	-	ND	ND	3	0.08	0
OR 0541	Soya bean oil, refined	0.018	-	USA	65.0	98	-	-	ND	ND	3	0.03	0
VO 0447	Sweet corn (corn-on-the-cob)	-	0.012	USA	65.0	367	200	JPN	200	3	2a	0.14	0
VO 0448	Tomato (fresh, juice, paste, peeled)	-	0.3	USA	65.0	391	123	USA	123	3	2a	2.94	3
JF 0448	Tomato juice	0.022	-	-	-	ND	-	-	ND	ND	3	ND	-
	Tomato paste	0.21	-	-	-	ND	-	-	ND	ND	ND	ND	-
	Wine only	0.018	-	AUS	67.0	1131	-	-	ND	ND	3	0.30	0

CHILDREN UP TO 6 YEARS

Maximum % of ARfD: 130%

Codex Code	Commodity	STMR or STMR-P mg/kg	HR or HR-P mg/kg	Large portion diet			Unit weight			Varia-bility factor	Case	IESTI µg/kg bw/day	% ARfD rounded
				Country	Body weight (kg)	Large portion, g/person	Unit weight (g)	Country	Unit weight, edible portion (g)				
FP 0226	Apple	-	0.3	USA	15.0	679	138	USA	127	3	2a	18.65	20
JF 0226	Apple juice	0.011	-	-	-	ND	-	-	ND	ND	ND	ND	-
VB 0400	Broccoli	-	0.14	USA	15.0	164	608	USA	474	3	2b	4.60	5
VB 0041	Cabbages, head	-	2.7	SAF	14.2	220	908	USA	717	3	2b	125.55	130
FM 0812	Cattle milk fat	1	-	NLD	17.0	35	-	-	ND	ND	3	2.04	2
VB 0404	Cauliflower (head)	-	0.14	NLD	17.0	209	1733	UNK	780	3	2b	5.17	5
PE 0840	Chicken eggs	-	0	FRA	17.8	134	-	-	ND	ND	1	0.00	0
VD 0524	Chick-pea (dry)	0.02	-	USA	15.0	34	-	-	ND	ND	3	0.05	0
SO 0691	Cotton seed	0.36	-	USA	15.0	1	-	-	ND	ND	3	0.02	0
OR 0691	Cotton seed oil, edible	0.013	-	USA	15.0	6	-	-	ND	ND	3	0.01	0
VC 0424	Cucumber	-	0.1	NLD	17.0	162	400	FRA	360	3	2b	2.86	3
MO 0105	Edible offal (mammalian)	-	0.027	FRA	17.8	203	-	-	ND	ND	1	0.31	0
VO 0440	Egg plant	-	0.3	JPN	15.9	219	548	USA	444	3	2b	12.41	10
FB 0269	Grapes (fresh, wine, dried)	-	1.5	JPN	15.9	388	125	FRA	118	3	2a	58.75	60
VL 0482	Lettuce, head	-	4.3	NLD	17.0	84	539	USA	512	3	2b	63.47	60
VL 0483	Lettuce, leaf	-	8.4	NLD	17.0	102		USA	0	1	1	50.40	50
MM 0095	Meat from mammals other than marine mammals: 20% as fat	-	0.91	AUS	19.0	52	-	-	ND	ND	1	2.50	2
MM 0095	Meat from mammals other than marine mammals: 80% as muscle	-	0.03	AUS	19.0	208	-	-	ND	ND	1	0.33	0
VC 0046	Melons, except watermelon	-	0.02	AUS	19.0	413	700	FRA	420	3	2b	1.30	1
ML 0106	Milks	0.048	-	USA	15.0	1286	-	-	ND	ND	3	4.11	4
VD 0536	Mung bean (dry)	0.015	-	-	-	ND	-	-	ND	ND	3	ND	-
FS 0247	Peach	-	0.18	AUS	19.0	315	110	FRA	99	3	2a	4.86	5
SO 0697	Peanut	0.01	-	USA	15.0	78	-	-	ND	ND	3	0.05	0
OR 0697	Peanut oil, edible	0.003	-	FRA	17.8	67	-	-	ND	ND	3	0.01	0
FP 0230	Pear	-	0.11	UNK	14.5	279	166	USA	151	3	2a	4.41	4
VO 0445	Peppers, sweet (incl. pim(i)ento)	-	0.21	AUS	19.0	60	172	UNK	160	3	2b	1.99	2
VO 0445	Peppers, sweet (incl. pim(i)ento)	-	0.21	AUS	19.0	60	119	USA	98	3	2b	1.99	2
VR 0589	Potato	-	0.01	SAF	14.2	300	122	USA	99	3	2a	0.35	0
PM 0110	Poultry meat: 10% as fat	-	0	AUS	19.0	22	-	-	ND	ND	1	0.00	0
PM 0110	Poultry meat: 90% as muscle	-	0	AUS	19.0	201	-	-	ND	ND	1	0.00	0
PO 0111	Poultry, edible offal of	-	0	USA	15.0	37	-	-	ND	ND	1	0.00	0
VD 0541	Soya bean (dry)	0.027	-	JPN	15.9	88	-	-	ND	ND	3	0.15	0
OR 0541	Soya bean oil, refined	0.018	-	USA	15.0	35	-	-	ND	ND	3	0.04	0

Annex 4

INDOXACARB (216) International estimate of short term intake (IESTI) for ARfD= 0.1 mg/kg bw

CHILDREN UP TO 6 YEARS

Maximum % of ARfD: 130%

Codex Code	Commodity	STMR or STMR-P mg/kg	HR or HR-P mg/kg	Large portion diet			Unit weight			Varia-bility factor	Case	IESTI µg/kg bw/day	% ARfD rounded
				Country	Body weight (kg)	Large portion, g/person	Unit weight (g)	Country	Unit weight, edible portion (g)				
VO 0447	Sweet corn (corn-on-the-cob)	-	0.012	UNK	14.5	161	200	JPN	200	3	2b	0.40	0
VO 0448	Tomato (fresh, juice, paste, peeled)	-	0.3	USA	15.0	159	123	USA	123	3	2a	8.10	8
FJ 0448	Tomato juice	0.022	-	-	-	ND	-	-	ND	ND	3	ND	-
	Tomato paste	0.21	-	-	-	ND	-	-	ND	ND	ND	ND	-
	Wine only	0.018	-	AUS	19.0	4	-	-	ND	ND	3	0.00	0

METHIOCARB (132) International estimate of short term intake (IESTI) for ARfD= 0.02 mg/kg bw

