Pesticide residues in food – 2004

FAO
PLANT
PRODUCTION
AND PROTECTION
PAPER

178

Report of the Joint Meeting of the FAO Panel of Experts on Pesticide Residues in Food and the Environment and the WHO Core Assessment Group on Pesticide Residues
Rome, Italy, 20 – 29 September 2004

WORLD HEALTH ORGANIZATION
FOOD AND AGRICULTURE ORGANIZATION OF THE UNITED NATIONS
Rome, 2004

The designations employed and the presentation of material in this information product do not imply the expression of any opinion whatsoever on the part of the Food and Agriculture Organization of the United Nations concerning the legal or development status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries.

ISBN 92-5-105242-5

All rights reserved. Reproduction and dissemination of material in this information product for educational or other non-commercial purposes are authorized without any prior written permission from the copyright holders provided the source is fully acknowledged. Reproduction of material in this information product for resale or other commercial purposes is prohibited without written permission of the copyright holders. Applications for such permission should be addressed to the Chief, Publishing Management Service, Information Division, FAO, Viale delle Terme di Caracalla, 00100 Rome, Italy or by e-mail to copyright@fao.org

© **FAO 2004**

CONTENTS

LIST OF PARTICIPANTS

2004 Joint FAO/WHO Meeting on Pesticide Residues
Rome, 20–29 September 2004

FAO Members

Dr Ursula Banasiak, Federal Institute for Risk Assessment, Thielallee 88-92, D-14195 Berlin, Germany
Tel.: (49 30) 8412 3337; Fax: (49 30) 8412 3260; E-mail: u.banasiak@bfr.bund.de

Dr Eloisa Dutra Caldas, University of Brasilia, College of Health Sciences, Pharmaceutical Sciences Department, Campus Universitàrio Darci Ribeiro, 70919-970 Brasília/DF, Brazil
Tel.: (55 61) 307 3671; Fax: (55 61) 273 0105; E-mail: eloisa@unb.br

Dr Stephen Funk, Health Effects Division (7509C), United States Environmental Protection Agency, 1200 Pennsylvania Ave NW, 7509C, Washington DC 20460, USA (*FAO Chairman*)
Tel.: (1 703) 305 5430; Fax: (1 703) 305 0871; E-mail: funk.steve@epa.gov

Mr Denis J. Hamilton, Principal Scientific Officer, Biosecurity, Department of Primary Industries and Fisheries, PO Box 46, Brisbane, QLD 4001, Australia (*FAO Rapporteur*)
Tel.: (61 7) 3239 3409; Fax: (61 7) 3211 3293; E-mail: denis.hamilton@dpi.qld.gov.au

Mr David Lunn, Programme Manager (Residues–Plants), Dairy and Plant Products Group, New Zealand Food Safety Authority, PO Box 2835, Wellington, New Zealand
Tel.: (644) 463 2654; Fax: (644) 463 2675; E-mail: dave.lunn@nzfsa.govt.nz

Dr Dugald MacLachlan, Australian Quarantine and Inspection Service, Australian Department of Agriculture, Fisheries and Forestry, Edmond Barton Building, Kingston, ACT 2601, Australia
Tel.: (61 2) 6272 3183; Fax: (61 2) 6271 6522; E-mail: dugald.maclachlan@aqis.gov.au

Dr Bernadette C. Ossendorp, Centre for Substances and Integrated Risk Assessment, National Institute of Public Health and the Environment (RIVM), Antonie van Leeuwenhoeklaan 9, PO Box 1, 3720 BA Bilthoven, Netherlands
Tel.: (31 30) 274 3970; Fax: (31 30) 274 4475; E-mail: bernadette.ossendorp@rivm.nl

Dr Yukiko Yamada, Research Planning and Coordination Division, National Food Research Institute, 2-1-12 Kannondai, Tsukuba 305-8642, Japan
Tel.: (81 3) 3502 2319; Fax: (81 3) 3597 0389; E-mail: yukiko.yamada@affrc.go.jp

WHO Members

Professor Alan R. Boobis, Experimental Medicine & Toxicology, Division of Medicine, Faculty of Medicine, Imperial College London, Hammersmith Campus, Ducane Road, London W12 0NN, England (*WHO Chairman*)
Tel.: (44 20) 8383 3221; Fax: (44 20) 8383 2066; E-mail: a.boobis@imperial.ac.uk

List of participants

Dr Les Davies, Science Strategy and Policy, Office of Chemical Safety, Australian Government Department of Health and Ageing, PO Box 100, Woden, ACT 2606, Australia
Tel.: (61 2) 6270 4378; Fax: (61 2) 6270 4353; E-mail: les.davies@health.gov.au

Dr Vicki L. Dellarco, United States Environmental Protection Agency, Office of Pesticide Programs (7509C), Health Effects Division, 401 M Street SW, Washington DC 20460, USA (*WHO Rapporteur*)
Tel.: (1 703) 305 1803; Fax: (1 703) 305 5147; E-mail: dellarco.vicki@epa.gov

Dr Helen Hakansson, Institute of Environmental Medicine, Karolinska Institutet, Unit of Environmental Health Risk Assessment, Box 210, Nobels väg 13, S-171 77 Stockholm, Sweden
Tel.: (46 8) 524 87527; Fax: (46 8) 34 38 49; E-mail: helen.hakansson@imm.ki.se

Dr Angelo Moretto, Dipartimento Medicina Ambientale e Sanità Pubblica, Università di Padova, via Giustiniani 2, 35128 Padova, Italy
Tel.: (39 049) 821 1377 / 2541; Fax: (39 049) 821 2550 / 2542; E-mail: angelo.moretto@unipd.it

Dr Roland Solecki, Pesticides and Biocides Division, Federal Institute for Risk Assessment, Thielallee 88-92, D-14195 Berlin, Germany
Tel.: (49 30) 8412 3232; Fax: (49 30) 8412 3260; E-mail: r.solecki@bfr.bund.de

Dr Maria Tasheva, Laboratory of Toxicology, National Center of Hygiene, Medical Ecology and Nutrition, 15 Dim. Nestorov Str., 1431 Sofia, Bulgaria
Tel.: (3592) 954 11 97; Fax: (3592) 954 11 97; E-mail: mtasheva@aster.net

Secretariat

Dr Arpàd Ambrus, Central Service for Plant Protection and and Soil Conservation, Plant and Soil Protection Directorate, Budaörsi ut 141-145, H-1118 Budapest, Hungary (*FAO Consultant*)
Tel.: (36 1) 309 1003; Fax: (36 1) 246 2955; E-mail: ambrus.arpad@ontsz.hu

Dr Andrew Bartholomaeus, Therapeutic Goods Administration, Commonwealth Department of Health and Ageing, MDP 122, PO Box 100, Woden, ACT 2602, Australia (*WHO Temporary Adviser*)
Tel.: (61 2) 62 32 8345; Fax: (61 2) 62 32 8355; E-mail: andrew.bartholomaeus@health.gov.au

Dr Lourdes Costarrica, Food and Nutrition Division, Food and Agriculture Organization of the United Nations (FAO), Viale delle Terme di Caracalla, 00100 Rome, Italy (*FAO Staff Member*)
Tel.: (39 06) 570 56060; Fax: (39 06) 570 54593; E-mail: lourdes.costarrica@fao.org

Mr Bernard Declercq, 13 impasse du court Riage, 91360 Epinay sur Orge, France (*FAO Consultant*)
Tel.: (33 1) 64488369; Fax: (33 1) 64488369; E-mail: bernard-declercq@wanadoo.fr

Dr Ghazi Dannan, Office of Pesticide Programs (7509C), United States Environmental Protection Agency, 1200 Pennsylvania Avenue NW, Washington DC 20460, USA (*WHO Temporary Adviser*)
Tel.: (1 703) 308 9549; Fax: (1 703) 305 5529; E-mail: dannan.ghazi@epa.gov

Dr Ian C. Dewhurst, Pesticides Safety Directorate, Mallard House, King's Pool, 3 Peasholme Green, York YO1 7PX, England (*WHO Temporary Adviser*)
Tel.: (44 1904) 455 890; Fax: (44 1904) 455 711; E-mail: ian.dewhurst@psd.defra.gsi.gov.uk

Dr Salwa Dogheim, Central Laboratory of Residue Analysis of Pesticides and Heavy Metals in Food, Agriculture Research Center, Ministry of Agriculture, 7 Mahalla Street, Heliopolis, Cairo, Egypt (*FAO Consultant*)
Tel.: (2012) 215 5201; Fax: (2012) 418 2814; E-mail: s.dogheim@link.net

Professor P.K. Gupta, Toxicology Consulting Services Inc., C-44 Rajinder nagar, Bareilly 243 122 (UP), India (*WHO Temporary Adviser*)
Tel.: (91 581) 2300 628; mobile (91 581) 310 4922; E-mail: drpkg_brly@sancharnet.in

Dr Yibing He, Pesticide Residue Division, Institute for the Control of Agrochemicals, Ministry of Agriculture, Building 22, Maizidian Street, Cheoyang District, Beijing 100026, China (*FAO Consultant*)
Tel.: (86 10) 659 36997; Fax: (86 10) 641 94017; E-mail: heyibing@agri.gov.cn

Dr H. Jeuring, Chairman, Codex Committee on Pesticide Residues, Senior Public Health Officer, Food and Consumer Product Safety Authority, PO Box 19506, 2500 CM The Hague, Netherlands (*WHO Temporary Adviser*)
Tel.: (31 70) 448 4848; Fax: (31 70) 448 4747; E-mail: hans.jeuring@vwa.nl

Mr Antony F. Machin, Boundary Corner, 2 Ullathorne Road, London SW16 1SN, England (*FAO Editor*)
Tel. & Fax: (44 208) 769 0435; E-mail: afmachin@clara.net

Dr Timothy C. Marrs, Food Standards Agency, Room 504C, Aviation House, 125 Kingsway, London WC2B 6NH, England (*WHO Temporary Adviser*)
Tel.: (44 207) 276 8507; Fax: (44 207) 276 8513; E-mail: tim.marrs@foodstandards.gsi.gov.uk

Dr Jeronimas Maskeliunas, Joint FAO/WHO Food Standards Programme, Food and Nutrition Division, Food and Agriculture Organization of the United Nations (FAO), Viale delle Terme di Caracalla, 00100 Rome, Italy (*FAO Staff Member*)
Tel.: (39 06) 570 53967; Fax: (39 06) 570 54593; E-mail: jeronimas.maskeliunas@fao.org

Dr Heidi Mattock, 9 rue Jules Verne, 67400 Illkirch-Graffenstaden, France (*WHO Editor*)
Tel.: (33 3) 88 66 07 34; E-mail: heidimattock@yahoo.com

Dr Douglas B. McGregor, 38 Shore Road, Aberdour, KY3 0TU, Scotland (*WHO Temporary Adviser*)
Tel.: (44 1383) 860901; Fax: 44 1583 860901; E-mail: mcgregortec@btinternet.com

Dr Rudolf Pfeil, Pesticides and Biocides Division, Federal Institute for Risk Assessment, Thielallee 88-92, D-14195 Berlin, Germany (*WHO Temporary Adviser*)
Tel.: (49 30) 8412 3828; Fax: (49 30) 8412 3260; E-mail: r.pfeil@bfr.bund.de

Mr Tsuyoshi Sakamoto, Agricultural Chemicals Inspection Station, 2-772 Suzuki-cho, Kodaira, Tokyo 187-0011, Japan (*FAO Consultant*)
Tel.: (81 42) 383 2151 (switchboard); Fax: (81 42) 385 3361; E-mail: t-sakamoto@acis.go.jp

Dr Atsuya Takagi, Division of Toxicology, Biological Safety Research Centre, National Institute of Health Sciences, 1-18-1 Kamiyoga, Setagaya-ku, Tokyo 158-8501, Japan (*WHO Temporary Adviser*)
Tel.: (81 3) 3700 1141 (ext 406); Fax: (81 3) 3700 9647; E-mail: takagi@nihs.go.jp

List of participants

Dr Amelia Tejada, Pesticide Management Group, Plant Protection Service, Plant Production and Protection Division, Food and Agriculture Organization of the United Nations (FAO), Viale delle Terme di Caracalla, 00100 Rome, Italy (*FAO Joint Secretary*)
Tel.: (39 06) 570 54010; Fax: (39 06) 570 56347; E-mail: amelia.tejada@fao.org

Dr Angelika Tritscher, International Programme on Chemical Safety, World Health Organization, 1211 Geneva 27, Switzerland (*WHO Joint Secretary*)
Tel: (41 22) 791 3569; Fax: (41 22) 791 4848; E-mail: tritschera@who.int

Dr Gero Vaagt, Pesticide Management Group, Food and Agriculture Organization of the United Nations (FAO), Viale delle Terme di Caracalla, 00100 Rome, Italy (*FAO Staff Member*)
Tel.: (39 06) 570 55757; Fax: (39 06) 570 56347; E-mail: gero.vaagt@fao.org

Dr Gerrit Wolterink, Centre for Substances & Risk Assessment, National Institute for Public Health and the Environment (RIVM), Antonie van Leeuwenhoeklaan 9, PO Box 1, 3720 BA Bilthoven, Netherlands (*WHO Temporary Adviser*)
Tel.: (31 30) 274 4531; Fax: (31 30) 274 4401; E-mail: gerrit.wolterink@rivm.nl

Dr Jürg Zarn, Swiss Federal Office of Public Health, Food Toxicology Section, Stauffacherstrasse 101, CH-8004 Zürich, Switzerland (*WHO Temporary Adviser*)
Tel.: (41 43) 322 21 93; Fax: (41 43) 322 21 99; E-mail: juerg.zarn@bag.admin.ch

ABBREVIATIONS

(Well-known abbreviations in general use and SI units are not included.)

*	at or about the limit of quantification
ADI	acceptable daily intake
ai	active ingredient
AMPA	ammonethylphosphonic acid
ARfD	acute reference dose
bw	body weight
CCN	Codex classification number (for compounds or commodities)
CCPR	Codex Committee on Pesticide Residues
CSAF	chemical-specific adjustment factor
CXL	Codex level
DT_{50}	time to 50% decomposition
DT_{90}	time to 90% decomposition
F_1	first filial generation
F_2	second filial generation
FAO	Food and Agricultural Organization of the United Nations
FOB	functional observational battery
GAP	good agricultural practice
GEMS/Food	Global Environment Monitoring System–Food Contamination Monitoring and Assessment Programme
GLP	good laboratory practice
HPLC	high-performance liquid chromatography
HR	highest level of residue in the edible portion of a commodity found in trials to estimate a maximum residue limit 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
IEDI	international estimated daily intake
IESTI	international estimated short-term dietary intake
ILO	International Labour Organisation
IUPAC	International Union of Pure and Applied Chemists
JECFA	Joint Expert Committee on Food Additives
ISO	International Standards Organization
JMPR	Joint Meeting on Pesticide Residues
LC_{50}	median lethal concentration
LD_{50}	median lethal dose
LOAEL	lowest-observed-adverse-effect level
LOQ	limit of quantification
MRL	maximum residue limit
NOAEC	no-observed-adverse-effect concentration
NOAEL	no-observed-adverse-effect level
OECD	Organisation for Economic Co-operation and Development
PHI	post-harvest interval
Po	the recommendation accommodates post-harvest treatment of the food commodity
PoP	the recommendation accommodates post-harvest treatment of the primary food commodity

Abbreviations

P_{ow}	octanol–water partition coefficient
ppm	parts per million
RAC	raw agricultural commodity
STMR	supervised trials median residue
STMR-P	supervised trials median residue in a processed commodity calculated by multiplying the STMR of the raw commodity by the corresponding processing factor
THPI	1,2,3,6-tetrahydrophthalimide
TMDI	theoretical maximum daily intake
TRR	total radiolabelled residue
UNEP	United Nations Environment Programme
US	United States of America
W	The previous recommendation is withdrawn.
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 2004 JOINT FAO/WHO MEETING OF EXPERTS

1. INTRODUCTION

A Joint Meeting of the FAO Panel of Experts on Pesticide Residues in Food and the Environment and the WHO Core Assessment Group (JMPR) was held at FAO Headquarters, Rome (Italy), from 20 to 29 September 2004. The Panel Members of FAO and WHO met in preparatory sessions on 15–19 September.

The Meeting was opened by Dr Mahmoud Solh, Director, Plant Production and Protection Division, Department of Agriculture, FAO. On behalf of FAO and WHO, Dr Solh welcomed and thanked the participants for providing their expertise and for the significant time and effort put into this important activity. He noted that on the Meeting agenda there were a number of important issues for consideration, that would result in recommendations to the Codex Committee on Pesticide Residues (CCPR), as well as to Member States. He emphasized the importance of the JMPR and the commitment of FAO/WHO to its continuous support to this very important statutory body which gives scientific advice to FAO, WHO, their member countries and Codex.

Dr Solh noted that the CCPR had once again referred to the JMPR in order to speed up the establishment of maximum residue limits (MRLs) and to refine dietary intake as a result of a critical review by the JMPR, evaluation of the Codex process and the work of the OECD Working Group on Pesticides. He highlighted some of the important activities: the pilot project on work-sharing on the basis of national and regional evaluations; refinements of dietary risk assessment to approximate a more realistic situation at national and international levels; implementation of the recommendations on the York and zoning meetings to conserve resources; establishment of templates for estimating long- and short-term dietary intake; and development of a probabilistic approach to intake assessment.

The Meeting was held in pursuance of recommendations made by previous Meetings and accepted by the governing bodies of FAO and WHO that studies should be undertaken jointly by experts to evaluate possible hazards to humans arising from the occurrence of residues of pesticides in foods. The reports of previous Joint Meetings (see Annex 6) contain information on acceptable daily intakes (ADIs), acute reference doses (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 (GAP). Maximum residue levels and supervised trials median residue (STMR) values were estimated for commodities of animal origin. The WHO Core Assessment Group was responsible for reviewing toxicological and related data and for estimating ADIs and, if necessary, ARfDs, when possible.

The Meeting evaluated 31 pesticides, including two new compounds and 12 compounds that were re-evaluated within the periodic review programme of the CCPR, for toxicity or residues, or both.

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

The Meeting devoted particular attention to estimating the dietary intakes (both short-term and long-term) of the pesticides reviewed in relation to their ADIs or ARfDs. In particular, for compounds undergoing a complete evaluation or re-evaluation, it distinguished between those for which the estimated intake is below the ADI and those for which the intake might exceed the ADI. Footnotes are used to indicate those pesticides for which the available information indicates that the ADI might be exceeded, and to denote specific commodities in which the available information indicates that the ARfD of the pesticide might be exceeded. A proposal to make this distinction and its rationale are described in detail in the reports of the 1997 JMPR (Annex 6, reference 80, section 2.3) and the 1999 JMPR (Annex 6,

reference 86, section 2.2). Additional considerations are described in the report of the 2000 JMPR (Annex 6, reference 89, sections 2.1–2.3).

2. GENERAL CONSIDERATIONS

2.1 Guidance on the establishment of acute reference doses

This item summarizes a document drafted by a Working Group of the JMPR WHO Core Assessment Group[1], and the reader is referred to that document for a more detailed consideration of the issues outlined below. The document provides guidance on the issues to be considered when determining whether it is necessary to establish an acute reference dose (ARfD) on the basis of the hazard profile of a chemical as well on particular end-points that may be particularly relevant to acute effects. Note that it is intended that the detailed document be updated on a regular basis as further experience in establishing ARfDs is gained.

Introduction

In 1998, the JMPR WHO Core Assessment Group published brief guidance on procedures for setting ArfDs[1]. At its meeting in 2001, the JMPR established an international Working Group to compile a table of all available ARfDs and to collate information from different national agencies about their approaches to setting ARfDs. On the basis of an analysis of this inventory and a comparison of the technical policy approaches to setting ARfDs in different countries, further guidance was drafted by the Working Group and published by the 2002 JMPR[2]. At the request of the 2003 JMPR, the Working Group elaborated further guidance, including: (1) detailed advice on interpretation of certain toxicological end-points (haematotoxicity, immunotoxity, neurotoxicity, kidney toxicity, liver effects, endocrine effects and developmental toxicity) that might be particularly relevant to acute exposure to pesticides; and (2) recommendations about the design and conduct of a suitable single-dose study that might be useful in identifying a more appropriate no-observed-adverse-effect level (NOAEL) for an acute end-point. This guidance is summarized below.

In 2002, the JMPR recognized that databases on consumption are available for daily intakes but that this information generally cannot be further divided into individual meals. Thus, the original definition of the ARfD was reworded from 'over a short period of time, usually during one meal or one day' to 'the amount that can be ingested in a period of 24 h or less' (see definition below).

The necessity for setting an ARfD should be considered for other chemicals to which the population may be exposed, such as non-agricultural pesticides, veterinary compounds and contaminants. If it is considered that an ARfD is necessary for such a compound, the guidance provided in this and the more detailed document should be of value. It is hoped that a harmonized approach will be followed in establishing acute health values for these other types of compounds.

Analysis of the inventory of ARfDs set by different agencies (1995–2002)

An analysis of the ARfDs set for pesticides by several regulatory agencies between 1995 and 2002 was summarized in a working paper used by the Working Group in developing the guidance document published by the 2002 JMPR. The purpose of this inventory was to identify any obvious differences in the derivation of toxicology threshold values, to identify different approaches to the selection of safety or uncertainty factors, and to give more detailed guidance on harmonization of acute risk assessments. This analysis indicated significant variations in decisions about the need to set an ARfD for a particular chemical, in the selected NOAELs and in safety factors, and hence ARfDs, for the same pesticide among different agencies. Most agencies have based some ARfDs on studies in humans, particularly for inhibitors of

[1] Annex 6, reference 83
[2] Annex 6, reference 95

acetylcholinesterase activity[3]. The database also indicated that the practice employed by the Meeting, of using safety factors of less than 100 (or 10) for carbamate insecticides, had not been followed by any other agency in 1995–2002. It was apparent from the analysis of the database that the current data package of toxicological studies generated for the active ingredients of pesticides is poorly suited to the establishment of ARfDs.

Acute dietary risk assessment

At the international level, only limited data on acute consumption are available. Adults and children aged 1–6 years are the only population groups for which acute dietary intakes can be estimated. Therefore, during the Meeting, the models for calculating acute dietary intake of pesticide residues were based on these two populations. Since it is generally not possible to model separately the intake of women of childbearing age, the establishment of separate ARfDs is not particularly useful. Therefore, the ARfD used for modelling the dietary intake of the general population should protect this subgroup adequately.

Except for those chemicals that would be very unlikely to leave residues in foodstuffs, it was concluded that the trigger for performing an acute dietary intake assessment should be toxicity concern.

If it is considered unnecessary to establish an ARfD, it can be concluded that short-term intake is unlikely to present a public health concern. Therefore, it is not necessary to estimate the short-term intake of such substances.

General guidance on the derivation of ARfDs

Most of the scientific concepts applying to the establishment of acceptable dietary intakes (ADIs) apply equally to the establishment of ARfDs. This section is mainly based on the recommendations of the 2002 JMPR but expands on that guidance in a number of areas. The following key issues are highlighted:

Definition of the ARfD

The following definition of the ARfD was adopted by the 2002 JMPR: "The ARfD of a chemical is an estimate of the amount of a substance in food and/or drinking-water, normally expressed on a body-weight basis, that can be ingested in a period of 24 h or less, without appreciable health risk to the consumer, on the basis of all the known facts at the time of the evaluation".

General considerations in setting an ARfD

The establishment of an ARfD should be considered for all pesticides whose uses may lead to residues in food and drinking-water. The suggested numerical cut-off for setting ARfDs for pesticides was about 5 mg/kg bw; i.e. if calculations indicated that an ARfD would be greater than this value, then it would not be necessary on practical grounds to set an ARfD, as residue levels necessary to achieve this intake would be highly unlikely to occur in practice.

Biological and toxicological considerations

The appropriateness or otherwise of using doses and end-points from short- and long-term studies to establish ARfDs, needs to be carefully considered. The pertinent biology of the system affected should be considered in order to determine whether an acute exposure might compromise the ability of the organ to compensate and maintain homeostasis. Particular weight should be given to observations and investigations at the beginning of studies of repeated doses. Isolated findings showing no specificity or clear pattern are not necessarily indications of toxicity. In the absence of information to the contrary, all toxic effects seen in repeat-dose studies should be evaluated for their relevance in establishing an ARfD. In studies on compounds showing acute toxicity after repeated doses, the adequacy of investigations (including the duration of the

[3] Until 2002, the United States Environmental Protection Agency had based only one value in their database on a study in humans, but there has been a policy change since that date.

follow-up of the animals to see if there are any delayed effects) must be shown to be adequate before it can be concluded that the compound does not have any acute toxic potential. The NOAEL from the most sensitive species should be used, unless there is evidence to demonstrate it is not appropriate for a human risk assessment.

Stepwise process in setting an ARfD

The first step is to consider whether, on the basis of the acute toxicity profile and potency of effects, an acute health value is really necessary. The following process for setting ARfDs is suggested:

1. Evaluate the total database on the substance and establish a toxicological profile for the active substance.
2. Consider the principles for not setting an ARfD:
    - No findings indicative of effects elicited by an acute exposure are seen at doses up to about 500 mg/kg bw per day; and/or
    - No substance-related mortalities are observed at doses of up to 1000 mg/kg bw in single-dose studies after oral administration.
    - If mortality is the only trigger, the cause of death should be confirmed as being relevant to human exposures.
    - If the above criteria do not exclude the setting of an ARfD, then further consideration should be given to setting a value, using the most appropriate end-point.
3. Select appropriate end-points for setting an ARfD
    - Select the toxicological end-points that are most relevant for a single (day) exposure.
    - Select the most relevant or adequate study in which these end-points have been adequately determined.
    - Identify the NOAELs for these end-points.
    - Select the most relevant end-point providing the lowest NOAEL.
    - Use an end-point from a repeat-dose study of toxicity if the critical effect of the compound has not been adequately evaluated in a single-dose study. This is likely to be a more conservative approach and should be stated. This does not mean that a safety factor other than the default value should be applied. A refinement of such a NOAEL (e.g. in a special single-dose study) may be necessary, if the acute intake estimation exceeds such a conservatively-established ARfD.
    - If after consideration of all the end-points, an ARfD is not set, justify and explain the reasons.
4. Select appropriate safety factors for setting an ARfD.

    Derive the ARfD using an appropriate safety factor(s).

Safety factors

The process of deriving ARfDs involves the determination of the most appropriate NOAEL and a safety factor (also called an uncertainty or assessment factor). These factors are used to extrapolate from data in animals to the average human and to allow for interindividual variation within the human population.

In determining the appropriate safety factor, a stepwise approach is proposed:

- Determine whether the database is adequate to support the derivation of a chemical-specific adjustment factor (CSAF)[4].
- If a specific factor cannot be derived, consider if there is any information to indicate reduced or increased uncertainty. If not, the 100-fold (or 10-fold) default should be used.

Whenever a safety factor other than a default is used, a clear explanation of the derivation of the factor must be provided.

Different ARfDs for different population subgroups

It is preferable to set a single ARfD to cover the whole population. It is important to ensure that any ARfDs established are adequate to protect the embryo and fetus from possible effects in utero. While an ARfD based on developmental effects (on the embryo or fetus) would necessarily apply to women of childbearing age, it is recognized that such an ARfD may be conservative and not relevant to other population subgroups. This is the case for children aged 1–6 years, for whom specific data on acute consumption are available (and thus can be modelled separately with respect to acute dietary intake of residues); the use of such a conservative ARfD for children who generally have a higher intake of food commodities per unit body weight compared with adults could lead to an unreasonably conservative acute dietary risk assessment. Thus, in those situations in which a developmental end-point drives a very conservative ARfD, it may be necessary to set a second value based on another non-developmental end-point.

Alternatively, if the prenatal developmental end-point is the only acute effect of concern, there may be no need to perform an acute dietary intake risk assessment for children. The single ARfD based on a developmental end-point (in the embryo or fetus) would only be used to model the acute dietary intake of the adult population, which includes women of childbearing age.

Use of human data

Human data from accidental or deliberate poisonings, biomarker monitoring studies, epidemiology studies, volunteer studies, and clinical trials on the same or structurally similar compounds can provide useful data to help establish ARfDs. The use of data from human volunteers in chemical risk assessment is a controversial issue, with a range of views held by different countries and individuals. However, it is recognized that the use of such data can reduce the level of uncertainty inherent in extrapolating from animal models. There needs to be adequate consideration of both scientific and ethical issues. The JMPR has considered human data at many of its meetings. The 2002 JMPR reaffirmed the principle that end-points from studies in human volunteers could be used to set intake standards if they had been conducted in accordance with relevant ethical guidelines. The study should be assessed for the quality and integrity of the data and the adequacy of the documentation of methods (including statistics and control values) and results. A poorly designed or conducted study in humans should not be used for risk assessment. Additionally, because the designs of studies in humans have some limitations in comparison with those in experimental animals, their use should always be considered in the context of the overall toxicological database.

ARfDs based on studies in humans should provide a sufficient margin of safety for toxicological end-points that cannot readily be addressed by such studies (e.g. developmental toxicity).

When an initial estimate of the ARfD is less than the established ADI

If an ARfD derived using the principles outlined in this guidance document has a numerical value that is lower than the existing ADI, then the ADI should be reconsidered.

---

[4] Draft guidance document for the use of chemical-specific adjustment factors (CSAFs) for interspecies differences and human variability in dose/concentration–response assessment. WHO/UNEP/ILO International Programme on Chemical Safety, July 2001 (WHO/PCS01.4) (http://www.who.int/ipcs/methods/harmonization/areas/uncertainty/en/print.html, accessed 15 October 2004)

Specific guidance on the derivation of ARfDs

Particular toxicology end-points that are relevant to the establishment of ARfDs are considered below. Note that this summary is not intended to comprehensively cover all potentially relevant end-points, but focuses on the interpretation of those that have proved to be problematic in reaching a decision as to whether an effect is relevant to an acute exposure.

Haematotoxicity

The induction of methaemoglobinaemia is considered to be a critical effect in acute responses to chemical exposure. For acute exposure to methaemoglobin-inducing xenobiotics, a level of 4% methaemoglobin (or higher) above the background level in dogs, or a statistically significant increase relative to the background level in rodents is considered to be relevant in setting an ARfD. Haemolytic anaemias induced by mechanical damage, immune mediated anaemia, oxidative injury to erythrocytes and non-oxidative damage are considered to be less relevant for the derivation of ARfDs since the severity of such effects appears generally to depend on prolonged exposure. If changes in haematological parameters are observed early in a repeat-dose study and do not appear to progress during the course of the study, then such effects can be considered to relate to acute exposure to the substance. In assessing whether effects observed in repeat-dose studies should be used for setting an ARfD, the mechanism of action must be evaluated. If known, this could provide arguments for selecting, or not selecting, the end-point for setting an ARfD.

Immunotoxicity

Data on immunotoxicity derived from short-term studies are not likely to be appropriate for setting a reference dose for limits on acute exposure. It is unlikely that an acute exposure will produce persistent effects on immune function because the cells of the immune system are constantly replaced and because of the inherent redundancy in the system (e.g. alternative mechanisms exisit to resist infection).

Neurotoxicity

The nervous system has a limited capacity for repair and regeneration. Therefore, any neurotoxicity seen in repeat-dose studies could be the result of a single exposure and may not be reparable, i.e. any evidence of neurotoxicity should be considered relevant to an ARfD assessment, unless it can be demonstrated that the effects are produced only after repeated exposures. In addition to long-term or irreversible effects associated with acute exposure, attention should be paid to transient effects, as these could be considered to be adverse under some circumstances.

Delayed neurotoxicity after single chemical exposures can occur, and thus any acute exposure study should have an adequate period of investigation.

In functional observation batteries (FOBs), a large amount of data is produced; interpretation of such studies should include a consideration not only of the statistical significance of results, but alos of the nature, severity, persistence, dose–response relationship and pattern of the effects. Isolated findings showing no specificity or clear pattern do not necessarily indicate neurotoxicity.

The most common neurotoxic end-point used to date in the derivation of ARfDs for pesticides is inhibition of acetylcholinesterase activity. The Meeting has previously defined criteria for the assessment of cholinesterase inhibition5; these apply equally to the setting of ADIs and ARfDs. For inhibition of acetylcholinesterase activity, a specific cut-off (20%) is used routinely to differentiate between adverse and non-adverse effects.

Effects on the kidney and liver

If effects on these organs cannot be discounted as being either adaptive or the result of prolonged exposure, an ARfD can be derived on the basis of these effects. Such an ARfD is likely to be conservative

[5] Annex 6, reference 83

and it may be possible to subsequently refine it using the results of an appropriately designed single-dose study. When interpreting data on liver and kidney toxicity in repeat-dose studies, one has to consider two important aspects; firstly, the type of effect observed and secondly, any information on correlations between exposure duration and effect.

For liver toxicity, it is considered that findings of increased serum cholesterol, cirrhosis, induced activity of metabolizing enzymes, regenerative hyperplasia, hepatocyte hypertrophy, fibrosis, or sclerosis in repeat-dose studies are, in isolation, either adaptive or the result of prolonged exposure and are therefore are not applicable for deriving an ARfD.

For kidney toxicity, it is considered that the following findings of toxicity targeted to the kidney in repeat-dose studies are, in isolation, the result of prolonged exposure and are not applicable for deriving an ARfD: increased organ weight; regenerative hyperplasia; altered serum calcium and phosphate concentrations.

All other findings of liver and kidney toxicity should be considered to be potentially relevant to the derivation of an ARfD.

Endocrine effects

In general, effects on the endocrine system, other than those affecting female reproduction, are considered to be unlikely to arise as a consequence of acute exposure. However, because the process of evaluating endocrine toxicity and mechanisms is an evolving one, the guidance on endocrine disruptor chemicals is considered to be interim.

Developmental effects

Any treatment-related adverse effect on fetuses or offspring that has resulted from exposure during any phase of development should be considered to be potentially appropriate to use in acute dietary risk assessment, despite the fact that the period of treatment typically consists of repeated dosing. ARfDs based on reductions in fetal body-weight gain may be conservative and should be evaluated in the context of all pertinent data, including other developmental effects. Consideration should be given to the degree of maternal toxicity when considering whether fetal effects may be occurring as a direct effect of the chemical; the presence of severe maternal toxicity means that a direct effect is less likely.

Single-dose study protocol

ARfDs established using existing databases of repeat-dose studies may be overly conservative and it may be possible to refine the ARfD by conducting an appropriately-designed single-dose study. The protocol for a proposed single-dose study of toxicity is outlined in the detailed document. Unlike a classical median lethal dose (LD_{50}) study, this protocol is not intended to investigate mortality and significant morbidity. On the contary, it is aimed at investigating a range of more subtle end-points which may arise after a single exposure, or during 1 day of dietary exposure to a test substance. In particular, it is tailored to see whether toxic effects observed in the standard package of repeat-dose studies may occur after single doses, and if so, at what level of exposure.

It is important to note that a specific study designed to enable an accurate ARfD to be set should only be undertaken after the toxicology profile of an active substance has been reasonably well documented and understood, and it is apparent that the available database is not adequate to allow the establishment of a reasonable ARfD. Furthermore, it is not intended that this test guideline should become a routine data requirement. It can, however, be utilized for those chemicals with limited databases that do not allow a clear determination of an appropriate reference dose.

The draft test protocol for the single oral dose study of toxicity will be submitted to the Organization for Economic Co-operation and Development (OECD) Working Group of National Co-ordinators to the Test Guidelines Programme. If it is considered appropriate to incorporate into the OECD test guidelines, it will be

useful in directing the conduct of studies directly relevant to the establishment of ARfDs for those chemicals which, because of their use pattern, have the potential to lead to residues in food and drinking-water.

Future considerations

It is intended that the detailed document drafted by the Working Group of the JMPR WHO Core Assessment Group be updated on a regular basis as further experience in establishing ARfDs is gained. For example, further more detailed guidance on specific end-points (e.g. emesis and diarrhoea in dogs) will be added as these issues are researched and assessed.

The introduction of a specific test protocol for a single-dose study of oral toxicity will aid the process of establishing ARfDs. Once introduced, the utility of such a test guideline will be evaluated by the Meeting. The detailed guidance document will be available from the JMPR Secretariat.

2.2 Definition of 'overall NOAEL'

During the toxicological evaluation of a compound, the Meeting often has available more than one study in which the same end-points have been addressed. In such situations, the dose spacing may be different, resulting in different NOAELs and lowest-observed-adverse-effect levels (LOAELs). The Meeting agreed that in such circumstances it might be appropriate to consider the studies together. When they are comparable, including consideration of study design, end-points addressed, and strain of animal, the 'overall NOAEL' should be the highest value identified in the available studies that provides a reasonable margin (≥ 2) over the lowest LOAEL, provided that due consideration is given to the shape of the dose–response curve.

2.3 Interim acute reference dose

The WHO Core Assessment Group is occasionally asked by the FAO Panel of Experts to establish an ARfD for compounds that were not scheduled for toxicological evaluation. In such cases, the ARfD is based on data available from previous evaluations and is used to perform an acute dietary risk assessment. The Meeting decided to call these values 'interim ARfDs' (in order to distinguish them from the ARfDs established for compounds that were scheduled for toxicological evaluation) and to publish the derivation of the interim ARfDs under general considerations. These interim ARfDs can be used in dietary risk assessments until they are replaced by a full evaluation, if this is considered necessary.