GENERAL POPULATION

Maximum % of ARfD: 50%

Codex Code	Commodity	STMR or STMR-P mg/kg	HR or HR-P mg/kg	Large portion diet			Unit weight			Variability factor	Case	IESTI µg/kg bw/day	% ARfD rounded
				Country	Body weight (kg)	Large portion, g/person	Unit weight (g)	Country	Unit weight, edible portion (g)				
VS 0620	Artichoke globe	-	0.01	FRA	62.3	534	230	FRA	99	3	2a	0.12	1
GC 0640	Barley (fresh, flour, beer)	0	-	NLD	63.0	378	-	-	ND	ND	3	0.00	0
VB 0402	Brussels sprouts	-	0.01	NLD	63.0	394	7	FRA	5	1	1	0.06	0
VB 0041	Cabbages, head	-	0.08	SAF	55.7	362	771	UNK	540	3	2b	1.56	8
VB 0404	Cauliflower (head)	-	0.08	UNK	70.1	579	1733	UNK	780	3	2b	1.98	10
TN 0666	Hazelnuts	-	0.04	AUS	67.0	70	-	-	ND	ND	1	0.04	0
VA 0384	Leek	-	0.33	FRA	62.3	374	100	FRA	50	3	2a	2.66	10
VL 0482	Lettuce, head	-	0.05	USA	65.0	213	754	UNK	558	3	2b	0.49	2
GC 0645	Maize (fresh, flour, oil)	0	-	FRA	62.3	260	-	-	ND	ND	3	0.00	0
VC 0046	Melons, except watermelon	-	0.02	USA	65.0	655	700	FRA	420	3	2a	0.46	2
VA 0385	Onion, bulb	-	0.35	FRA	62.3	306	165	UNK	150	3	2a	3.41	20
VP 0063	Peas (green pods & immature seeds)	-	0.05	JPN	52.6	63	-	-	ND	ND	ND	ND	-
VD 0072	Peas (dry)	0.05	-	FRA	62.3	445	-	-	ND	ND	3	0.36	2
VO 0445	Peppers, sweet (incl. pim(i)ento)	-	1.5	FRA	62.3	207	119	USA	98	3	2a	9.69	50
VR 0589	Potato	-	0.02	NLD	63.0	687	216	UNK	216	3	2a	0.36	2

METHIOCARB (132) International estimate of short term intake (IESTI) for ARfD= 0.02 mg/kg bw

GENERAL POPULATION

Maximum % of ARfD: 50%

Codex Code	Commodity	STMR or STMR-P mg/kg	HR or HR-P mg/kg	Large portion diet: Country	Large portion diet: Body weight (kg)	Large portion diet: Large portion, g/person	Unit weight: Unit weight (g)	Unit weight: Country	Unit weight: Unit weight, edible portion (g)	Variability factor	Case	IESTI µg/kg bw/day	% ARfD rounded
SO 0495	Rape seed	0	-	-	-	ND	-	-	ND	ND	3	ND	-
FB 0275	Strawberry	-	0.83	FRA	62.3	346	14	FRA	13	1	1	4.61	20
VR 0596	Sugar beet	-	0.01	-	-	ND	-	-	ND	ND	ND	ND	-
SO 0702	Sunflower seed	0	-	USA	65.0	193	-	-	ND	ND	3	0.00	0
GC 0654	Wheat	0	-	USA	65.0	383	-	-	ND	ND	3	0.00	0

METHIOCARB (132) International estimate of short term intake (IESTI) for ARfD= 0.02 mg/kg bw (20 µg/kg bw)

CHILDREN UP TO 6 YEARS

Maximum %ARfD: 70%

Codex Code	Commodity	STMR or STMR-P mg/kg	HR or HR-P mg/kg	Large portion diet: Country	Large portion diet: Body weight (kg)	Large portion diet: Large portion, g/person	Unit weight: Unit weight (g)	Unit weight: Country	Unit weight: Unit weight, edible portion (g)	Varia-bility factor	Case	IESTI µg/kg bw/day	% ARfD rounded
VS 0620	Artichoke globe	-	0.01	FRA	17.8	89	230	FRA	99	3	2b	0.15	1
GC 0640	Barley (fresh, flour, beer)	0	-	AUS	19.0	14	-	-	ND	ND	3	0.00	0
VB 0402	Brussels sprouts	-	0.01	NLD	17.0	213	7	FRA	5	1	1	0.13	1
VB 0041	Cabbages, head	-	0.08	SAF	14.2	220	771	UNK	540	3	2b	3.72	20
VB 0404	Cauliflower (head)	-	0.08	NLD	17.0	209	1733	UNK	780	3	2b	2.95	10
TN 0666	Hazelnuts	-	0.04	NLD	17.0	11	-	-	ND	ND	1	0.03	0
VA 0384	Leek	-	0.33	FRA	17.8	121	281	UNK	160	3	2b	6.75	30
VL 0482	Lettuce, head	-	0.05	NLD	17.0	84	754	UNK	558	3	2b	0.74	4
GC 0645	Maize (fresh, flour, oil)	0	-	FRA	17.8	148	-	-	ND	ND	3	0.00	0
VC 0046	Melons, except watermelon	-	0.02	AUS	19.0	413	700	FRA	420	3	2b	1.30	7
VA 0385	Onion, bulb	-	0.35	FRA	17.8	127	165	UNK	150	3	2b	7.50	40
VP 0063	Peas (green pods & immature seeds)	-	0.05	JPN	15.9	48	-	-	ND	ND	ND	ND	-
VD 0072	Peas (dry)	0.05	-	FRA	17.8	107	-	-	ND	ND	3	0.30	2

Annex 4

METHIOCARB (132) International estimate of short term intake (IESTI) for **CHILDREN UP TO 6 YEARS**

ARfD= 0.02 mg/kg bw (20 µg/kg bw)

Maximum %ARfD: 70%

Codex Code	Commodity	STMR or STMR-P mg/kg	HR or HR-P mg/kg	Large portion diet			Unit weight			Varia-bility factor	Case	IESTI µg/kg bw/day	% ARfD rounded
				Country	Body weight (kg)	Large portion, g/person	Unit weight (g)	Country	Unit weight, edible portion (g)				
VO 0445	Peppers, sweet (incl. pim(i)ento)	-	1.5	AUS	19.0	60	119	USA	98	3	2b	14.22	70
VR 0589	Potato	-	0.02	SAF	14.2	300	216	UNK	216	3	2a	1.03	5
SO 0495	Rape seed	0	-	-	-	ND	-	-	ND	ND	3	ND	-
FB 0275	Strawberry	-	0.83	AUS	19.0	176	14	FRA	13	1	1	7.70	40
VR 0596	Sugar beet	-	0.01	-	-	ND	-	-	ND	ND	ND	ND	-
SO 0702	Sunflower seed	0	-	USA	15.0	24	-	-	ND	ND	3	0.00	0
GC 0654	Wheat	0	-	USA	15.0	151	-	-	ND	ND	3	0.00	0

Annex 4

PHORATE : International estimate of short term intake (IESTI) for **GENERAL POPULATION**

ARfD= 0.003 mg/kg bw/day

Maximum % of ARfD: 50%

Codex Code	Commodity	STMR or STMR-P mg/kg	HR or HR-P mg/kg	Large portion diet			Unit weight		Unit weight, edible portion (g)	Variability factor	Case	IESTI µg/kg bw/day	% ARfD rounded
				Country	Body weight (kg)	Large portion, g/person	Unit weight (g)	Country					
VD 0071	Beans (dry)	0.05	-	FRA	62.3	255	-	-	ND	ND	3	0.21	7
PE 0840	Chicken eggs*	-	0	FRA	62.3	219	-	-	ND	ND	1	0.00	0
SB 0716	Coffee beans**	0.00335	-	NLD	63.0	66	-	-	ND	ND	3	0.00	0
VP 0526	Common bean (green pods and/or immature seeds)	-	0.05	NLD	63.0	431	-	-	ND	ND	1	0.34	10
SO 0691	Cotton seed	0	-	USA	65.0	3	-	-	ND	ND	3	0.00	0
MO 0105	Edible offal (mammalian)	-	0.02	FRA	62.3	277	-	-	ND	ND	1	0.09	3
CF 1255	Maize flour	0.046	-	AUS	67.0	90	-	-	ND	ND	3	0.06	2
GC 0645	Maize (fresh, flour, oil)***	0.02	-	FRA	62.3	260	-	-	ND	ND	3	0.08	3
OR 0645	Maize oil, edible****	0.0162	-	NLD	63.0	43	-	-	ND	ND	3	0.01	0
MM 0095	Meat from mammals other than marine mammals: 20% as fat	-	0.02	AUS	67.0	104	-	-	ND	ND	1	0.03	1
MM 0095	Meat from mammals other than marine mammals: 80% as muscle	-	0.02	AUS	67.0	417	-	-	ND	ND	1	0.12	4
ML 0106	Milks	0.005	-	USA	65.0	2466	-	-	ND	ND	3	0.19	6
VR 0589	Potato*****	-	0.0972	NLD	63.0	687	122	USA	122	3	2a	1.44	50
PM 0110	Poultry meat: 10% as fat	-	0	AUS	67.0	43	-	-	ND	ND	1	0.00	0
PM 0110	Poultry meat: 90% as muscle	-	0	AUS	67.0	388	-	-	ND	ND	1	0.00	0
GC 0651	Sorghum	0.05	-	USA	65.0	18	-	-	ND	ND	3	0.01	0
VD 0541	Soya bean (dry)	0.05	-	JPN	52.6	159	-	-	ND	ND	3	0.15	5
VR 0596	Sugar beet	-	0.05	-	-	ND	-	-	ND	ND	ND	ND	-

* HR for PE 0112, Eggs was used

** STMR-P for SM 0716 Coffee beans, roasted was used

*** there is no consumption data on maize (fresh) only

**** STMR-P for deodorized maize oil was used

***** HR-P for potatoes, microwaved with peel was used.

PHORATE : International estimate of short term intake (IESTI) for ARfD= 0.003 mg/kg bw/day

CHILDREN UP TO 6 YEARS

Maximum % of ARfD: 120%

Codex Code	Commodity	STMR or STMR-P mg/kg	HR or HR-P mg/kg	Large portion diet			Unit weight			Variability factor	Case	IESTI µg/kg bw/day	% ARfD rounded
				Country	Body weight (kg)	Large portion, g/person	Unit weight (g)	Country	Unit weight, edible portion (g)				
VD 0071	Beans (dry)	0.05	-	FRA	17.8	209	-	-	ND	ND	3	0.59	20
PE 0840	Chicken eggs*	-	0	FRA	17.8	134	-	-	ND	ND	1	0.00	0
SB 0716	Coffee beans**	0.00335	-	NLD	17.0	19	-	-	ND	ND	3	0.00	0
VP 0526	Common bean (green pods and/or immature seeds)	-	0.05	NLD	17.0	184	-	-	ND	ND	1	0.54	20
SO 0691	Cotton seed	0.05	-	USA	15.0	1	-	-	ND	ND	3	0.00	0
MO 0105	Edible offal (mammalian)	-	0.02	FRA	17.8	203	-	-	ND	ND	1	0.23	8
CF 1255	Maize flour	0.046	-	AUS	19.0	60	-	-	ND	ND	3	0.15	5
GC 0645	Maize (fresh, flour, oil)***	0.02	-	FRA	17.8	148	-	-	ND	ND	3	0.17	6
OR 0645	Maize oil, edible****	0.0162	-	FRA	17.8	21	-	-	ND	ND	3	0.02	1
MM 0095	Meat from mammals other than marine mammals: 20% as fat	-	0.02	AUS	19.0	52	-	-	ND	ND	1	0.05	2
MM 0095	Meat from mammals other than marine mammals: 80% as muscle	-	0.02	AUS	19.0	208	-	-	ND	ND	1	0.22	7
ML 0106	Milks	0.005	-	USA	15.0	1286	-	-	ND	ND	3	0.43	10
VR 0589	Potato*****	-	0.0972	SAF	14.2	300	122	USA	122	3	2a	3.72	120
PM 0110	Poultry meat: 10% as fat	-	0	AUS	19.0	22	-	-	ND	ND	1	0.00	0
PM 0110	Poultry meat: 90% as muscle	-	0	AUS	19.0	201	-	-	ND	ND	1	0.00	0
GC 0651	Sorghum	0.05	-	-	-	ND	-	-	ND	ND	3	ND	-
VD 0541	Soya bean (dry)	0.05	-	JPN	15.9	88	-	-	ND	ND	3	0.28	9
VR 0596	Sugar beet	-	0.05	-	-	ND	-	-	ND	ND	ND	ND	-

* HR for PE 0112, Eggs was used
** STMR-P for SM 0716 Coffee beans, roasted was used
*** there is no consumption data on maize (fresh) only
**** STMR-P for deodorized maize oil was used
***** HR-P for potatoes, microwaved with peel was used.