Setting an ARfD for propineb

At the present Meeting, the FAO Panel of Experts asked the WHO Core Assessment Group if an ARfD for propineb could be established on the basis of the data available to the 1993 JMPR. Propineb is metabolized to propylenethiourea, which forms part of the residue, and then to carbon disulfide. Propineb is of low acute toxicity (oral LD_{50}s in rats and mice are about 5 g/kg bw). The main effects of propineb are on the thyroid and on the nervous system.

The effects of propineb on the thyroid are mediated by propylenethiourea, which is similar to ethylenethiourea; these compounds block the accumulation of iodine by the thyroid gland. The 1993 JMPR took the view that those thyroid changes that were thought to be reversible, e.g. those observed in a study in rat could be considered adaptive. Furthermore, this effect is not appropriate for establishing an ARfD because of the buffering of thyroid hormone levels by homeostatic mechanisms. The existing ADI established by the JMPR (0–0.007 mg/kg bw per day) is based on the NOAEL (10 ppm, equal to 0.74 mg/kg bw per day) for decreased thyroxin and changes in thyroid weights in a short-term study of thyroid function in rats, with a 100-fold safety factor.

Propylenethiourea: The limited database on propylenethiourea was reviewed by the Meeting in 1993 when a temporary ADI of 0–0.0002 mg/kg bw was established. At this Meeting in 1993, no information was available on the metabolism of propylenethiourea. The temporary ADI was based on the LOAEL for liver tumours in a 2-year study in mice, with the application of a 1000-fold safety factor because of the inadequate database. The lowest dose in that study was considered to be a marginal effect level.

Carbon disulfide: Exposure to carbon disulfide is associated with cardiovascular disease, and carbon disulfide is also neurotoxic, producing demyelination, cerebellar atrophy and peripheral nerve abnormalities. Some or all of these effects are secondary to angiopathy. The effects on long axons might be caused by protein cross-linking. There is evidence from the clinical toxicology literature that carbon disulfide produces effects in humans after single, high-level exposures

Critical NOAELs for propineb: The neurotoxicity observed after repeated doses of propineb is considered to be potentially relevant to the establishment of an ARfD. The lowest NOAEL for neurotoxicity was identified in the multigeneration study in rats; the NOAEL in this study was 60 ppm, equivalent to 3 mg/kg bw per day on the basis of hind limb paralysis, and the LOAEL was 200 ppm, equivalent to 10 mg/kg bw per day. In the study of developmental toxicity in rats, the NOAEL for maternal toxicity was 10 mg/kg bw per day. Mild central neurotoxic effects were seen at 30 mg/kg bw per day in the dams. At the highest dose (100 mg/kg bw day), more serious central neurotoxicity was observed in the dams. Because of the shorter duration of dosing, the study of developmental toxicity in rats was considered to be more appropriate for the establishment of an ARfD than the multigeneration study in rats. Therefore the Meeting established an ARfD of 0.1 mg/kg bw, based on the NOAEL of 10 mg/kg bw per day from the study of developmental toxicity in rats, with a safety factor of 100. This should be considered to be an interim ARfD, until a full evaluation of the toxicological database has been conducted. Furthermore, this ARfD is probably conservative and could be refined using the results of an appropriate single-dose study.

2.4 Progress report on the JMPR work-sharing pilot project on trifloxystrobin

A FAO/WHO/OECD pilot project on work-sharing was conducted to test whether national and regional evaluations of pesticide residues and toxicology could be used as a basis for JMPR evaluations. The 2003 CCPR selected trifloxystrobin as the first compound for the project because it had been evaluated in Australia, Canada and the USA and by the European Commission and was scheduled for evaluation by the JMPR in 2004. Unfortunately, a Japanese evaluation was not available for the pilot project. Original data were also provided by the manufacturer.

The objective of work-sharing is to facilitate and expedite reviews by using national and regional evaluations, while maintaining independence and incorporating global perspectives. The pilot project was intended to promote, facilitate and formalize this practice, although it was not expected to save cost or time. Those would be the main goals in the future, with greater efficiency and more transparent evaluations.

Differences in the global applicability of evaluations of toxicological and residue data were noted: Studies on residues are often specific to particular registered uses, which differ from one country to another, while toxicological studies are generally globally relevant.

The data on the toxicology and residues of trifloxystrobin were evaluated by the 2004 JMPR, and experiences in work-sharing were assessed.

Experience in work-sharing on toxicological evaluations

The Australian monograph served as the ‘master’ evaluation and thus as the main basis for the JMPR monograph, because a preliminary review indicated that it was closest to the JMPR format. The sections on toxicokinetics, human data and metabolites were derived from the European Commission monograph, which was prepared by the United Kingdom.

In the first step, it was found that the manufacturer had submitted the same key toxicological studies on trifloxystrobin to all four agencies and to JMPR. In general, the national and regional reports described the methods and results of the studies in a reasonable level of detail.

The formats of the monographs and the amount of detail given in the study reviews differed substantially. The differences in the formats of the national evaluations made comparisons difficult, obviating importation of tables into the JMPR monograph. Tables in which the toxicological data from individual studies were summarized and the statistical analyses that supported the conclusions varied significantly in lay-out and detail, creating a great deal of work for the WHO temporary advisor.

In the next step, the study descriptions and selection of end-points in the Australian monograph were compared with those in the Canadian, US and European Commission monographs. This comparison revealed both similarities and differences in interpretations. When differences were found, JMPR experts made an independent evaluation of the original data and presented it to the JMPR. In only a few instances was it necessary to review the original data.

The process facilitated preparation of a transparent JMPR monograph, as the WHO evaluator could judge the results independently, usually without having to refer to the original studies. The evaluator could thus concentrate on areas of disagreement, helping to focus the JMPR deliberations. The evaluator also benefitted from others' insights into the significance of the effects seen in a study.

As trifloxystrobin represents relatively little hazard and has minimal toxicity, the national evaluations tended to differ on interpretation of the adversity of minor effects, such as changes in body weight and increases in liver weight.

The evaluations agreed reasonably well with regard to the selection and evaluation of key studies. Three studies with similar NOAELs were selected as pivotal for setting three ADI values, ranging from 0.038 to 0.1 mg/kg bw. Derivation of an ARfD was considered unnecessary in all the evaluations except for that of the US Environmental Protection Agency, which has a common practice of setting a separate ARfD for women of child-bearing age.

Experience in work-sharing on residue evaluations

The generic studies for residue reviews are: pesticide identity, physical and chemical properties, metabolism, environmental fate in soil and water–sediment systems, analytical methods, freezer storage stability, and fate of residues in processing and in feeding to farm animals. National and regional summaries and assessments of data on these subjects were taken into account. Supervised trials, which constitute the major part of a residue evaluation, were not included in this pilot project.

No one national or regional monograph could be used as the 'master' because of differences in the studies on trifloxystrobin. Furthermore, the studies in the dossier provided to JMPR were not all the same as those assessed at national and regional levels. The set of studies provided to the four national and regional authorities and to JMPR was identical only for metabolism in farm animals.

In the first step, a JMPR evaluation and an appraisal were prepared on the basis of the original studies provided by the company. In the second step, the evaluations of the studies in the national and regional reviews were compared with each other and with the JMPR evaluation. A 129-page report on the comparisons was prepared, which will be available on the FAO website.

The assessments of trifloxystrobin submitted by Australia and the European Commission were prepared in monograph format. In this format, excerpts from the applicant's dossier can be used (e.g. tables, metabolism schemes, some text), although the monograph does not include the applicant's proposals or recommendations. Independent, complete, final evaluations of a compound are made without considering registration purposes.

The assessments of trifloxystrobin submitted by Canada and the USA were presented in review format. In this approach, the scientific results are summarized and then the applicant's dossier is subjected to a critical review which includes discussions of the applicant's proposals and recommendations with regard to registration of specific plant protection products.

The trifloxystrobin example showed some similarities and some differences in the procedures and approaches used by national and regional agencies for evaluating residues. These resulted in some divergence on conclusions, such as those for residue definitions and processing factors. As JMPR considers the worldwide use of pesticides when recommending MRLs for food commodities in international trade, its approach is not necessarily the same as those of national and regional organizations, which operate within registration systems.

Conclusions and recommendations

Issues relevant for both toxicological and residue evaluations

- The availability of several national and regional evaluations was useful for both the WHO and the FAO evaluators, despite the problems encountered. FAO, WHO and OECD should thus consider means to facilitate the provision of national or regional evaluations to JMPR evaluators.
- Consideration of multiple national and regional evaluations should aid progress towards international harmonization of dossiers and evaluations.
- The evaluation process, including standardization of formats and guidelines, should be harmonized further internationally. Good progress has been attained in the toxicological evaluations, while more work is necessary to improve work-sharing for residue evaluations.
- A further JMPR pilot work-sharing project should have more flexible procedures, which should be reviewed when the formats and evaluation procedures have been harmonized in guidance documents.

Issues more closely relevant to toxicological evaluations

- The national and regional evaluations differed considerably in their level of detail in describing toxicological studies, and more guidance and harmonization in this area could improve work-sharing.
- More guidance is needed on the interpretation of specific toxicological data, such as on changes in body and organ weights, and on interpretation of effects on the liver as adaptive or adverse.
- The key advantage of considering multiple national and regional evaluations in the JMPR process is the rapid identification of agreements and disagreements in data interpretation, thus focusing resources on areas of disagreement.

Issues more closely relevant to residue evaluations

- The project requires further work, incorporating changes based on the experience with trifloxystrobin, before work-sharing, with its anticipated benefits, can be implemented routinely. The experience with trifloxystrobin indicates that JMPR cannot comprehensively accept national or regional conclusions or recommendations for the residue topics included in the pilot project.
- Further progress in international work-sharing could be made by separating the summaries of key data from the conclusions in the submitted studies in the national or regional evaluations for risk assessment and management. This could facilitate mutual exchange and acceptance of study summaries.
- Work-sharing should focus on mutual use of summaries of data validated at national, regional and international level, covering all aspects of the residue evaluation, including data from supervised trials. This would allow exchange of a valid database, thus saving time and potentially reducing the workload.
- Specific assessment results, such as the definition of residue, could be used on a case-by-case basis.

- The current workload of the JMPR precludes additional work by FAO Panel Members on this project, as it would be at the expense of normal residue evaluation commitments, which are regarded by Panel Members as the priority.

2.5 Comparison of JMPR recommendations and interim MRL recommendations from the CCPR pilot project

The 2004 CCPR agreed on the main steps of the procedure for establishing interim maximum residue limits (MRLs)[6]. These included a request to JMPR to compare its recommendations with the suggested interim MRLs for trifloxystrobin and fludioxonil and to comment on discrepancies, for the purposes of the pilot project; this would not be considered part of any normal procedure that might eventually evolve. The US Delegation to the CCPR, as Chair of the Pilot Project Working Group, provided FAO with detailed information on the chemicals nominated for interim MRLs. These included summaries of the proposed interim MRLs for fludioxonil and trifloxystrobin, as well as information on toxicology, residue chemistry and dietary risk assessment.

The table shows the proposed interim MRL and the corresponding JMPR recommended MRLs.

Commodity, CCN	Interim MRL recommendation (mg/kg)	JMPR MRL recommendation (mg/kg)	Comment on difference
Trifloxystrobin Interim definition: Plant and animal, trifloxystrobin + CGA321113 or (E,E)-methoxyimino{2-[1-(3-trifluoromethylphenyl)-ethylideneaminooxymethyl]phenyl}acetic acid JMPR definition: Plant, trifloxystrobin; animal, trifloxystrobin + CGA321113 or (E,E)-methoxyimino{2-[1-(3-trifluoromethyl-phenyl)ethylideneaminooxymethyl]phenyl}acetic acid			
Barley, GC640	0.3	0.5	High value from European Commission, 0.19 mg/kg. European Commission established 0.3 mg/kg (Tables B.7.49 and B.7.50) High value from JMPR, 0.40 mg/kg, based on trial in Germany, 1999
Grapes, FB269	3	3	
Grapes, dried, DF269	5	5	
Pome fruit, FP9	1	0.7	High value from European Commission, 0.44 mg/kg
Edible offal (mammalian), MO105	0.05	Kidney, MO98, 0.04* Liver, MO99, 0.05	Interim, wide scope JMPR, narrow scope
Eggs, PE112	0.04*	0.04*	
Meat (mammalian), MM95	0.04*	0.05 (fat)	Interpretation of feeding study: JMPR determined a maximum residue in fat of 0.038 mg/kg; 0.04 mg/kg is the LOQ (0.02 trifloxystrobin + 0.02 metabolite). Trifloxystrobin present in fat (0.05 mg/kg) at a feeding level of 20 ppm is approximately twice the US and JMPR calculated dietary intake of cattle. The 0.04 value is based on one feed item, barley, as compared with the much greater intake of the total treated commodities considered by the US and JMPR.
Milks, ML106	0.02*	0.02*	
Poultry, edible offal of	0.04*	0.04*	

[6] ALINORM 04/27/24, paragraphs 220–234

Commodity, CCN	Interim MRL recommendation (mg/kg)	JMPR MRL recommendation (mg/kg)	Comment on difference
Poultry meat	0.04*	0.04* (fat)	Interpretation of feeding study
Fludioxonil			
Interim definition: Plant, fludioxonil. Animal, fludioxonil + metabolites determined as 2,2-difluorobenzo[1,1]dioxole-4-carboxylic acid, calculated as fludioxonil			
JMPR definition: Same			
Herbs (fresh), HH726	10	Basil, HH722, 10 Chives, HH727, 10	JMPR restricted MRLs to specific herbs and did not extend them to all herbs.
Herbs (dry), HH726	65	Basil, dry, DH722, 50 Chives, dry, HH727, 50	JMPR considered two trials and a drying factor of 8, yielding 15 and 24 mg/kg. The interim approach considered one trial each on dried basil and dried chives, with residues of 23 and 31 mg/kg.
Blackberry, FB264	5	5	
Blueberry, FB20	2	2	
Broccoli, VB400	2	0.7	Same data set. US interim value based on US brassica head and stem subgroup 5A (with higher residues for cabbage).
Cabbage, head, VB41	2	2	
Carrot, VR577	1	0.7	Same data set. Interim MRL based on US tolerance of 0.75 mg/kg rounded up under JMPR rules; highest residue value, 0.46 mg/kg. JMPR reported highest residue of 0.42 mg./kg from same data set.
Wheat, GC643	0.02*	Cereal grains GC80, 0.05*	Interim based on seed treatments in the USA, with an LOQ of 0.02 mg/kg. JMPR based on 71 trials in Europe and the USA, with LOQs ranging from 0.01 to 0.05 mg/kg.
Rye, GC650	0.02*		
Spelt, GC4673	0.02*		
Triticale, GC653	0.02*		
Barley, GC640	0.02*		
Oats, GC647	0.02*		
Maize, GC645	0.02*		
Popcorn, GC656	0.02*		
Sorghum, GC651	0.02*		
Cotton-seed, SO691	0.05*	0.05*	
Currants, FB21	2		Interim based on translation of blueberry field trials (< 0.05–1.4 mg/kg) to the US bushberry subgroup 13B. JMPR did not make this translation.
Grapes, FB269	2	2	
Longan, FI342	1	None	Based on lychee
Lychee, FI343	1	None	Same data set (US). JMPR considered the three trials to be in excess of GAP.
Mustard greens, VL485	20	10	Same data set. Interim maximum residue value, 7.7 mg/kg; JMPR maximum residue, 7.1 mg/kg
Onion, VA385	0.2	0.5	Interim based on US data only, with maximum value of 0.11 mg/kg (0.06 mg/kg average for high field trial). Interim included European data, with maximum value of 0.34 mg/kg
Pistachio, TN675	0.1	0.2	Same data set (US). Although highest residue was 0.08 mg/kg, JMPR estimated 0.2 mg/kg on basis of small size of set (n = 3).

Commodity, CCN	Interim MRL recommendation (mg/kg)	JMPR MRL recommendation (mg/kg)	Comment on difference
Potato, VR589	0.02*	0.02	
Pulasan, FI357	1	None	Based on lychee
Rambutan, FI358	1	None	Based on lychee
Rape-seed, SO495	0.01*	0.02*	Interim based on translation of data on treatment of other seed (wheat), with an LOQ of 0.01 mg/kg. JMPR based on 15 trials in Europe, with an LOQ of 0.02 mg/kg.
Raspberry, FB272	5	5	
Soya, SO4723	0.01*	None	JMPR received no data. Interim based on seed treatment use and translation of data for wheat, lettuce, pea, cucumber and radish (all below LOQ)
Spanish lime, FI366	1	None	Based on lychee
Stone fruit, FS12	5	5	
Strawberry, FB275	2	3	Interim based on US data only, with maximum value of 1.3 mg/kg. JMPR included European data, with maximum of 1.9 mg/kg.
Sunflower seed, SO702	0.01*	None	JMPR received no data. Interim based on seed treatment use and translation of data for wheat, lettuce, pea, cucumber and radish (all < LOQ)
Sweet corn (corn-on-the-cob), VO447	0.02*	0.01*	Interim based on LOQ for cereal grain group. Codex does not consider sweet corn in the cereal grain group and evaluated data separately.
Watercress, VL473	10	10	
Meat (from mammals other than marine), MM95	0.01*	0.01*	
Edible offal (mammalian), MO105	0.05*	0.05	
Milks, ML106	0.01*	0.01	
Poultry meat, PM110	0.01*	0.01*	
Poultry, edible offal of, PO111	0.05*	0.05*	
Eggs, PE112	0.05*	0.05*	

LOQ, limit of quantification; GAP, good agricultural practice

Trifloxystrobin

The interim MRL recommendations are based on information and data compiled by the USA from both the European Union and the USA. The maximum residue levels recommended by the JMPR are based on an independent review of studies supplied by the manufacturer and include field trial data from more diverse sources: Australia, Brazil, Canada, Colombia, Costa Rica, Ecuador, Europe (Belgium, Denmark, France, Germany, Italy, The Netherlands, Spain, Switzerland, United Kingdom), Guatemala, Honduras, Mexico, South Africa, and the USA.

The interim MRLs are based on the residue definition in the USA, which is parent plus an acid metabolite. This differs fundamentally from the JMPR definition for enforcement for plant commodities, which is trifloxystrobin only. The residue definitions for dietary intake and for animal commodities are identical.

The manufacturer proposed, via the Pilot Project Working Group on the Interim MRL, only three commodities for this test exercise: grapes, barley and pome fruit, while the JMPR evaluation included an extensive array of plant commodities. Thus, only a limited comparison is possible.

The recommended interim MRLs and JMPR MRLs are similar for some commodities. The exceptions are mammalian meat (interim, 0.04 mg/kg; JMPR, 0.05 mg/kg), pome fruit (interim, 1 mg/kg; JMPR, 0.7 mg/kg) and barley (interim, 0.3 mg/kg; JMPR, 0.5 mg/kg). The discrepancy in the values for meat may be due to the fact that only barley was considered in the animal diet, as this was the only feed commodity suggested by the manufacturer for an interim MRL. The value of 0.04 mg/kg represents the limit of detection of the analytical method. JMPR estimated the intake of cattle at 6.3 ppm, and the USA estimated it at 12 mg/kg. The USA maintains a tolerance of 0.5 mg/kg on the basis of a long list of trifloxystrobin-treated commodities. The value was reduced to 0.04 mg/kg because barley was the only feed item being considered for an interim MRL. The reviews of both the USA and the JMPR considered the maximum residue level in beef fat to be 0.05 mg/kg, derived from a 20 ppm dietary burden of trifloxystrobin. Thus, the difference can be attributed to the limited interim MRL list; the values would both be 0.05 mg/kg with the longer list of animal feed commodities. The value of 0.05 mg/kg is appropriate on the basis of the animal feed items for which JMPR is proposing MRLs.

The interim MRL value of 1 mg/kg for pome fruit is based on the highest residue value of 0.44 mg/kg reported from Europe. The US tolerance is 0.5 mg/kg, based on a maximum residue value of 0.23 mg/kg. Under the JMPR system, the MRL would be either 0.7 mg/kg or 1 mg/kg. The Meeting selected 0.7 mg/kg in view of the large number of trials available (74) and the median of 0.11 mg/kg. These factors suggest that the MRL may be set near the maximum residue value, i.e. 0.7 mg/kg and not 1 mg/kg.

The interim MRL for barley is based on data from field trials considered by the European Commission in establishing a European Union MRL of 0.03 mg/kg. The JMPR considered additional data from field trials. A trial in Germany yielded a maximum residue value of 0.40 mg/kg. The 0.5 mg/kg value is appropriate when this additional information is considered.

The dietary risk assessments for the interim MRLs and for the JMPR MRLs indicated no concern. Using supervised trials median residue (STMR) values and an ADI of 0.04 mg/kg bw per day, the JMPR estimated the intake to be 1–2% of the ADI in regional diets. Using MRL values (for the limited list of commodities) and a reference dose of 0.038 mg/kg bw per day for long-term exposure (USA), the Interim Pilot Project estimated the intake in regional diets to be 0–6% of the ADI.

A calculation of dietary intake during short-term exposure similar to that of JMPR was performed within the Pilot Project, taking the proposed interim MRLs as residue levels and the ARfD determined in the USA (2.5 mg/kg bw per day). It should be noted that the end-point applies only to the subpopulation of females aged 13–49 years and is based on developmental toxicity. The calculation was performed for the general population, because the Codex system does not have data on the consumption of this subpopulation The ARfD was not exceeded for any commodity**.** The maximum exposure of the general population (used as a surrogate for women of child-bearing age) was 1% of the ARfD, from apples. The JMPR determined that an ARfD need not be established.

Fludioxonil

The interim MRLs recommended for fludioxonil are based solely on data from the USA, as the European Commission has not completed its evaluation of fludioxonil. The JMPR made an independent evaluation of studies provided by the manufacturer, which included field trials from Chile, Europe (Denmark, France, Greece, Hungary, Italy, Spain, Sweden, Switzerland), South Africa and the USA.

The residue definitions in the interim proposal and the JMPR recommendation are identical for plants and animals for both enforcement and dietary intake. The interim and the JMPR MRL recommendations

differed for currants, lychee, longan, pulasan, rambutan, Spanish lime, strawberry, sweet corn, broccoli, carrot, mustard greens, bulb onion, basil (dry), chives (dry), pistachio and cereal grains.

The interim MRL for *currants* is based on a translation of data from US blueberry field trials, in which the residue values ranged from < 0.05 to 1.4 mg/kg. Blueberries are the representative commodity for the US bushberry subgroup 13B. The JMPR had no data from trials conducted under GAP and did not consider a translation of data on blueberries to currants.

The interim MRLs for *lychee, longan, pulasan, rambutan* and *Spanish lime* are based on three US field trials with lychee. The JMPR received the same data set but considered that the three trials were conducted substantially in excess of US GAP. US GAP specifies a maximum of four applications, each at 0.25 kg ai/ha, with a 0 day PHI; however, in the trials, five or seven applications were made at the maximum rate, with an approximate 7-day re-treatment interval. On the basis of the results of decline studies conducted with other fruit crops, JMPR concluded that the extra applications might make a significant (25%) contribution to the residue.

The interim MRL proposal for *strawberry* is based on US data only, with a maximum value of 1.3 mg/kg. The JMPR considered both European and US data; the maximum value in the former was 1.9 mg/kg.

The interim MRL proposal for *sweet corn* is based on US data for cereal grains, with an LOQ of 0.01 mg/kg. The Codex System does not place sweet corn in the cereal grains group, and the JMPR evaluated data for sweet corn and field corn, with an LOQ of 0.02 mg/kg.

The same US data were used to derive the interim and the JMPR MRL recommendations for *broccoli.* The interim MRL is based on a high residue value of 0.53 mg/kg, found on one of two samples in one field trial. The value is also based on a US tolerance for the brassica head and stem subgroup 5A, which allows higher residue values for cabbage. The JMPR MRL was based on a high residue value of 0.36 mg/kg, which is the average for the two samples in the same field trial ([0.53 mg/kg + 0.19 mg/kg]/2). Under JMPR procedures, 0.5 mg/kg is an appropriate MRL.

The same US data were used to derive the interim and the JMPR MRL recommendations for *carrot.* The interim MRL is based on the US tolerance of 0.75 mg/kg, rounded under JMPR rules to 1 mg/kg. Residue values ranged from 0.04 to 0.42 mg/kg in the nine trials. JMPR considered 0.7 mg/kg to be an appropriate MRL estimate.

The same US data were used to derive the interim and the JMPR MRL recommendations for *mustard greens*. The residue values ranged from 0.06 to 7.1 mg/kg in seven trials. JMPR considered 10 mg/kg to be an appropriate MRL estimate. The proposed interim MRL value of 20 mg/kg does not seem appropriate, given the number of trials and the range of residue values.

The same US data were used to derive the interim and the JMPR MRL recommendations for *dried chives* and *dried basil*. The interim MRL of 65 mg/kg for dried herbs is based on the results of one trial each with basil and chives, with residues of 23 and 31 mg/kg, respectively. The recommended JMPR maximum residue level of 50 mg/kg for dried basil is based on two trials and a drying factor of 8 (from one trial), yielding values of 15 and 24 mg/kg. For dried chives, the recommended JMPR maximum residue level is based on two trials and a drying factor of 8 (from one trial), yielding values of 14 and 31 mg/kg. The recommended JMPR maximum residue level of 50 mg/kg is appropriate for both dried basil and dried chives. The JMPR considered that the limited data available on basil (two trials, one including drying) and chives (two trials, one including drying) were inadequate to recommend an MRL for the general category of dried herbs.

The same US data were used to derive the interim and the JMPR MRL recommendations for *pistachio* nuts. Three trials were conducted in the USA, with the highest residue being 0.08 mg/kg. The interim MRL recommendation is based on the US tolerance of 0.1 mg/kg. The JMPR considered that the number of data points was minimal and therefore estimated an MRL of 0.2 mg/kg.

The interim MRL recommendation for soya (oil seed) of 0.01 mg/kg is based on a translation of data from treatment of seeds for wheat, lettuce, pea, cucumber and radish. JMPR did not receive any data on soya seed treatment and did not translate data on rape or cereal grain.

The interim MLR for rape-seed is based on a translation of data from various seed treatments, with an LOQ of 0.01 mg/kg. The JMPR value is based on the results of trials on the treatment of rape-seed, with an LOQ of 0.02 mg/kg.

The various interim MRLs for cereal grains are based on field trials of seed treatment for wheat, maize and other crops in the USA and are set at the LOQ of 0.02 mg/kg. The JMPR recommendation for the maximum residue level for *cereal grain* is based on 71 seed treatment trials in Europe and the USA, with LOQs ranging from 0.01 to 0.05 mg/kg. The highest value was selected by the JMPR.

The dietary risk assessments with the interim and the JMPR MRLs found no dietary concern. Using STMR values and an ADI of 0.4 mg/kg bw per day, the JMPR estimated the intake at 0–1% of the ADI for regional diets. Using MRL values and a reference dose of 0.03 mg/kg bw per day for long-term exposure (US), the Interim Pilot Project estimated the intake to be 0–13% of the ADI for regional diets. Neither calculation indicates concern associated with long-term dietary intake by the general populations in the five regions of the Global Environment Monitoring System–Food Contamination Monitoring and Assessment Programme (GEMS/Food).

A calculation of dietary intake for short-term exposure similar to that of JMPR was performed in the USA, using the proposed interim MRLs as residue values and the ARfD as determined in the USA (1.0 mg/kg bw per day). It should be noted that the end-point applies only to the subpopulation of females aged 13–49 years. The calculation was performed for the general population, because the Codex system does not have data on the consumption of this subpopulation. The maximum exposure of the general population (used as a surrogate for women of child-bearing age) was 10% of the ARfD, from stone fruits. The JMPR considered that an ARfD need not be established. Both the Pilot Group for the Interim MRL and the JMPR concluded that there was no concern associated with short-term dietary intake from the uses considered.

General comments

Several significant differences in the approaches used by the Pilot Group for the Interim MRL and the JMPR become apparent during consideration of the maximum residue levels, because the JMPR uses the average for replicate samples or from replicate analyses, whereas the interim proposals are based on maximum values. This difference usually has only a minimal effect. The JMPR has access to a larger database of field trials and can thus make recommendations on the basis of wider use. The larger database might give rise to different estimates, even when the residue values are below the LOQ. Consideration of full studies from the manufacturer allows inclusion of results that might be considered ‘outliers’ by the European Commission, thereby giving rise to significantly different estimates of maximum residue levels. As crop groupings and extrapolations differ among classification systems, an interim proposal for a maximum residue level in a commodity that is based on a national crop group might be significantly different from that based on a single commodity by the JMPR.

The JMPR agrees with the goals of the project, namely to accelerate the process for establishing MRLs within the Codex system and the introduction of standards for pesticides that are safer alternatives for use on food and feed**.** The Meeting expressed concern over the meaning of the word ‘safer’, which could mean either less toxic (hazard) or a lower residue level (exposure), and the extent of the ‘safer’ designation, which could be either for human health (dietary intake) or for environmental effects. The CCPR has included a number of safeguards in the process, the most important being analyses of long-term and short-term dietary intake based on JMPR methods and consideration by the Codex Alimentarius Commission.

The JMPR considers that extensive use of the interim MRL process might create a serious problem. As the interim MRLs are limited to a period of 4 years, pesticides nominated in this process must be

scheduled for and reviewed by the JMPR within this period. If there are many nominations for interim MRLs for pesticides, the currently limited resources of the JMPR might mean that the evaluations of some of the pesticides might not be completed within the 4 years or that other priorities, such as periodic reviews and evaluations, might have to be severely curtailed.

2.6 Estimation of maximum residue levels of pesticides in or on spices on the basis of monitoring results

The setting of MRLs for spices on the basis of monitoring results was discussed by the CCPR on several occasions. The 2002 JMPR prepared guidelines for the submission of monitoring data for evaluation (xx). The CCPR at its Thirty-sixth Session proposed that commodity group A028 be subdivided into groups on the basis of the parts of plants from which they are obtained—seeds, fruits or berries, roots or rhizomes, bark, buds, arils and flower stigmas—and that MRLs for pesticides that had been evaluated within the Codex system should be set for these sub-groups rather than for each of the pesticide–spice combinations.[7]

The CCPR proposed that the MRL should cover at least 95% of the residue population at the 99% confidence level.[8]

The Meeting evaluated the data on residues provided but emphasized that estimating maximum, high and median residue values does not necessarily mean that the use of those compounds for use on spices is approved by the JMPR.

The Meeting considered the nature of monitoring results and identified the following principal differences from residue data derived from supervised field trials:

- The origin and treatment of the lots sampled are not known.
- The sampled commodity might be composed of the produce of several small fields.
- The residues in spice samples were determined by multi-residue procedures, and their contents were usually screened for organochlorine and organophosphorous compounds, which have relatively high LOQs.
- When residue values are reported as being below the LOQ, it is not necessarily true that the sampled commodity was not treated with or exposed to the pesticide.

Consequently, estimation of maximum residue levels for pesticides on the basis of monitoring results requires a different approach from that used for the evaluating the results of supervised field trials.

Basic principles for evaluating monitoring data

The Meeting assumed that the laboratories reported only valid results. Therefore, all residue data were taken into account as there was no scientific ground for excluding any value as an outlier due to the fact that no information was available on registered or approved uses or application conditions of the pesticides.

It is unlikely that all the sampled commodities were treated with the pesticides in the multi-residue screening procedure; therefore, the proportion of commodities treated with or exposed to a given pesticide was calculated from the ratio of samples containing detectable residues and the total number of samples analysed.

The distributions of residues were scattered or skewed upwards, and no distribution fitting appeared to be appropriate. Consequently, distribution-free statistics was used in estimating the maximum residue level, covering the 95th percentile of the population at the 95% confidence level. Thus, the estimated

[7] ALINORM 04/24, para 236
[8] CX/PR 04/13

maximum residue level encompasses at least 95% of the residues with 95% probability (in 95% of cases). To satisfy this requirement, a minimum of 58–59 samples is required.

STMR and the highest residue values can be calculated only from supervised trials. The corresponding values from the monitoring data are indicated as median and high residue values, and these can be used like the STMR and highest residue values for estimating short-term and long-term intake of residues.

In accordance with the recommendation of the CCPR, maximum, high and median residue values were estimated for pesticide residues in the spice subgroups shown in Table 1 if at least 58 samples belonging to one subgroup were analysed for the given pesticide. The minimum sample size of 58 provides 95% assurance of finding at least one residue value above the 95th percentile of the residue population in the sampled object. It is not, however, known how many of the measured values are above the 95th percentile and what percentile (95.1th, 99th or 99.9th) the highest residue represents. The 95th percentile of the sample does not necessarily represent the 95th percentile of the residue population in the sampled commodity, especially when the sample size is small.

The procedure used depended on the number of samples containing detectable residues.

- When no sample contained detectable residues, the highest reported LOQ value was used as the maximum residue level and the high residue value. The median residue value was calculated from the reported LOQ values.
- When a large number of samples (> 120) contained detectable residues, the sample size was sufficiently large to calculate the upper 95% one-tailed confidence limit of the population of residues, on the basis of binominal (distribution free) probability calculation.[9]

  The confidence limits calculated for pirimicarb residues in anise seeds (number of positive samples, 129) are illustrated in Figure 1. The data set contained 129 residue values with maximum and 95th percentile values of 1.4 and 0.68 mg/kg, respectively. The upper confidence limit of the 95th percentile is between 0.93 and 1.2 mg/kg. This would require an MRL of 1.2 mg/kg, but it is rounded up to 2 mg/kg according the general practice of the JMPR.

  When more detectable residue values are available (n = 343; max 10 values: 11, 9.4, 7, 6.9, 6.8, 6.8, 6.7, 6, 5.9, 4.4, mg/kg; 95th percentile of sample, 3.2 mg/kg; median, 0.5 mg/kg), the upper 95% confidence limit is lower than the maximum of residues observed, and the residue values above the upper confidence limit need not be considered for the maximum residue level. The situation is illustrated in Figure 2.

  As the upper 95% confidence limit is between 5.9 and 6 mg/kg, an MRL of 7 mg/kg would be appropriate. The highest three residue values (7, 9.4 and 11 mg/kg) were above the upper 95% confidence limit and did not influence the estimated limit.

3. A few samples (≤ 120) contained detectable residues. In such cases, the upper 95% confidence limit cannot be calculated from the 95th percentile value of the residues. Sufficient allowance should be given when the maximum residue level is estimated to be above the highest residue value observed. The situation is illustrated in Figure 3 by the example of dimethoate residues in anise (n = 61; maximum, 3 mg/kg; 95th percentile for all samples, 0.9 mg/kg). For the given residue population, the Meeting estimated a maximum residue level of 5 mg/kg.

[9] Hamilton DJ, Ambrus Á, Dieterle RM, Felsot Á, Harris C, Petersen B, Racke K, Wong SS, Gonzalez R, Tanaka K. Pesticide residues in food—Acute dietary intake. Pest Manag Sci 2004;60:311–39.

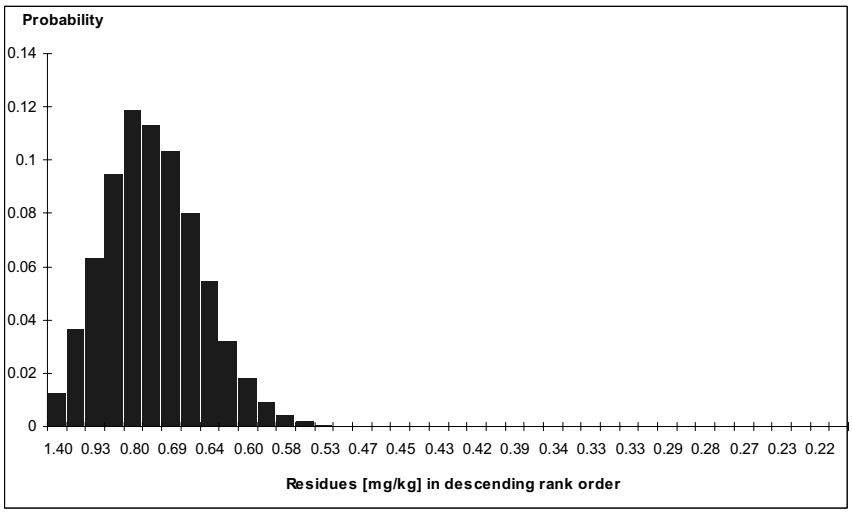


Figure 1. Upper 95% confidence limits for the 95th percentile of pirimicarb residues in anise seed (*n* = 129)

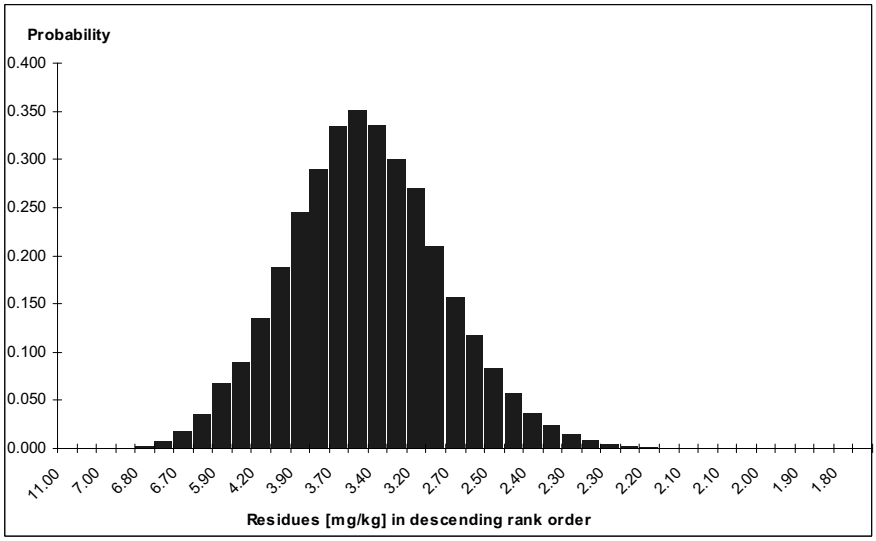


Figure 2. Upper 95% confidence limits for the 95th percentile of chlorpyrifos residues in cumin seed (*n* = 343)

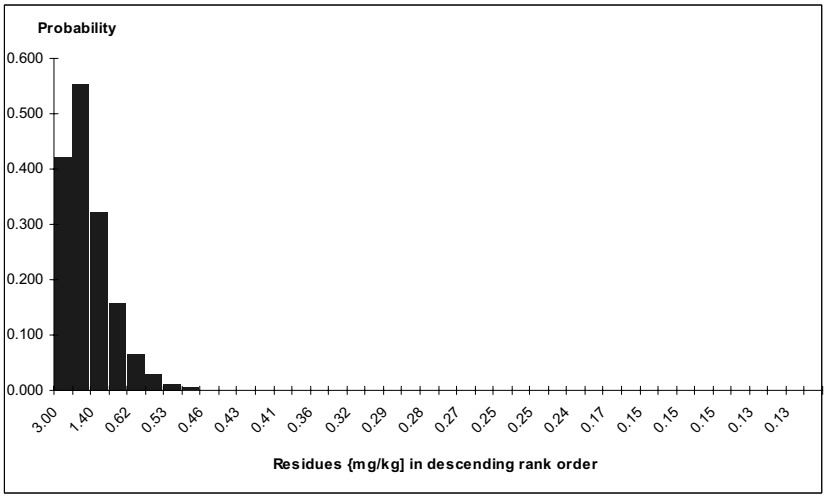


Figure 3. Distribution of estimated 95th percentile estimates of dimethoate residues in anise seed (*n* = 61)

Calculation of international estimated short-term dietary intake (IESTI) and international estimated daily intake (IEDI)

The revised subgroups of spices in group A28 do not all correspond to the consumption figures used for intake calculations. Therefore, the calculations were made with the combined amounts listed for spices in the GEMS/Food tables, in grams per day.