PYRETHRINS (063) International estimate of short term intake (IESTI) for **GENERAL POPULATION** ARfD= 0.2 mg/kg bw (200 µg/kg bw)

Maximum % of ARfD: 1%

Codex Code	Commodity	STMR or STMR-P mg/kg	HR or HR-P mg/kg	Large portion diet			Unit weight			Variability factor	Case	IESTI µg/kg bw/day	% ARfD rounded
				Country	Body weight (kg)	Large portion, g/person	Unit weight (g)	Country	Unit weight, edible portion (g)				
TN 0085	Tree nuts		0.5	JNP	52.6	107	-	-	-	-	1	1.02	1

PYRETHRINS (063) International estimate of short term intake (IESTI) for **CHILDREN UP TO 6 YEARS** ARfD= 0.2 mg/kg bw (200 µg/kg bw)

Maximum % of ARfD: 0%

Codex Code	Commodity	STMR or STMR-P mg/kg	HR or HR-P mg/kg	Large portion diet			Unit weight			Varia-bility factor	Case	IESTI µg/kg bw/day	% ARfD rounded
				Country	Body weight (kg)	Large portion, g/person	Unit weight (g)	Country	Unit weight, edible portion (g)				
TN 0085	Tree nuts		0.5	AUS	19.0	28	-	-	-	-	1	0.73	0

SULFURYL FLUORIDE (218) International estimate of short term intake (IESTI) for **GENERAL POPULATION** ARfD = 0.3 mg/kg bw

Maximum % of ARfD: 5%

Codex Code	Commodity	STMR or STMR-P mg/kg	HR or HR-P mg/kg	Large portion diet			Unit weight			Varia-bility factor	Case	IESTI µg/kg bw/day	% ARfD rounded
				Country	Body weight (kg)	Large portion, g/person	Unit weight (g)	Country	Unit weight, edible portion (g)				
TN 0660	Almonds	-	2.5	JPN	52.6	74	-	-	ND	ND	1	3.50	1
DF 0226	Apple, dried	-	0.04	AUS	67.0	10	-	-	ND	ND	1	0.01	0
DF 0240	Apricot, dried	-	0.04	AUS	67.0	31	-	-	ND	ND	1	0.02	0
GC 0640	Barley (fresh, flour, beer)	-	0.03	NLD	63.0	378	-	-	ND	ND	1	0.18	0
CM 0081	Bran, unprocessed of cereal grain (except buckwheat, cañihua, quinoa)	-	0.06	AUS	67.0	37	-	-	ND	ND	1	0.03	0
TN 0662	Brazil nut	-	2.5	NLD	63.0	23	-	-	ND	ND	1	0.90	0
GC 0641	Buckwheat	-	0.03	NLD	63.0	117	-	-	ND	ND	1	0.06	0

SULFURYL FLUORIDE (218) International estimate of short term intake (IESTI) for **GENERAL POPULATION**

ARfD = 0.3 mg/kg bw
Maximum % of ARfD: 5%

Codex Code	Commodity	STMR or STMR-P mg/kg	HR or HR-P mg/kg	Large portion diet			Unit weight			Varia-bility factor	Case	IESTI µg/kg bw/day	% ARfD rounded
				Country	Body weight (kg)	Large portion, g/person	Unit weight (g)	Country	Unit weight, edible portion (g)				
TN 0295	Cashew nut	-	2.5	AUS	67.0	150	-	-	ND	ND	1	5.60	2
TN 0664	Chestnuts	-	2.5	AUS	67.0	400	-	-	ND	ND	1	14.93	5
TN 0665	Coconut	-	2.5	AUS	67.0	84	-	-	ND	ND	ND	ND	-
DF 0295	Dates, dried or dried and candied	-	0.04	AUS	67.0	137	-	-	ND	ND	1	0.08	0
DF 0167	Dried fruits	-	0.04	FRA	62.3	138	-	-	ND	ND	1	0.09	0
DF 0297	Figs, dried or dried and candied	-	0.04	FRA	62.3	231	-	-	ND	ND	1	0.15	0
DF 0269	Grapes, dried (= currants, raisins and sultanas)	-	0.04	FRA	62.3	135	-	-	ND	ND	1	0.09	0
TN 0666	Hazelnuts	-	2.5	AUS	67.0	70	-	-	ND	ND	1	2.60	1
TN 0669	Macadamia nuts	-	2.5	USA	65.0	107	-	-	ND	ND	1	4.10	1
CF 1255	Maize flour	-	0.06	AUS	67.0	90	-	-	ND	ND	1	0.08	0
GC 0645	Maize (fresh)	-	0.03	-	-	ND	-	-	ND	ND	1	ND	-
GC 0646	Millet	-	0.03	AUS	67.0	101	-	-	ND	ND	1	0.05	0
GC 0647	Oats	-	0.03	FRA	62.3	305	-	-	ND	ND	1	0.15	0
TN 0672	Pecan	-	2.5	AUS	67.0	23	-	-	ND	ND	1	0.88	0
TN 0673	Pine nuts	-	2.5	AUS	67.0	47	-	-	ND	ND	1	1.75	1
TN 0675	Pistachio nut	-	2.5	AUS	67.0	300	-	-	ND	ND	1	11.20	4
GC 0656	Popcorn	-	0.03	JPN	52.6	175	-	-	ND	ND	1	0.10	0
DF 0014	Prunes	-	0.04	USA	65.0	303	6	FRA	5	1	1	0.19	0
GC 0649	Rice	-	0.03	FRA	62.3	312	-	-	ND	ND	1	0.15	0
CM 1206	Rice bran, unprocessed	-	0.06	AUS	67.0	50	-	-	ND	ND	1	0.04	0
CM 0649	Rice, husked	-	0.06	JPN	52.6	319	-	-	ND	ND	1	0.36	0
CM 1205	Rice, polished	-	0.06	JPN	52.6	402	-	-	ND	ND	1	0.46	0
GC 0650	Rye	-	0.03	NLD	63.0	77	-	-	ND	ND	1	0.04	0
CM 0650	Rye bran, unprocessed	-	0.06	-	-	ND	-	-	ND	ND	1	ND	-
CF 1250	Rye flour	-	0.06	FRA	62.3	115	-	-	ND	ND	1	0.11	0
CF 1251	Rye wholemeal	-	0.06	USA	65.0	33	-	-	ND	ND	1	0.03	0
GC 0651	Sorghum	-	0.03	USA	65.0	18	-	-	ND	ND	1	0.01	0
GC 0653	Triticale	-	0.03	-	-	ND	-	-	ND	ND	1	ND	-
TN 0678	Walnuts	-	2.5	FRA	62.3	136	-	-	ND	ND	1	5.45	2
GC 0654	Wheat	-	0.03	USA	65.0	383	-	-	ND	ND	1	0.18	0
CM 0654	Wheat bran, unprocessed	-	0.06	USA	65.0	80	-	-	ND	ND	1	0.07	0
CF 1211	Wheat flour	-	0.06	USA	65.0	365	-	-	ND	ND	1	0.34	0

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SULFURYL FLUORIDE (218) International estimate of short term intake (IESTI) for **GENERAL POPULATION**

ARfD = 0.3 mg/kg bw
Maximum % of ARfD: 5%

Codex Code	Commodity	STMR or STMR-P mg/kg	HR or HR-P mg/kg	Large portion diet			Unit weight			Varia-bility factor	Case	IESTI µg/kg bw/day	% ARfD rounded
				Country	Body weight (kg)	Large portion, g/person	Unit weight (g)	Country	Unit weight, edible portion (g)				
CF 1210	Wheat germ	-	0.06	FRA	62.3	207	-	-	ND	ND	1	0.20	0
CF 1212	Wheat wholemeal	-	0.06	USA	65.0	155	-	-	ND	ND	1	0.14	0
GC 0655	Wild rice	-	0.03	AUS	67.0	48	-	-	ND	ND	1	0.02	0

SULFURYL FLUORIDE (218) International estimate of short term intake (IESTI) for **CHILDREN UP TO 6 YEARS**

ARfD = 0.3 mg/kg bw
Maximum %ARfD: 3%

Codex Code	Commodity	STMR or STMR-P mg/kg	HR or HR-P mg/kg	Large portion diet			Unit weight			Variability factor	Case	IESTI µg/kg bw/day	% ARfD rounded
				Country	Body weight (kg)	Large portion, g/person	Unit weight (g)	Country	Unit weight, edible portion (g)				
TN 0660	Almonds	-	2.5	FRA	17.8	31	-	-	ND	ND	1	4.40	1
DF 0226	Apple, dried	-	0.04	AUS	19.0	4	-	-	ND	ND	1	0.01	0
DF 0240	Apricot, dried	-	0.04	AUS	19.0	24	-	-	ND	ND	1	0.05	0
GC 0640	Barley (fresh, flour, beer)	-	0.03	AUS	19.0	14	-	-	ND	ND	1	0.02	0
CM 0081	Bran, unprocessed of cereal grain (except buckwheat, cañihua, quinoa)	-	0.06	AUS	19.0	13	-	-	ND	ND	1	0.04	0
TN 0662	Brazil nut	-	2.5	-	-	ND	-	-	ND	ND	1	ND	-
GC 0641	Buckwheat	-	0.03	NLD	17.0	59	-	-	ND	ND	1	0.10	0
TN 0295	Cashew nut	-	2.5	AUS	19.0	36	-	-	ND	ND	1	4.78	2
TN 0664	Chestnuts	-	2.5	-	-	ND	-	-	ND	ND	1	ND	-
TN 0665	Coconut	-	2.5	NLD	17.0	17	-	-	ND	ND	ND	ND	-
DF 0295	Dates, dried or dried and candied	-	0.04	AUS	19.0	63	-	-	ND	ND	1	0.13	0
DF 0167	Dried fruits	-	0.04	FRA	17.8	101	-	-	ND	ND	1	0.23	0
DF 0297	Figs, dried or dried and candied	-	0.04	FRA	17.8	45	-	-	ND	ND	1	0.10	0
DF 0269	Grapes, dried (= currants, raisins and sultanas)	-	0.04	USA	15.0	59	-	-	ND	ND	1	0.16	0
TN 0666	Hazelnuts	-	2.5	NLD	17.0	11	-	-	ND	ND	1	1.63	1
TN 0669	Macadamia nuts	-	2.5	-	-	ND	-	-	ND	ND	1	ND	-
CF 1255	Maize flour	-	0.06	AUS	19.0	60	-	-	ND	ND	1	0.19	0
GC 0645	Maize (fresh)	-	0.03	-	-	ND	-	-	ND	ND	1	ND	-
GC 0646	Millet	-	0.03	-	-	ND	-	-	ND	ND	1	ND	-
GC 0647	Oats	-	0.03	USA	15.0	62	-	-	ND	ND	1	0.12	0

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SULFURYL FLUORIDE (218) International estimate of short term intake (IESTI) for **CHILDREN UP TO 6 YEARS**

ARfD = 0.3 mg/kg bw
Maximum %ARfD: 3%

Codex Code	Commodity	STMR or STMR-P mg/kg	HR or HR-P mg/kg	Large portion diet			Unit weight			Variability factor	Case	IESTI µg/kg bw/day	% ARfD rounded
				Country	Body weight (kg)	Large portion, g/person	Unit weight (g)	Country	Unit weight, edible portion (g)				
TN 0672	Pecan	-	2.5	AUS	19.0	22	-	-	ND	ND	1	2.92	1
TN 0673	Pine nuts	-	2.5	AUS	19.0	18	-	-	ND	ND	1	2.33	1
TN 0675	Pistachio nut	-	2.5	AUS	19.0	63	-	-	ND	ND	1	8.22	3
GC 0656	Popcorn	-	0.03	JPN	15.9	53	-	-	ND	ND	1	0.10	0
DF 0014	Prunes	-	0.04	AUS	19.0	170	6	FRA	5	1	1	0.36	0
GC 0649	Rice	-	0.03	FRA	17.8	223	-	-	ND	ND	1	0.38	0
CM 1206	Rice bran, unprocessed	-	0.06	USA	15.0	3	-	-	ND	ND	1	0.01	0
CM 0649	Rice, husked	-	0.06	FRA	17.8	223	-	-	ND	ND	1	0.75	0
CM 1205	Rice, polished	-	0.06	JPN	15.9	199	-	-	ND	ND	1	0.75	0
GC 0650	Rye	-	0.03	NLD	17.0	37	-	-	ND	ND	1	0.07	0
CM 0650	Rye bran, unprocessed	-	0.06	-	-	ND	-	-	ND	ND	1	ND	-
CF 1250	Rye flour	-	0.06	USA	15.0	18	-	-	ND	ND	1	0.07	0
CF 1251	Rye wholemeal	-	0.06	USA	15.0	10	-	-	ND	ND	1	0.04	0
GC 0651	Sorghum	-	0.03	-	-	ND	-	-	ND	ND	1	ND	-
GC 0653	Triticale	-	0.03	-	-	ND	-	-	ND	ND	1	ND	-
TN 0678	Walnuts	-	2.5	USA	15.0	6	-	-	ND	ND	1	0.93	0
GC 0654	Wheat	-	0.03	USA	15.0	151	-	-	ND	ND	1	0.30	0
CM 0654	Wheat bran, unprocessed	-	0.06	USA	15.0	30	-	-	ND	ND	1	0.12	0
CF 1211	Wheat flour	-	0.06	AUS	19.0	194	-	-	ND	ND	1	0.61	0
CF 1210	Wheat germ	-	0.06	USA	15.0	8	-	-	ND	ND	1	0.03	0
CF 1212	Wheat wholemeal	-	0.06	USA	15.0	74	-	-	ND	ND	1	0.29	0
GC 0655	Wild rice	-	0.03	AUS	19.0	34	-	-	ND	ND	1	0.05	0