The calculations of short-term intake were based on the highest value of residues of the given pesticide measured in any spice sample.

The IEDI was calculated only from the residue levels detected in the pesticide–spice commodity combination that made the highest contribution to intake of any of the subgroups. A factor for the proportion of treated commodities was calculated from the ratio of the number of samples containing detectable residues and that containing undetectable residues. Adjustment of the median residue value by this factor was one of the recommended procedures for refining intake calculations.[10]

Recommendations

The Meeting recommended that the CCPR accept the principle of setting MRLs on the basis of monitoring results covering the 95th percentile of the residue population at the 95% confidence level. This decision would facilitate use of the statistical procedures for estimating maximum residue levels and acceptance of recommended limits. It should be noted, however, that when MRLs are set at the 95th percentile with 95% confidence, the residue levels might exceed the MRLs in 5% of cases.

Monitoring results should not be used for estimating maximum residue levels that reflect post-harvest use, which results in much higher residue values than foliar application or exposure to spray drift.

Definition of spices

Spices (Group 028) are dried aromatic seeds, buds, roots, bark, pods, berries or other fruits from a variety of plants, rhizomes and flowers, or parts thereof, which are used in relatively small quantities for seasoning, flavouring or imparting aroma to foods. They are consumed in dried form after being added to or sprinkled on foods. The portion of the commodity to which the MRL applies (and which is analysed) is only the dried commodity as it moves in international trade.

Spices of interest and proposed subgroups

The Committee agreed that spices should be collected into smaller groups to facilitate the setting of group MRLs. On the basis of the above definition and after consultation with the spice trade industry, the spices of interest, grouped on the basis of the parts of plants from which they are obtained, are as shown in the table below.

[10] Hamilton D, Murray B, Ambrus Á, Baptista G, Ohlin B, Kovacicova J. Optimum use of available residue data in the estimation of dietary intake of pesticides. Pure Appl Chem 1997;69:1373–410.

Group 028—Spices (as modified by the CCPR at its Thirty-sixth Session, 2004; CX PR 04/13)

CCN[a]	Common name	Botanical name	Industry associations consulted
Seeds	Ajowan	*Carum ajowan*	ESA
	Bishop's weed	*Trachspermum ammi*	ISO , India
HS 771	Anise	*Pimpinella anisum*	ESA, ASTA (fruit in ISO, India)
	Black caraway	*Nigella satia*	ASTA
HS 624	Celery seed	*Apium gravveolens*	ASTA, ESA, (fruit in India, ISO)
HS 779	Coriander	*Coriandrum sativum*	ASTA, India (fruit in ESA)
HS 780	Cumin	*Cuminum cyminum*	ESA, ASTA (fruit in ISO, India)
HS 730	Dill	*Anethum graveolens*	ESA, ASTA, India (fruit in ISO)
HS 731	Fennel	*Foeniculum vulgare*	ESA, ASTA (fruit in India)
HS 782	Fenugreek	*Trigonella foenum graecum*	ESA, ASTA, India, ISO
HS 789	Nutmeg	*Myristica fragrans*	ESA, ASTA , India (kernel in ISO)
HS 4783	Poppy seed	*Papaver somniferum*	India
HS 4785	Sesame seed	*Sesamum indicum* or *orientale*	India
	Mustard seed		Proposed addition
Fruits and berries			
HS 4769	Allspice	*Pimenta dioica*	ESA, ASTA, ISO, India
	Anise pepper; Japan pepper	*Zanthoxylum piperitum* DC	ESA
	Candlenut	*Aleyrites moluccana*	Indonesia
HS 774	Caraway	*Carum carvi*	ESA, India, ISO (seed in ASTA)
HS 775	Cardamom	*Elettaria cardamomum*	ESA, ASTA, India, ISO
HS 786	Juniper	*Juniperus communis*	ASTA, ESA, India, ISO
HS 735	Lovage	*Levisticum officinale* Koch	ISO, India (root in ESA)
HS 790	Pepper (black, white, green)	*Piper nigrum*	ESA, ASTA, India, ISO
HS 791	Pepper, long	*Piper longum*	India, ISO
HS 792	Pimento	*Pimenta officinalis*	ESA, ASTA
	Pink pepper	*Schinus terebinthifolius*, *S. molle*	ASTA, ESA
	Sichuan pepper	*Zanthoxylum bungei* Planch	ESA
	Star anise	*Illicium verum*	ASTA, ESA, ISO, India
HS 795	Vanilla bean	*Vanilla planifolia*; or *tahitensis*	ESA, ASTA, ISO, India
Barks			
HS 4775	Cassia bark	*Cinnamomum aromaticum*	ASTA, ESA, India, ISO
HS 777	Cinnamon	*Cinnamomum zeylanicum*, *C. verum*	ESA, ASTA, India
	Tejpat	*Cinnamomum tamala*	India
Roots and rhizomes			
	Asafoetida	*Ferula assafoetida*	ESA, India, ISO
HS 781	Elecampane	*Inula helenium*	ESA
HS 784	Ginger	*Zingiber officinale*	ESA, ASTA, India, ISO
	Greater galangal; Siamese ginger	*Apinia galangaWilld*	ESA, India, ISO

CCN[a]	Common name	Botanical name	Industry associations consulted
	Lesser galangal	*Apinia officinarum* Hance	ESA, ISO
	Galangal	*Kaempferia galanga*	ESA, ISO
HS 772	Sweet flag	*Acorus calamus*	India, ISO
HS 794	Turmeric	*Curcuma longa*	ESA, ASTA, India, ISO
Buds			
HS 7743	Capers	*Capparis spinosa*	ESA, India, ISO
HS 778	Cloves	*Syyzgiunm aromaticum*; *Caryophyllus aromaticus*	ESA; ASTA, India , ISO
Flower stigmas			
	Saffron	*Crocus sativus*	ESA, India, ISO, ASTA, Spain, Malta
Arils			
HS 788	Mace	*Myristica fragrans*.	ISO, India, ASTA, ESA

CCN, Codex classification number; ASTA, American Spice Trade Association; ESA, European Spice Association; India, Indian Spices Board; ISO, International Standards Organization (specifically, ISO 676 Standard for Spices and Condiments)

[a] Those with a CCN are currently in the list of spices; others are additions to the list.

2.7 Revisited: MRLs for fat-soluble pesticides in milk and milk products

The 2003 JMPR reiterated its explanation of the rationale behind the expression of MRLs for fat-soluble pesticides in milk and milk products.[11] Nevertheless, the 2004 CCPR indicated that the procedure is still complex and considered that it was bound to introduce errors. For instance, the JMPR assumes that adding the suffix 'F' to an MRL for milk clearly implies that analysis for compliance testing must be conducted on the milk fat. The 2004 CCPR noted that the suffix 'F' means only that the specific rule for application of the MRL to the fat in milk products applies. It stated that the MRL applies to the milk as such and might therefore be determined for whole milk.

Currently, the JMPR follows the Codex convention of expressing the MRL for fat-soluble compounds in milk on the basis of the calculated whole product, assuming that all milks contain 4% fat.[12] The residue concentration is calculated for the whole product from the concentration measured in fat, and the MRL would be 1/25th of the residue concentration estimated for the milk fat. Many pesticides are, however, have intermediate solubility in fat; even if they are regarded as fat-soluble, they can be distributed equally between the fat and non-fat portions of milk. For example, if the ratio of residue concentrations between the fat and aqueous phases is 15:1 in milk with 4% fat, the ratio of residue mass distribution is about 2:3, meaning that most of the residue remains in the aqueous phase.

The Meeting decided that, for fat-soluble pesticides, two maximum residue levels will be estimated, if the data permit: one for whole milk and one for milk fat. For enforcement purposes, a comparison can be made either of the residue in milk fat with the MRL for milk (fat) or of the residue in whole milk with the MRL for milk. When needed, maximum residue levels for milk products can then be calculated from the two values, by taking into account the fat content of the milk product and the contribution from the non-fat fraction.

[11] Annex 6, reference 98

[12] FAO/WHO 2000: Codex Alimentarius Volume 2B, Pesticide Residues in Food—Maximum residue limits. Joint FAO/WHO Food Standards Programme, p. 4. Rome, 2000.

Analytical methods should be made available for both milk and milk fat (both with a practical LOQ). The fat should preferably be separated from the milk by physical means, not by chemical solvent extraction, because in solvent extraction residues are extracted from both the aqueous and the lipid phase. As in this way cream (containing 40–60% fat) and not 100% milk fat is obtained, the lipid content of the cream should also be reported. The Meeting requested the CCPR ad-hoc Working Group on Methods of Analysis to give further guidance on analytical methods for measuring residues of fat-soluble pesticide in milk. Estimation of maximum residue levels for spinosad in milk is given here as an example (see also this report).

The 2001 JMPR reported that residues were measured in 119 samples of milk and cream after direct treatment of dairy cows with spinosad, and that the mean quotient of the concentration in cream divided by the concentration in milk was 4.2. A plot of residue levels in whole milk versus residue levels in cream (Figure 4) showed that the residue level in milk was approximately 24% of that in cream (line of best fit through the origin). Data on spinosad residues in milk and cream from a study of feeding to dairy cows are summarised in Table 79 of the JMPR Residue Evaluations of 2001[13]. The mean quotient of the concentration in cream divided by the concentration in milk after feeding at levels of 1, 3 and 10 ppm was 4.0, in good agreement with the results of direct treatment.

The 2001 JMPR estimated a maximum residue level of spinosad in cattle milk of 1 mg/kg on the basis of the highest value in milk, 0.65 mg/kg, after direct treatment. The calculated concentration in cream would be 0.65 × 4.2 = 2.7 mg/kg. On the assumption that the cream in the feeding study was approximately 50% fat, the concentration in fat would be about 5 mg/kg.

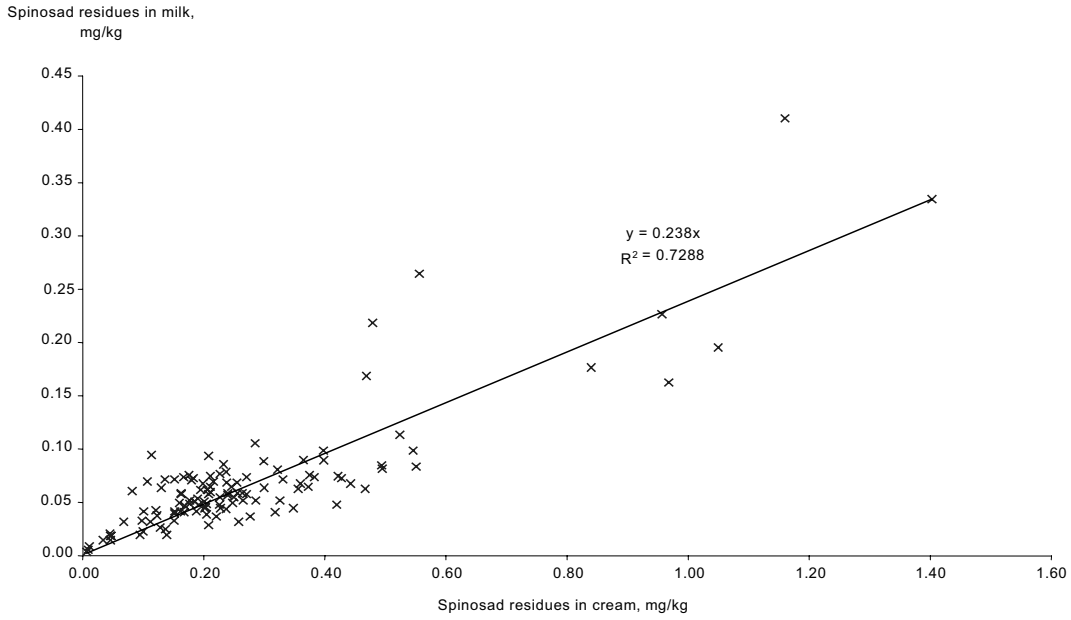


Figure 4. Residues of spinosad in milk and cream after direct treatment of dairy cows

The Meeting estimated a maximum residue level for spinosad residues in cattle milk fat of 5 mg/kg. The Meeting noted that the residue of this pesticide of intermediate fat solubility was estimated to be 8.4 times higher in milk fat than in milk, while the default factor would have been 25 when milk MRLs for fat-soluble pesticides are expressed as previously.

[13] Annex 6, reference 93

2.8 Revisited: Dietary burden of animals for estimation of MRLs for animal commodities

The 1997 JMPR developed guidance for estimating maximum residue and STMR levels for products of animal origin when residues are transferred from feed items. As a result of experience gained since that time, the Meeting agreed that animals could be exposed for extended periods to certain commodities such as fodder, grain and feeds treated post-harvest which contain residues at the highest level. The Meeting was informed that this situation pertains in Australia and probably in other regions of the world.

For example, on a farm on which 20 ha of an animal feed (forage, fodder or grain) were grown per year with a yield of 10 t/ha on a dry weight basis, enough would be produced to feed 333 head of cattle for 1 month. If the feed constituted less than 100% of the diet, more head of cattle could be fed for 1 month, or the duration of feeding might be longer.

In addition, in the experience of the Meeting, the residue levels of many pesticides on animal feed commodities decrease to only a limited extent during storage.

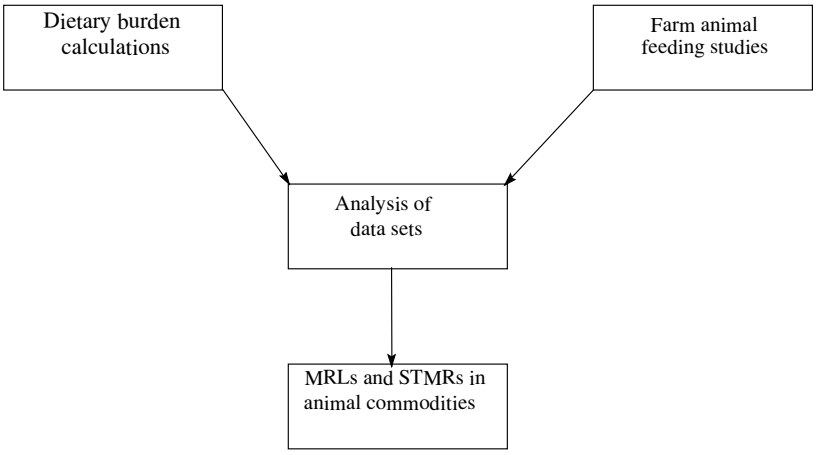
The Meeting agreed that the assumption of the 1986 JMPR, which was used in developing guidance in this area, that "it was unrealistic to assume that the theoretical maximum residue level would be achieved and maintained in the rations of food-producing animals receiving feeds produced on the farm" should no longer apply. Hence, the concept of the time required for residue levels to reach a plateau is also no longer required, thus simplifying estimation of dietary burden. It is recognized that it is unlikely that the individual ingredients of mixed feeds produced from commercially available ingredients would all contain residues at the theoretical maximum level; in these cases, the STMR should be applied to each of the components.

A revision of the relevant text in the *FAO Manual*, taking the above into account, will appear on the FAO website.

Residues arising from consumption of feed items

The 1986 JMPR explained its use of feeding studies with farm animals in estimating MRLs for foods of animal origin. It made the point that a sensible judgement must be made about the expected level of ingestion. The 2004 JMPR noted that it is realistic to assume that the theoretical maximum residue level would be achieved and maintained in the rations of food-producing animals receiving feeds grown on the farm for extended periods.

The estimation of residues that will arise in animal commodities is a two-pronged process, involving feeding studies with farm animals and calculations of dietary burden. These two sets of information are combined to estimate the residue levels that will be found in animal commodities in practice:



The following decision matrix is recommended for use in estimating maximum residue levels and STMR values:

Maximum residue level	STMR
Choose:	Choose:
feed commodity, highest residue or STMR-P (for dietary burden calculation)	feed commodity STMR or STMR-P (for dietary burden calculation)
highest residue level[1] (from feeding study in farm animals)	mean residue level[1] (from feeding study in farm animals)

STMR-P, supervised trials median residue in a processed commodity calculated by multiplying the STMR of the raw commodity by the corresponding processing factor

[1] Residue levels in tissues and eggs of the relevant group of animals in the feeding study. For milk, choose the mean residue in milk from the relevant group of animals in all cases.

The residue contribution of a feed commodity for estimating maximum residue levels is calculated from the percentage of the total diet and the highest residue level in raw agricultural commodity feed items. For processed commodities that are likely to originate from a number of farms, e.g. apple pomace, the STMR-P of the processed commodity is chosen as the likely highest residue value that will occur in practice.

Maximum residue levels in animal commodities are derived from the highest residue values in feed commodities, and STMRs for animal commodities are derived from the STMRs for feed commodities. Separate tables are made for each MRL and STMR estimate, in which all feed items, their Codex commodity group and the residue levels found in crop residue trials are listed. The basis of the residue level is provided; i.e. the basis of the maximum residue level estimate is the highest level for raw agricultural commodities and the STMR-P for processed commodities. The percentage dry matter in the feeds is derived from Appendix IX of the *FAO Manual*, 'Maximum proportion of agricultural commodities in animal feed', except when the data stipulate 100% dry matter. The residue of each feed commodity on a dry weight basis is then calculated.

Starting with the feed item with the highest residue level, the percentage of each feed in the livestock diet is allocated from Appendix IX. Usually, only one feed commodity from each Codex commodity group is used; if more than one is used, it is only up to the full percentage feed allocation for that group. Feeds are allocated a percentage of the diet for each animal until no more than 100% of the diet is used.

The residue contribution (mg/kg) of each feed is then calculated from the dry weight of the residue and the corresponding percentage of the diet. All residue contributions for each animal are then added to determine the total dietary burden.

The procedure illustrated in the diagram and described above is demonstrated in the following worked example for spinosad.

Maximum dietary burden of farm animals estimated for spinosad

Commodity	Codex commodity group	Residue (mg/kg)	Basis of residue value	Dry matter (%)	Residue dry weight (mg/kg)	Feed allocation in total diet (%)			Residue contribution of feeds (mg/kg)		
						Beef cattle	Dairy cattle	Poultry	Beef cattle	Dairy cattle	Poultry
Apple pomace, wet	AB	0.064	STMR-P	40	0.16	10			0.016		
Citrus pulp	AB	0.12	STMR-P	91	0.13						
Maize forage	AF	3.1	Highest	100	3.1	40	50		1.24	1.55	
Maize fodder	AS	2.1	Highest	100	2.1						

Commodity	Codex commodity group	Residue (mg/kg)	Basis of residue value	Dry matter (%)	Residue dry weight (mg/kg)	Feed allocation in total diet (%)			Residue contribution of feeds (mg/kg)		
						Beef cattle	Dairy cattle	Poultry	Beef cattle	Dairy cattle	Poultry
Wheat straw and fodder, dry	AS	0.83	Highest	100	0.83						
Sorghum	GC	0.68	Highest	86	1.2	40	40	80	0.27	0.27	0.544
Almond hulls	AM	1.1	Highest	90	2.2	10	10		0.11	0.11	
Cotton-seed hulls		0.0020	STMR-P	90	0.0022						
Cotton-seed meal		0.0017	STMR-P	88	0.0019			20			0.0004
					Total	100	100	100			
						Maximum dietary burden			1.64	1.93	0.54

STMR dietary burden of farm animals estimated for spinosad

Commodity	Codex commodity group	Residue (mg/kg)	Basis of residue value	Dry matter (%)	Residue dry weight (mg/kg)	Feed allocation in total diet (%)			Residue contribution of feeds (mg/kg)		
						Beef cattle	Dairy cattle	Poultry	Beef cattle	Dairy cattle	Poultry
Apple pomace wet	AB	0.064	STMR-P	40	0.16	10			0.016		
Citrus pulp	AB	0.12	STMR-P	91	0.13						
Maize forage	AF	0.70	STMR	100	0.70	40	50		0.28	0.35	
Maize fodder	AS	0.46	STMR	100	0.46						
Wheat straw and fodder, dry	AS	0.215	STMR	100	0.22						
Sorghum	GC	0.165	STMR	86	0.19	40	40	80	0.08	0.08	0.15
Almond hulls	AM	0.56	STMR	90	0.62	10	10		0.062	0.062	
Cotton seed hulls	SO	0.0020	STMR-P	90	0.0022						
Cotton seed meal	SO	0.0017	STMR-P	88	0.0019			20			0.00039
					Total	100	100	100			
						STMR dietary burden			0.43	0.49	0.15

The poultry dietary burdens are not discussed further in this example.

Use of the results of farm animal feeding studies and dietary burdens to estimate maximum residue levels and STMR values for commodities of animal origin

The calculations of dietary burden are compared with the feeding levels in studies of farm animals to estimate maximum residue levels and STMR values on the basis of the following guidelines.

- When a feeding level in a feeding study matches the dietary burden, the residue levels reported in the study can be used directly as estimates of residue levels in tissues, milk and eggs resulting from the dietary burden.
- When a feeding levels in a feeding study differs from the dietary burden, the resulting residues in tissues, milk and eggs can be estimated by interpolation between the closest feeding levels.

- When the dietary burden is below the lowest feeding level in the study, the resulting residues in tissues, milk and eggs can be estimated by applying the transfer factor (residue level in milk or tissue ÷ residue level in diet) at the lowest feeding level to the dietary burden.
- When the dietary burdens of beef and dairy cattle are different, the higher value should be used for calculating the residues in muscle, fat, liver and kidney.
- For estimating maximum and highest residue levels in meat, fat, liver, kidney and eggs, the highest residue level found in an animal in the relevant feeding group of the study should be used.
- For estimating STMR values in meat, fat, liver, kidney and eggs, the mean residue levels in animals in the relevant feeding group of the study are used.
- For estimating maximum residue levels and STMRs in milk, the mean residue levels in the animals in the relevant feeding group of the study are used.
- No more than about 30% above the highest feeding level can be extrapolated to a dietary burden.

The feeding levels in the farm animal feeding studies are entered into a table with the calculations of dietary burden and analysed on the basis of the above guidelines.

In the example of spinosad, the maximum dietary burdens of beef and dairy cattle are 1.6 and 1.9 mg/kg, respectively. Therefore, the levels of residues in tissues and milk are taken by interpolation from the 1 and 3 ppm feeding levels in the study.

The STMR dietary burdens (0.43 and 0.49 mg/kg) are below the lowest feeding level, 1 ppm. Therefore, the resulting residues in tissues and milk are calculated by applying the transfer factors at the lowest feeding level to the STMR dietary burdens.

The highest residue level in an individual tissue from an animal in the relevant feeding group is used with the highest dietary burden of residue to calculate the probable highest residue level in animal commodities. The mean tissue residue in the animals in the relevant feeding group is used with the STMR dietary burden to estimate the STMR values for animal commodities. For milk, the mean plateau residue level in milk from the relevant feeding group was used to estimate both the maximum residue level and the STMR.

The estimated dietary burden of spinosad was 1.6 mg/kg for beef cattle and 1.9 mg/kg for an actual feeding level of 3 ppm in the transfer study. The STMR value was 0.43 mg/kg for beef cattle and 0.49 mg/kg for dairy cattle for an actual feeding level of 1 ppm. The mean spinosad residue level in milk from dairy cattle was 0.13 mg/kg, while the value interpolated from the dietary burden and the feeding levels and the residue levels found in the transfer study was 0.087. The highest tissue residue levels in individual dairy cattle in the relevant feeding group were 1.7 mg/kg in fat (interpolated value, 1.1 mg/kg), 0.069 mg/kg in muscle (0.044 mg/kg), 0.44 mg/kg in liver (0.28 mg/kg) and 0.26 mg/kg in kidney (0.16 mg/kg). The mean residues in dairy cattle tissue (or milk) in the relevant feeding group were 0.044 mg/kg in milk (interpolated value, 0.022 mg/kg), 0.65 mg/kg in fat (0.32 mg/kg), 0.020 mg/kg in muscle (0.010 mg/kg), 0.13 mg/kg in liver (0.064 mg/kg) and 0.065 mg/kg in kidney (0.032 mg/kg).

As the STMR burden of dairy cattle exceeds that of beef cattle, it is used as the maximum residue level and the estimated STMR for fat, muscle, liver and kidney.

The highest residue levels expected in tissues and milk are: 1.1 mg/kg in fat, 0.16 mg/kg in kidney, 0.28 mg/kg in liver and 0.087 mg/kg in milk. The proposed STMR values are: 0.010 mg/kg in cattle meat, 0.032 mg/kg in cattle kidney, 0.064 mg/kg in cattle liver and 0.022 mg/kg in milk.

2.9 Statistical methods for estimating MRLs

The Meeting was informed of developments in the use of statistics to estimate the maximum residue level. A group of experts was formed in the USA, consisting of persons involved in MRL setting in the countries of the North American Free Trade Association and the European Food Safety Authority. They investigated the available procedures, primarily those used in the European Union, and decided to pursue a procedure in which a log normal distribution of data is assumed and the lower 95% upper confidence limit on the 95th percentile or the point estimate of the 99th percentile from normal Q–Q plots is used as an approximation of the maximum residue level. The plots give visual evidence of the degree of log normal behaviour of particular residue values. Some comparisons were made of the results obtained from application of this procedure and of the procedure used currently by the JMPR for data sets on fludioxonil. In most cases, there was good agreement. Small data sets often result in estimates of maximum residue levels that are considerably above the maximum. Statistically, this results from the uncertainty associated with few data points.

It was emphasized that any statistical system must be easy to use (spreadsheet) and be based on accepted statistical principles. Such systems might assist evaluators but could never replace professional judgement.

The method is still being developed. The Meeting expressed interest in receiving spreadsheets and documentation for evaluation, when available, and will await further developments.

2.10 Application of the recommendations of the OECD project on minimum data requirements to the work of the JMPR

The 2003 JMPR noted that some of the recommendations of the OECD York Workshop[14] and the FAO/OECD Zoning Steering Group were used routinely. The JMPR first considered the activities of the York Workshop at its 1999 Meeting, and subsequent Meetings have incorporated the Workshop recommendation into their work where practical. For example, as a result of the York Workshop, the JMPR has considered glasshouse trials conducted worldwide at the same GAP equivalent. Likewise, post-harvest trials conducted throughout the world at the same GAP are considered equivalent. The York Workshop also provided limited recommendations on crop translations, and the JMPR has been using that guidance routinely. It is noted, however, that the Zoning Steering Group addressed only foliar uses and that the York workshops considered primarily foliar and post-harvest uses. There is no guidance on soil treatment, seed treatment or use of herbicides. It was agreed that a pilot study would be conducted for the 2004 JMPR, in which the effect of full implementation of the recommendations would be considered for a new compound evaluation. Fludioxonil was selected.

The York Workshop and the follow-up Zoning Steering Group offered guidance that is potentially useful in two areas. First, they assigned the minimum number of trials required for evaluating a given pesticide–commodity combination for a maximum residue level, on the basis of three criteria: (1) the significance of the item in the diet of the general population; (2) the significance of the item in trade; and (3) the number of zones in which the commodity is grown. Unfortunately, the Workshop failed to define two of the three criteria adequately. It suggested that an item is 'significant' if its consumption represents $\geq 0.5\%$ of the total diet in any region. Importance in trade and the criteria for designating zones were not defined, and the subsequent Zoning Steering Group did not find a correlation between climatic growing regions and crop residue levels. The Zoning Steering Group suggested that a definition of zones based on climate, e.g. temperate–wet, temperate–dry, cold and tropical, was not relevant.

[14] *Minimum data requirements for establishing Maximum Residue Limits (MRLs) and import tolerances*, Doc. 2734/SANCO/99

In view of the undefined criteria, the Meeting found it difficult to implement the scheme in determining the minimum number of trials required for a given pesticide–commodity combination. In the absence of guidance, the Meeting based the required number of trial on one or several zones where the likelihood of the crop being grown in substantial quantity in very different geographic and agricultural practice areas was considered. Likewise, the Meeting used its best collective opinion in deciding on the significance of the commodity in trade. The Meeting considered significance relative to international trade and not local or regional trade; thus, a commodity might be of substantial economic importance to a nation or region but not significant on the global scale.

The second area of assistance was in defining representative commodities for crop groups and listing some acceptable translations of data. For example, the York Workshop decided that field trial data for orange or grapefruit and mandarin or lemon could be used to represent all citrus fruit and that data for tomato and pepper could be extrapolated to okra and eggplant. This aspect was not, however, completed; for example, no recommendations were made for leafy vegetables. The Meeting noted that the Codex classification system for food and feed items is currently undergoing a limited revision, and this may be of assistance.

The Meeting compiled a list of commodities for which the following information was available: recommendations on maximum residue levels for fludioxonil, the number of trials available at GAP, the decision of the JMPR, the apparent requirements under the York Workshop criteria, and the result of application of the York Workshop criteria. The list is shown below.

Maximum residue level recommendations for fludioxonil

Commodity	No. of trials at GAP	JMPR MRL recommendation	OECD minimum database			
			Assumptions			Recommendation
			No. of zones	Significant in trade (T), diet (D)	No. of trials	
Pears	7	Yes	2–3	D	8	No
Stone fruit	11	Yes (Po)	Po	T, D	8	Yes
Grapes	18	Yes	2–3	T, D	12	Yes
Strawberry	25	Yes	2–3	D	8	Yes
Raspberry	4	Yes	2–3		4	Yes
Blackberry	0	Yes, translation of raspberry				Yes (translation)
Dewberry	0	Yes, translation of raspberry				Yes (translation)
Blueberry	8	Yes	2–3		4	Yes
Spring onions	3	Yes	2–3		4	No
Bulb onions	13	Yes	2–3	D	8	Yes
Broccoli	7	Yes	2–3	D	8	No
Cabbage	6	Yes	2–3	D	8	No
Cucumber	13	Yes	2–3	D	8	Yes
Summer squash	2	Yes (support from cucumber)	2–3		4	No
Tomato	16	Yes	2–3	T, D	12	Yes
Bell pepper	10	Yes	2–3	T, D	12	Yes
Eggplant	4	Yes	2–3		3	Yes
Sweet corn (on-the-cob)	8	Yes	2–3	D	8	Yes
Lettuce, head	17	Yes	2–3	T, D	12	Yes
Watercress	2	Yes (support from mustard greens)	2–3		3	No

Commodity	No. of trials at GAP	JMPR MRL recommendation	OECD minimum database			
			Assumptions			Recommendation
			No. of zones	Significant in trade (T), diet (D)	No. of trials	
Mustard greens	7	Yes (support form watercress)	2–3		3	Yes
Bean pod with seed	22	Yes	2–3	T, D	12	Yes
Pea with pod	0	Translation from bean with pod				Yes (translation)
Peas (succulent)	6	Yes	2–3	T, D	12	No
Pea and bean (dry)	5	Yes	2–3	D	8	No
Potato	17	Yes	2–3	T, D	12	Yes
Carrot	7	Yes	2–3	D	8	No
Asparagus	2	No	2–3		3	No
Cereal grains	71	Yes (wheat, rye, barley, maize, sorghum)	> 3	T, D	16	Yes
Pistachio nuts	3	Yes	1		3	Yes
Rape-seed	15	Yes	2–3	T	8	Yes
Cotton-seed	8	Yes	2–3	T, D	12	No
Chives	2	Yes	1		3	No
Basil	2	Yes	1		3	No
Maize forage	7	Yes	> 3	N/A	10	No
Fodder and straw of cereal grains	50	Yes	> 3	N/A	10	Yes

Po, the recommednation accommodates post-harvest treatment of the food commodity; N/A, not applicable

[1] Crops with no trials at GAP are not listed.

The Meeting noted that it had extended estimates of maximum residue levels to commodities for which use of the OECD guidance would not have so indicated (cotton-seed, basil, chives, peas, peas and beans (dry), watercress, summer squash, broccoli, cabbage, green onions, pears). These assignments were based, however, on application of criteria that are not defined or only partially described. For example, if one zone were assumed (rather than two or three), use of the OECD guidance would have led to maximum residue level recommendations for all commodities except the herbs, summer squash and watercress.

These evaluations of additional commodities for maximum residue levels are the result of independent scientific judgement by the JMPR. For example, the Meeting considered six or seven trials (in cabbage, pear, broccoli) conducted under GAP and properly documented to be acceptable.

Although the Meeting usually requires a minimum of three or four trials for a minor commodity, it considered two fully documented trials under GAP adequate for the herbs chives and basil. As these commodities are herbs, their consumption is extremely low and pesticide residues on them would not usually pose a hazard. Because the maximum residue level was based on only two trials, the Meeting estimated a considerably higher level than the highest residue level: The high residue level for chives was 3.9 mg/kg, and the Meeting estimated a maximum residue level of 10 mg/kg.

The Meeting considered five trials to be adequate for establishing maximum residue levels for dry beans and dry peas, as the residues were below the LOQ. The OECD recommendations suggest eight trials.

A similar situation existed for cotton-seed. The GAP is for seed treatment use, and all the residue levels were below the LOQ. Metabolism studies after seed treatment and other seed treatment trials predict residues below the LOQ. Thus, the Meeting considered five trials to be acceptable, although the York Workshop would have required eight.

The Meeting also noted that, while the York Workshop provided some information on the translation of residue values for one commodity to another, it did not provide for the mutual support of other commodities with similar use patterns. In the present example, the Meeting agreed to use data on cucumber to support the MRL for summer squash (zucchini) and to use data on mustard greens to support the value for watercress. This is common practice by many national governments and is based on similarities in crop morphology. The York Workshop did provide for the translation of data on raspberry to blackberry and dewberry and the translation of data on bean with pod to pea with pod.

The Meeting recalled the conclusion of the Zoning Steering Group, that trials on a given commodity conducted at the same GAP with similar residues on day 0 be considered equivalent regardless of geographic location. The Group suggested that application method, crop type and local agricultural practices are major contributors to differences in residue levels among trials conducted under the same GAP. Climate has only a minor direct effect. The JMPR suggested, therefore, that hypothetical zones (not geographical zones) be developed on the basis of crop type and variations in agricultural practice. For example, wheat is grown in a relatively uniform manner worldwide (one zone), while grapes are grown under a variety of conditions (of crop height, leaf numbers and plant density; multiple zones).

The Meeting concluded that some of the recommendations of the York Workshop and Zoning Steering Group used by the JMPR will continue to be considered as auxiliary advice but that substantial additional work is required to make the recommendations generally applicable as guidance. Areas in which additional effort is needed include: (1) defining significance in trade, perhaps with a table of commodities and their classifications; (2) determining the criteria for zones and the number of zones for each commodity; (3) extending the list of commodity translations for the purpose of recommending a maximum residue level for one commodity on the basis of available field trial data for another commodity; and (4) completing the list of representative crops for the purpose of recommending group maximum residue levels.

2.11 Alignment within one year of toxicological and residue evaluations for new and periodically reviewed compounds

When a new compound or one undergoing periodic review is evaluated, it is generally preferable to conduct the toxicological and residue reviews in the same year. Practical problems may, however, arise; e.g. when the residue definition is uncertain, the residue evaluation cannot proceed satisfactorily or efficiently. In such cases, it is preferable that the toxicological evaluation precede the residue evaluation.