SULFURYL FLUORIDE (218) International estimate of short term intake (IESTI) for **CHILDREN UP TO 6 YEARS**

ARfD =0.3 mg/kg bw
Maximum %ARfD: 3%

Codex Code	Commodity	STMR or STMR-P mg/kg	HR or HR-P mg/kg	Large portion diet			Unit weight			Variability factor	Case	IESTI µg/kg bw/day	% ARfD rounded
				Country	Body weight (kg)	Large portion, g/person	Unit weight (g)	Country	Unit weight, edible portion (g)				
TN 0660	Almonds	-	2.5	FRA	17.8	31	-	-	ND	ND	1	4.40	1
DF 0226	Apple, dried	-	0.04	AUS	19.0	4	-	-	ND	ND	1	0.01	0
DF 0240	Apricot, dried	-	0.04	AUS	19.0	24	-	-	ND	ND	1	0.05	0
GC 0640	Barley (fresh, flour, beer)	-	0.03	AUS	19.0	14	-	-	ND	ND	1	0.02	0
CM 0081	Bran, unprocessed of cereal grain (except buckwheat, cañihua, quinoa)	-	0.06	AUS	19.0	13	-	-	ND	ND	1	0.04	0
TN 0662	Brazil nut	-	2.5	-	-	ND	-	-	ND	ND	1	ND	-
GC 0641	Buckwheat	-	0.03	NLD	17.0	59	-	-	ND	ND	1	0.10	0
TN 0295	Cashew nut	-	2.5	AUS	19.0	36	-	-	ND	ND	1	4.78	2
TN 0664	Chestnuts	-	2.5	-	-	ND	-	-	ND	ND	1	ND	-
TN 0665	Coconut	-	2.5	NLD	17.0	17	-	-	ND	ND	ND	ND	-
DF 0295	Dates, dried or dried and candied	-	0.04	AUS	19.0	63	-	-	ND	ND	1	0.13	0
DF 0167	Dried fruits	-	0.04	FRA	17.8	101	-	-	ND	ND	1	0.23	0
DF 0297	Figs, dried or dried and candied	-	0.04	FRA	17.8	45	-	-	ND	ND	1	0.10	0
DF 0269	Grapes, dried (= currants, raisins and sultanas)	-	0.04	USA	15.0	59	-	-	ND	ND	1	0.16	0
TN 0666	Hazelnuts	-	2.5	NLD	17.0	11	-	-	ND	ND	1	1.63	1
TN 0669	Macadamia nuts	-	2.5	-	-	ND	-	-	ND	ND	1	ND	-
CF 1255	Maize flour	-	0.06	AUS	19.0	60	-	-	ND	ND	1	0.19	0
GC 0645	Maize (fresh)	-	0.03	-	-	ND	-	-	ND	ND	1	ND	-
GC 0646	Millet	-	0.03	-	-	ND	-	-	ND	ND	1	ND	-
GC 0647	Oats	-	0.03	USA	15.0	62	-	-	ND	ND	1	0.12	0
TN 0672	Pecan	-	2.5	AUS	19.0	22	-	-	ND	ND	1	2.92	1
TN 0673	Pine nuts	-	2.5	AUS	19.0	18	-	-	ND	ND	1	2.33	1
TN 0675	Pistachio nut	-	2.5	AUS	19.0	63	-	-	ND	ND	1	8.22	3
GC 0656	Popcorn	-	0.03	JPN	15.9	53	-	-	ND	ND	1	0.10	0
DF 0014	Prunes	-	0.04	AUS	19.0	170	6	FRA	5	1	1	0.36	0
GC 0649	Rice	-	0.03	FRA	17.8	223	-	-	ND	ND	1	0.38	0
CM 1206	Rice bran, unprocessed	-	0.06	USA	15.0	3	-	-	ND	ND	1	0.01	0
CM 0649	Rice, husked	-	0.06	FRA	17.8	223	-	-	ND	ND	1	0.75	0
CM 1205	Rice, polished	-	0.06	JPN	15.9	199	-	-	ND	ND	1	0.75	0

SULFURYL FLUORIDE (218) International estimate of short term intake (IESTI) for **CHILDREN UP TO 6 YEARS**

ARfD =0.3 mg/kg bw
Maximum %ARfD: 3%

Codex Code	Commodity	STMR or STMR-P mg/kg	HR or HR-P mg/kg	Large portion diet			Unit weight			Variability factor	Case	IESTI µg/kg bw/day	% ARfD rounded
				Country	Body weight (kg)	Large portion, g/person	Unit weight (g)	Country	Unit weight, edible portion (g)				
GC 0650	Rye	-	0.03	NLD	17.0	37	-	-	ND	ND	1	0.07	0
CM 0650	Rye bran, unprocessed	-	0.06	-	-	ND	-	-	ND	ND	1	ND	-
CF 1250	Rye flour	-	0.06	USA	15.0	18	-	-	ND	ND	1	0.07	0
CF 1251	Rye wholemeal	-	0.06	USA	15.0	10	-	-	ND	ND	1	0.04	0
GC 0651	Sorghum	-	0.03	-	-	ND	-	-	ND	ND	1	ND	-
GC 0653	Triticale	-	0.03	-	-	ND	-	-	ND	ND	1	ND	-
TN 0678	Walnuts	-	2.5	USA	15.0	6	-	-	ND	ND	1	0.93	0
GC 0654	Wheat	-	0.03	USA	15.0	151	-	-	ND	ND	1	0.30	0
CM 0654	Wheat bran, unprocessed	-	0.06	USA	15.0	30	-	-	ND	ND	1	0.12	0
CF 1211	Wheat flour	-	0.06	AUS	19.0	194	-	-	ND	ND	1	0.61	0
CF 1210	Wheat germ	-	0.06	USA	15.0	8	-	-	ND	ND	1	0.03	0
CF 1212	Wheat wholemeal	-	0.06	USA	15.0	74	-	-	ND	ND	1	0.29	0
GC 0655	Wild rice	-	0.03	AUS	19.0	34	-	-	ND	ND	1	0.05	0