The Meeting recommended that the toxicological and residue evaluations of new compounds or those undergoing periodic review be scheduled for the same year, when practical. When the residue definition is problematic (e.g. different residue definitions in different national and regional registration systems), the toxicological evaluation should be scheduled 1 year ahead of the residue evaluation.

3. DIETARY RISK ASSESSMENT FOR PESTICIDE RESIDUES IN FOOD

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 abd previous Meetings. Dietary intakes were calculated by multiplying the concentrations of residues (STMR or STMR-P values or recommended MRLs) by the average daily per capita consumption estimated for each commodity on the basis of the GEMS/Food diet[1,2]. International estimated daily intakes (IEDIs) were derived when STMR or STMR-P values were available, and theoretical maximum daily intakes (TMDIs) were calculated when only existing or recommended MRLs were available. Codex MRLs that have been recommended by the JMPR for withdrawal were not included in the estimates.

Long-term dietary intakes are expressed as a percentage of the ADI for a 60-kg person, with the exception of the intake calculated for the Far Eastern diet, in which a body weight of 55 kg is used. The estimates are summarized in Table 1. 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 some conservative assumptions used in the assessments. The detailed calculations of long-term dietary intake are given in Annex 3.

The Meeting drew attention to the use of residue levels in muscle tissue for estimating dietary intake of residues in meat of fat-soluble compounds. Previously, residue levels in trimmable fat, with adjustment by a default factor, were used to estimate dietary intake from meat.

Assessments of long-term risk for betazone, captan, carbofuran, fenpropimorph, fenpyroximate, folpet, dimepthipin, methamidophos and pirimiphos-methyl were considered by previous meetings. For these compounds, the recommendations made at this Meeting will not significantly affect the previous assessments.

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.[1]

Table 1. Summary of risk assessments of long-term dietary intake conducted by the 2001 JMPR

Compound		ADI	Intake range (% of	Type of assessment
Codex code	Name	(mg/ kg bw)	maximum ADI)	
017	Chlorpyrifos	0–0.01	3–30	IEDI
149	Ethoprophos	0–0.0004	5–10	IEDI
037	Fenitrothion	0–0.05	110–330	IEDI
211	Fludioxonil	0–0.4	0–1	IEDI
158	Glyphosate	0–1	1	TMDI
049	Malathion	0–0.3	0	IEDI
212	Metalaxyl/ Metalaxyl M	0–0.08	2–10	TMDI
094	Methomyl	0–0.02	1–20	IEDI
166	Oxydemeton methyl	0–0.0003	3–30	IEDI
057	Paraquat	0–0.005	2–5	IEDI
112	Phorate	0–0.0007	40–200	TMDI
101	Pirimicarb	0–0.02	3–20	TMDI

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

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

Compound		ADI	Intake range (% of	Type of assessment
Codex code	Name	(mg/kg)	maximum ADI	
142	Prochloraz	0–0.01	7–10	IEDI
160	Propiconazole	0–0.07	0–1	TMDI
105	Propineb [1]	0–0.007	4–30	IEDI
210	Pyraclostrobin	0–0.03	0–3	IEDI
203	Spinosad	0–0.02	9–30	IEDI
133	Triadimefon	0–0.03	1–6	TMDI
168	Triadimenol	0–0.03	1–20	TMDI
213	Trifloxystrobin	0–0.04	1–2	IEDI

Spices and dried chili peppers

Long-term dietary intake (IEDI) from the consumption of spices was calculated for 28 pesticides for which recommendations were made at the present Meeting on the basis of monitoring data (General item 2.6; Annex 5). For these compounds, the additional contributions to the IEDI from the consumption of spices were < 1% of the respective ADIs for all GEMS/Food regional diets.

The Meeting also calculated TMDIs from the consumption of dried chili peppers using maximum residue levels estimated at this Meeting for 46 pesticides, on the basis of MRLs for peppers (Annex 5). The TMDIs for carbaryl and dimethoate were > 100 % of the respective ADIs in at least one regional diet.

The TMDIs were > 5–100% of the respective ADIs in at least one regional diet for acephate, azinphos-methyl, carbendazim, chlorothalonil, chlorpyrifos, chlorpyrifos-methyl, cyhexatin, cyromazine, dicofol, ethephon, ethoprophos, fenarimol, methamidophos, methomyl, monocrotophos, oxamyl, phosphamidon, procymidone, profenofos, tebufenozide and vinclozolin. For these compounds, a long-term intake calculation based on all uses should be performed before the risk assessment can be finalized.

The TMDIs were ≤ 5% of the respective ADIs in all regional diets for abamectin, benalaxyl, cyfluthrin, cypermethrin, diazinon, dichlofluanid, dinocap, dithiocarbamates, fenpropathrin, fenvalerate, imidacloprid, metalaxyl, methoxyfenozide, permethrin, piperonyl butoxide, propamocarb, pyrethrins, quintozene, spinosad, tebuconazole, tolylfluanid, triadimefon and triadimenol. The Meeting agreed that the intake of these compounds through consumption of dried chili peppers would not significantly affect the risk assessment based on all other uses of the compounds.

Assessment of risk from short-term dietary exposure

Risks associated with short-term dietary intake were assessed for compounds for which STMR and highest residue values were estimated at the present and previous Meetings and for which acute reference doses (ARfDs) has been established, in commodities for which data on consumption were available. The procedures used for calculating the short-term intake are described in detail in sections 2.10 and 3 of the report of the 2003 JMPR.[3]

A risk assessment for short-term dietary intake was conducted for each commodity–compound combination by assessing the IESTI as a percentage of the ARfD. When the maximum residue level was estimated for a Codex commodity group (e.g. citrus fruits), intakes were calculated for individual commodities within the group.

On the basis of data received by the present or previous Meetings, the establishment of an ARfD for bentazone, metalaxyl M, fludioxinil, glyphosate, spinosad, trifloxystrobin was considered unnecessary. The intake of these compounds was therefore not estimated.

An ARfD might be necessary for pirimiphos-methyl but has not yet been established. Therefore, the short-term risk assessment could not be finalized. The Meeting recommended that this compound be evaluated for the establishment of ARfDs in the near future.

[3] Annex 6, reference 98

ARfDs were established for phorate, pirimicarb, propiconazole, triadimefon and triadimenol, but short-term intakes were not calculated as STMR and highest residue values were not available for these compounds.

On the basis of data received by the present Meeting, the establishment of ARfDs for captan and folpet was considered necessary only for women of child-bearing age. The corresponding IESTI could, however, be calculated only from the consumption data available for the general population.

The recommendation made for methamidophos at the present Meeting does not affect the previous assessment for this compound.

The short-term intakes, as percentages of the ArfDs, of the general population and of children are summarized in Table 2. 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 some conservative assumptions used in the assessments. The detailed calculations of short-term dietary intakes are given in Annex 4.

Table 2. Summary of risk assessments of short-term dietary intake conducted by the 2004 JMPR

Compound		ARfD (mg/kg bw)	Commodity	Percentage of ARfD	
Codex code	Name			General population	Children ≤ 6 years
			Grape	150	–
007	Captan	0.3[1]	Other 19 commodities	0–100	–
096	Carbofuran	0.009	All 20 commodities	1–50	0–100
017	Chlorpyrifos	0.1	All 7 commodities	0–10	0–40
151	Dimethipin	0.2	All 12 commodities	0	0–1
149	Ethoprophos	0.05	All 11 commodities	0–1	0–3
037	Fenitrothion	0.04	Maize	80	160
			Wheat bran, unprocessed	90	150
			Wholemeal bread	50	120
			Other 22 commodities	0–100	0–80
188	Fenpropimorph	0.2	All 15 commodities	0–7	0–10
193	Fenpyroximate	0.01	Apple	50	130
			Grape	120	310
			Other 7 commodities	0–10	0–30
041	Folpet	0.2[1]	Lettuce, head	190	–
			Other 9 commodities	1–100	–
049	Malathion	2	6 commodities	0–4	0–10
094	Methomyl	0.02	Pepper	20	20
166	Oxydemeton methyl	0.002	Apple	50	130
			Cabbage, head	50	120
			Grape	80	220
			Orange	30	120
			Other 16 commodities	0–30	0–90
057	Paraquat	0.006	All 44 commodities	0–20	0–50
142	Prochloraz	0.1	Mushroom	130	150
			Other 46 commodities	0–30	0–70
105	Propineb	0.1[2]	Pepper	110	120
			Other 12 commodities	0–30	0–90
210	Pyraclostrobin	0.05	All 37 commodities	0–30	0–90

[1] Applies only to women of child-bearing age
[2] Interim ARfD

Spices and dried chili peppers

Short-term dietary risk assessments from the consumption of spices were performed for 12 pesticides for which recommendations were made at the present Meeting on the basis of monitoring data (item 2.6, Annex 5), when ARfD values were available. The IESTI ranged from 0 to 30 % of the ARfD for both the general population and children for azinphos-methyl, chlorpyrifos, diazinon, dimethoate, disulfoton, endosulfan, fenitrothion, malathion, methamidophos, parathion-methyl and phosalone. The intake of mevinphos represented 170% of the ARfD for the general population and 160% for children.

Short-term dietary risk assessments from the consumption of dried chilli peppers were performed for 14 pesticides for which ARfD values were established, using the maximum residue level estimated by the present Meeting. The intakes ranged from 0 to 100% of the respective ARfDs for the general population and children for acephate, carbaryl, chlorpyrifos, diazinon, ethephon, ethoprophos, imidacloprid, methamidophos, methoxyfenozide, pyrethrins and tolyfluanid. The intakes were 120% of the ARfD for both populations for dimethoate. They were 260% of the ARfD for the general population and 270% for children for oxamyl.

4. EVALUATION OF DATA FOR ESTABLISHING VALUES FOR ACCEPTABLE DAILY INTAKES AND ACUTE REFERENCE DOSES FOR HUMANS, MAXIMUM RESIDUE LIMITS AND SUPERVISED TRIAL MEDIAN RESIDUE LEVELS

4.1 BENTAZONE (172)

TOXICOLOGY

Evaluation for an acute reference dose

Bentazone is a herbicide that was first evaluated by the JMPR in 1991, when an ADI of 0–0.1 mg/kg bw was allocated on the basis of the NOAEL of 9 mg/kg bw per day in a long-term study in rats and a safety factor of 100. Further data were made available to the 1998 JMPR, including observations in humans and a 90-day study in rats fed with 6-hydroxybentazone, a metabolite of bentazone. Data from studies of genotoxicity with 6-hydroxybentazone were also supplied. It was concluded that 6-hydroxybentazone was less toxic than bentazone, and the ADI of 0–0.1 mg/kg bw was maintained. Data were not evaluated to establish an ARfD. The present Meeting re-evaluated some of the previously evaluated data in order to establish an ARfD, and two cases of acute human poisoning were described.

The oral median lethal dose (LD_{50}) for bentazone was 1200–2500 mg/kg bw in rats. In 13-week studies in mice, rats and dogs, interference with blood clotting was a consistently observed effect. There was prolongation of the prothrombin and partial thromboplastin times in mice and rats, and prolongation of the prothrombin and bleeding time in dogs. Additionally, extramedullary haematopoiesis, haemorrhage and haemosiderosis were found in mice at autopsy. Toxicological effects in rats were less dramatic, the NOAEL being identified on the basis of clinical chemistry changes. In dogs, clinical effects, such as hyperactivity, ataxia, prostration and tremor, were seen. At the highest dose in dogs, at histopathological examination of tissues post mortem there was congestion and necrosis in the liver, together with fatty change and, in the spleen, evidence of extramedullary haematopoiesis. Fatty change in the myocardium and cloudy swelling of the renal tubular cells were also observed. The NOAEL for the study in mice was 400 ppm (equal to 90 mg/kg bw per day) on the basis of prolonged prothrombin and partial thromboplastin times at higher dietary concentrations. The NOAEL for the study in rats was 400 ppm (equal to 25.3 mg/kg bw per day) on the basis of clinical chemistry changes observed at the next highest dietary concentration. In the study in dogs, the NOAEL was 300 ppm (equal to 12.0 mg/kg bw per day) on the basis of clinical effects observed at higher dietary concentrations. Three deaths were observed at the highest dose in weeks 11 and 12 of the study. In a 1-year study in dogs, clinical signs (emaciation, dehydration, hyperaemia, alopecia and diarrhoea, which was occasionally bloody) were seen at the highest dietary concentration. The NOAEL for the study was 400 ppm (equal to 13.1 mg/kg bw per day) on the basis of clinical signs, weight loss and anaemia at the highest dietary concentration. It was not considered appropriate to set an ARfD on the clinical signs, reduced body weight or haematological changes occurring in dogs, since significant clinical effects were not seen early in these two studies.

Three studies of developmental toxicity in rats treated by gavage (two studies) or by dietary administration (one study) were evaluated by the Meeting. In the earlier study of rats treated by gavage, neither maternal nor fetal toxicity was seen at any dose; the NOAEL for both maternal and fetal toxicity was thus 200 mg/kg bw per day, the highest dose tested. In the later study in rats treated by gavage, in which higher doses were administered, the NOAEL was 100 mg/kg bw per day on the basis of maternal toxicity (decreased food consumption) and fetal toxicity (postimplantation loss, reduced fetal weight and incompletely ossified fetal skeletons). In the study of developmental toxicity in rats given diets containing bentazone, the NOAEL for maternal toxicity was 4000 ppm (equal to 324 mg/kg per day) on the basis of decreased weight gain and food consumption at 8000 ppm. The NOAEL for fetal toxicity was also 4000 ppm

(equal to 324 mg/kg bw per day) on the basis of decreased fetal weights and fetal liver petechiae at 8000 ppm. Bentazone was not teratogenic in any of the studies of developmental toxicity in rats. The Meeting assessed two studies of developmental toxicity in rabbits. In one study, the NOAEL for maternal and fetal toxicity was 150 mg/kg bw per day, the highest dose tested; neither maternal nor fetal toxicity was observed at any dose. In the second study, which was conducted using higher doses than the earlier study, the NOAEL for maternal toxicity was 150 mg/kg bw per day on the basis of reduction in maternal food consumption at 375 mg/kg bw per day. Postimplantation loss was increased at 375 mg/kg bw per day and there was total implantation loss in one dam. Bentazone was not teratogenic in either study of developmental toxicity in rabbits.

Two case reports of fatal self-poisoning in humans were characterized by vomiting, diarrhea, drowsiness and death from cardiac arrest.

Toxicological evaluation

The Meeting concluded that the establishment of an ARfD was unnecessary. An addendum to the toxicological monograph was prepared

Estimate of acute reference dose

Unnecessary

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

Further observations in humans

DIETARY RISK ASSESSMENT

Short-term intake

The 2004 JMPR decided that it was not necessary to establish an ARfD for bentazone. The Meeting therefore concluded that the short-term dietary intake of bentazone residues is unlikely to present a public health concern.

4.2 CAPTAN (007)

TOXICOLOGY

Evaluation for an acute reference dose

Captan is a fungicide used for the control of fungal diseases in crops. The JMPR evaluated captan in 1963, 1965, 1969, 1973, 1978, 1982, 1984, 1990 and 1995. Toxicological monographs were prepared in 1963, 1965 and 1969 and addenda to the monographs were prepared in 1973, 1977, 1978, 1982, 1984, 1990 and 1995. In 1984, an ADI of 0–0.1 mg/kg bw was established on the basis of a NOAEL of 12.5 mg/kg bw per day in studies of reproductive toxicity in rats and monkeys. The present Meeting considered the requirement for an ARfD, based on data from the previous evaluations for JMPR and from new studies.

In mice treated orally with captan, the captan molecule is largely degraded to 1,2,3,6-tetrahydrophthalimide (THPI) and thiophosgene (via thiocarbonyl chloride) in the stomach before reaching the duodenum. No captan was detected in blood or urine. Studies of metabolism in vitro with human blood

revealed that captan is rapidly degraded to THPI, with a calculated half-life of 1–4 s. Thiophosgene is detoxified by reaction with, e.g. cysteine or glutathione and is ultimately rapidly excreted.

The acute oral toxicity of captan in rats is low (LD_{50}, > 5000 mg/kg bw). Mice fed diets containing captan at a concentration of 3000 ppm, equal to 440 mg/kg bw per day, for 28 days showed an initial reduction in food consumption of about 37%. Food consumption gradually recovered over the first week of treatment, although it remained lower that that of controls throughout the 4-week treatment period. After 1 day, no treatment-related macroscopic and microscopic changes were observed in the duodenum or any other tissue examined. From day 3 onwards, the duodenum showed crypt cell hyperplasia, shortening of villi and a general disorganization of the villus enterocytes. From day 7 onward, immature cells were seen at the villus tips.

In a 28-day range-finding study in which dogs were given captan at doses of 30 to 1000 mg/kg bw per day, dose-related emesis, reduced body-weight gain and food consumption were observed in all treatment groups. No other clinical signs were observed. Haematological parameters and histopathology of the duodenum were within normal limits.

In a study from the published literature, the teratogenic effects of a number of phthalimide derivatives, including captan, were tested in pregnant golden hamsters. The Meeting noted that this study had major limitations (e.g. small number of animals per dose, limited reporting of the data) and is therefore of limited value. It does, however, suggest that developmental effects may occur after a single exposure to captan, albeit at maternally toxic doses.

In a study of developmental toxicity in rats treated by gavage, captan was not teratogenic. The NOAEL for maternal toxicity was 18 mg/kg bw per day on the basis of a reduction in body weight and food consumption. The NOAEL for offspring toxicity was 90 mg/kg bw per day on the basis of the reduction in fetal body weight and an increased incidence of skeletal variations.

In a study in rabbits treated by gavage, the NOAEL for maternal toxicity was 10 mg/kg bw per day on the basis of a markedly reduced body-weight gain and reduced food consumption at 30 mg/kg bw per day. The NOAEL for embryo- and fetotoxicity was 10 mg/kg bw per day on the basis of increases in skeletal variations at 30 and 100 mg/kg bw per day. At 100 mg/kg bw per day, increased incidences of early and late intra-uterine deaths were observed, as were increased incidences of several malformations. The NOAEL for these effects was 30 mg/kg bw per day. Multiple malformations observed in two fetuses in the group receiving the intermediate dose were considered to be incidental. In another study in rabbits treated by gavage, the NOAEL for maternal toxicity was 10 mg/kg bw per day on the basis of reduced body-weight gain and food consumption at 40 mg/kg bw per day. On the basis of the increase in postimplantation losses and the increase in incidence of minor skeletal variations at 160 mg/kg bw per day, the NOAEL for embryo- and fetotoxicity was 40 mg/kg bw per day. In a third study in rabbits treated by gavage, the NOAEL for maternal toxicity was 12 mg/kg bw per day on the basis of reductions in body-weight gain during the initial phase of treatment. The NOAEL for embryo- and fetotoxicity was 25 mg/kg bw per day on the basis of a reduction in fetal body weight at 60 mg/kg bw per day. The Meeting considered that maternal toxicity and the associated increases in skeletal variations and fetal body-weight reductions observed were likely to be caused by high local concentrations of captan produced by administration by gavage and are not considered to be relevant to dietary exposure.

While few data on humans are available, captan is known to have caused allergic dermatitis and eye irritation in humans. After ingesting 7.5 g of Captan 50 WP, which is a suspension of captan mixed with water (ratio, 50%), a 17-year-old woman (body weight not reported) experienced some clinical signs, which started 3 h after ingestion and recovered within 72 h. Assuming a body weight of 50–60 kg, this intake equates to a dose of 62.5–75 mg/kg bw.

Toxicological evaluation

Other than developmental effects, captan produced no toxicological effects that might be considered to be a consequence of acute exposure. The Meeting concluded that it was not necessary to establish an ARfD for the general population, including children aged 1–6 years for whom separate data on dietary intake are available. The Meeting concluded that it might be necessary to establish an ARfD to protect the embryo or fetus from possible effects in utero. Such an ARfD would apply to women of childbearing age.

The maternal toxicity and associated increases in skeletal variations and fetal body-weight reductions observed in studies of developmental toxicity in rabbits are likely to be caused by high local concentrations of captan and are not considered to be relevant to dietary exposure. However, the observed intra-uterine deaths and fetal malformations could not, with confidence, be attributed to maternal toxicity.

The Meeting concluded that the database was insufficient (in particular, with regard to the absence of studies on the developmental effects of THPI) to establish the mode of action by which the increased incidences of intra-uterine deaths and of fetuses with malformations, observed at 100 mg/kg bw per day (NOAEL, 30 mg/kg bw per day) in rabbits, were induced. As a consequence, their relevance for deriving an ARfD could not be dismissed. Therefore the Meeting established an ARfD of 0.3 mg/kg bw, based on a NOAEL of 30 mg/kg bw per day for increased incidences of intra-uterine deaths and malformations at 100 mg/kg bw per day in the study in rabbits and a safety factor of 100. The use of a safety factor of 100 was considered to be conservative; although the mode of action by which the developmental effects were induced is uncertain, they are possibly secondary to maternal toxicity. The ARfD also covers the effects observed in the case report in humans. The Meeting noted that it might be possible to refine the ARfD using the results of an appropriately designed study.

An addendum to the toxicological monograph was prepared.

Estimate of acute reference dose

0.3 mg/kg bw for women of childbearing age

Unnecessary for the general population

DIETARY RISK ASSESSMENT

Short-term intake

The Meeting established an ARfD (0.3 mg/kg bw) for captan for women of childbearing age and decided that an ARfD was unnecessary for the general population including children aged 1–6 years. Women of childbearing age are also part of the general population.

In the absence of relevant studies on the developmental effects of THPI, the Meeting was unable to determine whether or not THPI should be excluded from the residue for dietary risk assessment. The Meeting was not able to finalize the risk assessment before an evaluation of the residue definition for risk assessment and associated residue values for dietary intake estimation had been completed.

4.3 CARBOFURAN (096)/ CARBOSULFAN (145)

RESIDUE AND ANALYTICAL ASPECTS

Carbofuran, resulting from use of carbosulfan, was reviewed for residue levels within the periodic review programme in 1997. When the compound was re-evaluated by the JMPR in 2002 and 2003, short-term

risks were assessed for commodities for which recommendations had been made at those Meetings: rice, sweet corn, maize and potato. The CCPR at its Thirty-fifth Session, taking into account concerns expressed by the Delegation of Australia and the Observer from the European Commission, requested GEMS/Food to perform a full short-term intake assessment of carbofuran, to include all the commodities not evaluated previously for which recommendations existed. The assessment was presented to the CCPR at its Thirty-sixth Session (CX/PR 03/4). Except for the consumption of oranges (sweet and sour) by children, none of the IESTI value exceeded the ARfD of 0.009 mg/kg bw. The assessment was conducted with the highest residue (HR) level in the edible portion of 0.5 mg/kg, recommended by the 1997 JMPR for oranges, sweet, sour, from a residue data set in whole orange derived from 53 supervised trials conducted with carbosulfan according to GAP. A maximum residue level of 0.5 mg/kg and a STMR of 0.1 mg/kg were also recommended.

At its Thirty-sixth Session, the Committee noted (ALINORM 04/27/24) that the European Commission had established an ARfD 10 times lower than that established by JMPR. The Committee decided to return to Step 6 the draft MRLs for cantaloupe; cucumber; mandarin; oranges, sweet, sour; squash, summer; and sweet corn (corn-on-the-cob) to address concern about short-term intake.

For the purposes of dietary intake, the residue definition for carbofuran arising from use of carbosulfan and carbofuran is carbofuran + free and conjugated 3-OH carbofuran, expressed as carbofuran. The analytical methods include an acid hydrolysis step to release the conjugate.

At the present Meeting, data on residues in orange pulp in supervised trials conducted with carbosulfan and submitted to the 1997 JMPR were evaluated.

Results of supervised trials on crops

Six trials in Spain conducted according to GAP with carbosulfan in orange, evaluated by the 1997 JMPR, showed residue levels of carbamates (carbosulfan, carbofuran or 3-OH carbofuran) of < 0.05 mg/kg at 0 days (four trials), 45 days (six trials) and 105 days (four trials). The post-harvest interval (PHI) is 110 days. The residue levels in peel ranged from 0.21 to 0.84 mg/kg 45 days after the last application (two trials) and from < 0.05 to 0.25 mg/kg within 110 days' PHI (four trials).

The Meeting agreed that it is unlikely that residues of carbamates arising from the use of carbosulfan will be present in orange pulp at levels higher than the LOQ (0.05 mg/kg). The Meeting estimated an STMR and a highest residue level of 0.05 mg/kg for carbofuran in orange, sweet, sour.

This estimate is supported by a study on metabolism evaluated by the 1997 JMPR, in which the pulp of oranges treated with ^{14}C-carbosulfan contained no more than 0.3% of the total radioactive residues 30 days after treatment.

DIETARY RISK ASSESSMENT

Long-term intake

The Meeting agreed that the STMR in the edible portion of orange estimated by the present Meeting would result in a lower IEDI than that calculated by the 2002 JMPR. The Meeting confirmed the previous conclusion that the long-term intake of carbofuran residues arising from use of carbosulfan and/or carbofuran on the commodities considered by the JMPR is unlikely to present a public heath concern.

Short-term intake

The IESTI of carbofuran, was calculated for all the commodities not evaluated previously, including citrus. The IESTI represented 1–50% of the ARfD for the general population and 1–100% of that for

children. The Meeting concluded that the short-term intake of carbofuran residues in the commodities evaluated at this Meeting is unlikely to present a public health concern.

4.4 CHLORPYRIFOS (017)

RESIDUE AND ANALYTICAL ASPECTS

At its Twenty-fifth Session in 1993 (ALINORM 93/24A para. 251), the CCPR identified chlorpyrifos as a candidate for periodic review. At its Twenty-ninth Session in 1997, it scheduled periodic reviews for toxicology in 1999 and for residue chemistry in 2000. The 1999 toxicology review confirmed the ADI of 0.01 mg/kg bw and also established an ARfD of 0.1 mg/kg bw. In the 2000 residue chemistry review, information was supplied on the identity and physical properties of the active ingredient and technical material, metabolism in plants and animals, environmental fate, storage stability, animal feeding studies, field trials, GAP (national labels) and fate of residues in processing.

Chlorpyrifos was scheduled for re-evaluation in 2004 for consideration of maximum residue levels in cotton, potato, rice and soya bean. No MRLs were recommended by the 2000 JMPR on these commodities because of lack of relevant GAP labels or insufficient residue data. Relevant GAP labels and additional residue data to support proposed Codex MRLs in these commodities were submitted to the Meeting for evaluation. The CCPR at its Thirty-sixth Session in 2004 agreed that JMPR would review data from India to support establishment of a maximum residue level on tea. Information was submitted by the Government of India for this purpose.

Methods of analysis

Methods for enforcement, data collection and monitoring of chlorpyrifos in different matrices were submitted and evaluated by JMPR in 2000. Additional methods were submitted to the present Meeting for the analysis of cotton-seed, potato, rice and soya bean. Various extraction and clean-up methods are followed by gas chromatography with flame photometric detection. The LOQ for chlorpyrifos is 0.01 mg/kg in all matrices.

The method of analysis for chlorpyrifos in tea was submitted by the Government of India. Residues in the cleaned extract were quantified by gas chromatography with flame-photometric or electron-capture detection. The LOQ is 0.02 mg/kg tea.

Results of supervised trials on crops

Cotton-seed

Supervised field trials on cotton were conducted at three sites in Australia in 2000 to provide additional residue data for consideration of MRLs for this crop. Bridging studies were conducted with a water-dispersible granule containing 750 g ai/kg and with an emulsifiable concentrate containing 300 g ai/l. Three foliar broadcast applications of each formulation were made at a rate of 1.5 kg ai/ha per application at a 5–8-day interval. A twofold rate of 3.0 kg ai/ha per application was also included. The applications were made at growth stages from late flowering to 15% of the bolls opened, with the last application 17 or 28 days before harvest. Although two sites in Australia have an early PHI (17 days), the residue levels in cotton-seed in these trials were included for MRL consideration because they were within the range of those in all trials. The trials conformed with Australian GAP (0.15–1.5 kg ai/ha in three applications and a 28-day PHI with either formulation). The highest residue level in replicate plots was chosen for estimating the STMR as a worst-case scenario.

Two supervised field trials on cotton were conducted at two sites in Brazil in 1992. Data on residues from the trials were submitted to JMPR in 2000 and accepted as meeting GAP. Briefly, the trials were conducted with an emulsifiable concentrate containing 480 g ai/l at a rate of either 0.96 or 1.92 kg ai/ha (twofold rate) per application. Foliar broadcast applications were made twice in one trial and three times in the other. In 2000, three additional supervised field trials on cotton were conducted at three sites in Brazil, with three foliar broadcast applications of the same emulsifiable concentrate at a rate of 0.96 or 1.92 kg ai/ha per application. The applications were made at growth stages from plant emergence to 30% of the bolls opened. Two replicate plots were used per treatment in each field site. Samples were hand-harvested from control and treated plots at 0, 7 (or 5), 14 (or 15), 21 (or 22) and 28 days after the last application and ginned to generate the cotton-seed (undelinted) samples. The trials conformed with Brazilian GAP (0.14–0.96 kg ai/ha in one to three applications and a 21-day PHI).

Supervised field trials on cotton were conducted in the USA in 1973, 1974 and 1986. Data on residue levels from these trials were submitted to JMPR 2000, and three of the trials were accepted as meeting GAP. Briefly, the trials were conducted with an emulsifiable concentrate containing 480 g ai/l applied as foliar broadcast applications. At a site in Mississippi in 1973, nine applications were made at a rate of either 1.12 or 2.24 kg ai/ha per application. Samples were hand-harvested 0, 3, 7 and 14 days after the last application and ginned to generate undelinted cotton-seed. At another site in Mississippi in 1974, two applications were made at a rate of 0.28 kg ai/ha per application, followed by 12 applications each at 1.12 kg ai/ha. Undelinted cotton-seed samples were generated similarly 15 days after the last application. At a site in California in 1986, five applications were made at 1.12 kg ai/ha, and undelinted cotton-seed samples were generated 14 days after the last application.

On the basis of the trials that conformed to GAP, the chlorpyrifos residue levels, in ranked order (median underlined), was: 0.01 (two), 0.02, 0.03 (two), 0.05, <u>0.07</u> (four), 0.11, 0.12, 0.16 and 0.18 mg/kg. The Meeting estimated a maximum residue level of 0.3 mg/kg for cotton-seed, an STMR of 0.07 mg/kg and a highest residue level of 0.18 mg/kg from the supervised trial in the USA in 1986.

Potato

The 2000 JMPR considered data on residues from supervised trials on potatoes, but did not establish MRLs because there were insufficient trials at GAP to estimate the STMR or maximum residue level. Additional data from supervised trials after at-plant application (soil in-furrow) on potatoes were generated in Brazil and submitted to the present Meeting. The proposed MRL from the data on residues after at-plant application would also cover residue levels after foliar application. The data previously summarized for at-plant application were provided again to allow evaluation of residue levels in all supervised trials conducted in Brazil. Four supervised field trials on potatoes were conducted in 1993–94 in Brazil. The data from these trials were submitted to the JMPR in 2000 and accepted as meeting GAP. The trials were conducted with either a granular formulation containing 100 g ai/kg or an emulsifiable concentrate containing 450 g ai/l. A single application was made to soil in-furrow at planting, at a rate of 1.5, 3.0 or 6.0 kg ai/ha for the granular formulation and 2.9 or 5.9 kg ai/ha for the emulsifiable concentrate.

In 1999–2000, seven supervised field trials on potatoes were conducted in Brazil to provide additional data on residue levels for MRLs. Four trials were conducted with the granular formulation at a rate of 3 or 6 kg ai/ha, and three trials were conducted with the emulsifiable concentrate at a rate of 2.7 or 5.4 kg ai/ha. Three replicate plots were maintained for each treatment. A single application of each formulation was made to soil in-furrow at planting. Three samples of potatoes were collected manually at normal harvest from the control and treated plots 100–124 days after application. The highest residue level in replicate plots was chosen for estimating the STMR as a worst-case scenario.

On the basis of at-plant treatment in trials conforming to GAP, the chlorpyrifos residue levels, in ranked order, were: 0.02, 0.03, 0.10, 0.13, 0.29, <u>0.51</u>, 0.57, 0.58, 0.65, 0.69 and 0.87 mg/kg. The Meeting estimated a maximum residue level of 2 mg/kg for potato, an STMR of 0.51 mg/kg and a highest residue level of 0.87 mg/kg.

Rice

The 2000 JMPR considered data on residues from supervised trials on rice, but did not establish MRLs because no trials were conducted at the relevant GAP. Relevant GAP in Colombia, the Philippines and Viet Nam was made available to support the results of the supervised trials submitted to the JMPR in 2000. Some additional data from supervised trials on rice, generated in India and Thailand since 2000, were submitted to the present Meeting. Supervised trials were thus conducted in Colombia, India, the Philippines, Thailand and Viet Nam.

In Colombia, two supervised field trials on rice were conducted in 1998 at two sites. Data on residue levels from these two trials were submitted to the JMPR in 2000. Briefly, the trials were conducted with an emulsifiable concentrate containing 480 g ai/l, applied three times to upland rice. The first application was made at a rate of 0.96 kg ai/ha after germination, followed by a second application at 0.72 kg ai/ha when the plants were at tillering crop growth stage; the final application was made at a rate of 0.34 kg ai/ha 20–21 days before harvest, when 100% of pinnacles were present. Three replicate plots were maintained for each trial. Rice samples from the control and treated plots were hand-harvested 20–21 days after the last application. The supervised trials conformed to Colombian GAP (0.34–0.96 kg ai/ha in a maximum of three applications and 20-day PHI).

In the Philippines, two supervised field trials on rice were conducted in 1998 at two sites. An emulsifiable concentrate containing 300 g ai/l was applied three times at a rate of 0.3 kg ai/ha per application. Data on residue levels in these two trials were submitted to JMPR 2000. The first two applications were made 25 and 40 days after transplantation, and the last application was made 25 days before harvest. Rice grain and straw samples from the control and treated plots were harvested 25 days after the last application. The supervised trials conformed to GAP in the Philippines, which is 0.30 kg ai/ha in a maximum of three applications and 25 days' PHI.

In Viet Nam, two supervised field trials on rice were conducted in 1998 at two sites. Data on residue levels in these two trials were submitted to the JMPR in 2000. Briefly, the trials were conducted with an emulsifiable concentrate containing 300 g ai/l, applied at a rate of 0.42 kg ai/ha. Rice grain and straw samples from the control and treated plots were harvested 10 days after the last application. The supervised trials conformed to GAP in Viet Nam, which is 0.3–0.42 kg ai/ha in one application and 28 days' PHI.

In Thailand, three supervised field trials on rice were conducted in 2002. An emulsifiable concentrate of chlorpyrifos containing 400 g ai/l was applied three times as a foliar application at a rate of 400 g ai/ha per application. The first application was made at mid-booting, and the final one at seed formation. Samples of rice grain and straw from the control and treated plots were hand-harvested 7, 14 and 21 days after the last application. The GAP in Thailand is 0.40 kg ai/ha, with an unspecified number of applications and 7–14 days' PHI.

In India, three supervised field trials on rice were conducted at three sites in 2002. An emulsifiable concentrate of chlorpyrifos containing 200 g ai/l was applied as a foliar application at a single rate of 375 g ai/ha. Samples of grain and straw from the control and treated plots were taken 14 (or 15), 21 and 30 days after application. As the labels were not available in English, the Meeting did not evaluate the data from India.

On the basis of trials on rice conforming to GAP, the chlorpyrifos residue levels, in ranked order, were: 0.02 (two), 0.08 (two), 0.09, 0.15, 0.16, 0.19 and 0.28 mg/kg. The Meeting estimated a maximum residue level of 0.5 mg/kg for rice, an STMR of 0.12 mg/kg and a highest residue level of 0.28 mg/kg.

Soya bean

The 2000 JMPR considered data from supervised trials on soya beans, but did not establish MRLs because the data from accepted GAP trials were insufficient for estimating the STMR or maximum residue level. Additional data from supervised trials conducted in 1994–96 on soya beans in Brazil were submitted to

the Meeting. The data from the five trials conducted in the USA according to GAP were provided again to the Meeting.

In Brazil, two field trials were conducted in 1992–93 with an emulsifiable concentrate containing 480 g ai/l, applied three times at either 0.48 or 0.96 kg ai/ha (twofold label rate) per application. Soya beans from the control and treated plots were hand-harvested 20–21 days after the last application. In 1992–93, an additional supervised field trial was conducted with the emulsifiable concentrate applied three times at 0.48 or 0.96 kg ai/ha per application. Soya beans from the control and treated plots were hand-harvested 21 days after application. In 1995, one supervised field trial was conducted in Brazil with the emulsifiable concentrate applied at either 0.34 or 0.77 kg ai/ha. Soya beans from the control and treated plots were harvested 21 days after application. Brazilian GAP is 0.12–0.48 kg ai/ha with one to two applications and 21 days' PHI. The supervised trials represent the worst-case scenario. The residue levels were below the LOQ (< 0.01 mg/kg) in all trials conducted at either the maximum or twice the maximum label rate or in single or triple applications.

In the USA, supervised field trials on soya beans were conducted in 1975–76. Data on residue levels from these trials were submitted to the JMPR in 2000, and five trials were accepted as meeting GAP. Briefly, the trials were conducted with an emulsifiable concentrate containing 480 g ai/l applied once as a directed broadcast spray at crop emergence, followed by three to four foliar broadcast applications during the growing season. The application rates were 0.56–2.2 kg ai/ha at emergence and 0.56–1.1 kg ai/ha at each foliar application. Soya beans were collected from the control and treated plots at normal harvest, 28–31 days after the last application. For replicate plots, the highest residue level was chosen for consideration of the MRL, as a worst-case scenario.

On the basis of trials conforming to GAP, the chlorpyrifos residue levels, in ranked order, were: <u>≤ 0.01</u> (six), 0.01 (two) and 0.05 mg/kg. The Meeting estimated a maximum residue level of 0.1 mg/kg for soya bean, an STMR of 0.01 mg/kg and a highest residue level of 0.05 mg/kg.

Tea

Six supervised field trials were conducted in 1995, 1996, 1998 and 1999 at various sites in India. A chlorpyrifos emulsifiable concentrate containing 200 g/l was applied once at a rate of 0.20 kg ai/ha (0.05 kg ai/hl, 400 l/ha water), which complied with GAP for chlorpyrifos on tea as submitted by the Government.

On the basis of trials conforming to GAP in India, the chlorpyrifos residue levels in tea, in ranked order, were: 0.03, 0.15, <u>0.19</u>, <u>0.57</u>, 0.77 and 1.13 mg/kg. The Meeting estimated a maximum residue level of 2.0 mg/kg for tea, an STMR of 0.34 mg/kg and a highest residue levelof 1.13 mg/kg.

Fate of residues during processing

Studies on processing of cotton-seed, rice and soya beans were submitted but not evaluated by the JMPR in 2000 because no MRLs were established for the raw agricultural commodities of these crops. The processing studies were resubmitted to the present Meeting for evaluation of residue levels in processed products of these raw agricultural commodities. The processing factors and estimated STMR-Ps for cotton-seed, rice and soya bean are summarized below:

Processed commodity	Processing factor	STMR (mg/kg) (RAC)	STMR-P (mg/kg)
Cotton hulls	0.7	0.07	0.05
Cotton-seed meal	0.1	0.07	< 0.01
Cotton-seed oil, crude	1.4	0.07	0.10
Cotton-seed oil, refined	0.2	0.07	0.01
Rice hulls	2.44	0.12	0.29
Rice bran	1.80	0.12	0.22
Rice husked	0.13	0.12	0.016

Processed commodity	Processing factor	STMR (mg/kg) (RAC)	STMR-P (mg/kg)
Polished rice	0.07	0.12	0.008
Soya bean meal	< 0.2	0.01	< 0.002
Soya bean crude oil	0.4	0.01	0.004
Soya bean refined oil	0.4	0.01	0.004
Soya bean refined	0.5	0.01	0.005

STMR-P, STMR of raw agricultural commodity × processing factor of processed product

Residues in animal commodities

The 2000 JMPR estimated the dietary burden of chlorpyrifos in farm animals and poultry in cases in which calculations from the MRLs yielded maximum theoretical dietary intakes, and calculations from STMR values for feed allowed estimation of STMR values for animal commodities. The present Meeting concluded that the contribution of residues to feed, calculated for the uses considered this year, would not increase the dietary burden assessed by the 2000 JMPR. The Meeting maintained the recommendations of the 2000 JMPR.

DIETARY RISK ASSESSMENT

Long-term intake

IEDIs for chlorpyrifos were calculated for the five GEMS/Food regional diets from the STMRs and STMR-Ps estimated by this Meeting, in addition to those for 61 commodities from the JMPR 2000 evaluation. The IEDIs were 3–30% of the maximum ADI (0–0.01 mg/kg bw), as shown in Annex 3. The Meeting concluded that the intake of residues of chlorpyrifos resulting from uses that have been considered by the JMPR is unlikely to present a public health concern.

Short-term intake

The IESTI for chlorpyrifos was calculated for the commodities for which MRLs, STMR values and highest residue values were estimated and for which data on consumption (large portion and unit weight) were available. The results are shown in Annex 4.

The ARfD for chlorpyrifos is 0.1 mg/kg bw. The short-term intakes were calculated for commodities for which highest residues or HR-Ps were estimated by the present Meeting. The calculated short-term intakes were < 100% of the ARfDs for children (0–40%) and for the general population (0–10%). The Meeting concluded that the intake of residues of chlorpyrifos resulting from uses that have been considered by the JMPR is unlikely to present a public health concern for consumers.

.

4.5 DIMETHIPIN (151)

TOXICOLOGY

Evaluation for an acute reference dose

The 1999 JMPR established an ARfD for dimethipin of 0.02 mg/kg bw on the basis of a NOAEL of 20 mg/kg bw per day and a LOAEL of 40 mg/kg bw per day for skeletal malformations (increased incidence of fetuses and of litters containing fetuses with scoliosis and 27 presacral vertebrae) in a study of developmental toxicity in rabbits, and using a safety factor of 1000 in consideration of the nature of the

effects caused. The 2002 JMPR concluded that the 1000-fold safety factor might be excessive and that the ARfD of dimethipin should be reconsidered on the basis of appropiate data.

The present Meeting reconsidered the ARfD for dimethipin. The study of developmental toxicity in rabbits was re-evaluated in the light of a larger set of historical control data for Dutch belted rabbits, provided by the sponsor.

In a study of developmental toxicity in rabbits, does treated with dimethipin at a dose of 40 mg/kg bw per day showed body-weight loss on days 6–12 of gestation and decreased body-weight gain on days 6–28 of gestation. Fetal and litter incidences of scoliosis were 0% and 0% in the controls and 4.0% and 23.1% at 40 mg/kg bw per day, respectively. The observed incidence of scoliosis at 40 mg/kg bw per day was at the upper bound of that for historical controls (i.e. fetal and litter incidences of 4.1 and 20%, respectively). The NOAEL for both maternal and developmental toxicity was 20 mg/kg bw per day.

Toxicological evaluation

The Meeting established an ARfD of 0.2 mg/kg bw on the basis of the NOAEL of 20 mg/kg bw per day in the study of developmental toxicity in rabbits and a safety factor of 100. The Meeting considered that a safety factor of 100 was adequate, since the observed developmental toxicity was at the upper range of the historical control incidence and was possibly secondary to maternal toxicity.

An addendum to the toxicological monograph was prepared.

Estimate of acute reference dose

0.2 mg/kg bw

DIETARY RISK ASSESSMENT

Short-term intake

The Meeting established an ARfD (0.2 mg/kg bw) for dimethipin. The 2001 JMPR had calculated the IESTI for dimethipin for 12 food commodities (and their processed fractions) for which MRLs were estimated and for which consumption data were available, using the previous ARfD of 0.02 mg/kg bw. The IESTI represented 0% of the ARfD for the general population and 0–1% of the ARfD for children. The Meeting concluded that the short-term intake of residues of dimethipin from uses that have been considered by the JMPR is unlikely to present a public health concern.

4.6 DITHIOCARBAMATES (105)

RESIDUE AND ANALYTICAL ASPECTS

Propineb was evaluated by the present Meeting within the CCPR periodic review programme, and the recommendations for MRLs, STMRs and highest residue levels are discussed in the appraisal of that compound. Recommended MRLs for dithiocarbamates arising from use of propineb are consolidated here.

The 1996 JMPR recommended MRLs for dithiocarbamates in almond hulls, almond, pecan, pome fruits and stone fruits which were based on residue data for ziram. The 1996 JMPR also recommended that estimates of maximum residue levels for dithiocarbamates, which relied primarily on data for ziram, should be temporary until the relevant data on environmental fate had been evaluated.

In view of the decision of the 2003 JMPR that data on environmental fate need be reviewed only when they directly affect estimation of maximum residue levels, the Meeting decided to withdraw its requirement for information on the environmental fate of ziram in soil and in water–sediment systems.

4.7 ETHOPROPHOS (149)

RESIDUE AND ANALYTICAL ASPECTS

Ethoprophos, a nematicide and soil-insecticide, was evaluated for residues in 1984 and 1987. The toxicology of ethoprophos was reviewed within the periodic review programme by the 1999 JMPR. Ethoprophos was listed as a priority by the the CCPR at its Thirtieth Session (Alinorm 99/24 App VII) for for periodic review of residues by the 2001 JMPR. The manufacturer requested postponement of the residue evaluation.

The Meeting received information on identity; metabolism and environmental fate; analysis of residues; use pattern; residues resulting from supervised trials on strawberry, banana, cucumber, melon, pepper, tomato, potato, sweet potato and sugar-cane; fate of residues during storage and in processing; residues in food in commerce or at consumption; and national maximum residue limits.

Metabolism

Animals

The Meeting received information on the fate of [1-ethyl-^{14}C]ethoprophos rats, lactating goats and laying hens dosed orally.

Studies on metabolism in laboratory animal (rats) were evaluated by the WHO Expert Group of the 1999 JMPR, which concluded that ^{14}C-ethoprophos is rapidly and virtually completely absorbed, metabolized and excreted after oral administration to rats. The main route of excretion was urine (51–56%), but significant proportions were excreted in expired air (about 15%) and faeces (10–14%). Little radiolabel was found in tissues at 168 h, representing less than 2.5% of the dose, and the highest concentrations were found in excretory organs (liver, kidneys and lungs). There was no evidence that bioaccumulation would occur after repeated doses. Ethoprophos was metabolized by dealkylation of one or both *S*-propyl groups, followed by conjugation.

Lactating goats given feed containing ^{14}C-ethoprophos at a concentration of 32 ppm excreted 78% of the administered radiolabel in urine (including cage rinse), 3.6% in faeces (including the gastrointestinal tract and contents) and 1.7% in milk; 3.9% of the administered dose was found in tissues. During the 7-day dosing period, 2% of the applied radiolabel was found in expired air. The highest concentration of radioactive residues was found in liver (8.8 mg/kg), while kidney contained 0.93 mg/kg, milk 0.49 mg/kg, muscle 0.095 mg/kg and fat 0.051 mg/kg. The total recovery of the administered dose was 88%.

The majority of the radiolabel in liver and kidney remained in the post-extraction solids, and enzyme and acid digests of these solids co-chromatographed with amino acid standards. Radiolabelled amino acids can be formed by hydrolysis of ethoprophos to ethanol and subsequently to acetaldehyde, acetate, acetyl coenzyme A and amino acids (tricarboxylic acid cycle). Thin-layer chromatography of the polar liver extract showed three radioactive spots, representing 1.1%, 1.4% and 0.45 % of the total radioactive residues (TRR). The first spot co-chromatographed with *O*-ethyl-*S*-propyl phosphorothioate and ethyl phosphate, while the other two spots did not co-chromatograph with any of the reference markers used. The parent compound was not found. Radioactivity in the kidney extract was not characterized.

Most of the radioactivity in muscle was released from the post-extracted solids by acid or base treatment, while that in fat was distributed approximately equally between the extracted and unextracted fractions. The radiolabel in the post-extracted solids could be released by enzyme digestion. No further characterization of muscle or fat fractions was attempted owing to the low levels of radioactivity.

The residue levels in milk reached a plateau on the first day of treatment, with an average level over days 0–7 of 0.49 mg/kg (maximum, 0.68 mg/kg). The radioactivity in the chloroform extract of milk (55% TRR) co-chromatographed with standards of the fatty acids palmitic acid, oleic acid and stearic acid, which were poorly resolved. Radiolabelled fatty acids can be formed by hydrolysis of ethoprophos to ethanol. No parent compound was found.

When laying hens were given feed containing ^{14}C-ethoprophos at a concentration of 2.1 ppm for 7 days, 48% of the total administered radioactivity was recovered in excreta (including the gastrointestinal tract and contents), 1.0% in egg whites, 9.3% in egg yolks, 3.6% in expired volatiles and 3.2% in tissues and blood. The total recovery of the administered radioactivity was 64%. The highest concentration of radioactive residues was found in liver, at 1.2 mg/kg, followed by kidney at 0.42 mg/kg; 0.069 mg/kg radioactive residue was found in fat and 0.010 mg/kg in muscle. A maximum residue level of 0.64 mg/kg was found in egg yolk and 0.029 mg/kg in egg white.

As in goats, most of the radioactivity in liver and kidney remained in the post-extracted solids. Enzyme and acid digests of these solids co-chromatographed with amino acid standards. Thin-layer chromatography of the polar extract of liver contained three radioactive zones, representing 1.9%, 0.95% and 2.0% TRR. The first zone contained *O*-ethyl-*S*-propyl phosphorothioate or ethyl phosphate, the second zone did not co-chromatograph with any of the reference markers used, and the third zone co-chromatographed with *O*-ethyl-*O*-methyl-*S*-propyl phosphorothioate or *O*-ethyl-*S*-methyl-*S*-propyl phosphorodithioate. No parent compound was found.

Most of the radioactivity in muscle was released from the post-extracted solids by acid or base treatment, while that in fat was present mainly in the organic extract. The radiolabel could be released from the post-extracted solids by enzyme digestion. No further characterization of muscle or fat fractions was attempted owing to the low levels of radioactivity.

The radioactive residue level reached a plateau in egg whites on the third day of treatment, but no plateau was reached in egg yolks during the 7-day treatment. The average concentrations found were 0.021 mg/kg in egg whites (average over days 3–7; maximum, 0.029 mg/kg) and 0.30 mg/kg in egg yolks (average over days 0–7; maximum, 0.64 mg/kg). In egg yolks, 84% was extractable in hexane and 11% in chloroform. The hexane fraction of egg yolks co-chromatographed with the fatty acids palmitic, myristic, oleic and stearic acid, which were poorly resolved. No parent compound was found.

The metabolism of ethoprophos in laboratory animals was similar to that in farm animals.

Plants

The Meeting received information on the fate of ethoprophos labelled with ^{14}C in the ethyl or the propyl group after soil treatment before planting of pulses or oil seeds (French beans), cereals (maize), root and tuber vegetables (potatoes) and leafy crops (cabbage).

In a greenhouse, *French bean* bedding plants (variety Contender) were planted in clay pots filled with steam-sterilized soil treated with [α-^{14}C-ethyl]- or [α-^{14}C-propyl]ethoprophos. The compound was applied as a granule formulation at 14.3 mg ai/kg soil. The plants were grown for 63 days and were sampled at weekly intervals from day 7 onwards. The residue levels in soil extracts decreased with time, while the total residues in the bean plants increased with time, from 2.2% of the total applied radioactivity to 13% with the ethyl label and from 0.58% to 8.3% with the propyl label between days 7 and 63. Mainly extractable residues were found early in the study, while unextracted residues predominated (> 57%) from day 21 onwards. In mthanol:water extracts of the bean plants, the main compounds were *O*-ethyl-*S*-propyl phosphorothioate and ethyl phosphate. In dichloromethane extracts, the main compounds were the parent (maximum, 13%) and

ethyl propyl sulfide (maximum, 9.2%). The amount of parent compound decreased with time after application and contributed < 10% from day 28 onwards. Minor amounts of propyl disulfide, ethyl propyl sulfoxide (plus methyl propyl sulfoxide) and ethyl propyl sulfone (plus methyl propyl sulfone) were present at some sampling times.

In a greenhouse, *maize seeds* were planted in clay pots filled with steam-sterilized soil treated with [α-^{14}C-ethyl]- or [β-^{14}C-propyl]ethoprophos. Ethoprophos was applied as a granule formulation at 14.3 mg ai/kg soil. Maize plants were grown for 100 days and were sampled at 10-day intervals from day 18 onwards. The residue levels in soil extracts were constant, while those in maize plants increased from 0.96% of the applied radiolabel to 74% for the ethyl label and from 0.26% to 34% with the propyl label between days 18 and 100. Most of the extractable residues in the maize plants were found early in the study, while unextracted residues predominated (> 67%) from day 38 onwards. In methanol:water extracts of the maize plants, the main compounds were *O*-ethyl-*S*-propyl phosphorothioate and ethyl phosphate. In dichloromethane extracts, the main compounds were the parent (maximum, 40% TRR) and ethyl propyl sulfide (maximum, 7.6% TRR). The amount of parent compound decreased over time and contributed < 10% from day 48 onwards. Small amounts of propyl disulfide, ethyl propyl sulfoxide (plus methyl propyl sulfoxide) and ethyl propyl sulfone (plus methyl propyl sulfone) were present at some sampling times. The ethyl label was found mainly on ethyl phosphate.

In a second study on *maize*, silt loam was treated with [1-ethyl-^{14}C]ethoprophos (emulsifiable concentrate formulation) at a rate of 13 kg ai/ha in plastic-lined wooden boxes placed in the field. The actual concentration in the soil was 10 mg ai/kg. The application mixture was incorporated to a depth of 10 cm. Sweet maize seeds (variety Early extra sweet) were planted 3 days after soil treatment and were sampled at the green forage stage (soil, whole plant), at maturity (shanks, husks, silks, grain, empty cobs) and at the fodder stage (soil, senescent stalks without cobs). The TRR was 2.2 mg/kg in maize forage, 0.27 mg/kg in maize cobs, 0.25 mg/kg in grain, 0.79 mg/kg in husks and 1.4 mg/kg in fodder. Most of the TRR in these matrices was solvent-extractable. Acid or base hydrolysis released a further 6–14% TRR from forage, grain, cobs and fodder; however, 13% TRR in forage and 40% TRR in grain, cobs and fodder remained unextracted. Ethyl phosphate was the main metabolite detected in green forage, grain and fodder (10%, 35% and 8.9%, respectively). Parent ethoprophos and its metabolite *O*-ethyl-*S*-propyl phosphorothioate were also present in small amounts in forage and fodder. The extracts of forage and fodder further tentatively contained < 1% each of *O*-ethyl-*O*-methyl-*S*-propyl phosphorothioate and *O*-ethyl-*S*-methyl-*S*-propyl phosphorodithioate.

Silt loam was treated with [1-ethyl-^{14}C]ethoprophos (emulsifiable concentrate formulation) at a rate of 13 kg ai/ha in plastic-lined wooden boxes placed in the field. The actual concentration in the soil was 15 mg ai/kg. The mixture was incorporated to a depth of 10 cm. *Potatoes* (variety Kenebeck) were planted 3 days after soil treatment, and soil and plants were sampled at the 'new potato' stage and at maturity. The TRR was 0.24–0.54 mg/kg in tubers and 1.1–3.8 mg/kg in vines. Most of the TRR was extracted with aqueous methanol. Acid or base hydrolysis solubilized a further 17% of the radioactivity in the vines, while 31% TRR in vines and 23% TRR in tubers remained unextracted. In both vines and the tubers, the main metabolite was ethylphosphate (12% and 38% TRR, respectively). Parent ethoprophos, *O*-ethyl-*S*-propyl phosphorothioate and *O*-ethyl-*O*-methyl-*S*-propyl phosphorothioate (the latter tentatively) were present in small amounts in the vines but were not detected in tubers.

To determine the nature of the unextracted residues in potatoes, sandy loam was treated with [1-ethyl-^{14}C]ethoprophos (emulsifiable concentrate formulation) at a dose rate of 13 kg ai/ha in plastic-lined wooden boxes placed in the field. The mixture was incorporated to a depth of 10 cm; the actual concentration in the soil was 5.9 mg ai/kg. Potatoes (minituber variety Kennebec) were planted 3 days after soil treatment and were harvested 118 days (new potato tubers) or 167 days after treatment (mature potatoes). The TRR and extractability were comparable with those in the first study. A sequential extraction scheme showed that 41% TRR in new potato tubers consisted of solvent-extractable residues, 11% TRR was present in starch, 8.5% TRR in protein, 4.4% TRR in pectin, 3.7% TRR in lignin, 8.2% in hemicellulose and 8.8% TRR in cellulose. The unextracted radioactive residue associated with starch was shown to be ^{14}C-glucose.

Silt loam was treated with [1-ethyl-^{14}C]ethoprophos (emulsifiable concentrate) at a rate of 11 kg ai/ha in plastic-lined wooden boxes placed in the field. The actual concentration in the soil was 7.6 mg ai/kg. The mixture was incorporated to a depth of 7.6 cm. *Cabbage* bedding plants (variety Stonehead) were planted 2 days after soil treatment, and soil and plants were sampled at the leafy stage and at maturity. The TRR was 16 mg/kg in leafy cabbage and 3.1 mg/kg in head cabbage. Most of the TRR was extractable, and ethylphosphate was the main metabolite found in both leafy and head cabbage extracts (21% and 24%, respectively). Ethoprophos and *O*-ethyl-*S*-propyl phosphorothioate were present at 0.3–4% in both types of cabbage, and *O*-ethyl-*O*-methyl-*S*-propyl phosphorothioate and *O*-ethyl-*S*-methyl-*S*-propyl phosphorodithioate were tentatively identified at 0.4–1.7%. A supplementary characterization study showed that most of the unextractable radioactive residues in cabbage were incorporated into plant structural components, mainly in lignin (38%).

The metabolism of ethoprophos in plants appears to be qualitatively similar to that in animals; however, the toxicologically significant metabolites *O*-ethyl-*O*-methyl-*S*-propyl phosphorothioate and *O*-ethyl-*S*-methyl-*S*-propyl phosphorodithioate were tentatively identified in hen liver, maize green forage and fodder, potato vines and cabbage heads, but not in rats or goats.

Environmental fate

Soil

The Meeting received information on aerobic degradation in soil and studies on rotational crops (confined and field).

The route and rate of degradation of [1-^{14}C-propyl]ethoprophos was investigated in three studies in different soils under aerobic conditions in the dark at 10 °C and 20–25 °C. On the basis of an application rate of 10.5 kg ai/ha in the field, the test substance was applied at a nominal concentration of 10–14 mg ai/kg dry weight of soil. The main degradation product in soil under aerobic conditions was $^{14}CO_2$, which accounted for 54–60% of the applied radioactivity after 90 days at 22–25 °C and 43–50% after 110 days at 10 °C. Most of the radioactivity in the extracts was associated with unchanged ethoprophos, representing 90–94% on day 0 and 7.2–9.4% on day 90 at 22 °C. One major metabolite was identified as *O*-ethyl-*S*-propyl phosphorothioate (maximum, 3.6–7.9% of the applied radioactivity); two minor metabolites were *O*-ethyl-*O*-methyl-*S*-propyl phosphorothioate (maximum, 0.7%) and *O*-ethyl-*S*-methyl-*S*-propyl phosphorodithioate (maximum, 0.3%). The half-life of ethoprophos at ambient temperature was 10–25 days, while that at 10 °C was two to three times longer.

In a study of a confined rotational crop, a sandy loam soil was sprayed with [1-ethyl-^{14}C]ethoprophos as an emulsifiable concentrate at a rate equivalent to 13.4 kg ai/ha and thus incorporated into the top 10 cm of soil. The soil was placed in boxes inside a screened enclosure, which was heated and covered with plastic during the winter months. The soil was left fallow for 30–365 days after treatment. *Wheat* (variety Anza), *spinach* (variety Polka) and *radish* (variety Cherry Belle) were each planted 30, 120 and 365 days after treatment, and immature and mature crops were harvested at each planting interval. Soil samples were collected at application, at each planting and at each harvest. The TRR in rotational crops was generally much lower after a plant-back interval of 365 days than that after a plant-back interval of 30 days; e.g. mature wheat straw contained a radioactive residue level of 47 mg/kg after a plant-back interval of 30 days and 0.65 mg/kg after a plant-back interval of 365 days. Crops harvested when immature showed similar extractability, while the total extractability from mature wheat was generally lower than that from mature spinach or radish. Some of the remaining solids could be hydrolysed by acid or alkaline treatment; however, 1.9–42% TRR remained unextractable, with the highest portion in wheat chaff 365 days after treatment.

Parent ethoprophos was present in extracts of immature and early maturing crops (radish) at both the 120-day and the 30-day plant-back interval. The parent compound was not found in mature wheat or spinach at the 120-day plant-back interval or in any crop at the 365-day plant-back interval. The main component in each crop matrix was ethyl phosphate, but *O*-ethyl-*S*-propyl phosphorothioate was also found. Many

unidentified compounds were found, some at levels > 10% TRR or 0.05 mg/kg. After hydrolysis of immature spinach extracts from the 120-day plant-back interval, two of the unknown compounds (12% and 8.5% TRR) were found to be conjugates of ethyl phosphate. The levels of the remaining unknown compounds were not sufficient for structural identification. The main component in acid and base hydrolysates of the crops was the parent compound (0.13 mg/kg in mature wheat straw at the 120 day plant-back interval). Most of the remaining radiocarbon was associated with *O*-ethyl-*O*-methyl-*S*-propyl phosphorothioate (0.02 mg/kg). Unextractable residues were characterized in mature wheat straw. General incorporation into cellular components was 40% TRR in extractable residues, 7.7% TRR in starch, 1.5% TRR in protein, 1.9% TRR in pectin, 11% TRR in lignin, 14% TRR in hemi-cellulose, 10% TRR in cellulose and 22% TRR in insoluble residue; the overall recovery was 105%.

In a field study of rotational crops, unlabelled ethoprophos was applied once as an emulsifiable concentrate to sandy loam before planting at an actual rate of 13.5 kg ai/ha. The rotational crops were root vegetables (radish roots), leafy crops (radish leaves, red leaf lettuce, collards), cereals (forage, grain and straw from winter wheat, spring wheat and sorghum) and pulses or oil seeds (forage, grain and straw from cow peas, wando peas, green peas and soya beans and mustard forage). The crops were planted 1, 4, 8 and 12 months after application at two sites. Sample extracts were analysed for ethoprophos and *O*-ethyl-*S*-propyl phosphorothioate by gas chromatography with flame photometry detection. The residue levels were below the LOQ of 0.01 mg/kg in all treated samples from both test sites, except in radish root and radish leaves. The highest level of parent compound found in radish root was in samples taken at the plant-back interval of 31 days with harvest 32 days after planting, at 0.023 mg/kg; in the same samples, the highest level of *O*-ethyl-*S*-propyl phosphorothioate was 0.039 mg/kg. The presence of ethoprophos and *O*-ethyl-*S*-propyl phosphorothioate in radish root and tops was confirmed by gas chromatography–mass spectrometry but at levels at least an order of magnitude lower than those measured by gas chromatography with flame photometry detection.

Methods of analysis

The Meeting received information on enforcement and monitoring methods for the determination of ethoprophos in foodstuffs of plant and animal origin and on the analytical methods used in studies of rotational crops, supervised trials and studies of storage stability, processing and monitoring for determination of ethoprophos and the metabolite *O*-ethyl-*S*-propyl phosphorothioate in foodstuffs of plant origin.

Five enforcement methods were submitted. Ethoprophos can be determined by the Dutch multi-residue method MRM-1 (validated for non-fatty matrices, quantification by gas chromatography with nitrogen–phosphorus or mass spectrometry detection; LOQ, 0.01–0.05 mg/kg) and with the German multi-residue methods DFG-S8 (validated for fruits and vegetables, quantification by gas chromatography with electron capture or alkali flame ionization detection; LOQ, 0.02 mg/kg) and DFG-S19 (validated for foodstuffs of plant and animal origin, quantification with gas chromatography with flame photometry, mass spectrometry or PFP detection, depending on the module used; LOQ, 0.01 mg/kg). Ethoprophos could not be determined by the multi-residue protocols of the US Food and Drug Administration. Method AR 271-01 was proposed as an enforcement method for determination of ethoprophos in milk, egg, meat, fat and liver and is considered valid in the range 0.01–0.1 mg/kg (quantification by gas chromatography with flame photometric detection).

All the methods used in the various studies were based on extraction with hexane, methanol, acetone, ethyl acetate, acetonitrile or petroleum ether:acetone, followed by a clean-up and determination by gas chromatography with MC, flame photometry, nitrogen–phosphorus, flame photometric, mass spectrometry, electron capture or tandem mass spectrometry detection. The LOQs ranged from 0.005 mg/kg to 0.05 mg/kg, 0.01 mg/kg being the most common.

Stability of residues in stored analytical samples

The Meeting received data on the stability of residues in crops with a high water content (pineapple, broccoli, cabbage, potato, sweet potato, tomato), in dry crops with starch and protein (maize), in dry crops with fat or oil, starch and protein (peanut), in special cases (sugar-cane, tobacco (green, cured)), in processed commodities (pineapple juice, peanut crude oil, peanut refined oil, maize crude oil, maize refined oil, maize starch, refined cane sugar) and in feed remains (pineapple bran, pineapple feed pulp, peanut hulls, peanut meal, peanut vine, dry peanut hay, maize meal, maize forage, maize fodder, maize grain dust, sugar-cane molasses) stored frozen. Crops with a high water and a high acid content (citrus fruits) were not investigated.

The freezer storage stability of ethoprophos depends on the matrix. Parent ethoprophos was found to be stable at –20 °C for a maximum of 9 months in broccoli and pineapple fruit, but for at least 9–12 months in other crops with a high water content (cabbage, sweet potato, potato, peanut vine, maize forage). In another study, the parent compound was stable for at least 19 months in tomato and potato. It was stable for at least 12 months in dry crops with starch and protein (maize grain) and for a maximum of 12 months in tobacco and peanut nutmeat. Ethoprophos was not stable in peanut hay. Ethoprophos and *O*-ethyl-*S*-propyl phosphorothioate were stable at –20 °C for at least 15 months in sugar-cane and its processed commodities. No general conclusions can be drawn for processed commodities and remains.

The results showed that, in general, *O*-ethyl-*S*-propyl phosphorothioate is not stable at –20 °C for < 1 month, although longer storage times are possible for some crops.

Definition of the residue

Ethoprophos is metabolized rapidly in rats and livestock and was not found in edible tissues. In metabolism studies with labelled compounds, most of the radioactivity was found to be incorporated into natural components, such as fatty acids and amino acids. Low levels of *O*-ethyl-*S*-propyl phosphorothioate or ethyl phosphate were identified in goat and hen liver, and *O*-ethyl-*O*-methyl-*S*-propyl phosphorothioate and *O*-ethyl-*S*-methyl-*S*-propyl phosphorodithioate were tentatively identified in hen liver at low levels. The main route of metabolism in livestock is hydrolysis of the P–S bond, yielding *O*-ethyl-*S*-propyl phosphorothioate and propyl sulfide, with hydrolysis of *O*-ethyl-*S*-propyl phosphorothioate to ethyl phosphate; the ethyl moiety can be split off and become incorporated into natural components like amino acids and fatty acids.

Although ethoprophos is not found in edible tissues, the Meeting agreed that, in the absence of a better indicator, the parent should be considered the compound of interest in animal commodities, both for enforcement and for dietary risk assessment. The log octanol–water partition coefficient (P_{ow}) of 2.99 indicates that the residue is not fat-soluble.

The main route of metabolism is similar in plant and animals, although other routes differ. Propylsulfide in plants can react with a parent molecule to yield ethylpropyl sulfide and propyl disulfide, while propylsulfide is methylated in rats.

In edible plant parts (mature maize grain, potato and cabbage), the major residue is ethyl phosphate, which is considered not to be toxicologically relevant and is thus not included in the residue definition for dietary risk assessment. Furthermore, ethyl phosphate is formed by several other organophosphate pesticides (e.g. parathion) and can therefore not be used for enforcement purposes. Ethylpropyl sulfide, which was found in amounts similar to the parent compound in French beans, was not found in rats; however, it behaves similarly to methylpropyl sulfide, which was detected in rats. It is not expected that this metabolite will be toxicologically significant.

Possible candidates for the residue definition are the parent, *O*-ethyl-*S*-propyl phosphorothioate, *O*-ethyl-*O*-methyl-*S*-propyl phosphorothioate and *O*-ethyl-*S*-methyl-*S*-propyl phosphorodithioate.

As reported by the 1999 JMPR, *O*-ethyl-*S*-propyl phosphorothioate, *O*-ethyl-*O*-methyl-*S*-propyl phosphorothioate and *O*-ethyl-*S*-methyl-*S*-propyl phosphorodithioate were tested for toxicity and for their ability to inhibit cholinesterase activity in female rats given single oral doses. The last two metabolites had approximately the same cholinergic toxicity as the parent compound, while the first was less toxic than the parent. As *O*-ethyl-*S*-propyl phosphorothioate is less toxic than the parent compound in rats, is rapidly converted to ethyl phosphate and is not found in mature maize grain, potato tubers or mature cabbage heads, the Meeting decided not to include this metabolite in either residue definition. The two remaining metabolites were not detected in mature maize grain or potato tubers but were tentatively identified in mature cabbage heads. These metabolites were also tentatively identified in animal feedstuffs (maize forage and fodder), although they were not identified in rats. It is possible that the molecules are artefacts formed during extraction with methanol. In view of the low levels found in the metabolism studies, the Meeting decided not to include *O*-ethyl-*O*-methyl-*S*-propyl phosphorothioate or *O*-ethyl-*S*-methyl-*S*-propyl phosphorodithioate in either residue definition.

Definition of the residue for compliance with MRLs and for estimating dietary intake: ethoprophos, for both plant and animal commodities.

Results of supervised residue trials on crops

Supervised trials were available for stawberry, banana, cucumber, melon, pepper, tomato, potato and sugar-cane, but none were provided for the remaining commodities that currently have a Codex level (CXL). Therefore, the Meeting decided to withdraw the current recommendations for beetroot, cabbage head, gherkin, grape, lettuce head, maize, maize fodder, onion bulb, peanut, peanut fodder, pea (pods and succulent or immature seeds), pineapple, pineapple fodder, pineapple forage, soya bean and soya bean fodder.

Berries and other small fruit

Strawberry

Ethoprophos is registered in Austria and Spain for use on strawberry with granule and emulsifiable concentrate formulations at the pre-planting or planting stages. Four trials on strawberry were conducted in Italy in 1996–98 at two sites. Application was by drip irrigation with emulsifiable concentrates throughout the growing season but before the fruits had formed. Although drip irrigation is usually the critical GAP and no residues were detected in the trials, the application rate stated on the available labels was 6 kg ai/ha, while that used in the trials was only 1.8–3.5 kg ai/ha: None of the trials was conducted according to GAP.

The Meeting agreed that the available data were insufficient to estimate a maximum residue level for ethoprophos in strawberry.

Assorted tropical and sub-tropical fruits minus inedible peel

Banana

Trials on bananas were reported to the Meeting from Brazil (GAP: 3.0 g ai/tree, two applications, 3-day PHI), Costa Rica (GAP for Central America: 2.9–3.0 g ai/tree, one application, 30-day PHI), Côte d'Ivoire (GAP: 4.0–8.0 g ai/tree, two to three applications, PHI not specified) and the Phillipines (GAP: 4.0–5.0 g ai/tree, two applications, PHI not specified).

In one trial in the Côte d'Ivoire, the residue levels in banana were below the LOQ (< 0.02 mg/kg).

None of the 20 Costa Rican trials was conducted according to GAP in Central America, as 15 involved overdosing, 14 involved more than one treatment or residues were measured at a PHI of < 30 days. As residue levels above the LOQ were not measured in any of the trials, the Meeting decided that the six trials with a PHI of ≤ 30 days could be considered for estimating the MRL. The residue levels in banana were < 0.02 mg/kg in all six trials.

The two trials in Brazil did not comply to GAP (overdosing, with only one application), and no residues were found. The five trials in the Philippines were also not conducted according to GAP (underdosing). In two of the trials, residue levels of 0.0065 mg/kg and 0.013 mg/kg were found in pulp.

The Meeting decided to combine the results of the trial in the Côte d'Ivoire and of the six trials in Costa Rica to estimate the maximum residue level for banana. The levels in all seven trials were < 0.02 mg/kg. The Meeting agreed to withdraw the previously recommended maximum residue level for banana of 0.02* mg/kg and to replaced it by a recommendation of 0.02 mg/kg. The Meeting estimated an STMR and a highest residue level for ethoprophos in banana of 0.02 mg/kg.

Fruiting vegetables, cucurbits

Cucumber

Indoor trials on cucumber in which soil received overall treatment before planting or at transplanting with a granule formulation were reported from Canada and The Netherlands. No GAP was reported for either country. In the five Canadian trials, conducted according to US GAP (12–15 kg ai/ha), the residue levels were < 0.01 mg/kg. In four of the six Dutch trials conducted according to Italian, Portuguese or Spanish GAP (3–10 kg ai/ha, 30–60-day PHI), the residue levels in cucumber were < 0.01 mg/kg.

Seventeen outdoor trials on cucumber, with overall soil treatment with a granule formulation before planting or at transplanting, were reported from the USA. In the five conducted according to US GAP, the residue levels were < 0.005 and < 0.02 (four) mg/kg.

Nine indoor trials on cucumber in which soil received spray treatment with emulsifiable concentrate formulations pre- and post-planting were reported from southern Europe (France, Greece, Italy, Portugal and Spain). The trials were evaluated against Spanish GAP (6.0 kg ai/ha, one application, 60-day PHI). All the trials involved overdosing. In one trial in which ethoprophos was applied after planting, an actual residue level of 0.0090 mg/kg was found at 21 days PHI; however, all trials at the correct PHI showed residue levels of < 0.005 mg/kg.

Ten outdoor trials on cucumber in which soil received spray treatment with emulsifiable concentrate formulations before or at planting were reported from the USA. All the trials were conducted according to US GAP, but the results of one trial was excluded from evaluation as the samples were purportedly mislabelled. The residue levels were < 0.01 (nine) mg/kg.

Eight indoor trials on cucumber in which soil was treated with emulsifiable concentrate formulations by drip irrigation after planting or transplanting were reported from southern Europe (France, Italy and Spain). The trials complied with Spanish GAP (0.6 kg ai/ha, 1–10 applications, maximum total of 6 kg ai/ha, 60-day PHI), except that the latest PHI for which residue levels were reported was 14–15 days. On these days, the residue levels were < 0.005 (six), < 0.01 and 0.012 mg/kg.