TERBUFOS (167) International estimate of short term intake (IESTI) for **GENERAL POPULATION**

Acute RfD= 0.002 mg/kg bw (2 µg/kg bw)
Maximum % of ARfD: 30%

Codex Code	Commodity	STMR or STMR-P mg/kg	HR or HR-P mg/kg	Large portion diet			Unit weight			Variability factor	Case	IESTI µg/kg bw/day	% acute RfD rounded
				Country	Body weight (kg)	Large portion, g/person	Unit weight (g)	Country	Unit weight, edible portion (g)				
FI 0327	Banana	-	0.02	SAF	55.7	613	900	FRA	612	3	2a	0.66	30%
FI 0327	Banana	-	0.02	SAF	55.7	613	720	JPN	720	3	2b	0.66	30%
FI 0327	Banana	-	0.02	SAF	55.7	613	909	UNK	600	3	2a	0.65	30%
FI 0327	Banana	-	0.02	SAF	55.7	613	708	USA	481	3	2a	0.57	30%
FI 0327	Banana	-	0.02	SAF	55.7	613	1218	SWE	767	3	2b	0.66	30%

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MF 0812	Cattle fat	-	0.05	USA	65.0	60	-	-	ND	ND	1	0.05	2%
PE 0840	Chicken eggs	-	0.01	FRA	62.3	219	-	-	ND	ND	1	0.04	2%
SB 0716	Coffee beans	0.05	-	NLD	63.0	66	-	-	ND	ND	3	0.05	3%
PE 0841	Duck eggs	-	0.01	AUS	67.0	135	-	-	ND	ND	1	0.02	1%
MO 0105	Edible offal (mammalian)	-	0.05	FRA	62.3	277	-	-	ND	ND	1	0.22	10%
MF 0814	Goat fat	-	0.05	USA	65.0	18	-	-	ND	ND	1	0.01	1%
GC 0645	Maize (fresh, flour, oil)	0.01	-	FRA	62.3	260	-	-	ND	ND	3	0.04	3%
MM 0095	Meat from mammals other than marine mammals	-	0.05	AUS	67.0	521	-	-	ND	ND	1	0.39	20%
ML 0106	Milks	0.01	-	USA	65.0	2466	-	-	ND	ND	3	0.38	20%
PM 0110	Poultry meat	-	0.05	AUS	67.0	431	-	-	ND	ND	1	0.32	20%
PO 0113	Poultry skin	-	0.05	AUS	67.0	28	-	-	ND	ND	1	0.02	1%
PO 0111	Poultry, edible offal of	-	0.05	USA	65.0	248	-	-	ND	ND	1	0.19	10%
PF 0111	Poultry, fats	-	0.05	FRA	62.3	46	-	-	ND	ND	1	0.04	2%
MF 0822	Sheep fat	-	0.05	USA	65.0	54	-	-	ND	ND	1	0.04	2%
GC 0651	Sorghum	0	-	USA	65.0	18	-	-	ND	ND	3	0.00	0%
VR 0596	Sugar beet	-	0.01	-	-	ND	-	-	ND	ND	ND	ND	-
VO 0447	Sweet corn (corn-on-the-cob)	-	0.01	USA	65.0	367	200	JPN	200	3	2a	0.59	6%
VO 0447	Sweet corn (corn-on-the-cob)	-	0.01	USA	65.0	367	215	UNK	125	3	2a	0.47	5%

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TERBUFOS (167) International estimate of short term intake (IESTI) for **CHILDREN**

ARfD=0.002 mg/kg bw (2 μg/kg bw)

Maximum %ARfD: ug/kg bw) 30%

Codex Code	Commodity	STMR or STMR-P mg/kg	HR or HR-P mg/kg	Large portion diet			Unit weight			Variability factor	Case	IESTI μg/kg bw/day	% acute RfD rounded
				Country	Body weight (kg)	Large portion, g/person	Unit weight, g	Country	Unit weight, edible portion, g				
FI 0327	Banana	-	0.02	JPN	15.9	312	708	USA	481	3	2b	1.18	60%
PE 0840	Chicken eggs	-	0.01	FRA	17.8	134	-	-	ND	ND	1	0.08	4%
SB 0716	Coffee beans	0.05	-	NLD	17.0	19	-	-	ND	ND	3	0.06	3%
MO 0105	Edible offal (mammalian)	-	0.05	FRA	17.8	203	-	-	ND	ND	1	0.57	30%
GC 0645	Maize (fresh, flour, oil)	0.01	-	FRA	17.8	148	-	-	ND	ND	3	0.08	4%
MM 0095	Meat from mammals other than marine mammals	-	0.05	AUS	19.0	261	-	-	ND	ND	1	0.69	30%
ML 0106	Milks	0.01	-	USA	15.0	1286	-	-	ND	ND	3	0.86	40%
PM 0110	Poultry meat	-	0.05	AUS	19.0	224	-	-	ND	ND	1	0.59	30%
PO 0111	Poultry, edible offal of	-	0.05	USA	15.0	37	-	-	ND	ND	1	0.12	6%
GC 0651	Sorghum	0	-	-	-	ND	-	-	ND	ND	3	ND	-
VR 0596	Sugar beet	-	0.01	-	-	ND	-	-	ND	ND	ND	ND	-
VO 0447	Sweet corn (corn-on-the-cob)	-	0.01	UNK	14.5	161	200	JPN	200	3	2b	0.33	20%

ANNEX 5: REPORTS AND OTHER DOCUMENTS RESULTING FROM PREVIOUS JOINT MEETINGS OF THE FAO PANEL OF EXPERTS ON PESTICIDE RESIDUES IN FOOD AND THE ENVIRONMENT AND THE WHO EXPERT GROUPS ON PESTICIDE RESIDUES