The Meeting concluded that, irrespective of the method of application and the site (indoors or outdoors), the residue levels would not be expected to exceed the enforcement LOQ of 0.01 mg/kg. The Meeting agreed to withdraw the previously recommended maximum residue level for cucumber of 0.02* mg/kg and to replace it by a recommendation of 0.01 mg/kg. The Meeting estimated an STMR and a highest residue level for ethoprophos in cucumber of 0.01 mg/kg.

Melon

Nine outdoor trials on melon involving overall soil treatment with granule formulations before, at and after planting were reported from southern Europe (France, Italy and Spain). The trials were compared with Portuguese GAP (8 kg ai/ha, 56-day PHI). The residue levels were < 0.005 (seven), 0.0055 and 0.010 mg/kg. The levels in melon pulp (edible portion) were $\underline{< 0.005}$ (eight) and 0.012 mg/kg.

Eight outdoor trials on melon involving post-transplanting drip irrigation with emulsifiable concentrate formulations were reported from southern Europe (France, Italy and Spain); however, there is no GAP for drip irrigation on melon in southern Europe.

On the basis of the trials of overall soil treatment, the Meeting agreed to withdraw the previously recommended maximum residue level for melon, except watermelon, of 0.02* mg/kg and to replace it by a recommendation of 0.02 mg/kg. The Meeting estimated an STMR of 0.005 mg/kg and a highest residue level of 0.012 mg/kg for ethoprophos in the edible portion of melon.

Fruiting vegetables other than cucurbits

Pepper

Eleven indoor trials on sweet pepper involving overall soil treatment with granule formulations before or at planting were reported from southern Europe (France, Greece, Italy and Spain). The trials were evaluated against Spanish GAP (6.0–8.0 kg ai/ha, one application, 60-day PHI). The residue levels were: < 0.005 (nine), 0.007 and 0.027 mg/kg.

A further 12 trials from southern Europe on green and sweet pepper involved application of ethoprophos as an emulsifiable concentrate formulation by post-planting drip irrigation. Ten could be evaluated against Italian GAP (1.7–3.5 kg ai/ha, three to four applications, 30-day PHI). The residue levels were: < 0.005 (four), < 0.01 (two), 0.006, 0.0068, 0.007 and 0.044 mg/kg. Two trials on green pepper yielded higher residue levels, but the latest sampling was at a PHI of 14–15 days.

The Meeting decided to combine the results of all the trials, yielding residue levels, in ranked order, of: < 0.005 (13), < 0.01 (two), 0.006, 0.0068, 0.007 (two), 0.027 and 0.044 mg/kg.

The Meeting agreed to withdraw the previously recommended maximum residue level for pepper of 0.02* mg/kg and to replace it by a recommendation of 0.05 mg/kg for sweet pepper. The Meeting estimated an STMR of 0.005 and a highest residue level of 0.044 mg/kg for ethoprophos on sweet peppers.

Tomato

Six trials on tomato fruit involving overall soil treatment with granule formulations before or after planting were reported from Brazil (two, no GAP), The Netherlands (indoors) and the USA (three, no GAP). The dose used in the Dutch trial was twice that of Spanish GAP, but no residue level above the LOQ was found (< 0.01 mg/kg).

In 20 trials in southern Europe on tomato fruit, ethoprophos was applied as an emulsifiable concentrate formulation by post-planting drip irrigation or band spraying. The 13 trials conducted according to Italian GAP (1.7–3.5 kg ai/ha, three to four applications, total maximum of 8.6 kg ai/ha, 30-day PHI) or Spanish GAP (0.8–2.0 kg ai/ha, several applications, total maximum of 6 kg ai/ha, 60-day PHI) yielded residue levels of < 0.005 (four) and < 0.01 (nine) mg/kg.

On the basis of the trials conducted in southern Europe, the Meeting estimated a maximum residue level of 0.01* mg/kg, an STMR of 0.005 mg/kg and a highest residue level of 0.01 mg/kg for ethoprophos on tomato.

Root and tuber vegetables

Potato

The results of 62 trials were available in which ethoprophos was applied to potatoes after overall soil treatment or band application with granule formulations before or at planting. Ware potatoes are normally harvested within 90–120 days after application at or a few days before planting. Early maturing potatoes 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. On most labels, no PHI is indicated, as treatment is made before or at planting, and the potatoes are harvested when they are ready. In

trials in which the time of maturity of the potataoes was not indicated, the residue level measured at the shortest PHI was used for evaluation.

Three Dutch trials were evaluated against Dutch GAP (overall application, pre-planting: 4–10 kg ai/ha; band application at planting, 2.5 kg ai/ha), all yielding < 0.02 mg/kg. In 19 German trials evaluated against Dutch GAP, the residue levels were: < 0.01 (10), 0.0076, 0.012 (two), 0.014, 0.016, 0.017 (two), 0.02 and 0.03 mg/kg.

Three of four trials in the United Kingdom in 1995 suffered from abnormal weather conditions, resulting in retarded growth of the tubers. As residues were found in control samples (up to 0.096 mg/kg in one trial), these trials were excluded from evaluation. The remaining 14 trials in the United Kingdom could not be evaluated against that country's GAP (overall application, pre-planting: 6.6–11 kg ai/ha; band application pre-planting, 4.0–6.0 kg ai/ha; 56-day PHI) because the PHI was longer. Eleven of the trials could be evaluated against Dutch GAP, yielding residue levels of: < 0.005 (seven), 0.005 and < 0.01 (three) mg/kg.

Five French trials could be compared to French GAP (overall application, pre-planting: 6–10 kg ai/ha), yielding residue levels of: < 0.005 (two), < 0.01 (two) and 0.011 mg/kg.

One Spanish trial was evaluated against Spanish GAP (overall application, pre-planting: 6–8 kg ai/ha), yielding a residue level of < 0.01 mg/kg.

Two Greek trials could not be compared with Greek GAP (overall application, pre- or at planting: 8–10 kg ai/ha; 60-day PHI) because of the specified PHI. When they were evaluated against Spanish GAP, the residue levels were < 0.02 mg/kg in both.

Fourteen trials in the USA with a granule formulation were compared with US GAP (pre-planting until prior to crop emergence: overall application, 4.5–13 kg ai/ha; band application, 10 kg ai/treated ha = 3.4 kg ai/ha). In the 12 that complied with GAP, the residue levels were: < 0.01 and < 0.02 (11) mg/kg. In three trials in the USA with an emulsifiable concentrate formulation, which complied with US GAP, the residue levels were < 0.01 (two) and < 0.02 mg/kg.

The Meeting decided to combine the residue levels from all the studies, yielding, in ranked order: < 0.005 (nine), 0.005, $\underline{\leq 0.01}$ (19), < 0.02 (17), 0.0076, 0.011, 0.012 (two), 0.014, 0.016, 0.017 (two), 0.02 and 0.03 mg/kg. The Meeting estimated a maximum residue level of 0.05 mg/kg, an STMR of 0.01 mg/kg and a highest residue level of 0.03 mg/kg.

For assessing the risk to consumers of short-term intake, the possible residue level in single units is more important than the average residue level in a lot, which is the residue level in a representative composite sample. The concept of a variability factor was introduced to describe the relationship between the level in a high-residue unit and the typical or average level in the whole batch. The concept was refined to a more precise definition: the residue level in the 97.5th percentile unit divided by the mean residue level for the lot. There is a relation between the number of data from field trials, the proportion (percentile) of the population covered and the confidence level. The 2003 Meeting determined a method for calculating the variability factor on the basis of probabilities of random sampling from a population, making no assumptions as to the type of distribution.

In four of the trials on potato, residue levels were measured in individual units. Two were among the trials conducted in the United Kingdom in 1995 that were considered unreliable (see above). In a trial in France in 2001, 48 of 50 samples had undetectable residues, making the result unsuitable for calculation of a variability factor. In the fourth trial, conducted in the United Kingdom in 1999, 88 of 100 samples contained finite residue levels, so that a variability factor could be calculated. Applying the method referred to above to the 100 individual values available and using the 97.5th percentile in the calculation, the best estimate of the variability factor is 4.1 when the 12 data points below the LOQ are assumed to be at the LOQ, and 4.2 when those values are assumed to be 0. The 95% confidence limits on these estimates are 2.63 – > 5.6 and 2.75 – > 5.6, respectively. The Meeting decided to use the default variability factor of 3 in calculating the short-term

intake of ethoprophos, as this value was within the confidence interval of the calculated factor, and the default factor was based on a much larger database.

Sweet potato

The Meeting received the results of four trials on sweet potato in the USA, three of which complied to US GAP (3.3–4.4 kg ai/ha). The residue levels were < 0.01 (two) and 0.014 mg/kg. Three trials is insufficient for recommending a maximum residue level, but the Meeting decided to extrapolate the data on potato to sweet potato, because GAP is similar for the two crops.

On the basis of the trials on potato, the Meeting estimated a maximum residue level of 0.05 mg/kg, an STMR of 0.01 mg/kg and a highest residue level of 0.03 mg/kg for sweet potato.

Grasses for sugar or syrup production

Sugar-cane

Fourteen trials were available in which ethoprophos in granule formulations was applied to sugar-cane in the open furrow at planting. Of these, nine trials from the USA complied to US GAP (band application: 2.2–4.6 kg ai/ha; 10–27 kg ai/treated ha). In all cases, the residue level was below the LOQ (< 0.02 mg/kg). Three trials in India were evaluated against Indonesian GAP (band application, pre-planting: 1.0–2.0 kg ai/ha), yielding residue levels of < 0.01 mg/kg. The two trials in Brazil with application after planting had no matching GAP.

The Meeting decided to combine the results of the trials in India and the USA, yielding residue levels, in ranked order, of: < 0.01 (three) and < 0.02 (nine) mg/kg. The Meeting estimated a maximum residue level of 0.02 mg/kg, an STMR of 0.02 mg/kg and a highest residue levelof 0.02 mg/kg for ethoprophos on sugar-cane.

Miscellaneous fodder and forage crops (group 052)

Sugar-cane leaves

In the three trials on sugar-cane in India, the residue levels in leaves were < 0.01 mg/kg. In three of the trials in the USA, the residue levels in leaves were < 0.02 mg/kg.

The Meeting estimated an STMR and a highest residue level of 0.02 mg/kg for ethoprophos on sugar-cane forage.

Fate of residues during processing

The Meeting received information on the fate of residues during commercial storage of bananas. After successive storage at 10 °C and 20 °C for fruit ripening, the residue level remained within 80–130% of the original level.

The Meeting received information on the fate of incurred residues of ethoprophos during the processing of potatoes and sugar-cane.

In the first study on potato, the raw agricultural commodity and the processed fractions (washed tubers, wash water, peeled tuber, wet peel, dry peel, flakes, chips) did not contain residues (< 0.01 mg/kg ethoprophos and < 0.01 mg/kg *O*-ethyl-*S*-propyl phosphorothioate). In the second study, no residues were found (< 0.005 mg/kg ethoprophos) in the raw agricultural commodity or in processed fractions (peeled and baked potato). Nevertheless, residues were found in potato peel, at 0.022 and 0.062 mg/kg (average, 0.042 mg/kg) in variety Maris Peer and 0.009 and 0.011 mg/kg (average, 0.010 mg/kg) in variety Desiree. As

the raw agricultural commodity did not contain residues, no processing factors for potato could be calculated; however, it can be concluded tentatively that the residue concentrates in peel and not in potato pulp.

After treatment with ethoprophos at planting, a 2-t batch of sugar-cane was processed into bagasse, mixed juice, clarified juice, mud, syrup, raw sugar and molasses according to commercial practices in a pilot plant. No quantifiable residues (< 0.02 mg/kg) were found in the raw agricultural commodity or its processed fractions. In a second study, in which ethoprophos was applied at planting, no residues (< 0.01 mg/kg) were detected in sugar-cane stalks or juice. Even when an exaggerated dose rate was used, in a third study, no residues (< 0.01 mg/kg) were found in stalks, bagasse, mixed juice, clarified juice, clarifier mud, syrup, molasses or sugar. Therefore, no processing factors for sugar-cane could be calculated.

The Meeting also received information on the distribution of residues in peel and pulp fractions of banana and melon. The results of two trials on banana in which residues were found at harvest indicate that ethoprophos tends to concentrate in the pulp fraction of banana. The results of six trials on melon in which residues were found at harvest indicate that ethoprophos is present in both peel and pulp fractions. Generally, the peel fractions contained slightly higher residue levels.

Residues in animal commodities

Dietary burden of farm animals

The Meeting estimated the dietary burden of ethoprophos residues in farm animals from the diets listed in Appendix IX of the *FAO Manual*. Only one feed commodity from each Codex Commodity Group was used, in this case potato culls (group VR). Calculation from highest residue 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.

On the basis of a highest residue value of 0.03 mg/kg and 20% dry matter in potato culls, the maximum contribution of residue to the dietary burden would be 0.11 mg/kg for beef cattle given feed containing 75% potato culls and 0.06 mg/kg for dairy cattle given feed containing 40% potato culls.

On the basis of an STMR of 0.01 mg/kg and 20% dry matter, the mean dietary burden of beef cattle given feed containing 75% potato culls would be 0.038 mg/kg, and that of dairy cattle given feed containing 40% culls would be 0.02 mg/kg.

Maximum residue levels

The results of the metabolism study in lactating goats given feed containing 32 ppm ethoprophos indicate that no residues are to be expected in mammalian commodities at a maximum dietary burden of 0.11 mg/kg. As laying hens are not exposed to ethoprophos, no maximum residue levels for poultry commodities are required.

The Meeting estimated a maximum residue level of 0.01* mg/kg in mammalian meat, offal and milks, and STMR and highest residue values of 0.

DIETARY RISK ASSESSMENT

Long-term intake

The IEDIs of ethoprophos, on the basis of the STMRs estimated for 11 commodities, for the five GEMS/Food regional diets represented 5–10% of the maximum ADI (0–0.0004 mg/kg bw), see Annex 3. The Meeting concluded that the long-term intake of residues of ethoprophos resulting from uses that have been considered by JMPR is unlikely to present a public health concern.

Short-term intake

The IESTIs for ethoprophos were calculated for 11 food commodities for which maximum residue levels had been estimated and for which consumption data were available. The results are shown in Annex 4.

The IESTI represented 0–1% of the ARfD (0.05 mg/kg bw) for the general population and 0–3% of the ARfD for children. The Meeting concluded that the short-term intake of residues of ethoprophos resulting from uses that have been considered by the JMPR is unlikely to present a public health concern.

4.8 FENITROTHION (037)

RESIDUE AND ANALYTICAL ASPECTS

Fenitrothion was evaluated for residues within the periodic review programme of the CCPR by the 2003 JMPR, which recommended an MRL of 10 mg/kg (accommodating post-harvest treatment, Po) for cereals. The Meeting indicated that additional information on metabolism in cereals (including rice) after pre-harvest treatment, a validated analytical method for the determination of fenitrothion in animal commodities, freezer storage stability of residues in animal commodities, farm animal transfer studies and a processing study on rice were desirable. At the present Meeting, an undertaking was given to submit additional data to support uses on apple, pear and soya bean (dried seed), as these are important traded commodities.

The CCPR at its Thirty-sixth Session agreed to retain the existing MRLs for meat (0.05* mg/kg, fat), milks (0.002* mg/kg), unprocessed rice bran (20 mg/kg), polished rice (1 mg/kg), processed wheat bran (2 mg/kg), unprocessed wheat bran (20 mg/kg), wheat flour (2 mg/kg) and wheat wholemeal (5 mg/kg).

The data submitted to address the outstanding points are summarized below.

Metabolism

Animals

No additional data were submitted.

Plants

The 2003 JMPR evaluated the fate of fenitrothion after spray application to grapes and tomato (crop category fruits) and the fate of fenitrothion in stored rice. The Meeting received two additional studies on the fate of fenitrothion after pre-harvest spray application to rice under simulated paddy growing conditions.

In the first study, rice plants (variety Hatsushimo) were transplanted to a paddy field which had been prepared in a vinyl tent. The rice plants were sprayed once at 0.375 kg ai/ha with a ^{32}P-fenitrothion emulsifiable concentrate formulation. At various intervals after application, rice plants were sampled at random by cutting down at the base and separating the leaf sheath and leaf blade. At normal harvest, mature grains were harvested and separated into bran and polished rice.

In mature rice grain, the main metabolite was phosphoric acid, while phosphorothionic acid, dimethylphosphorothioic acid and parent were also found. The residue levels were 7–33 times higher in rice bran than in polished rice. Fenitrooxon, desmethylfenitrothion, desmethylfenitrooxon, dimethylphosphoric acid, monomethylphosphorothioic acid and monomethylphosphoric acid were not detected. In rice grains from plants (varieties Kin-nampu, Ginga, Aichi-asahi) treated with unlabelled fenitrothion, the parent compound could not be detected in rice bran or in polished rice (< 0.1 mg/kg), but 3-methyl-4-nitrophenol was found in rice bran of the varieties Kin-nampu and Aichi-asahi.

In a second study, rice (variety Nihonbare) was grown in a glasshouse under conditions simulating growth in a rice paddy. Rice seedlings were planted in pots filled with soil and flooded with 3–5 cm water throughout the study. The rice was treated with four spray applications of an emulsifiable concentrate formulation containing [phenyl-^{14}C]fenitrothion at a nominal dose rate of 0.75 kg ai/ha per application 81 (2 months after planting), 28, 21 and 14 days before mature harvest. Twelve days before harvest, water was withheld from the plants. Rice plants, soil and root samples were collected, and the plants were separated into unhulled whole grain and straw (leaf and stem). The unhulled whole grain was further processed to brown rice and chaff (hulls). The brown rice was further processed to give 90% (w/w) polished rice and 11% (w/w) bran.

A high proportion of the radioactivity was extractable (65–89% TRR). Fenitrothion was detectable in all rice fractions, at 0.003–0.3 mg/kg. The major metabolite in unhulled whole grain, brown rice, polished rice, chaff, bran and straw was 3-methyl-4-nitrophenol, at 0.09–3.9 mg/kg fenitrothion equivalents, and this compound was present in a mixture of free and conjugated forms. The conjugates were hydrolysed to the free form by enzymatic (β-glucosidase) and acid hydrolyses. Fenitrothion was present at levels of 0.30 mg/kg in unhulled whole grain rice, 0.027 mg/kg in brown rice and 0.003 mg/kg in polished rice.

The percentage transference would be equivalent to 8.9% for brown rice and 1.0% for polished rice. Fenitrooxon was present at levels of 0.14 mg/kg in unhulled whole grain rice and 0.009 mg/kg in brown rice; it was not detected in polished rice. Fenitrooxon was also found in bran at 0.042 mg/kg, chaff at 0.84 mg/kg and straw at 0.27 mg/kg. Most of the radioactivity in the post-extracted solids was released by acid or base hydrolysis. 3-Methyl-4-nitrophenol was detected in all the hydrolysates except that of polished rice. Minor amounts (< 2.5% TRR) of aminofenitrothion, fenitrooxon, fenitrothion S-isomer and fenitrothion were also released on hydrolysis. In polished rice, only fenitrothion S-isomer was found.

Environmental fate

No additional data were submitted.

Methods of analysis

The 2003 JMPR evaluated enforcement and monitoring methods for plant commodities. The Meeting received two additional analytical methods intended for enforcement and monitoring for animal commodities (RRC 78-32 and RRC 78-32A).

Method RRC 78-32 is used for the determination of fenitrothion (parent), fenitrooxon, aminofenitrothion and 3-methyl-4-nitrophenol in milk, cream and cattle tissues. Method RRC 78-32A is a modification for eggs and poultry tissues. In this appraisal, the focus is on parent compound. Cattle milk, cream and tissue, and eggs and poultry tissues were extracted with acetone or acetonitrile:methanol:water and cleaned, and fenitrothion was determined by gas chromatography–flame photometry detection. The reported LOQ was 0.01 mg/kg for cattle milk and cream and 0.05 mg/kg for eggs and cattle and poultry tissues. The method is considered to be outdated because of the use of glass gas chromatography columns.

The Meeting received information on analytical methods for the determination of parent in foodstuffs of plant, animal or environmental origin as used in various additionally submitted study reports (residue trials, storage stability of analytical samples, processing studies, feeding studies). Fenitrothion was determined by gas chromatography with flame photometry, nitrogen–phosphorus or FT detection. The reported LOQs ranged from 0.001 mg/kg to 0.1 mg/kg.

Stability of residues in stored analytical samples

The 2003 JMPR evaluated the stability in storage of residues in dry crops with starch and protein (grain of wheat, barley, rice) and in rice straw. The Meeting received additional data on the stability of

residues in crops with a high water content (apple, green soya bean, green broad bean) and dry crops with starch and protein (dry seeds of soya bean, kidney bean, pea).

The Meeting concluded that fenitrothion residues are stable at –20 °C for at least 192 days in apples, for at least 155 days in legumes, for at least 149 days in cereals and for at least 98 days in pulses. In several trials, however, samples were stored at –15 °C, –10 °C, +5 °C or +10 °C. Information on the stability of the samples under these conditions was not available.

Definition of the residue

The 2003 JMPR proposed fenitrothion as the residue definition for compliance with MRLs and for dietary intake, for both plant and animal commodities. The residue is not fat-soluble.

The supported uses of fenitrothion at that time were pre-harvest application on cereals and post-harvest application on stored cereal grains. The 2003 Meeting concluded that the available studies were adequate only for post-harvest uses on stored cereal grains; to support pre-harvest uses on cereals, relevant metabolism studies were required.

The manufacturer now wishes to support use on pome fruit and soya bean. The 2003 JMPR evaluated studies of metabolism in grape and tomato after pre-harvest use. The main metabolites were 3-methyl-4-nitrophenol and its conjugates. Two studies on metabolism in rice after pre-harvest use of fenitrothion were made available to the present Meeting.

The studies confirm that the main metabolite is 3-methyl-4-nitrophenol (free and conjugated). The parent compound was found in the raw agricultural commodity and in all processed fractions (unhulled whole rice grain, brown rice, polished rice, bran, hulls and rice straw). In addition, fenitrooxon was found in unhulled whole rice grain (0.14 mg/kg), brown rice (0.009 mg/kg), bran (0.042 mg/kg), hulls (0.84 mg/kg) and straw (0.27 mg/kg). Fenitrooxon should be considered for inclusion in the residue definition for dietary intake, as the 2000 JMPR concluded that it is the most important metabolite with respect to toxicity. As it is found in small amounts in brown rice and not at all in polished rice (the edible portions for humans), however, the Meeting decided not to include fenitrooxon in the residue definition for dietary intake.

Fenitrothion S-isomer and aminofenitrothion, metabolites that were found but not discussed previously, were present in such small amounts that the Meeting concluded that their inclusion in the residue definition was unnecessary.

Therefore, the Meeting concluded that the residue definition as proposed by the 2003 JMPR do not require alteration.

Definition of the residue for compliance with MRLs and for estimating dietary intake: fenitrothion, for both plant and animal commodities.

Results of supervised trials on crops

The Meeting received information on supervised trials on apple, pear, green broad bean, green soya bean, dry soya bean, dry beans and dry peas.

In 2003, the Meeting summarized the results of supervised trials of pre-harvest treatment on cereal grains (rice, wheat, barley, triticale) in Japan and Australia. In some trials, pre-harvest treatment was combined with seed treatment before planting. The trials were not evaluated at that time, because information on metabolism after pre-harvest treatment was lacking.

Pome fruit

Nineteen trials on apple and two trials on pear were conducted in Canada in 1972–73. As there is no GAP in Canada or in the USA, the trials could not be evaluated.

In six of 24 trials on apple conducted in Japan in 1989–95, the analytical samples excluded hulls, pedicels, stylar scars and cores. As the Codex commodity for which the maximum residue level is estimated is the whole fruit, the trials could not be evaluated. In the remaining 18 trials, only pedicels, stylar scars and cores were removed. The Meeting decided that this deviation from the Codex commodity definition was acceptable, and it evaluated the trials. GAP in Japan is three applications of 0.025–0.050 kg ai/ha, with a PHI of 30 days. In two trials, residues were found in control samples, and those trials could not be evaluated.

The residue levels in trials meeting GAP were, in ranked order: < 0.01, 0.01 (three), 0.02 (two), 0.04, 0.08, 0.10 (two), 0.11, 0.12 and 0.41 mg/kg. The Meeting decided to withdraw the currently recommended maximum residue level for apple and replace it by 0.5 mg/kg, with an STMR of 0.04 mg/kg and a highest residue value of 0.41 mg/kg.

There were only two trials on pear, and neither complied with GAP. Furthermore, Japanese GAP allows six applications on pear and only three on apple. The Meeting decided to maintain withdrawal of the recommendation for pear.

Legume vegetables

Three trials on green broad beans (seeds only) and seven trials on green soya beans (seeds or beans with pods) were conducted in 1971–95 in Japan. There is no Japanese GAP for broad beans. Japanese GAP for soya beans (dry and green) is foliar spray treatment at 0.025–0.050 kg ai/ha, four applications, 21-day PHI. Two trials in which the portion analysed was green soya bean in the pod and which were conducted according to GAP yielded residue levels of 0.12 mg/kg and 0.18 mg/kg. Two trials is insufficient to estimate a MRL for soya bean, immature seeds.

Pulses

Nineteen trials on dry harvested soya beans, four trials on beans and two indoor trials on peas were carried out in 1971–90 in Japan. Japanese GAP is described above, except that when fenitrothion is applied by foliar spray from an unmanned helicopter, the dose is 0.50 kg ai/ha. In all but four trials, the PHI exceeded that specified for GAP. In the four trials, the residue levels were: 0.004 (two) and < 0.01 (two) mg/kg. The Meeting decided that four trials is insufficient to estimate a MRL for soya bean, dry.

Cereal grains

The 2003 Meeting received information from supervised trials on pre-harvest treatment of cereal grains (rice, wheat, barley, triticale) in Australia and Japan. Because of lack of data on metabolism in cereal grains after pre-harvest treatment, the trials could not be evaluated at that time. As the present Meeting received the requested data, the trials can now be evaluated.

Sixteen trials on rice were conducted in Japan in 1993–96 (see 2003 JMPR). In the trials conducted in 1993–95, seeds were soaked in a fenitrothion solution for 24 h before planting and then given four applications of fenitrothion from a knapsack sprayer during the growing season. In the trials performed in 1996, fenitrothion was applied four times from an unmanned helicopter, without prior soaking of the seeds. Fenitrothion is registered in Japan for pre-harvest use on rice at a maximum of four foliar spray applications of 0.375–0.90 kg ai/ha and a PHI of 21 days. The residue levels in the trials complying with Japanese GAP were: < 0.01 (four), 0.01 (two), 0.02, 0.03, 0.04, 0.05, 0.06, 0.07, 0.08, 0.09, 0.10 and 0.12 mg/kg.

Four trials on *winter wheat* were conducted in Australia in 2001 and in Japan in 1993. In these trials, fenitrothion was applied three times from a knapsack sprayer or a boom sprayer. Fenitrothion is registered in Australia for pre-harvest use on cereals with a maximum of three applications of 0.27–0.55 kg ai/ha (interval ≥ 14 days) and a PHI of 14 days; in Japan, it is registered for pre-harvest use on wheat with a single application of 0.45–0.60 kg ai/ha and a PHI of 7 days. The Australian trials were at Australian GAP and yielded residue levels of 0.10 and 0.21 mg/kg. The trials in Japan did not comply completely with Japanese GAP (three applications instead of one), but the results were evaluated. The residue levels were < 0.01 and 0.30 mg/kg.

Three trials on *winter barley* were conducted in Australia in 2001 and in Japan in 1993. Fenitrothion was applied three times from a knapsack sprayer or a hand-held boom sprayer. In Australia, fenitrothion is registered for pre-harvest use on cereals with a maximum of three applications of 0.27–0.55 kg ai/ha (interval ≥ 14 days) and a PHI of 14 days. In Japan, fenitrothion is not registered for use on barley. The Australian trial was at Australian GAP and yielded a residue level of < 0.06 mg/kg.

One trial on *winter triticale* was conducted in Australia in 2001, in which fenitrothion was applied three times from a hand-held boom sprayer. The trial was at the Australian GAP for cereal and yielded a residue levek of 0.08 mg/kg.

The Meeting decided to combine the results of all the trials on cereals residue, to yield residue levels, in ranked order, of: < 0.01 (five), < 0.06, 0.01 (two), 0.02, 0.03, 0.04, 0.05, 0.06, 0.07, 0.08 (two), 0.09, 0.10 (two), 0.12, 0.21 and 0.30 mg/kg. As the residue levels resulting from pre-harvest treatment were lower than those after post-harvest treatment, the Meeting decided to maintain the current recommendations for cereal grain of 10 mg/kg (Po), an STMR of 5 mg/kg and a highest residue of 7.6 mg/kg.

Straw, fodder and forage of cereal grains and grasses

Two trials on *rice* were conducted in Japan in 1993 according to Japanese GAP. The residue levels in straw were 0.31 and 0.44 mg/kg.

Two trials on *winter wheat* were conducted in Australia in 2001 according to Australian GAP. The residue levels in straw were 1.2 and 4.1 mg/kg.

One trial on *winter barley* was conducted in Australia in 2001 according to Australian GAP. The residue level in straw was 0.41 mg/kg.

One trial on *winter triticale* was conducted in Australia in 2001 according to Australian GAP. The residue level in straw was 2.0 mg/kg.

The Meeting decided that there were insufficient data to estimate a maximum residue level in cereal straw.

Fate of residues during processing

The 2003 JMPR evaluated the fate of fenitrothion during simulated processing, in stored rice during polishing and cooking and in stored wheat during milling and baking. The Meeting received three additional studies on the fate of fenitrothion after post-harvest treatment of rice during polishing and cooking and in barley during malting.

Rice stored for up to 12 months after post-harvest treatment with fenitrothion at 2–15 g ai/t was separated into polished rice and bran. The polished rice was washed and cooked for 10–15 min at normal to 2.5 atm pressure. Parent compound was analysed in all processed products. The calculated processing factors were 0.11–0.15 for polished rice (mean, 0.14), 6.6–7.2 for bran (mean, 6.9), 0.041–0.049 for washed polished rice (mean, 0.046) and 0.0060–0.033 for cooked washed polished rice (mean, 0.020).

Paddy rice stored for up to 6 months after post-harvest treatment with fenitrothion at 15 g ai/t was processed into husked rice, polished rice and bran. Husked and polished rice were cooked for 25 min. Parent compound was analysed in all processed products. The calculated processing factors were 0.18 for husked rice, 0.08 for polished rice, 0.11 for cooked husked rice and 0.04 for cooked polished rice.

Paddy rice was processed into husked rice, polished rice, hulls and bran. Parent compound was analysed in all processed products. The calculated processing factors were 0.031–0.64 for husked rice (mean, 0.17), < 0.002–0.087 for polished rice (mean, 0.018), 0.12–10 for hulls (mean, 4.3) and 0.018–2.0 for bran (mean, 0.61).

Barley stored for up to 6 months after post-harvest treatment with 15 g ai/t fenitrothion was processed into malt and was analysed for parent. The calculated processing factors were 0.16-0.24 for malt (mean 0.20).

The table below summarizes the processing factors for wheat, barley and rice commodities. The information on wheat was discussed by the 2003 JMPR. Three studies were available on the processing of rice, yielding different results. As details of the growing conditions, treatments, storage and processing were absent or partial, the Meeting could not judge which study was the most representative of household processing. Therefore, maximum processing factors were used. Processing factors used for the calculation of maximum residue levels and STMR-Ps are underlined.

Commodity	Processing factor (range)	No. of trials	Processing factor (mean)	STMR-P (mg/kg)	HR-P (mg/kg)
Wheat bran	3.9–4.0	2	<u>3.95</u>	19.75	30.02
Wheat flour	0.21–0.26	2	<u>0.235</u>	1.175	1.786
White bread	0.089–0.11	2	<u>0.10</u>	0.5[a]	0.76
Wholemeal bread	0.33–0.43	2	<u>0.38</u>	1.9	2.888
Barley malt	0.16–0.24	2	<u>0.20</u>	1	1.52
Husked rice	0.031–<u>0.64</u>	22	0.17	3.2	4.864
Polished rice	< 0.002–<u>0.15</u>	26	0.039	0.75	1.14
Rice hulls	0.12–<u>10</u>	21	4.3	50	76
Rice bran	0.018–<u>7.2</u>	23	1.7	36	54.72
Cooked husked rice	<u>0.11</u>	1		0.55	0.836
Cooked polished rice	<u>0.04</u>	1		0.2	0.304
Washed polished rice	0.041–0.049	4	<u>0.046</u>	0.23	0.3496
Cooked, washed, polished rice	0.0060–0.033	13	<u>0.020</u>	0.1	0.152

[a] The Meeting noted that the 2003 Report incorrectly reported an STMR-P of 0.05 mg/kg in white bread.

Using the highest residue level for cereal grains (7.6 mg/kg) and the processing factors indicated above, the Meeting estimated maximum residue levels of 30 mg/kg in wheat bran and 60 mg/kg in rice bran. The Meeting decided to withdraw the current recommendations for 1 mg/kg in polished rice, 2 mg/kg in wheat flour, 1 mg/kg in white bread and 3 mg/kg in wholemeal bread (accommodating post-harvest treatment, PoP), because the MRL would be lower than that of the raw agricultural commodity.

Using the STMR for cereal grains (5 mg/kg), the Meeting estimated STMR-Ps for wheat bran, wheat flour, white bread, wholemeal bread, barley malt, husked rice, polished rice, rice hulls, rice bran, cooked husked rice, cooked polished rice, washed polished rice and cooked washed polished rice, as shown in the table above.

Furthermore, using the highest residue level for cereal grains (7.6 mg/kg), the Meeting estimated HR-Ps for wheat bran, wheat flour, white bread, wholemeal bread, barley malt, husked rice, polished rice, rice hulls, rice bran, cooked husked rice, cooked polished rice, washed polished rice and cooked washed polished rice, as shown in the table above.

The Meeting decided to use the STMR-P and HR-P values for cooked husked rice and cooked polished rice in calculating the dietary intake of fenitrothion from rice.

Residues in animal commodities

Dietary burden of farm animals

The Meeting estimated the dietary burden of fenitrothion residues in farm animals from the diets listed in Appendix IX of the *FAO Manual*. Only one feed commodity from each Codex Commodity Group is used; therefore, the calculation includes wheat grain, but no other cereals, and rice bran, but not rice hulls. Calculation from the highest residue 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	Codex code	Residue (mg/kg)	Basis	Dry matter (%)	Residue, dry wt (mg/kg)	Dietary content (%)			Residue contribution of feeds (mg/kg)		
						Beef cattle	Dairy cattle	Poultry	Beef cattle	Dairy cattle	Poultry
Rice bran	CM	36	STMR-P	90	40						
Rice hulls	CM	50	STMR-P	90	55.6						
Wheat milled by-products[a]	CF	19.75	STMR-P	88	22.44	40	50	50	8.98	11.22	11.22
Wheat grain	GC	7.6	Highest residue	89	8.54						
Total						40	50	50	8.98	11.22	11.22

[a] Use of wheat bran

Estimated mean dietary burden of farm animals

Commodity	Codex code	Residue (mg/kg)	Basis	Dry matter (%)	Residue, dry wt (mg/kg)	Dietary content (%)			Residue contribution of feeds (mg/kg)		
						Beef cattle	Dairy cattle	Poultry	Beef cattle	Dairy cattle	Poultry
Rice bran	CM	36	STMR-P	90	40						
Rice hulls	CM	50	STMR-P	90	55.6						
Wheat milled by-products [a]	CF	19.75	STMR-P	88	22.44	40	50	50	8.98	11.22	11.22
Wheat grain	GC	5	STMR	89	5.62						
Total						40	50	50	8.98	11.22	11.22

[a] Use of wheat bran

Residues in grazing animals and feeding studies

The 2003 JMPR evaluated the fate of fenitrothion residues in cattle grazing on fenitrothion-treated grass and in cattle fed fenitrothion-treated corn. The Meeting received an additional study on cattle grazing on pasture treated with fenitrothion, a feeding study in lactating dairy cattle and a feeding study in laying hens.

Fenitrothion as technical material was applied by air to a 120-ha paddock by the ultra-low volume technique at the rate of 0.508 kg ai/ha. There were 28 *cattle* on the pastures when the application was made, and 38 were brought to the treated pastures immediately after spraying. Four cattle were maintained as controls, with no exposure to fenitrothion. The cattle were allowed to graze on the sprayed pasture for varying periods and were slaughtered within 1 day after removal from the paddock, 2, 4, 7, 14 or 21 days after treatment. Samples of subcutaneous and perirenal fat, meat (neck muscle) and liver were taken for analysis. Some cattle were removed from the treated pasture and were grazed on clean pasture for 2, 4 or 7 days before slaughter to determine the effect on the residue levels of this procedure. Soil and pasture were sampled on days –3, 0, 1, 2, 4, 7, 10, 14 and 21 and analysed for fenitrothion residues. The worst-case estimate of total exposure (pasture + soil + deposition) of the cattle on the day of spraying was 800–900 mg of fenitrothion per animal. As the total intake of dry matter from the pasture was assumed to be 10 kg/day, the exposure corresponds to a fenitrothion content of approximately 90 ppm.

Data on residues found in the pasture indicate a half-life for fenitrothion of 1–2 days, which declined with time; the decay during the first period appeared to be faster than that during later periods on a per hour basis. About 50% of the fenitrothion was gone within 1 day, 75% within 3 days and 90% within 6 days. Data on residues in the soil indicated a half-life for fenitrothion of 2–3 days. The residue levels in all animal commodities were below the LOQ (< 0.2 mg/kg for fat, < 0.02 mg/kg for muscle and liver).

Groups of three *lactating cows* received feed containing fenitrothion at a concentration of 0, 10, 30 or 100 ppm for 28 days. All animals were milked twice daily, and composite milk samples from the morning and afternoon milkings on days –1, 0, 3, 7, 14, 21 and 28 were analysed for residues. Cream was analysed separately; the cream content of the milk was 5–8% and the butterfat content was 3–5%. The levels of residues of fenitrothion in milk were below the LOQ of 0.01 mg/kg for all groups. Residues were measured in cream at some times (scattered among groups), but the levels were never higher than 0.01 mg/kg. Samples of liver, kidney, muscle (cardiac, hind-quarter and front-quarter) and fat (omental and perirenal) were taken. Residue levels above the LOQ of 0.05 mg/kg were not found in any sample at any feed level.

Layer and broiler *hens* received feed containing fenitrothion at 0, 10, 30 or 100 ppm for 28 days. Egg samples were collected twice a week from each group and frozen until ready for analysis. Eggs from birds in the same dose group were combined. Half of the hens at each dietary concentration were killed on day 14, and the remaining hens were killed on day 28 of the study. Samples of red muscle, white muscle, liver and fat were taken at both times. The residue levels in all tissue samples taken on days 14 and 28 were below the limit of determination of 0.05 mg/kg. No residues of fenitrothion were found in eggs taken over the 28-day period.

Maximum residue levels

The calculated dietary burden of dairy cattle is 11.22 mg/kg, and that of beef cattle is 8.98 mg/kg. In the feeding study with cattle described above, no residues were found at levels above the LOQ (0.05 mg/kg) in muscle, fat, liver or kidney at dietary concentrations of 10, 30 and 100 mg/kg. Therefore, no residues at levels above the LOQ are to be expected at the calculated dietary burden. The levels of residues of fenitrothion in milk were below the LOQ of 0.01 mg/kg.

The calculated dietary burden of poultry is 11.22 mg/kg. In the feeding study in poultry, no residues were detected in muscle, liver, fat or eggs (< 0.05 mg/kg) at dietary concentrations of 10, 30 and 100 mg/kg.

The Meeting recommended maximum residue levels of 0.05* mg/kg in meat (from mammals other than marine mammals), in edible offal (mammalian), in poultry meat and in eggs. The Meeting also recommended a maximum residue level of 0.01 mg/kg in milks. The STMR and the highest residue values for muscle, fat, liver, kidney, poultry meat and fat are estimated to be 0 mg/kg.

DIETARY RISK ASSESSMENT

Long-term intake

The IEDIs of fenitrothion, on the basis of the STMRs estimated for 12 commodities, for the five GEMS/Food regional diets represented 110–330% of the maximum ADI (0–0.005 mg/kg bw), see Annex 3. The information provided to the JMPR precludes an estimate that the dietary intake would be below the ADI.

The Meeting noted that the calculations of long-term intake were conservative, as they did not take into account the reduction in residue levels obtained by processing cereal grains, except for processing of wheat, barley and rice. The Meeting extrapolated processing data on wheat to rye. Information on processing of barley (uses besides beer), maize, millet and sorghum would be particularly useful for refining the intake calculations.

Short-term intake

The IESTIs for fenitrothion were calculated for 25 food commodities for which maximum residue levels had been estimated and for which consumption data were available. The results are shown in Annex 4.

The IESTI represented 0–100% of the ARfD (0.04 mg/kg bw) for the general population and 0–160% of the ARfD for children. The values 120%, 150% and 160% represent the estimated short-term intake of wholemeal bread, wheat bran (unprocessed) and maize (fresh, flour), respectively, by children. The Meeting concluded that the short-term intake of residues of fenitrothion from uses other than on these three commodities that have been considered by the JMPR is unlikely to present a public health concern.

The Meeting noted that the intake calculations were conservative, as they did not take into account the reduction in residue levels obtained by processing cereal grains, except for processing of wheat, barley and rice. Information on processing of maize would be particularly useful for refining the intake calculations. Nevertheless, the exceedences found for children in the consumption of wheat bran and wholemeal bread cannot be further refined.

The Meeting noted that the ADI and the ARfD for fenitrothion were established by the 2000 JMPR. At that time, the concepts of overall NOAEL (see item 2.3) and of compound-specific adjustment factors (see item 2.1) had not been fully developed. In addition, the process of establishing ARfDs was at an early stage of development. In view of these considerations, the Meeting concluded that a review of the toxicological database of fenitrothion, taking into account the new concepts, could lead to a refinement of the ADI and the ARfD.

4.9 FENPROPIMORPH (188)

TOXICOLOGY

Evaluation for an acute reference dose

Fenpropimorph is a morpholine fungicide with systemic activity, interfering with sterol biosynthesis. It was first evaluated by the 1994 JMPR, which established an ADI of 0–0.003 mg/kg bw on the basis of a NOAEL of 10 ppm, equal to 0.3 mg/kg bw per day, in a 2-year study of toxicity and carcinogenicity in rats. At the 2001 JMPR, an ARfD of 1 mg/kg bw was established on the basis of a NOAEL of 100 mg/kg bw per day in an acute neurotoxicity study in rats. In 2002, the Government of Germany asked the Meeting to reconsider the ARfD established for fenpropimorph by the 2001 JMPR, because this Government considered the NOAEL of 15 mg/kg bw per day for teratogenicity in the rabbit to be a more appropriate basis for the ARfD. The present review was undertaken to determine the appropriate end-point and NOAEL for

establishing an ARfD and to evaluate a new screening study of pre- and postnatal developmental toxicity in rats, which was submitted to the present Meeting.

Fenpropimorph is of low acute toxicity; in rats, the oral LD_{50} was 1500–3500 mg/kg bw, the dermal LD_{50} was 4300 mg/kg bw, and the inhalation LC_{50} was 2.9 mg/l of air.

In a study of acute neurotoxicity in rats, the NOAEL was 100 mg/kg bw per day on the basis of clinical and behavioural signs observed at doses of 500 and 1500 mg/kg bw per day.

In a screening study of pre- and postnatal developmental toxicity in rats, the NOAEL for maternal toxicity was < 5 mg/kg bw per day on the basis of decreased food consumption during pregnancy and lactation and reduced body-weight gain during pregnancy, at all doses. The NOAEL for developmental toxicity was < 5 mg/kg bw per day on the basis of reduced body weight or body-weight gain in pups at all doses during lactation.

In a study of prenatal developmental toxicity in rats, an increased incidence of cleft palate (14 fetuses from seven litters) was observed at the highest dose of 160 mg/kg bw per day. At this dose, severe maternal toxicity, including mortality, was found. The NOAEL for developmental toxicity was 40 mg/kg bw per day, while the NOAEL for maternal toxicity was 10 mg/kg bw per day.

In a study of prenatal developmental toxicity in Himalayan rabbits, severe maternal toxicity, including mortality, was found at 60 mg/kg bw per day, the highest dose tested. The number of early resorptions and dead fetuses was increased such that only one fetus survived. This fetus had several abnormalities, including syndactyly of the forelimbs, an anomalous position of the hindlimbs and micromelia, fusion of individual sternebrae and reduced weight and length. At 36 mg/kg bw per day, the clinical signs in dams (diarrhoea, salivation) were less severe and occurred at a lower incidence than at the highest dose. Two animals aborted and three were killed *in extremis*. The number of postimplantation losses was slightly increased at this dose. Six fetuses from two litters had pseudoankylosis, a skeletal variation. The NOAEL was 12 mg/kg bw per day for both maternal toxicity and developmental toxicity.

In a study of prenatal developmental toxicity in Russian rabbits, maternal toxicity (swelling of the anus, reduction of food consumption and of body weight or body-weight gain, weight loss) was observed only at the highest dose tested, 30 mg/kg bw per day. There were no effects on pre- or postimplantation loss, number of live or dead fetuses per litter and sex ratio. Mean gravid uterus weight and weights of male fetuses were significantly reduced at the highest dose. There was an increase in the total number of malformations (21 fetuses from four litters) and in findings described as ‘anomalies’ (36 fetuses from 13 litters). The malformations occurred mainly in the litters of three dams that showed marked signs of toxicity during treatment. Twenty fetuses from three litters had shortened fore- and hindlimbs, and four fetuses from two litters had a cleft palate. Furthermore, position anomalies were observed in the forelimbs in twenty-five fetuses from seven litters and in the hindlimbs in eight fetuses from three litters. The NOAEL was 15 mg/kg bw per day for both maternal toxicity and developmental toxicity.

Toxicological evaluation

The Meeting established an ARfD of 0.2 mg/kg bw on the basis of an overall NOAEL of 15 mg/kg bw per day for embryo- and fetotoxicity and teratogenicity in two studies of prenatal developmental toxicity in rabbits and using a safety factor of 100. The LOAEL of 5 mg/kg bw per day for decreased body-weight gain in pups in the screening study of pre- and postnatal developmental toxicity in rats is related to repeated pre- and postnatal exposure and is therefore not considered to be an appropriate basis for establishing an ARfD.

Levels relevant to risk assessment

Species	Study	Effect	NOAEL	LOAEL
Rat	Acute neurotoxicity	Neurotoxicity	100 mg/kg bw per day	500 mg/kg bw per day
	Screening for pre- and postnatal developmental toxicity	Maternal toxicity	< 5 mg/kg bw per day	5 mg/kg bw per day
		Developmental toxicity	< 5 mg/kg bw per day[a]	5 mg/kg bw per day[a]
	Prenatal developmental toxicity	Maternal toxicity	10 mg/kg bw per day	40 mg/kg bw per day
		Developmental toxicity	40 mg/kg bw per day	160 mg/kg bw per day
Rabbit	Prenatal developmental toxicity	Maternal toxicity	12 mg/kg bw per day	36 mg/kg bw per day
		Developmental toxicity	12 mg/kg bw per day	36 mg/kg bw per day
	Prenatal developmental toxicity	Maternal toxicity	15 mg/kg bw per day	30 mg/kg bw per day
		Developmental toxicity	15 mg/kg bw per day	30 mg/kg bw per day

[a] Effect considered not relevant for a single exposure

Estimate of acute reference dose

0.2 mg/kg bw

DIETARY RISK ASSESSMENT

Short-term intake

The Meeting estimated an ARfD of 0.2 mg/kg bw for fenpropimorph. The 2001 JMPR had calculated the IESTI for fenpropimorph for 16 food commodities (and their processed fractions) for which MRLs were estimated and for which consumption data were available using the previous ARfD of 1 mg/kg bw.

The IESTI represented 0–7% of the ARfD for the general population and 0–10% of the ARfD for children.

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

4.10 FENPYROXIMATE (193)

TOXICOLOGY

Evaluation for an acute reference dose

Fenpyroximate is a phenoxypyrazole acaricide. Fenpyroximate was evaluated by the 1995 JMPR, when an ADI of 0–0.01 mg/kg bw was established on the basis of a NOAEL of 1 mg/kg bw per day in a 104-week study in rats and a safety factor of 100. The critical effect in that study was a reduction in body-weight gain. Fenpyroximate was re-evaluated by the present Meeting in order to determine an ARfD.

The acute oral LD_{50} of fenpyroximate was 245 and 480 mg/kg bw in male and female rats, respectively. The toxic effects of fenpyroximate include diarrhoea, failure to gain weight and haematological and clinical chemistry changes. In short-term (range-finding) dietary studies in mice, the effects of fenpyroximate were mainly limited to decreases in food consumption and reduced body-weight gain. The

NOAELs for the two studies were 20 ppm (equal to 2.58 and 3.07 mg/kg bw per day in males and females, respectively) and 80 ppm (equal to 10.8 mg/kg bw per day in males and 11.7 mg/kg bw per day in females). In a 13-week dietary study in rats, effects were seen on body-weight gain, food consumption and haematological and clinical chemistry parameters. The NOAEL for the study was 20 ppm, equal to 1.30 mg/kg bw per day in males and 1.65 mg/kg bw per day in females. In a 13-week study in dogs given capsules containing fenpyroximate, weight loss or decreased weight gain, decreased food consumption and diarrhoea were seen. No NOAEL was identified in this study and the LOAEL was 2 mg/kg bw per day, on the basis of diarrhoea occurring at all doses. This was considered to be a minimal effect level and occurred from the beginning of the study. In a dietary study of reproductive toxicity in rats, parental toxicity comprised reduced body-weight gain and food consumption in both sexes and increased testicular and epididymal weights in males. Offspring toxicity consisted of reduced body-weight gain. A reduction in conception rate and fertility index was observed in one generation only. The NOAELs for parental, offspring and reproductive toxicity were all 30 ppm (equal to 1.99 mg/kg bw per day in parental males, 2.44 mg/kg bw per day in parental females, 2.33 mg/kg bw per day in F_1 males and 2.82 mg/kg bw per day in F_1 females). In a study of developmental toxicity in rats treated by gavage, effects were seen on maternal body weight, while increases in thoracic ribs were found in fetuses. The NOAEL for both effects was 5 mg/kg bw per day. In preliminary and substantive studies of the developmental toxicity of fenpyroximate in rabbits treated by gavage, reduced maternal body weight and food consumption was seen at the higher doses. These effects were not considered relevant for establishing an ARfD. The NOAEL for maternal toxicity was 1 mg/kg bw day. Significant elevations in the frequency of unilateral and bilateral slightly folded retinas were observed in the fetuses at 5 mg/kg bw per day. No other evidence of fetotoxicity was observed and the biological significance of this finding is unclear.

Toxicological evaluation

The Meeting established an ARfD of 0.01 mg/kg bw on the basis of the a minimal LOAEL of 2 mg/kg bw per day for the induction of diarrhoea at the beginning of a 13-week study of toxicity in dogs. It was unclear whether the diarrhoea was the result of a direct irritant or pharmacological effect of fenpyroximate. A safety factor of 200 was used since no NOAEL was identified. This ARfD is probably conservative and could be refined using the results of an appropriately designed study.

An addendum to the toxicological monograph was prepared

Estimate of acute reference dose

0.01 mg/kg bw

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

Appropriately designed single-dose study

DIETARY RISK ASSESSMENT

Short-term intake

The Meeting established an ARfD of 0.01 mg/kg bw for fenpyroximate. The 1999 JMPR had calculated the IESTI for fenpyroximate for 10 food commodities (and their processed fractions) for which MRLs were estimated and for which consumption data were available, but was not able to finalize the risk assessment because an ARfD was not available.

The IESTI represented 0–120% of the ARfD for the general population and 0–310% of the ARfD for children. The value 120% represents the estimated short-term intake of grapes by the general population. The values 130% and 310% represent the estimated short-term intakes of apples and grapes by children.

The Meeting concluded that the short-term intake of residues of fenpyroximate from uses, other than on apple and grape, that have been considered by the JMPR is unlikely to present a public health concern.

4.11 FLUDIOXONIL (211)

TOXICOLOGY

Fludioxonil is the ISO approved name for a new phenylpyrrole fungicide, 4-(2,2-difluoro-1,3-benzodioxol-4-yl)pyrrole-3-carbonitrile (IUPAC), that interferes with glucose transport across fungal membranes. Fludioxonil has not been evaluated previously by the JMPR.

After oral administration of radiolabelled fludioxonil, the radiolabel is rapidly and extensively (approximately 80% of the administered dose) absorbed, widely distributed, extensively metabolized and rapidly excreted, primarily in the faeces (approximately 80%) via the bile (approximately 70%), with a small amount being excreted in the urine (approximately 20%). The maximum blood concentration is reached within 1 h after administration. Elimination is biphasic, with half-lives of between 2 and 5 h for the first phase and between 30 and 60 h for the second phase. Fludioxonil is rapidly cleared from the blood and tissues, and there is consequently negligible potential for accumulation. The metabolism of fludioxonil proceeds primarily through oxidation of the pyrrole ring, leading to one major (57% of the administered dose) and one minor (4% of the administered dose) oxo-pyrrole metabolite. Hydroxylation of the phenyl ring yields the corresponding phenol metabolite, which represents 2% of the administered dose. These phase I metabolites are subsequently excreted as glucuronyl and sulfate conjugates and, together with unabsorbed and unchanged fludioxonil excreted in faeces, account for approximately 75% of the administered dose. The dimerization of the hydroxy pyrole metabolite produces a metabolite of an intense blue colour.

The dermal absorption of fludioxonil, excluding material bound to the skin, is low in rats in vivo (< 5%) and in human skin in vitro (< 0.5%). In a study of dermal penetration in rats in vitro, values for dermal absorption at low levels of application were comparable to those obtained in a study performed in vivo (< 2%), but at higher levels significantly overestimated absorption in vivo (38%).

Fludioxonil has low acute toxicity in rats when administered by oral, dermal or inhalation routes, producing no deaths at 5000 and 2000 mg/kg bw and 2.6 mg/l of air, respectively, the highest doses tested. There were also no deaths in mice given fludioxonil at 5000 mg/kg bw by gavage. Fludioxonil is a slight eye irritant in rabbits, but is neither a skin irritant in rabbits nor a skin sensitizer in guinea-pigs (Magnusson & Kligman maximization assay).

In studies with repeated doses in mice and rats, the liver (necrosis, centrilobular hypertrophy, increased serum cholesterol and 5´nucleotidase), the kidneys (nephropathy, inflammation, cysts) and haematopoietic system (mild anaemia) were the principal targets. Such effects often set the LOAELs for these studies, together with reduced body-weight gains. In mice, these effects were observed after 90 days of treatment at 450 mg/kg bw per day and at 590 mg/kg bw per day in one 18-month study, but not at 360 mg/kg bw per day in another such study. In rats, effects were seen at doses of ≥ 400 mg/kg bw per day in short-term studies and at 110 mg/kg bw per day in a 2-year study; lower body-weight gains were also observed at these doses. Liver toxicity was generally manifested by increased concentrations of serum cholesterol and bilirubin and centrilobular hypertrophy and/or necrosis. Anaemia in mice (at > 590 mg/kg bw per day for 18 months) and rats (at 1300 mg/kg bw per day for 3 months) was seen at doses greater than the LOAEL. In dogs, anaemia was observed at the LOAEL (at 290 mg/kg bw per day for 3 months, but only after 4 weeks of treatment; and at a dose of 300 mg/kg bw per day for 12 months). No haematological effects were observed in shorter studies in mice (at ≤ 1050 mg/kg bw per day for 90 days) or rats (at ≤ 2500 mg/kg bw per day for 20 days and at ≤ 1000 mg/kg bw per day for 28 days)

Blue discolouration of the urine, perineal fur, kidneys and gastrointestinal tract were common observations in all species. These effects were secondary to the formation of the blue metabolite in quantities that were sufficient, at high doses, to stain the various tissues. The effect is not toxicologically significant and was disregarded in identifying NOAELs from studies in which it was observed.

Fludioxonil gave negative results in assays for reverse mutation in *S. typhimurium* and *E. coli*, gene mutation in Chinese hamster V79 cells, unscheduled DNA synthesis in rat hepatocytes, micronucleus formation in bone marrow of rats and mice in vivo and chromosome aberration in Chinese hamsters in vivo. Fludioxonil was clastogenic in Chinese hamster ovary cells (CCL61) in vitro at non-cytotoxic concentrations. There was no evidence of heritable genetic damage in an assay for dominant lethal mutations in mice.

The Meeting concluded that fludioxonil is unlikely to be genotoxic in vivo.

The carcinogenicity potential of fludioxonil was examined in a study in rats and in two studies in mice. While the incidence of lymphomas was slightly increased in females in one study in mice receiving diets containing fludioxonil at a concentration of 3000 ppm (equal to 360 mg/kg bw per day), no increase was observed in a concurrent life-time study in mice given diets containing fludioxonil at dietary concentrations of up to 7000 ppm (1000 mg/kg bw per day). Lymphoma is a common finding in ageing female CD-1 mice, and the historical incidence at the laboratory conducting these studies was 13–32%, which encompasses the incidence noted in females at 3000 ppm (30%). Given the high background rate of this finding and the lack of any increase in the other study by the same authors using higher doses, the Meeting concluded that the apparent increase in lymphomas observed in one study in mice was incidental. There was no evidence of carcinogenic potential with fludioxonil in the study in rats. The overall NOAELs in the long-term studies were 112 and 37 mg/kg bw per day in mice and rats respectively.

On the basis of the above consideration and on the lack of genotoxic potential in vivo, the Meeting concluded that fludioxonil is unlikely to pose a carcinogenic risk to humans.

In a two-generation study of reproductive toxicity in rats, at a dose of 210 mg/kg bw per day, adult males had reduced body-weight gains and food consumption and pups had lower body-weight gains. The NOAEL for parental and pup toxicity was 21 mg/kg bw per day. The NOAEL for effects on reproductive performance was 21 mg/kg bw per day on the basis of reduced pup weights. As no effects on body-weight gain, or any other parameter, were seen in adult rats at 37 mg/kg bw per day in a 2-year study, the NOAEL for parental animals in the study of reproductive toxicity can also be considered to be > 37 mg/kg bw per day. The NOAEL of 21 mg/kg bw per day for pup toxicity was based on effects observed at 210 mg/kg bw per day. These effects were relatively mild and the dose–response relationship appears to be shallow (12% decrease in body-weight gain over the dose range of 190 mg/kg bw per day, or a 1%, or less, decrease in body-weight gain per dose increment of 16 mg/kg bw per day). Assuming a linear dose–response relationship between 21 and 210 mg/kg bw per day, then at the proposed overall NOAEL for rats of 37 mg/kg bw per day, a decrease in body-weight gain of ≤ 1% would be predicted in pups; this would not be interpreted as being an adverse effect. Consequently, the use of an overall NOAEL of 37 mg/kg bw per day is also appropriate for pup toxicity. In a study of developmental toxicity in rabbits and another in rats, fludioxonil was neither teratogenic nor fetotoxic and fetal weights were unaffected at doses of up to 1000 and 300 mg/kg bw per day, respectively. Maternal toxicity in these studies was limited to reduced body-weight gain at 1000 and 300 mg/kg bw per day in rats and rabbits, respectively.

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

Studies of acute oral toxicity and genotoxicity with a range of plant metabolites of fludioxonil showed that these metabolites are of low acute oral toxicity and are not genotoxic. The NOAEL in a 90-day study in rats given diets containing a photolytic/hydrolytic degradation product of fludioxonil found in soil and water was 800 ppm (equal to 58 mg/kg bw per day), on the basis of increased relative kidney weight and tubular casts at ≥ 2500 ppm (in males) and minimal to slight atrophy of the olfactory epithelium at ≥ 2500 ppm.

Toxicological evaluation

The Meeting established an ADI of 0–0.4 mg/kg bw based on a NOAEL of 37 mg/kg bw per day in a 2-year dietary study in rats and a 100-fold safety factor.

Although effects on the kidneys occurred after relatively short periods of exposure, the Meeting concluded that such effects were unlikely to result from a single exposure. Consequently, the Meeting concluded that an ARfD for fludioxonil was unnecessary.

A toxicological monograph was prepared.

Levels relevant to risk assessment

Species	Study	Effect	NOAEL	LOAEL
Mouse	18 month study of toxicity and carcinogenicity[a]	Toxicity	1000 ppm, equal to 112 mg/kg bw per day	3000 ppm, equal to 360 mg/kg bw per day
		Carcinogenicity	3000 ppm equal to 360 mg/kg bw per day[b]	—
Rat	2-year study of toxicity and carcinogenicity[a]	Toxicity	1000 ppm, equal to 37 mg/kg bw per day	3000 ppm, equal to 110 mg/kg bw per day
		Carcinogenicity	3000 ppm, equal to 110 mg/kg bw per day[b]	—
	Two-generation study of reproductive toxicity[a]	Parental toxicity	300 ppm, equal to 21 mg/kg bw per day[d]	3000 ppm, equal to 210 mg/kg bw per day
		Embryo- and fetotoxicity	300 ppm, equal to 21 mg/kg bw per day[d]	3000 ppm, equal to 210 mg/kg bw per day
	Developmental toxicity[c]	Maternal toxicity	100 mg/kg bw per day	1000 mg/kg bw per day
		Embryo- and fetotoxicity	1000 mg/kg bw per day[b]	—
Rabbit	Developmental toxicity[c]	Maternal toxicity	100 mg/kg bw per day	300 mg/kg bw per day
		Embryo- and fetotoxicity	300 mg/kg bw per day[b]	—
Dog	12-month study of toxicity[a,e]	Toxicity	1000 ppm, equal to 33 mg/kg bw per day	8000 ppm, equal to 300 mg/kg bw per day

[a] Diet
[b] Highest dose tested
[c] Gavage
[d] The NOAEL of 21 mg/kg bw per day in this study was adjusted upwards to 37 mg/kg bw per day on the basis of an absence of effects in 90-day and 2-year studies in rats at 64 and 37 mg/kg bw per day, respectively. Additionally, interpolation of the reduced weight gain in pups in the study of reproductive toxicity indicated a probably non-adverse, reduction in weight gain of 1% or less at the higher NOAEL of 37 mg/kg bw per day.
[e] The LOAEL for this study was 300 mg/kg bw per day. Owing to the wide dose spacing used for this study, the NOAEL is conservative; hence the slightly higher NOAEL obtained in the 2-year study in rats was selected for establishment of the ADI.

Estimate of acceptable daily intake for humans

0–0.4 mg/kg bw

Estimate of acute reference dose

Unnecessary

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

Further observations in humans

Critical end-points forsetting guidance values for exposure to fludioxonil

Absorption, distribution, excretion and metabolism in animals	
Rate and extent of oral absorption	Rapid, approximately 80%
Dermal absorption	Poor, < 10% in the rat in vivo; 1% or less in human skin in vitro
Distribution	Extensive
Rate and extent of excretion	Largely complete within 24 h; approximately 10% in urine and 80% in the faeces; 70% of the administered dose was excreted in the bile
Potential for accumulation	Low, no evidence of accumulation
Metabolism in mammals	Extensively metabolized, involving primarily oxidation of the pyrrole ring leading to a major (57% of the administered dose) and a minor (4% of the administered dose) oxo-pyrrole metabolite, followed by glucuronyl- and sulfate conjugation
Toxicologically significant compounds (animals, plants and the environment)	Parent compound and metabolites
Acute toxicity	
Rat, LD_{50}, oral	> 5000 mg/kg bw (no deaths)
Rat, LD_{50}, dermal	> 2000 mg/kg bw (no deaths)
Rat, LC_{50}, inhalation	> 2.6 mg/l (no deaths)
Rabbit, dermal irritation	Not irritating
Rabbit, eye irritation	Slight irritant
Skin sensitization	Not sensitizing (Magnusson & Kligman test)
Short-term studies of toxicity	
Target/critical effect	Damage to liver (rats and dogs) and kidney (mice and rats)
Lowest relevant oral NOAEL	1000 ppm, equal to 33 mg/kg bw per day (12-month study in dogs)
Lowest relevant dermal NOAEL	200 mg/kg bw per day (rats)
Lowest relevant inhalation NOAEC	—
Genotoxicity	Unlikely to pose a genotoxic risk in vivo
Long-term studies of toxicity and carcinogenicity	
Target/critical effect	Reduced body-weight gains and liver necrosis in rats, liver and kidney damage in mice
Lowest relevant NOAEL	1000 ppm, equal to 37 mg/kg bw per day, in rats
Carcinogenicity	Not carcinogenic in rats or mice; unlikely to pose a carcinogenic risk to humans
Reproductive toxicity	
Reproductive target/critical effect	Reduced pup weight gains in rats at parentally toxic doses
Lowest relevant reproductive NOAEL	300 ppm, equal to 21 mg/kg bw per day
Developmental target/critical effect	None
Lowest relevant developmental NOAEL	300 mg/kg bw per day (the highest dose tested in rabbits)
Neurotoxicity/delayed neurotoxicity	No evidence of neurotoxicity in any study conducted
Other toxicological studies	Studies on plant metabolites and a photolytic/hydrolytic degradation product of fludioxonil indicated that these were of no greater toxicity than the parent compound
Medical data	Medical monitoring since 1992 of employees engaged in the manufacture of fludioxonil, or its formulation, into products has not revealed any adverse health effects

Summary	***Value***	***Study***	***Safety factor***
ADI	0–0.4 mg/kg bw	2-year study in rats (liver effects and reduced body-weight gains)	100
ARfD	Unnecessary	—	—

RESIDUE AND ANALYTICAL ASPECTS

Fludioxonil, or 4-(2,2-difluorobenzo[1,3]dioxol-4-yl)-1*H*-pyrrole-3-carbonitrile, is a fungicide that belongs to the chemical class phenylpyrroles. It functions by blocking the protein kinase which catalyses the phosphorylation of a regulatory enzyme of glycerol synthesis. It is specific for a limited number of fungi. It was evaluated for the first time by the 2004 Joint Meeting.

Metabolism

Animals

The metabolism of ^{14}C-pyrrole-labelled fludioxonil was studied in goats and laying hens. Two goats were given radiolabelled fludioxonil orally at a level equivalent to 100 ppm in the feed for 4 consecutive days. The levels of radioactive residue, calculated as fludioxonil, were: 0.07 mg/kg in tenderloin muscle, 0.19 mg/kg in fat, 5.8 mg/kg in liver, 2.9 mg/kg in kidney and 2.2 mg/kg in milk on day 4. Organic solvents released 35% of the TRR in liver, 76% in muscle, 50% in kidney, 35% in liver, 87% in fat and 90% in milk. Protease treatment of the solid residues from solvent extraction of liver, kidney and muscle released 75–91% of the remaining activity. Less than half of this released activity was characterized as proteins by derivatization with 2,4-dinitrofluorobenzene.

The main component identified in muscle was fludioxonil, representing 24% and 43% of the TRR in the two goats. Likewise, fludioxonil was the main component of the residue in omental fat, representing 83% TRR. The main identified metabolite in muscle was the sulfate conjugate of the 2-hydroxy or 5-hydroxy derivative of fludioxonil (22% or 2% TRR). Minor metabolites identified in muscle (< 10% TRR) included the 2-*O*-glucuronide derivative of fludioxonil and the 5-*O*-glucuronide derivative of fludioxonil. (The position numbers refer to the pyrrole ring.) About 50% of the residue in muscle and 83% of the residue in fat were identified.

Multiple components were found in kidney and liver. The following were identified in kidney: 2-*O*-glucuronide derivative of fludioxonil (23% TRR); 7′-*O*-glucuronide derivative (8% TRR); 5-*O*-glucuronide derivative (15% TRR); fludioxonil (2% TRR); and 2- or 5-*O*-sulfate ester (0.7% TRR), for a total identification of 48%. In liver, only fludioxonil was identified (14% TRR). Two labile compounds (24% TRR) were also encountered. No compounds without the pyrrole–phenyl linkage were identified.

On the basis of the identified and characterized residues, the Meeting concluded that the metabolism of fludioxonil via the oral route in goats involves oxidation of the pyrrole ring at the 2 and 5 positions, followed by rapid conversion to sulfate and glucuronide conjugates. A minor route involves oxidation of the benzodioxol ring at the 7′ position and conversion to the glucuronide conjugate. Evidence was also found for substantial incorporation into natural products, including proteins, in kidney and liver.

Five laying hens were given gelatin capsules containing [^{14}C-pyrrole]fludioxonil for 8 consecutive days at a rate equivalent to about 89 ppm in the feed. The vast majority of the radiolabelled residue was eliminated in the excreta (88–102% of the total administered dose). The levels of radioactive residues, calculated as fludioxonil, in the tissues and eggs were as follows: liver, 8.9 mg/kg; muscle, 0.12 mg/kg; skin with fat, 0.25 mg/kg; peritoneal fat, 0.17 mg/kg; egg yolk, 1.8 mg/kg (day 7); egg white, 0.054 mg/kg (day 7).

A series of organic solvent extractions released 61% TRR in liver, 33% in kidney, 62% in muscle, 42% in skin with fat, 74% in egg white and 83% in egg yolk. The solids remaining after solvent extraction of liver (33% TRR), kidney (54%) and muscle (34%) were solubilized with protease and characterized by treatment with 2,4-dinitrofluorobenzene. Protease solubilized 54% of the unextracted activity in liver, 63% of that in kidney and 67% of that in muscle. About 25% of the released radioactivity (< 10% TRR) was derivatized by 2,4-dinitrofluorobenzene at pH 2, indicating the terminal amino group of amino acids.

Alkaline hydrolysis (15% KOH, 95 ^{o}C) released all the remaining radioactivity from the solvent-extracted liver (33% TRR), but it could be characterized only as acidic, polar compounds.

About 69% of the TRR in eggs, 24% in liver, 14% in kidney, 44% in muscle and 29% in skin with fat were identified. The main metabolites identified in eggs were the sulfate conjugate of the 1-hydroxy derivative of fludioxonil (40% TRR) , the succinamic acid derivative (10% TRR) and the sulfate conjugate of the 2-hydroxy or 5-hydroxy derivative (13% TRR). Fludioxonil was a minor component (2.1% TRR) in eggs. The succinamic acid derivative was the only significant metabolite identified in liver, at about 6% TRR. The metabolites identified in kidney were the glucuronide conjugate of the 2-hydroxy or 5-hydroxy derivative (4.7% TRR), fludioxonil (2.6% TRR) and the 7′-hydroxy derivative (2.8% TRR). The main components identified in breast muscle were fludioxonil (29% TRR) and the sulfate conjugate of the 1-hydroxy derivative. A similar situation existed for skin with attached fat, which contained fludioxonil (9.8%) and the sulfate conjugate of the 1-hydroxy derivative (14%).

On the basis of the characterizations and identifications made in the study of metabolism in hens, the Meeting concluded that metabolism in poultry involves oxidation at the C-2, C-5 and N-1 positions in the pyrrole ring and at the C-7′ of the benzodioxol ring. This is followed by the formation of sulfate or glucuronide conjugates. The C-2 hydroxypyrrole further oxidizes to the 2,5-dioxo-2,5-dihydro pyrrole and succinamic acid derivatives. The last two compounds are unique to poultry. The remaining metabolites found in the hen and all the metabolites in ruminants were also found in rats. The studies of metabolism in rats were reviewed by the WHO Expert Group of the 2004 JMPR.

Plants

The metabolism of radiolabelled fludioxonil resulting from its foliar application has been studied in grape, tomato, peach, green onion and head lettuce. Grape vines were sprayed three times at 3-week intervals with [pyrrole-4-C^{14}] fludioxonil at a rate of 500 g ai/ha per application. Samples of grapes and leaves were taken at intervals, immediately after the first application, up to grape maturity 35 days after the final application. Grapes at maturity contained 2.5–2.8 mg/kg of radiolabelled residue, calculated as fludioxonil. About 57% of the TRR was a surface residue, released by a methanol–water rinse; another 32% of the TRR was released by solvent extraction. The leaves at maturity contained 5.2 mg/kg of radiolabelled residue, 52% as a surface residue and 44% solvent extracted.

The residues in grapes and leaves were extensively identified. In grapes at maturity, seven compounds were identified, but only fludioxonil at 70% TRR exceeded 2% TRR. The metabolites included the succinamic acid derivative (< 1% TRR), the 3-hydroxy succinamic acid derivative (< 1% TRR), the glucose conjugate of 2-hydroxyacetamide benzodioxol (< 1% TRR), 2-hydroxyacetamide benodioxol (< 1% TRR), the 2-hydroxy-5-oxo derivative (2% TRR), the 2,5-dioxo derivative (< 1% TRR) and the 1-hydroxy-2,5-dioxo derivative (< 1% TRR). Similar metabolites were identified in leaves, fludioxonil representing 69% of the TRR; no other metabolite exceeded 6% TRR.

The metabolism of [pyrrole-4-^{14}C]fludioxonil was studied in greenhouse tomato plants that were sprayed three times at 2-week intervals with a wettable powder formulation at a single application rate of 750 g ai/ha. Forty days after the last application, leaves and tomatoes were sampled. The leaves contained a fludioxonil-equivalent radiolabelled residue level of 7.0 mg/kg, and the tomatoes contained 0.28 mg/kg. Of the residue on tomatoes, 41% was on the surface. Rinsing and solvent extraction released 95% of the residues in tomatoes and 95% of those in leaves. About 73% of the tomato residue and 69% of the leaf residue was fludioxonil. Five metabolites, representing 3.6% of the TRR in tomato, were identified. These were the same metabolites as in grapes, except that the 2,5-dioxopyrrole derivative was not found and the benzodioxole-4-carboxylic acid derivative was present but at below the LOQ (< 0.001 mg/kg).

The metabolism of [phenyl-U-^{14}C]fludioxonil was studied in peaches. Three foliar applications at 30-day intervals were made at 130 and 1300 g ai/ha, starting at petal fall. Mature fruit was collected 28 days after the second treatment. In a second trial, two applications, 950 and 2860 g ai/ha, were made at a 35-day interval, starting at petal fall. Samples of immature and mature fruits were taken 30 and 114 days after the second application. The radiolabelled residue level, calculated as fludioxonil, was 0.083 mg/kg and

0.98 mg/kg in the first trial after application at 130 and 1300 g ai/ha, respectively. The residue level on mature peaches in the second trial was 0.26 mg/kg (114-day PHI).