1. Principles governing consumer safety in relation to pesticide residues. Report of a meeting of a WHO Expert Committee on Pesticide Residues held jointly with the FAO Panel of Experts on the Use of Pesticides in Agriculture. FAO Plant Production and Protection Division Report, No. PL/1961/11; WHO Technical Report Series, No. 240, 1962.
2. Evaluation of the toxicity of pesticide residues in food. Report of a Joint Meeting of the FAO Committee on Pesticides in Agriculture and the WHO Expert Committee on Pesticide Residues. FAO Meeting Report, No. PL/1963/13; WHO/Food Add./23, 1964.
3. Evaluation of the toxicity of pesticide residues in food. Report of the Second Joint Meeting of the FAO Committee on Pesticides in Agriculture and the WHO Expert Committee on Pesticide Residues. FAO Meeting Report, No. PL/1965/10; WHO/Food Add./26.65, 1965.
4. Evaluation of the toxicity of pesticide residues in food. FAO Meeting Report, No. PL/1965/10/1; WHO/Food Add./27.65, 1965.
5. Evaluation of the hazards to consumers resulting from the use of fumigants in the protection of food. FAO Meeting Report, No. PL/1965/10/2; WHO/Food Add./28.65, 1965.
6. Pesticide residues in food. Joint report of the FAO Working Party on Pesticide Residues and the WHO Expert Committee on Pesticide Residues. FAO Agricultural Studies, No. 73; WHO Technical Report Series, No. 370, 1967.
7. Evaluation of some pesticide residues in food. FAO/PL:CP/15; WHO/Food Add./67.32, 1967.
8. Pesticide residues. Report of the 1967 Joint Meeting of the FAO Working Party and the WHO Expert Committee. FAO Meeting Report, No. PL:1967/M/11; WHO Technical Report Series, No. 391, 1968.
9. 1967 Evaluations of some pesticide residues in food. FAO/PL:1967/M/11/1; WHO/Food Add./68.30, 1968.
10. Pesticide residues in food. Report of the 1968 Joint Meeting of the FAO Working Party of Experts on Pesticide Residues and the WHO Expert Committee on Pesticide Residues. FAO Agricultural Studies, No. 78; WHO Technical Report Series, No. 417, 1968.
11. 1968 Evaluations of some pesticide residues in food. FAO/PL:1968/M/9/1; WHO/Food Add./69.35, 1969.
12. Pesticide residues in food. Report of the 1969 Joint Meeting of the FAO Working Party of Experts on Pesticide Residues and the WHO Expert Group on Pesticide Residues. FAO Agricultural Studies, No. 84; WHO Technical Report Series, No. 458, 1970.
13. 1969 Evaluations of some pesticide residues in food. FAO/PL:1969/M/17/1; WHO/Food Add./70.38, 1970.
14. Pesticide residues in food. Report of the 1970 Joint Meeting of the FAO Working Party of Experts on Pesticide Residues and the WHO Expert Committee on Pesticide Residues. FAO Agricultural Studies, No. 87; WHO Technical Report Series, No. 4574, 1971.
15. 1970 Evaluations of some pesticide residues in food. AGP:1970/M/12/1; WHO/Food Add./71.42, 1971.
16. Pesticide residues in food. Report of the 1971 Joint Meeting of the FAO Working Party of Experts on Pesticide Residues and the WHO Expert Committee on Pesticide Residues. FAO

Agricultural Studies, No. 88; WHO Technical Report Series, No. 502, 1972.

17. 1971 Evaluations of some pesticide residues in food. AGP:1971/M/9/1; WHO Pesticide Residue Series, No. 1, 1972.

18. Pesticide residues in food. Report of the 1972 Joint Meeting of the FAO Working Party of Experts on Pesticide Residues and the WHO Expert Committee on Pesticide Residues. FAO Agricultural Studies, No. 90; WHO Technical Report Series, No. 525, 1973.

19. 1972 Evaluations of some pesticide residues in food. AGP:1972/M/9/1; WHO Pesticide Residue Series, No. 2, 1973.

20. Pesticide residues in food. Report of the 1973 Joint Meeting of the FAO Working Party of Experts on Pesticide Residues and the WHO Expert Committee on Pesticide Residues. FAO Agricultural Studies, No. 92; WHO Technical Report Series, No. 545, 1974.

21. 1973 Evaluations of some pesticide residues in food. FAO/AGP/1973/M/9/1; WHO Pesticide Residue Series, No. 3, 1974.

22. Pesticide residues in food. Report of the 1974 Joint Meeting of the FAO Working Party of Experts on Pesticide Residues and the WHO Expert Committee on Pesticide Residues. FAO Agricultural Studies, No. 97; WHO Technical Report Series, No. 574, 1975.

23. 1974 Evaluations of some pesticide residues in food. FAO/AGP/1974/M/11; WHO Pesticide Residue Series, No. 4, 1975.

24. Pesticide residues in food. Report of the 1975 Joint Meeting of the FAO Working Party of Experts on Pesticide Residues and the WHO Expert Committee on Pesticide Residues. FAO Plant Production and Protection Series, No. 1; WHO Technical Report Series, No. 592, 1976.

25. 1975 Evaluations of some pesticide residues in food. AGP:1975/M/13; WHO Pesticide Residue Series, No. 5, 1976.

26. Pesticide residues in food. Report of the 1976 Joint Meeting of the FAO Panel of Experts on Pesticide Residues and the Environment and the WHO Expert Group on Pesticide Residues. FAO Food and Nutrition Series, No. 9; FAO Plant Production and Protection Series, No. 8; WHO Technical Report Series, No. 612, 1977.

27. 1976 Evaluations of some pesticide residues in food. AGP:1976/M/14, 1977.

28. Pesticide residues in food—1977. Report of the Joint Meeting of the FAO Panel of Experts on Pesticide Residues and Environment and the WHO Expert Group on Pesticide Residues. FAO Plant Production and Protection Paper 10 Rev, 1978.

29. Pesticide residues in food: 1977 evaluations. FAO Plant Production and Protection Paper 10 Suppl., 1978.

30. Pesticide residues in food—1978. Report of the Joint Meeting of the FAO Panel of Experts on Pesticide Residues and Environment and the WHO Expert Group on Pesticide Residues. FAO Plant Production and Protection Paper 15, 1979.

31. Pesticide residues in food: 1978 evaluations. FAO Plant Production and Protection Paper 15 Suppl., 1979.

32. Pesticide residues in food—1979. Report of the Joint Meeting of the FAO Panel of Experts on Pesticide Residues in Food and the Environment and the WHO Expert Group on Pesticide Residues. FAO Plant Production and Protection Paper 20, 1980.

33. Pesticide residues in food: 1979 evaluations. FAO Plant Production and Protection Paper 20 Suppl., 1980

34. Pesticide residues in food—1980. Report of the Joint Meeting of the FAO Panel of Experts on Pesticide Residues in Food and the Environment and the WHO Expert Group on Pesticide

Residues. FAO Plant Production and Protection Paper 26, 1981.

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