Extraction with acetonitrile:water:acetic acid (80:20:1, v/v) released ≥ 88% TRR in all cases. Analyses were conducted on extracts from 28-day peaches treated at 130 and 1300 g ai/ha in the first trial and on 114-day peaches from the second trial. Fludioxonil was the main component in all cases, ranging from 22% TRR to 62% TRR. Eight metabolites were identified in the 114-day PHI peaches, of which four are also grape or tomato metabolites (succinamic acid derivative, 3% TRR; 2-hydroxy-5-oxo derivative, 1.4% TRR; 2-hydroxy-5-oxo derivative, 1% TRR; benzodioxole-4-carboxylic, 1% TRR). The other metabolites included oxidized fludioxonil glucose conjugates at 7% TRR and an oxirane-2-carboxylic acid derivative at 3% TRR. About 54% of the TRR in peach was identified.

The metabolism of [phenyl-U-^{14}C]fludioxonil on green onions was studied after radiolabelled fludioxonil was applied twice at a 14-day interval at a rate of 560 or 680 g ai/ha and at 2800 or 3380 g ai/ha. Samples were taken at maturity (14-day PHI) and at other intervals. TRR as fludioxonil represented 1.6 mg/kg on the onions given the 560 or 680 kg ai/ha treatment and 10 mg/kg on those given the 2800 or 3380 g ai/ha treatment. After the 2800 or 3380 g ai/ha treatment, 51% of the TRR was souble in organic solvents and 21% in water.

The metabolitic profiles were qualitatively similar at the two treatment levels and at the various sampling intervals. In the onions treated at 2800 or 3380 g ai/ha at mature harvest (14-day PHI), fludioxonil comprised 49% of the TRR. Six metabolites were identified, but none represented > 2% TRR. These were the same metabolites identified in the studies of grape, tomato and peach metabolism.

The metabolism of [pyrrole-4-^{14}C]fludioxonil on head lettuce was studied after three foliar treatments at 10-day intervals at 200 g ai/ha. A second experiment was conducted at 600 g ai/ha per application. With a 6-day PHI, the TRR calculated as fludioxonil was 1.3 mg/kg after treatment at 200 g ai/ha and 5.8 mg/kg at 600 g ai/ha treated. Almost 100% of the radioactivity was extracted with methanol:water. Fludioxonil was the main component (68% TRR after the 200 g ai/ha treatment, 80% after the 600 g ai/ha treatment).

Six metabolites, four of which corresponded to metabolites in the studies of tomato, grape and peach, were identified. No metabolite exceeded 3% TRR. Metabolites unique to head lettuce were lactic acid conjugates of fludioxonil (1–2% TRR).

Several studies were also conducted on metabolism after seed treatment. Seed potatoes were treated with [pyrrole-4-^{14}C]fludioxonil at a rate of 2.5 g ai/100 kg seed. The pieces were planted, and mature potatoes were harvested after 95 days. The tuber contained 0.006 mg/kg radiolabelled residue, calculated as fludioxonil. Fludioxonil represented 21% of the TRR.

Rice seeds were soaked in a [pyrrole-4-^{14}C]fludioxonil solution equivalent to 6.5 kg ai/100 kg seed. Rice plants were grown in a glasshouse and harvested at maturity, 152 days after treatment. Stalks, hulls and seeds contained ≤ 0.002 mg/kg radiolabelled residue as fludioxonil equivalents.

The metabolism of [pyrrole-4-^{14}C]fludioxonil was studied in field-grown spring wheat plants treated at 7.4 g ai/100 kg seed. Plants were harvested 48 days (ear emergence), 83 days (milky stage) and 106 days (maturity) after treatment. At 48 days, stalks contained 0.005 mg/kg of radioactive residue (calculated as fludioxonil). At 83 days, stalks contained 0.004 mg/kg and ears contained 0.002 mg/kg. At maturity, stalks contained 0.015 mg/kg, husks contained 0.005 mg/kg, and grain contained 0.003 mg/kg.

Cotton-seed was treated at a rate of 2.5 or 5.0 g ai/100 kg seeds with [pyrrole-4-^{14}C]fludioxonil and then planted in sandy loam soil in pots. Plants were sampled at maturity, 186 days after treatment. Cotton-seed treated at 5.0 g ai/100 kg seed contained 0.003 mg/kg TRR, and those treated at 2.5 g ai/100 kg contained 0.012 mg/kg. Only 20–30% of the radioactivity could be extracted.

Soya bean seeds were treated with [pyrrole-4-^{14}C]fludioxonil at a rate of 5.0 g ai/100 kg seed and grown to mature plants in a greenhouse. The plants were sampled at intervals of 28 days after planting (sixth

node stage), 38 days (mid- to full bloom stage) and 133 days (maturity). Soya bean forage (sixth node) contained 0.096 mg/kg TRR, calculated as fludioxonil. Soya bean hay (mid-flowering) contained 0.041 mg/kg. At maturity, stalks contained 0.005 mg/kg, dry beans contained 0.015 mg/kg, and dry hulls contained 0.012 mg/kg. The main tentatively identified component in forage and hay was 6-hydroxy-2*H*-chromeno[3,4-*c*]pyrrol-4-one, representing 2% TRR.

The metabolism of fludioxonil in and on plants after foliar and seed treatment is adequately understood. Generally, the residue concentrations resulting from seed treatment were too low to permit extraction and identification. The numerous studies of foliar application indicate a similar metabolic pathway, showing fludioxonil as the main component of the residue.

The pathway is characterized by the generation of a large number of metabolites and proceeds mainly through oxidation. Each metabolite represents < 10% TRR. With the exception of oxidation at the 7′-C of the benzoldioxol ring, the oxidations and conjugations occur at the C-2, C-5 and N-1 positions of the pyrrole ring. Ultimately, cleavage of the pyrrole ring, probably via the formation of succinamic acid derivatives, results in formation of 2,2-difluorobenzo[1,3]dioxole metabolites. In studies with pyrrole- or phenyl-labelled ^{14}C-fludioxonil, no metabolites were found, indicating cleavage of the bond between the phenyl and pyrrole ring.

No information was provided on the degradation of fludioxonil when applied post-harvest. Nevertheless, the use of both short and long PHIs in the trial on metabolism in peaches after foliar application provides some indication of the fate of fludioxonil when applied to fruit post-harvest. The study of metabolism in peach shows that the main constituent in the residue is fludioxonil.

Soil

The degradation of fludioxonil on soil exposed to light is rapid, with a half-life of < 1 day for the component of fludioxonil on the surface. On the basis of isolated and identified degradates in studies of radiolabelled compound, it would appear that fludioxonil degrades to 4-(2,2-difluorobenzo[1,3]dioxol-4-yl)-2,5-dioxo-2,5-dihyrdo-1*H*-pyrrole-3-carbonitrile or the 2,5-dioxo derivative of fludioxonil. This metabolite undergoes epoxidation at the C-3 to C-4 position and pyrrole ring opening to give 3-carbamoyl-2-cyano-3-(2,2-difluorobenzo[1,3]dioxol-4-yl)oxirane-2-carboxylic acid. The latter degrades to 2,2-difluoro-benzo[1,3]-dioxole-4-carboxylic acid, a compound found in the studies of rotational crops (see below).

The breakdown of fludioxonil in soil under aerobic conditions with no exposure to light is slow. Mineralization to carbon dioxide is the main route of breakdown (4–45% of applied radioactivity). Some unextractable residues (8–27%) also form. The half-life in sandy loam soil is approximately 250 days.

Four studies of confined rotational crops were conducted with [pyrrole-4-^{14}C]fludioxonil. In the first study, soil was sprayed with [pyrrole-4-^{14}C]fludioxonil at a rate of 750 g ai/ha, and lettuce, winter wheat, sugar beets and maize were planted after intervals of 90, 140, 320 and 345 days, respectively. Lettuce at maturity (152 days post-treatment) contained 0.006 mg/kg radiolabelled residue, winter wheat stems and grain contained 0.008 and 0.002 mg/kg 429 days post-treatment, sugar beet roots and tops contained 0.001 and < 0.001 mg/kg, respectively, and maize stalks and grain contained 0.005 and < 0.001 mg/kg, respectively, at maturity (519 days after treatment). The concentrations of residue were too low to pursue isolation and identification.

In a follow-up study, spring wheat, mustard and turnips were planted 33 days after application of [pyrrole-4-^{14}C]fludioxonil to bare ground at a rate of 120 g ai/ha. At maturity, the residue levels were < 0.01 mg/kg (TRR) in the turnips and mustard greens and 0.006 mg/kg in wheat grain. In 25% mature wheat forage (109 days post-treatment) and in wheat straw (175 days post-treatment), however, the residue levels were 0.058 and 0.12 mg/kg, respectively. The following components were identified in immature wheat forage: fludioxonil (2.4% TRR, 0.001 mg/kg), 6-hydroxy-2*H*-chromeno[3,4-*c*]pyrrol-4-one (11% TRR, 0.006 mg/kg, tentative identification), 4-hydroxy-2,5-dione derivative (4.2% TRR, 0.002 mg/kg), 2,5-dioxo derivative (< 0.001 mg/kg, tentative identification), 2,2-difluoro-benzo[1,3]dioxole-4-carboxylic acid (2.3%

TRR, 0.001 mg/kg, tentative identification) and 2-(2,2-difluorobenzo[1,3]dioxol-4-yl)-2-hydroxyacetamide (< 0.001 mg/kg, tentative identification). Fludioxonil (< 0.001 mg/kg) and similar metabolites at similar concentrations were detected in wheat straw. This work was confirmed by another experiment conducted at 60 g ai/ha.

In a final trial, [phenyl-U-^{14}C]fludioxonil was sprayed onto bare ground at a rate of 1120 g ai/ha. Rotational crops of spring wheat, mustard and radishes were planted 30, 90 and 210 days after treatment and grown to normal maturity. Radish tubers contained 0.14, 0.019 and 0.019 mg/kg of radiolabelled residue at plant-back intervals of 30, 90 and 210 days, about 50% of which could be extracted with organic solvents and water. Mustard greens contained 0.033, 0.044 and 0.050 mg/kg at 30, 90 and 120 days after treatment. Mature wheat straw contained 0.36, 0.14 and 0.11 mg/kg radiolabelled residues, and grain contained 0.058, 0.021 and 0.019 at 30, 90 and 120 days plant-back, of which about 40% from straw and 20% from grain was extractable.

The main metabolite identified in the various commodities was 2,2-difluorobenzo[1,3]dioxole-4-carboxylic acid, at levels ranging from 4.4% TRR in mature wheat straw (30-day plant-back) to 38% TRR (radish tuber, 90-day plant-back). Fludioxonil generally represented < 4% TRR (≤ 0.001 mg/kg) in all matrices except mature radish tuber (30-day plant-back), in which it represented 12% TRR or 0.016 mg/kg.

Field rotational crop studies were conducted in which fludioxonil was applied four times to bare soil at 280 g ai/ha per application, followed at plant-back intervals of 30, 90, 150 and 210 days by sowing of wheat, turnips and leaf lettuce. The mature crops contained no detectable residues of fludioxonil at any plant-back interval, with a LOQ of 0.01 mg/kg.

The nature and extent of the residue in rotational crops after use of fludioxonil on the primary crop is adequately delineated. Similar patterns were observed with pyrrole- and phenyl-labelled ^{14}C-fludioxonil, although somewhat greater concentrations of residue were encountered with the phenyl label. In these trials, fludioxonil was not taken up into rotational crops at plant-back intervals as short as 30 days. The metabolism of fludioxonil in the crops was apparently the same as that seen in target crop studies, but this conclusion is speculative as little or no residue was generally found. Primarily on the basis of the confined study with [phenyl-U-^{14}C]fludioxonil, the metabolism and degradation of this compound is characterized by oxidation and cleavage of the pyrrole ring. No metabolites of cleavage of the bond between the phenyl and the pyrrole ring were observed. The proposed metabolic and degradation pathway is that suggested for foliar application of fludioxonil.

The Meeting concluded that the presence of fludioxonil residues in succeeding (rotational) crops from foliar applications is unlikely.

Methods of analysis

The Committee concluded that adequate analytical methods exist for both monitoring and enforcing MRLs and for gathering data in supervised field trials and processing studies. Methods REM-133/AG631A and AG-597 are suitable for the determination of fludioxonil in samples of plant origin. The methods are fully validated for a range of crops and crop types. In addition, fludioxonil residues can be determined in samples of plant origin by European multi-residue method DG S17.

Method REM-133 involves high-performance liquid chromatography (HPLC) with ultraviolet detection (268 nm). Only fludioxonil is determined. Samples are extracted and then placed on a phenyl solid-phase extraction cartridge and eluted with the appropriate solvent. The samples are analysed by HPLC with column switching (C-18 and phenyl). The validated LOQ is 0.01–0.04 mg/kg. In some European field trials, method REM 133 was modified by the use of only one HPLC column (amino) with a fluorescence detector (excitation, 265 nm; emission, 312 nm). The method was radiovalidated. In this method, 89% of the total radioactivity was solubilized, and 66% of the fludioxonil determined in the metabolism study was identified.

Method AG-597 is another HPLC method with ultraviolet detection (268 nm). Only fludioxonil is determined. Samples are extracted and then cleaned-up by silica solid-phase extraction. Analysis is usually conducted on an amino or a C18 column. The method was validated with a wide array of commodities, with limits of determination of 0.01–0.02 mg/kg, except for sorghum grain, for which the limit was 0.05 mg/kg. The method was validated by the US Environmental Protection Agency. Liquid chromatography with mass spectrometry can be used for confirmation, with quantification on ion 247.

A European multi-residue method based on DFG S19 was developed for an array of plant commodities. Extracts are separated by gel permeation chromatography and analysed by capillary gas chromatography with a mass selective detector, monitoring ions 248, 154 and 127. The method was validated for fludioxonil only at 0.02 mg/kg for tomato, orange, wheat and rape and at 0.01 mg/kg for grape wine.

The Meeting concluded that an adequate method exists for the determination of fludioxonil and certain metabolites in livestock commodities (meat, milk, poultry, eggs). In the HPLC method, fludioxonil and metabolites are converted to 2,2-difluoro-1,3-benzodioxole-4-carboxylic acid. The resulting residue is quantified by external calibration against standards of this conversion product, with HPLC and a ultraviolet detector (230 nm). Column switching is used, and alternate columns are specified as a confirmatory procedure. The method was validated at 0.01 mg/kg for muscle and milk and at 0.05 mg/kg for eggs, fat, liver and kidney.

Stability of residues in stored analytical samples

The Meeting concluded that fludioxonil is stable in an array of stored frozen commodities. No degradation of fludioxonil was observed in any frozen commodity throughout the duration of the studies. Fludioxonil is stable for at least 24 months in frozen samples of the following commodities: cereal grains, cereal straw, apple, tomato, grape, pea, rape-seed, maize grain, maize meal, sorghum hay, potato tuber and potato flake. Fludioxonil is stable for at least 12 months in frozen broccoli, cabbage and carrots and for 9 months in frozen chives. Fludioxonil is also stable for at least 3 months in frozen peach, plum, cherry and blueberry.

The Meeting also concluded that fludioxonil and metabolites, determined as 2,2-difluoro-1,3-benzodioxole-4-carboxylic acid, are stable for at least 12 months in frozen muscle and for at least 18 months in frozen liver, milk and eggs.

Definition of the residue

The results of the studies of metabolism after both seed treatment and foliar treatment show that the main identified component of the radiolabelled residue is fludioxonil. The identified metabolites generally represent < 10% of the TRR. The toxicological evaluation did not reveal any metabolites of special concern relative to the parent. The Meeting concluded that the residue definition for plant commodities for compliance with MRLs and for estimation of dietary intake is fludioxonil.

In the analytical methods for plant commodities, HPLC with ultraviolet detection or gas chromatography with mass spectrometry detection, only fludioxonil is determined.

The results of the studies of metabolism in goats and hens were similar. In goats, the main identified metabolite in meat, fat and liver was fludioxonil, representing 33%, 83% and 14% TRR, respectively. The main metabolite in milk and kidney was the pyrrole carbonitrile-*O*-glucuronide, representing 65% and 31% TRR, respectively, and the parent was absent. In hens, fludioxonil was present in muscle (7.9–28.% TRR) and skin plus attached fat (9.8%). It accounted for 1.2% of the TRR in liver, 2.6% in kidney and 2.2% in egg yolk (equivalent to 2.1% egg TRR). The main identified component of the radioactive residue in eggs and fat was the sulfate conjugate of 4-(2,2-difluorobenzo[1,3]dioxol-4-yl)-1-hydroxy-1*H*-pyrrole-3-carbonitrile. The benzene–pyrrole linkage was intact in all the identified metabolites. The toxicological evaluation did not reveal any metabolites of particular concern relative to the parent.

The P_{ow} for fludioxonil is 4.1, suggesting that fludioxonil is fat-soluble. In goats, the radioactive residue represented 0.07 mg/kg TRR in muscle and 0.26 mg/kg in fat. The main component in muscle and fat was fludioxonil (24–43% TRR in muscle and 83% in fat). The Meeting concluded that the fludioxonil residue is fat-soluble, but it also noted the lack of information on milk fat from both the metabolism and the feeding study.

In the validated analytical method for fludioxonil, fludioxonil and pyrrole-derivative metabolites are converted to 2,2-difluorobenzo[1,3]dioxole-4-carboxylic acid.

The Meeting concluded that the residue definition of the residue for livestock commodities (for compliance with MRLs and for estimation of dietary intake) is the sum of fludioxonil and its benzopyrrole metabolites, determined as 2,2-difluoro-benzo[1,3]dioxole-4-carboxylic acid and expressed as fludioxonil.

Results of supervised trials on crops

Supervised trials were conducted with foliar treatment, seed treatment and post-harvest treatment of a variety of crops worldwide.

Citrus fruit

Citrus (orange, lemon, grapefruit) was treated by post-harvest dip (120 g ai/hl) or spray (1000 g ai/250 000 kg fruit) in 28 trials conducted in the USA. GAP specifies a maximum of two treatments, one on entering storage and a second on exit of storage for market distribution, at a single application rate of 500 g ai/250 000 kg fruit (2 mg/kg; 0.85 kg ai/hl for droplet-type applications with a low-volume concentrate, 0.24 kg ai/hl for high-volume jet-type sprays) and 0.06 kg ai/hl for 30-s dip treatments. All trials were conducted at twice GAP in a single-application dip or high-volume spray, and nine of the trials included a second application at twice GAP with a re-treatment interval of 0 days. In the absence of data on residue level decline during storage of citrus, the Meeting considered application at twice GAP an approximation of the practical situation of two treatments at GAP with a variable interval between applications.

The residue levels on orange (six trials; one treatment at twice GAP), in ranked order, were: 0.48, 0.90, 1, 1.4, 2.2 and 2.8 mg/kg. The levels on lemon (seven trials; one treatment at twice GAP) were: 0.46, 0.54, 1., 1.1 (two), 2.9 and 3.2 mg/kg, and those on grapefruit (six trials; one treatment at twice GAP) were: 0.51, 0.94, 0.95, 1.4, 3.8 and 5.2 mg/kg. The nine trials consisting of two sequential applications, each at twice the GAP application rate, were considered exaggerations and were not used; the residue levels ranged from 0.52 mg/kg to 6.0 mg/kg.

The Meeting decided to combine the data; the residue levels on citrus (19 trials; one treatment at twice GAP single rate), in ranked order, were: 0.46, 0.48, 0.51, 0.54, 0.90, 0.94, 0.95, 1 (two), 1.1 (two), 1.4 (two), 2.2, 2.8, 2.9, 3.2, 3.8 and 5.2 mg/kg. Data on residues in pulp were available from only one trial on oranges, in which flesh and peel contained approximately equal concentrations of fludioxonil. The Meeting estimated a maximum residue level for whole citrus of 7 mg/kg and an STMR of 1.1 mg/kg.

Pome fruit

Apples were treated by post-harvest dip or spray in the USA with a 50% wettable powder formulation. GAP specifies a maximum of two treatments, one on entering storage and a second on exit from storage for market distribution, at a single application rate of 500 g ai/250 000 kg fruit (2 mg/kg; 0.85 kg ai/hl for droplet-type applications with a low-volume concentrate, 0.24 kg ai/hl for high-volume jet-type sprays) and 0.06 kg ai/hl for dip treatments of approximately 30 s. Seven trials were conducted at approximately the GAP rate (single application), and two trials were conducted at the GAP rate with two sequential applications: dip at 0.06 kg ai/hl, followed by packing-line spray at 2.5 mg/kg (125% GAP). As GAP specifies two treatments, the Meeting regarded the two trials conducted with two applications as an approximation of GAP. The residue levels were 2.0 and 2.2 mg/kg. The Meeting considered two trials inadequate for estimating a maximum residue level.

Pears were treated by post-harvest dip or spray treatment in the USA with a 50% wettable powder formulation. GAP is identical to that for apples. Twelve trials were conducted, but only two were conducted with two applications: 0.048 kg ai/hl drench (80% dip GAP), followed by a packing-line spray at 0.2–0.6 kg ai/hl or 2.2–6.6 mg/kg fruit (110–300% GAP). As GAP specifies two treatments, the Meeting regarded the two trials conducted with two applications as an approximation of GAP. The residue levels (with an exaggerated rate for the second application) were 1.6 and 2.8 mg/kg. The Meeting considered two trials insufficient for estimating a maximum residue level.

The Meeting considered combining the post-harvest trials on pear and apple (same GAP) for mutual support, but considered four trials insufficient for these commodities.

Pears received foliar treatment with a 25% water-dispersible granule formulation in seven trials conducted at GAP (three in Italy , three in Spain and one in France). The GAPs are as follows: Italy, 0.02 kg ai/hl, 0.25 kg ai/ha, three applications, 14-day PHI; Spain, 0.025 kg ai/ha, 0.25 kg ai/ha, three applications, 7-day PHI. No GAP was available for France, and the GAP of Spain was applied to all trials (7-day PHI). The residue levels, in ranked order, were: 0.14, 0.15, 0.18, 0.21, 0.28, 0.32 and 0.36 mg/kg. The Meeting estimated a maximum residue level of 0.7 mg/kg and an STMR of 0.21 mg/kg.

Stone fruit

In seven post-harvest treatment trials (spray or dip), *peaches* were treated at the GAP of 0.06 kg ai/hl with a 50% wettable powder formulation. The residue levels on peaches after treatment (no storage interval), in ranked order, were: 0.37, 0.42, 1.6, 2.2, 2.8, 3.4 and 3.6 mg/kg

Trials of foliar application of fludioxonil (62.5% water-dispersible granules, 25% fludioxonil) were conducted in France, Italy and Spain. The relevant GAPs are: France, 0.015 kg ai/hl, 14-day PHI; Italy, 0.015 kg ai/hl, 0.25 kg ai/ha, two applications, 14-day PHI. No GAP was available for Spain, and the GAP of Italy was applied. The residue levels in 11 trials at GAP, in ranked order, were: 0.02, 0.04 (two), 0.08 (two), 0.11, 0.23 (two), 0.29 and 0.33 mg/kg. The data set on post-harvest treatment contained the highest residue values and was used to estimate the maximum residue level and the STMR.

Post-harvest treatment of *plums* was investigated in two trials in the USA. GAP is spray application at 0.06 kg ai/hl of a 50% wettable powder formulation. The results were 0.10 and 0.92 mg/kg. As the results for post-harvest treatment of plums were not statistically significantly different from those for peaches with the same GAP, the populations can be combined for mutual support.

Trials of foliar application of fludioxonil (22.5% water-dispersible granules, 25% fludioxonil) to plums were conducted in France, Italy, Germany and Switzerland. The relevant GAPs are: France, 0.012 kg ai/hl, 0.12 kg ai/ha, three applications, 14-day PHI; Italy, 0.025 kg ai/hl, 0.25 kg ai/ha, two applications, 14-day PHI; Switzerland, 0.3 kg ai/ha, two applications, PHI not specified. GAP in Germany was not available, and the GAP of Italy was applied. In 12 trials at GAP, the residue levels, in ranked order, were: < 0.02, 0.03, 0.04, 0.05, 0.06 (two), 0.065, 0.07, 0.09, 0.10, 0.11 and 0.17 mg/kg. The data set on post-harvest treatment contained the highest residue values and was used to estimate the maximum residue level and the STMR.

Post-harvest treatment of *cherries* was investigated in two trials in the USA. GAP is spray application at 0.06 kg ai/hl of a 50% wettable powder formulation. The reside levels were 0.19 and 0.68 mg/kg. As the results for post-harvest treatment of cherries were not statistically significantly different from those for peaches, with the same GAP, the populations can be combined for mutual support.

A 25% water-dispersible granule formulation of fludioxonil was applied as a foliar spray to cherries in Europe. In six trials, the residue levels ranged from 0.16 to 0.43 mg/kg after a treatment rate of 0.019 kg ai/hl and a PHI of 7 days. No GAP was provided for any country in Europe.

The results for post-harvest treatment (GAP, dip or spray at 0.06 kg ai/hl) of peaches, plums and cherries were combined. The residue levels in the 11 trials, in ranked order, were: 0.10, 0.19, 0.37, 0.42, 0.68,

0.92, 1.6, 2.2, 2.8, 3.4 and 3.6 mg/kg. The Meeting estimated a maximum residue level of 5 mg/kg and an STMR of 0.80 mg/kg for stone fruit.

Berries and other small fruit

Grape

Trials on foliar treatment of grape vines were available from Chile, France, Germany, Greece, Italy , South Africa, Spain and Switzerland. The relevant GAPs (25% water-dispersible granules) are: Chile, 0.25 kg ai/ha, two applications, 7-day PHI; France, 0.3 kg ai/ha, two applications, 60-day PHI; Germany, 0.015 kg ai/hl, 0.24 kg ai/ha, two applications, 35-day PHI; Italy, 0.02 kg ai/hl, 0.2 kg ai/ha, two applications, 21-day PHI; Spain, 0.25 kg ai/ha, two applications, 21-day PHI; Switzerland, 0.3 kg ai/ha, one application, early season. The residue values at the GAP of Chile, in ranked order, were: 0.18, 0.24 and 0.28 (two) mg/kg. The trials in France (northern), Germany and Switzerland were evaluated against the GAP of Germany, resulting in six trials in Germany (0.17, 0.20, 0.21, 0.24, 0.28, 0.31 mg/kg) and five trials in Switzerland (0.90, 0.99, 1.4, 1.6 (two) mg/kg) at GAP and combined: 0.17, 0.20, 0.21, 0.24, 0.28, 0.31, 0.90, 0.99, 1.4 and 1.6 (two) mg/kg. The GAP of Spain was used to evaluate the trials in Greece, Italy and Spain. The residue levels in two trials in Spain and one in Italy at this GAP were 0.22, 0.41 and 0.43 mg/kg. The Meeting combined the 18 values for Chile, Germany and Switzerland, Spain and Italy (same population) and found a ranked order of: 0.17, 0.18, 0.20, 0.21, 0.22, 0.24 (two), 0.28 (three), 0.31, 0.41, 0.43, 0.90, 0.99, 1.4 and 1.6 (two) mg/kg. The Meeting estimated a maximum residue level of 2 mg/kg and an STMR of 0.28 mg/kg.

Strawberry

Foliar applications of a 50% wettable powder formulation were made to strawberries in the USA, and of a 25% water-dispersible granule formulation in Europe (glasshouse and outdoor). The relevant GAPs are: France, 0.25 kg ai/ha, one application, 3-day PHI; Germany, 0.125 kg ai/hl, 0.25 kg ai/ha, three applications, 7-day PHI; Italy, 0.02 kg ai/hl, 0.2 kg ai/ha, three applications, 7-day PHI; Spain, 0.25 kg ai/ha, three applications, 7-day PHI; Switzerland, 0.025 kg ai/hl, 0.3 kg ai/ha, two applications, 14-day PHI; USA, 0.25 kg ai/ha, four applications, 0-day PHI. The values from the eight trials in the USA in ranked order were: 0.22, 0.43, 0.54, 0.62, 1.0, 1.2 (two) and 1.3 mg/kg. At GAP of Spain and Germany (0.25 kg ai/ha, three applications, 7-day PHI), the values from outdoor trials in Germany were 0.04 and 0.05 (two) mg/kg; those in Switzerland were 0.13 (two) mg/kg; those in France were 0.09, 0.25, 0.61 and 0.77 mg/kg; that in Italy was 0.14 mg/kg; those in Spain were 0.64 and 0.83 mg/kg; and that in the United Kingdom was 0.11 mg/kg. These 13 values may be combined: 0.04, 0.05 (two), 0.09, 0.11, 0.13 (two), 0.14, 0.25, 0.61, 0.64, 0.77 and 0.83 mg/kg. When the European and US populations were combined, the residue levels, in ranked order, were: 0.04, 0.05 (two), 0.09, 0.11, 0.13 (two), 0.14, 0.22, 0.25, 0.43, 0.54, 0.61, 0.62, 0.64, 0.77, 0.83, 1.0, 1.2 (two) and 1.3 mg/kg.

Indoor trials were also conducted in France, Italy, Spain and Switzerland. The ranked order of residue values evaluated against the GAP of Italy was: 0.11, 0.21, 0.27 and 1.9 mg/kg.

When the results of the indoor and outdoor trials were combined, the residue levels in the 25 trials, in ranked order, were: 0.04, 0.05 (two), 0.09, 0.11 (two), 0.13 (two), 0.14, 0.21, 0.22, 0.25, 0.27, 0.43, 0.54, 0.61, 0.62, 0.64, 0.77, 0.83, 1.0, 1.2 (two), 1.3 and 1.9 mg/kg. The Meeting estimated a maximum residue level of 3 mg/kg and an STMR of 0.27 mg/kg.

Raspberry

Foliar applications of a 25% water-dispersible granule formulation of fludioxonil were made to raspberries in Germany and the USA. The relevant GAPs are: Switzerland, 0.025 kg ai/hl, 0.32 kg ai/ha, two applications, 14-day PHI; and USA, 0.25 kg ai/ha, four applications, 0-day PHI. The residue levels, in ranked order, were: 0.19, 0.24 (two) and 0.30 mg/kg in Germany and 0.96, 1.0 (three) and 3.6 mg/kg in the USA.

The Meeting estimated a maximum residue level of 5 mg/kg and an STMR of 1.0 mg/kg for raspberries and extrapolated the values to blackberry and dewberry on the basis of the trials in the USA, which had the highest values.

Blueberry

Foliar applications of a 25% water-dispersible granule formulation of fludioxonil were made to blueberries in Germany and the USA. The relevant GAP is: USA, 0.25 kg ai/ha, four applications, 0-day PHI. No GAP was available for Germany or other European countries. The residue levels in ranked order at GAP in the USÂ were: < 0.05, 0.14, 0.26, 0.52, 0.68, 0.84, 0.90 and 1.4 mg/kg. The Meeting estimated a maximum residue level of 2 mg/kg and an STMR of 0.60 mg/kg.

Black and red currant

Foliar application of a 25% water-dispersible granule formulation of fludioxonil was made to black currants in four trials and to red currants in one trial in Germany. As no GAP is available for Germany or other European countries, the Meeting could not estimate an STMR or maximum residue level.

Assorted tropical andsubtropical fruits

Lychee

Fludioxonil (25% water-dispersible granules) was applied as a foliar spray to lychee in the USA, where GAP is: 0.25 kg ai/ha, four applications, 0-day PHI. The residue levels in ranked order were: 0.81, 0.92 and 1.4 mg/kg. The Meeting noted that five or seven applications were made at about 7-day intervals and that the extra one or three applications would have been made ≤ 21 days before harvest. On the basis of studies of decline in other fruit crops, they might have made a significant contribution (about 25%) to the final residue level. Therefore, the Meeting did not estimate a maximum residue level or an STMR.

Kiwi

Kiwi fruit in the USA were treated post-harvest at 0.06 kg ai/hl with a wettable powder formulation. GAP specifies application of a 50% wettable powder formulation as a dip at 0.06 kg ai/hl for 30 s or as a low-volume application with a control droplet-type application at 0.24 kg ai/hl or 2.5 mg/kg fruit. Trials were conducted, with two methods (dip, spray) at two locations and a single method (dip) at a third. The ranked order of residue levels in the five trials was: 1.6, 5.2, 7.2, 8.6 and 9.0 mg/kg. The Meeting estimated mg/kg a maximum residue level of 15 mg/kg and an STMR of 7.2 mg/kg for kiwi fruit.

Pomegranate

Pomegranate in the USA were treated post-harvest at 0.06 kg ai/hl with a wettable powder formulation. The residue levels were 0.65 and 0.95 mg/kg; however, there is no GAP, and the Meeting could not estimate a maximum residue level or an STMR.

Bulb vegetables

Green (spring) onions

Fludioxonil was applied as a foliar spray of a wettable powder formulation to green onions in the USA. The relevant GAP is 0.25 kg ai/ha, four applications, 7-day PHI. The residue levels in ranked order were 0.14, 0.59 and 3.0 mg/kg. The Meeting estimated a maximum residue level of 5 mg/kg and an STMR of 0.59 mg/kg.

Bulb onion

Fludioxonil (wettable powder formulation) was applied as a foliar spray to onions in France, Italy, Germany and Switzerland and in the USA. The relevant GAPs are: Austria, 0.25 kg ai/ha, three applications, 7-day PHI; Switzerland, 0.25 kg ai/ha, two applications, unspecified PHI; and USA, 0.25 kg ai/ha, four applications, 7-day PHI. GAP in Switzerland (assumed 0-day PHI) was applied to the other European

countries in the absence of a GAP for southern Europe. The residue levels in trials on bulb onions (fresh) at the Swiss GAP were: France, < 0.02, 0.05 and 0.06 mg/kg; and Italy, < 0.02, 0.04, 0.07 and 0.34 mg/kg. The levels in three trials on bulb onions (dry) in the USA at US GAP were: < 0.02 (three), 0.04 (two) and 0.06 mg/kg. The Meeting combined the data sets for Europe and the USA and found a ranked order of residue levels of: < 0.02 (five), 0.04 (three), 0.05, 0.06 (two), 0.07 and 0.34 mg/kg. The Meeting estimated a maximum residue level of 0.5 mg/kg and an STMR of 0.04 mg/kg.

Brassica vegetables

Broccoli

Fludioxonil (water-dispersible granule formulation) was applied as a foliar spray to broccoli in Canada and the USA. The relevant GAP is: 0.25 kg ai/ha, four applications, 7-day PHI. The residue levels in seven trials at US GAP, in ranked order, were: 0.07, 0.10, 0.18, 0.23, 0.26, 0.34 and 0.36 mg/kg. The Meeting estimated a maximum residue level of 0.7 mg/kg and an STMR of 0.23 mg/kg.

Cabbage

Fludioxonil (water-dispersible granule formulation) was applied as a foliar spray to cabbage in the USA. The relevant GAP is: 0.25 kg ai/ha, four applications, 7-day PHI. The residue levels in ranked order on cabbage with wrapper leaves in six trials at GAP were: 0.17, 0.17, 0.21, 0.27, 0.5 and 1.2 mg/kg. The Meeting estimated a maximum residue level of 2 mg/kg and an STMR of 0.24 mg/kg.

Fruiting vegetables

Cucumber

A 25% water-dispersible granule formulation of fludioxonil was applied as a foliar spray (glasshouse and field) to cucumbers in Greece, Spain and Switzerland. The relevant GAPs are: Italy, 0.02 kg ai/hl, 0.20 kg ai/ha, three applications, 7-day PHI; Spain, 0.025 kg ai/hl, three applications, 7-day PHI; Switzerland, 0.025 kg ai/hl, 3-day PHI. GAP for Greece was not available, and that of of Italy and Spain was used. The results from the 10 glasshouse trials (seven in Spain, one in Greece, two in Switzerland) in ranked order were: < 0.02, 0.02 (two), 0.06 (two), 0.07, 0.08 (two), 0.11 and 0.14 mg/kg. The results from the field trials (one in Greece, two in Spain) were: < 0.02, 0.02 and 0.03 mg/kg. The populations are not statistically significantly different, and the combined results are: < 0.02 (two), 0.02 (three), 0.03, 0.06 (two), 0.07, 0.08 (two), 0.11 and 0.14 mg/kg. The Meeting estimated a maximum residue level of 0.3 mg/kg and an STMR of 0.06 mg/kg.

Summer squash (zucchini)

Two indoor trials were conducted on zucchini in Italy. The relevant GAP is: 25% water-dispersible granule, 0.02 kg ai/hl, 0.20 kg ai/ha, three applications, 7-day PHI. The residue levels were 0.05 and 0.06 mg/kg. The Meeting agreed to use the results for cucumber as support for summer squash. The residue levels in ranked order were: < 0.02 (two), 0.02 (three), 0.03, 0.05, 0.06 (three), 0.07, 0.08 (two), 0.11 and 0.14 mg/kg. The Meeting estimated a maximum residue level of 0.3 mg/kg and an STMR of 0.06 mg/kg.

Cantaloupe

A 50% wettable powder formulation was applied to cantaloupe vines (three times 0.28 kg ai/ha, 0.84 kg ai/ha total, 14-day PHI) in the USA by drip irrigation. GAP specifies drip irrigation application of a 50% wettable powder formulation at a rate of 0.28 kg ai/ha. The total seasonal application is limited to 0.84 kg ai/ha, and the PHI is 14 days. The residue levels in ranked order were: < 0.02 (two) and 0.02 (two) mg/kg. The Meeting estimated a maximum residue level of 0.03 mg/kg and an STMR of 0.02 mg/kg for whole melon. No information was available on the residue in pulp.

Tomato

Fludioxonil (25% water-dispersible granules) was applied as a foliar spray in glasshouses (11 trials) and in the field (two trials) in Greece, Spain, Switzerland and the United Kingdom. The relevant GAPs are: