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Pesticide residues in food 2018

Joint FAO/WHO Meeting on Pesticide Residues

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Joint FAO/WHO Meeting on Pesticide Residues

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
Berlin, Germany, 18–27 September 2018

FOOD AND AGRICULTURE ORGANIZATION OF THE UNITED NATIONS
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Contents

R, residue and analytical aspects; T, toxicological evaluation

* New compound

** Evaluated within the periodic review programme of the Codex Committee on Pesticide Residues

List of participants

2018 Joint FAO/WHO Meeting on Pesticide Residues

Berlin, Germany, pre-meeting 13-17 September, and joint meeting 18–27 September 2018

Mr Davide Arcella, Evidence Management Unit (DATA) European Food Safety Authority (EFSA) Via Carlo Magno 1/a, I-43126 Parma, Italy *(WHO Expert)*

Ms Janis Baines, Canberra, Australian Capital Territory, Australia *(WHO Expert)*

Professor Alan R. Boobis, Centre for Pharmacology & Therapeutics, Department of Medicine, Faculty of Medicine, Imperial College London, Hammersmith Campus Ducane Road, London W12 0NN, United Kingdom *(WHO Expert)*

Ms Marloes Busschers, Senior Regulatory Toxicologists, Charles River, PO Box 3476, 5203 DL S-Hertogenbosch, The Netherlands *(WHO Expert)*

Dr Carl E. Cerniglia, Director, Division of Microbiology, National Center for Toxicological Research, HFT-250, US Food and Drug Administration (FDA), 3900 NCTR Road, Jefferson, AR 72079, USA *(WHO Expert)*

Dr Julian Cudmore, Chemistry Team, Health & Safety Executive Chemicals Regulation Division, Room 1E, Mallard House Kings Pool, 3, Peasholme Green, York, YO1 7PX, United Kingdom *(FAO Expert)*

Dr Esther de Jong, Board for the authorisation of plant protection products and biocides. Bemmekomseweg 41, 6717 LL Ede, The Netherlands. *(WHO Expert)*

Dr Ian Dewhurst, Sunnycroft, Leavening, North Yorkshire Y017 9SA, United Kingdom

Dr Mike Dinovi, Supervisory Chemist, CFSAN US Food and Drug Administration 5001 Campus Drive HF5-255, College Park MD 20704, USA *(WHO Expert)*

Dr Michael Doherty, US EPA Office of Pesticide Programs, Health Effects Division Rm 10347 One Potomac Yard, 2777 S, Crystal Drive Arlington, VA 22202, USA *(FAO Chairman)*

Professor Eloisa Dutra Caldas, University of Brasilia, College of Health Sciences, Pharmaceutical Sciences Department, Campus Universitario Darci Ribeiro, Brazil *(FAO Expert)*

Dr David Eastmond, Department of Mollecular, Cell and Systems Biology 2109 Biological Sciences Building University of California, Riverside, California 92521, USA *(WHO Expert)*

Dr Jochen Heidler, Federal Institute for Risk Assessment Unit Residues and Analytical Methods Department Pesticide Safety, Max-Dohrn-Straße 8–10, 10589 Berlin, Germany *(FAO Expert)*

Dr Paul Humphrey, Residues and Trade Section, Scientific Assessment and Chemical Review Program, Australian Pesticides and Veterinary Medicines Authority (APVMA), 18 Worland Street Symonston ACT 2609, Australia *(FAO Expert)*

Mr Makoto Irie, Agricultural Chemicals Office, Plant Products Safety Division, Food Safety and Consumer Affairs Bureau, Ministry of Agriculture, Forestry and Fisheries, 1-2-1 Kasumigaseki, Chiyoda-ku, Tokyo 100-8950, Japan *(FAO Expert)*

Dr Debabrata Kanungo, Chairman Scientific Panel on Residues of Pesticides, Food Safety and Standard Authority of India Nityakshetra 294/Sector-21D, Faridabad 121005, India *(WHO Expert)*

Dr April Kluever, Toxicologist DFCN, CFSAN US Food and Drug Administration (FDA) 4300 River Rd; HFS-275 College Park, MD 20740, USA *(WHO Expert)*

Dr Jean-Charles Leblanc, French Agency for Food, Environmental and Occupational Health and Safety, 14 rue Pierre et Marie Curie 94701 Maisons-Alfort, France *(WHO Expert)*

Dr Mi-Gyung Lee, Dept. of Food Science & Biotechnology, College of Natural Science, Andong National University, #1375 Gyeongdong-ro, Andong-si, Gyeongbuk 760-749, Republic of Korea, *(FAO Expert)*

Ms Kimberley Low, Health Evaluation Directorate Pest Management Regulatory Agency Sir Charles Tupper Building 2720 Riverside Drive Ottawa, Ontario K1A 0K9, Canada *(WHO Expert)*

Mr David Lunn, Principal Adviser (Residues), Plant, Food & Environment Directorate, Ministry for Primary Industries, PO Box 2526, Wellington, New Zealand (*FAO Rapporteur*)

Dr Dugald MacLachlan, Australian Government Department of Agriculture and Water Resources, GPO Box 858, Canberra, ACT 2601, Australia *(FAO Expert)*

Ms Karin Mahieu, National Institute of Public Health and Environment Centre for Nutrition Prevention and Health Services, Department of Food Safety P.O. Box 1, 3720 BA Bilthoven, The Netherlands *(FAO Expert)*

Dr Farag Mahmoud Malhat, Central Agricultural Pesticide, Laboratory, Pesticide Residues, Environmental Pollution Department, 7-Nadi El-Saad St., Dokki, Giza, 12618, Egypt *(FAO Expert)*

Professor Angelo Moretto, Department of Biomedical and Clinical Sciences, University of Milan, Director, International Centre for Pesticides and Health Risk Prevention, ASST Fatebenefratelli Sacco, Via GB Grassi 74, 20157 Milano, Italy (*WHO Expert*)

Dr Lars Niemann, German Federal Institute for Risk Assessment, Dept Safety of Pesticides D - 10589 Berlin, Max-Dohrn-Strasse. 8-10, Germany (*WHO Expert*)

Dr Canping Pan, Department of Applied Chemistry College of Science, China Agricultural University, Yuanminyuan Western Road No. 2, Beijing, 2100193, China, *(FAO Expert)*

Dr Chris Schyvens, Health Assessment Team, Scientific Assessment and Chemical Review Program, Australian Pesticides and Veterinary Medicines Authority (APVMA) 18 Wormald Street, Symonston ACT 2609, Australia (*WHO Expert*)

Dr Prakashchandra V. Shah, Chief, Chemistry, Inerts and Toxicology Assessment Branch, Registration Division (MDTS 7505P), Office of Pesticide Programs, US EPA, 1200 Pennsylvania Avenue NW, Washington DC 20460, USA (*WHO Expert*)

Mr Christian Sieke, Federal Institute for Risk Assessment Unit Residues and Analytical Methods Department Pesticide Safety, Max-Dohrn-Straße 8–10, 10589 Berlin, Germany *(FAO Expert)*

Ms Monique Thomas, Pest Management Regulatory Agency, Health Canada, 2720 Riverside Drive, Ottawa, Ontario K1A 0K9, Canada *(FAO Expert)*

Dr Luca Tosti, International Centre for Pesticides and Health Risk Prevention (ICPS), Asst Fatebenefratelli Sacco, Polo Universitario, Padiglione 17, Via G.B. Grassi 74, 20157 Milano, Italy (*WHO Expert*)

Ms Julie Van Alstine, Risk Assessment Branch 6, Health Effects Division, Office of Pesticide Programs, USA Environmental Protection Agency, MC 7509P – Washington DC – USA *(FAO Expert)*

Ms Trijntje van der Velde-Koerts, Centre for Nutrition, Prevention and Health Services (VPZ)" of the RIVM, Antonie van Leeuwenhoeklaan 9, PO Box 1, 3720 BA Bilthoven, The Netherlands *(FAO Expert)*

Dr Takahiro Watanabe, National Institute of Health Sciences - Ministry of Health, Labour and Welfare, Japan *(FAO Expert)*

Dr Gerrit Wolterink, Centre for Nutrition, Prevention and Health Services (VPZ), National Institute for Public Health and the Environment, Antonie van Leeuwenhoeklaan 9, 3720 BA Bilthoven, The Netherlands, (*(WHO Expert)*

Dr Yukiko Yamada, Ministry of Agriculture, Forestry and Fisheries, 1-2-1 Kasumigaseki, Chiyoda-ku, Tokyo

100-8950, Japan, *(FAO Expert)*

Dr Guibiao Ye, Institute for the Control of Agrochemicals, Ministry of Agriculture, P. R. China, Maizidian 22, Chaoyang District, Beijing 100125, China *(FAO Expert)*

Dr Midori Yoshida, Commissioner, Food Safety Commission, Cabinet Office, Japan, Akasaka Park Bld. 22 Fl., 5-2-20 Akasaka Minato-ku, Tokyo 107-6122, Japan *(WHO Expert)*

Dr Katsuhiko Yoshizawa, Mukogawa Women's University, 6-46 Ikebiraki-cho, Nishinomiya, Hyogo 663-8558, Japan *(WHO Expert)*

Dr Jürg Zarn, Federal Food Safety and Veterinary Office FSVO, Schwarzenburgstrasse 155, CH-3003 Bern, Switzerland *(WHO Expert)*

Secretariat:

Ms Emanuela Aquilini, Plant Production and Protection Division, Food and Agriculture Organization of the United Nations, Viale delle Terme di Caracalla, 00153 Rome, Italy *(FAO JMPR Secretariat)*

Mr Kevin Bodnaruk, West Pymble, NSW 2073, Australia (*FAO Editor)*

Ms Grazia Chiu, Plant Production and Protection Division, Food and Agriculture Organization of the United Nations, Viale delle Terme di Caracalla, 00153 Rome, Italy *(FAO JMPR Secretariat)*

Ms Myoengsin Choi, Food Standards Officer, Joint FAO/WHO Food Standards Programme, Food and Agriculture Organization of the United Nations, Viale delle Terme di Caracalla, 00153 Rome, Italy *(Codex Secretariat)*

Dr Jeevan Khurana, Usingen, 61250, Germany (*FAO Editor*)

Dr Xiongwu Qiao, Shanxi Academy of Agricultural Sciences, 81 Longcheng Street, Taiyuan, Shanxi, 030031, China (*CCPR Chairman*)

Ms Marla Sheffer, Orleans, Ontario K1E 2K5, Canada *(WHO Editor*)

Dr Philippe Verger, JMPR Joint Secretary, Department of Food Safety and Zoonoses (FOS), World Health Organization, 1211 Geneva 27, Switzerland (WHO JMPR Secretariat)

Ms Yong Zhen Yang, Plant Production and Protection Division, Food and Agriculture Organization of the United Nations, Viale delle Terme di Caracalla, 00153 Rome, Italy *(FAO JMPR Secretariat)*

Dr Vittorio Fattori*, Agriculture and Consumer Protection Department, Food and Agriculture Organization of the United Nations, Viale delle Terme di Caracalla, 00153 Rome, Italy (*JECFA FAO Secretariat*).

Dr Markus Lipp*, Agriculture and Consumer Protection Department, Food and Agriculture Organization of the United Nations, Viale delle Terme di Caracalla, 00153 Rome, Italy (*JECFA FAO Secretariat*).

* Participated in discussion in the topic on the harmonisation of residue definitions

Abbreviations

AD	Administered Dose
ADI	Acceptable Daily Intake
Ache	Acetylcholinesterase
ALP	Alkaline Phosphatase
APTT	Activated Partial Thromboplastin Time
AR	Applied Radioactivity
Arfd	Acute Reference Dose
APTT	Activated Partial Thromboplastin Time
AUC	Area under the Plasma Concentration–Time Curve
BBCH	**B**iologische **B**undesanstalt, Bundessortenamt Und **Ch**emische Industrie
BMD	Benchmark Dosing
$BMDL_{10}$	Lower Confidence Limit on the Benchmark Dose for A 10% Response
Bw	Body Weight
CAR	Constitutive Androstane Receptor
CAS	Chemical Abstracts Service
CCPR	Codex Committee on Pesticide Residues
Cgap	Critical GAP
Cifocoss	Chronic Individual Food Consumption – Summary Statistics
C_{max}	Maximum Concentration in Blood or Plasma
CYP	Cytochrome P450
DALA	Days after Last Application
DAT	Days after Treatment
DM	Dry Matter
DNA	Deoxyribonucleic Acid
DRA	Dietary Risk Assessment
DT_{50}	Time Required For 50% Dissipation of the Initial Concentration
DT_{90}	Time Required For 90% Dissipation of the Initial Concentration
EFSA	European Food Safety Authority
EHC 240	Environmental Health Criteria 240 Monograph
EU	European Union
F_0	Parental Generation
F_1	First Filial Generation

F_2	Second Filial Generation
FAO	Food and Agriculture Organization of the United Nations
FOB	Functional Observational Battery
GAP	Good Agricultural Practice
GC-ECD	Gas Chromatography – Electron Capture Detector
GECDE	Global Estimate of Chronic Dietary Exposure
GEMS	Global Environment Monitoring System – Food Contamination Monitoring and Assessment Programme
GGT	Gamma-Glutamyl Transferase
GLP	Good Laboratory Practice
Har	Human Androgen Receptor
Herα	Human Estrogen Receptor Alpha
HR	Highest Residue Level in the Edible Portion of A Commodity
HR-P	Highest Residue Level in a Processed Commodity
IEDI	International Estimated Daily Intake
IESTI	International Estimate of Short-Term Dietary Intake
IUPAC	International Union of Pure and Applied Chemistry
IPCS	International Programme on Chemical Safety
ISO	International Organization for Standardization
IUPAC	International Union of Pure and Applied Chemistry
JECFA	Joint FAO/WHO Expert Committee on Food Additives
JMPR	Joint FAO/WHO Meeting on Pesticide Residues
LC_{50}	Median Lethal Concentration
LC-MS/MS	Liquid Chromatography-Tandem Mass Spectrometry
LD_{50}	Median Lethal Dose
LOAEL	Lowest-Observed-Adverse-Effect Level
LOD	Limit of Detection
Log P_{ow}	Octanol-Water Partition Coefficient
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
OIE	World Organisation for Animal Health

Pam	Pesticide Analytical Manual
PBI	Plant-Back Interval
PES	Post-Extraction Solids
Pf	Processing Factor
PHI	Pre-Harvest Interval
POD	Point Of Departure
Ppm	Parts Per Million
PXR	Pregnane X Receptor
RAC	Raw Agricultural Commodity
RTI	Re-Treatment Interval
STMR	Supervised Trials Median Residue
STMR-P	Supervised Trials Median Residue In A Processed Commodity
T_4	Thyroxine
TCP	Trichlorophenol
T_{max}	Time to Reach Maximum Concentration
TRR	Total Radioactive Residues
TSH	Thyroid-Stimulating Hormone
TTC	Threshold of Toxicological Concern
UL	Uniformly Labelled
USA	USA of America
USEPA	USA Environmental Protection Agency
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 authorisation 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 2018 joint FAO/WHO meeting of experts

1. Introduction

The Joint FAO/WHO Meeting on Pesticide Residues (JMPR) was taken place at the headquarters of the Federal Institute for Risk Assessment (BfR) in Berlin, Germany, from 18 to 27 September 2018. The meeting was opened by Dr Roland Solecki, Head of the BfR Department of Pesticides Safety. Over 50 participants from five continents participated in the Meeting.

On behalf of the President of the BfR, Dr Solecki welcomed the JMPR Meeting being held in Berlin. He highlighted that it was the first time the JMPR had been hosted by a national government authority in its 55 year history of assessing consumer health risks of pesticide residues in foods and feeds, and recommending maximum residue levels to the Codex Alimentarius Commission. He remarked, that experts from the BfR, and its predecessor organizations had a long history of participation in the the work of the JMPR and had contributed to both the development of, and international harmonization of many assessment concepts. From that perspective he considered the hosting of the 2018 JMPR another important initiative in that process. The BfR is the scientific body of the Federal Republic of Germany and provides expert reports and opinions on risks related to food ingestion and exposure to consumers including risk assessments of industrial chemicals, food additives, biocides and pesticides. Dr Solecki indicated that the BfR held the view that international harmonization was extremely important, as it forms the basis for national and international acceptance of risk assessments.

He also highlighted that such hosting of the JMPR Meeting would provide opportunities for national competent authorities of Codex Members, to improve linkages and strengthen relationships with the JMPR. Such collaboration would help facilitate a better understanding of the working principles of the JMPR and contribute to the further harmonization of risk assessment principles. The JMPR Secretariats expressed their appreciation to BfR for hosting this meeting and for all the support of BfR to the work of JMPR. The experience gained from this meeting would benefit the JMPR Secretariats for future co-organizing the meeting with other national authorities.

During the meeting, the FAO Panel of Experts on Pesticide Residues in Food was responsible for reviewing residue and analytical aspects of the pesticides under consideration, including data on their metabolism, fate in the environment and use patterns, and for estimating the maximum levels of residues that might occur as a result of use of the pesticides according to good agricultural practice. The methodologies are described in detail in the FAO Manual on the submission and evaluation of pesticide residue data for the estimation of maximum residue levels in food and feed (2016) hereafter referred to as the FAO manual. The WHO Core Assessment Group on Pesticide Residues was responsible for reviewing toxicological and related data in order to establish acceptable daily intakes (ADIs) and acute reference doses (ARfDs), where necessary and possible.

The Meeting evaluated 29 pesticides, including eight new compounds and three compounds that were re-evaluated for toxicity or residues, or both, within the periodic review programme of the Codex Committee on Pesticide Residues (CCPR). The Meeting established ADIs and ARfDs, estimated maximum residue levels and recommended them for use by CCPR, and estimated supervised trials median residue (STMR) and highest residue (HR) levels as a basis for estimating dietary exposures.

The Meeting also estimated the dietary exposures (both short-term and long-term) of the pesticides reviewed and, on this basis, performed a dietary risk assessment in relation to the relevant ADI and where necessary ARfD. Cases in which ADIs or ARfDs may be exceeded were clearly indicated in order to facilitate the decision-making process by CCPR.

The Meeting considered general items addressing procedures for the evaluation and risk assessment of pesticide residues used to recommend maximum residue levels.

1.1 Declaration of interests

The Secretariat informed the Meeting that all experts participating in the 2018 JMPR had completed declaration of interest forms and that no conflicts had been identified.

2. General considerations

2.1 Toxicological profiling of compounds and less-than-lifetime dietary exposure assessment

The 2015 meeting of JMPR (see section 2.2 of the 2015 JMPR meeting report, "Short-term lifetime exposures") raised concerns about the risk characterization of less-than-lifetime exposures (i.e. exposures that are longer than 1 day but shorter than a lifetime) to pesticide residues over a season or a life-stage – specifically, the possibility that dietary exposures above the acceptable daily intake (ADI) over short time frames could result in adverse effects in both normal and susceptible subpopulations when the lifetime (long-term or chronic) estimated dietary exposure was below the ADI.

A joint JMPR / Joint FAO/WHO Expert Committee on Food Additives (JECFA) working group meeting was held in October 2017 to explore methods for a harmonized approach to chronic dietary exposure assessments for compounds used as both pesticides and veterinary drugs. The JMPR/JECFA working group concluded that there is a need to better align the dietary exposure model to be used as part of the risk assessment process with the toxicological profile of the compounds and confirmed that the choice of an appropriate exposure model is determined by the toxicological end-point of concern (which includes the time to onset). Following the working group meeting, JECFA, at its eighty-fifth meeting, developed a draft decision-tree to be used to generate a toxicological profile of the chemical of interest (Figure 1).

As a follow-up, the present Meeting discussed options for the risk assessment of pesticide residues with such toxicological profiles.

Toxicological considerations

The draft decision-tree, together with the wider issue of how best to profile the toxicological effects of pesticides to enable better alignment of the exposure assessment, was discussed at a 1-day meeting of toxicological and exposure experts immediately preceding the 2018 JMPR (the "pre-meeting").

It was agreed at the pre-meeting that the subpopulations for whom dietary exposures over a season or life-stage might result in short-term exceedances of the ADI that were potentially of toxicological concern were the embryo or fetus (developmental toxicity), infants and young children (0–6 years) (offspring toxicity) and adults who were high consumers of foods containing the pesticide residue. In the draft decision-tree, the factor of 3 used in the decision points to identify populations of toxicological concern was based on the ratio of the 97.5th percentile exposure to the mean dietary exposure for consumers. The pre-meeting observed that when comparing points of departure (PODs) across studies, it is necessary to consider the respective power of the toxicological studies. For example, fewer animals are used in a 90-day study of toxicity in rats than in a 2-year study. It was recommended that PODs should be considered similar if they are within one order of magnitude of each other (i.e. differ by less than 10-fold), based on toxicological rather than exposure considerations. It was therefore proposed that the decision-tree be revised to use a factor of 10 (rather than 3) as the trigger at the decision points.

In the draft decision-tree, the first decision point was identification of the end-point used as the basis of the ADI. Once this toxicological effect was identified as being of potential concern (e.g. offspring toxicity), the risk characterization would be completed by comparing exposure in the relevant subpopulation with the ADI. However, it is still possible that estimated dietary exposures for one or both of the remaining subpopulation groups (from the original decision point) could exceed the ADI on a short-term basis. Hence, it was agreed that all three scenarios should be assessed for all compounds.

The pre-meeting discussed which studies should be used to profile less-than-lifetime exposure. It was noted that for the majority of compounds, adequate information on their toxicological effects would be available only in the rat, and hence this should be the species of preference for such comparisons. However, if suitable information is available in other species, this should also be assessed. Data on the dog would not normally be suitable for this purpose, as both the 3-month and the 1-year studies cover only a small fraction of the lifespan of this species[1] and thus are not adequate to assess toxicity after chronic (long-term) exposure. As it is rare for a critical no-observed-adverse-effect level (NOAEL) to change between 2 and 4 weeks of exposure, there should be sufficient information from rat (and mouse) studies conducted for 4–104 weeks to enable assessment of whether there is any specific concern for less-than-lifetime exposure. The pre-meeting therefore recommended that for such assessments, when applying the decision-tree, the PODs from studies in rats with a duration of 4 weeks, 90 days and 2 years (or 1 year) should be compared to assess less-than-lifetime exposure. Additional information on less-than-lifetime exposures might be available from other studies in the database, such as parental animals in studies of developmental or reproductive toxicity or repeated-dose neurotoxicity.

Although there was some concern about how test article intake decreases on a body weight basis as the age of the animals increases (due to changes in feed consumption in grams per kilogram of body weight with ageing, particularly up to 20 weeks of age), the pre-meeting agreed that doses should be compared on a milligram per kilogram of body weight per day basis, as this is the dose metric used in establishing the ADI. It was noted that, to some extent, this age-related change in exposure would be taken into account by the proposed factor of 10 used in the comparison of PODs. It was also noted that care should be taken when comparing PODs determined using different dosing regimens, particularly when comparing gavage and dietary dosing, as would often be the case in a comparison of a developmental toxicity study with a chronic (long-term) toxicity study in rats.

When the basis of the ADI is the critical POD from a study in dogs (a 3-month and/or a 12-month study), this already represents less-than-lifetime exposure. Hence, comparison of the POD in the 2-year rat study with that in the dog study can be used to determine whether there are any additional concerns for less-than-lifetime exposure. In general, if the POD in the 2-year rat study is more than 10-fold higher than the POD in the study in dogs on which the ADI is based, no further assessment of this scenario would be necessary. Comparison with the PODs for developmental and offspring toxicity in the rat would still be necessary.

For compounds for which an acute reference dose (ARfD) is considered necessary, if the POD on which the ARfD is based is numerically the same as the POD on which the ADI is based, there will be no concern for less-than-lifetime exposure if acute exposures (i.e. exposures that are less than 24 hours in duration) of both children and the general population are not of concern (i.e. the estimate of acute exposure is less than the ARfD). The pre-meeting noted that this would also be true when the POD on which the ARfD is based is slightly higher than the POD on which the ADI is based (i.e. POD [ARfD] / POD [ADI] > 1), but the appropriate margin would need to be determined by analysis of a suitable data set.

The pre-meeting discussed the issue of pesticide metabolites that are more toxic than the parent compound. In the majority of cases, data from long-term studies will not be available for metabolites. If it is possible to reach a conclusion on the potency of the metabolite relative to that of the parent compound, the toxicological profile of the metabolite will be qualitatively the same as that of the parent compound, and a potency factor can be used in the risk characterization. Otherwise, the decision-tree should be applied – if possible, and to the extent possible – for the metabolite.

[1] WHO (2015). Guidance document for WHO monographers and reviewers. Geneva: World Health Organization (http://www.who.int/foodsafety/publications/JMPR-guidance-document/en/).

In summary, it was agreed that the draft decision-tree required revision to better reflect uncertainty in the respective health-based guidance values, and that all three toxicological/exposure scenarios (developmental, offspring, less-than-lifetime) should be considered, regardless of the basis of the ADI. The draft decision-tree will be revised to address these and any other concerns raised in future consultation with JECFA experts.

In preparation for the 2018 JMPR, WHO monographers undertook a pilot exercise using the draft decision-tree developed by JECFA following the JMPR/JECFA working group meeting in 2017 (see Figure.1). The results of the toxicological profiling of compounds were presented and discussed at the pre-meeting. In general, the decision-tree was easy to follow, although a few issues were identified. These were discussed at the pre-meeting and resolved as noted above. It was agreed that for the purpose of the 2018 JMPR, the results of this exercise – i.e. using the draft decision-tree with a factor of 3 for the comparisons, but following the specific clarifications above – would be included in the report of the 2018 meeting (Table 1). ***This table is for illustrative purposes only and should not be interpreted as a definitive toxicological profiling of these substances.***

Dietary exposure considerations

JMPR has used the average of the estimated chronic dietary exposure for the general population for the comparison with the ADI, which may not be suitable for assessing less-than-lifetime risk. The current approach used by other groups, such as JECFA, is to compare estimated chronic dietary exposures with the ADI for the general population and to compare less-than-lifetime exposures with the ADI for subpopulation groups, including high consumers.

The Meeting currently calculates long-term (chronic) mean dietary exposure estimates for the general population based on the WHO Global Environment Monitoring System – Food Contamination Monitoring and Assessment Programme (GEMS/Food) consumption cluster diets (international estimated daily intake, or IEDI); these estimates are compared with the ADI to characterise the risk for each pesticide residue. The GEMS/Food diets consist of multi-annual FAO supply utilization account data averaged over the general population for each country; the data have been grouped into 17 clusters that capture, for each cluster diet, the amount of food available for consumption per capita (apparent food consumption), expressed in grams per day. However, owing to the nature of the FAO supply utilization account data used, the IEDI calculation cannot provide information for specific age/sex population groups or for high consumers of foods containing the pesticide residue of interest that may be required for assessing less-than-lifetime exposures.

As part of the trial exercise, the global estimate of chronic dietary exposure (GECDE) model developed by JECFA (veterinary drugs) in 2011[2] was used for estimating less-than-lifetime dietary exposure to pesticide residues for population subgroups of toxicological concern as identified using the decision-tree for toxicological profiling, such as high consumers in the adult population, women of childbearing age, and infants and young children (0–6 years). The GECDE model is based on summary statistics derived from individual food consumption data from representative national surveys and takes account of consumption of one commodity at a high level (for consumers only) plus consumption of the remaining commodities at a population mean level.

Food consumption data suitable for use in the GECDE model are available in the WHO Chronic Individual Food Consumption – summary statistics (CIFOCOss) database, which contains summary food

[2] FAO/WHO (2012). Joint FAO/WHO Expert Meeting on Dietary Exposure Assessment Methodologies for Residues of Veterinary Drugs. Final Report including Report of Stakeholder Meeting. Geneva: World Health Organization (http://www.fao.org/fileadmin/user_upload/agns/pdf/jecfa/Dietary_Exposure_Assessment_Methodologies_for_Residues_of_Veterinary_Drugs.pdf).

consumption data derived from national surveys that have two or more records per survey participant. Food consumption data (as reported) in each survey are averaged over the number of records prior to deriving summary statistics for the general population or subpopulation groups of interest and for consumers of each food only. The summary data are suitable for use in chronic dietary exposure assessments using the GECDE; in some cases, however, factors were required to convert the food consumption data as reported to raw commodity equivalents prior to use. It is not possible to derive an overall mean for an "exposed" consumer (i.e. people who have eaten one or more of the foods containing a pesticide residue) from the available summary statistics.

For each pesticide evaluated at this Meeting, results for the IEDI are reported in Chapter 4. As part of the pilot of trialling use of the decision-tree for toxicological profiling for new evaluations, estimated dietary exposures for the mean for the general population and the GECDE for population groups of toxicological concern were also derived using CIFOCOss survey data for each country. The results are summarised in Table 2, for illustrative purposes only.

Generally, the results using individual consumption data from national surveys in the CIFOCOss database to estimate mean dietary exposure to a specified residue for the general population were lower than the highest IEDI cluster estimate from the 17 cluster diets. Dietary exposure estimates from the high consumer GECDE model were of the same order of magnitude as the highest IEDI cluster estimate for the majority of pesticide residues considered in this exercise. However, for some subpopulation groups, the estimated dietary exposure using the GECDE was higher than the highest IEDI cluster estimate.

Conclusions

The Meeting agreed that the decision-tree is a useful approach, but that further work is necessary. The WHO Secretariat for JECFA and JMPR will convene an electronic working group to finalize the approach.

The Meeting noted that it would be useful to consider reporting potential dietary exposures based on national survey data in addition to the IEDI results at future JMPR meetings where there is an identified concern about less-than-lifetime exposures, as it provides additional information on subpopulation groups that is of use to risk assessors and risk managers. The Meeting considered that the GECDE could be a suitable model for this purpose. However, further work is required on a wider range of pesticides before the Meeting can include this approach in JMPR's general procedures. Work is also required to improve the consistency of coding of foods in each country survey as submitted to WHO for inclusion in the CIFOCOss database. The Meeting noted that WHO is currently updating this database using FoodEx2 coding only for foods reported as consumed, which should address this issue in the future.

The Meeting recommended that the applicability of these considerations to the harmonization of risk assessments of chemicals used as pesticides and as veterinary drugs, particularly those with dual use, should be further discussed with JECFA.

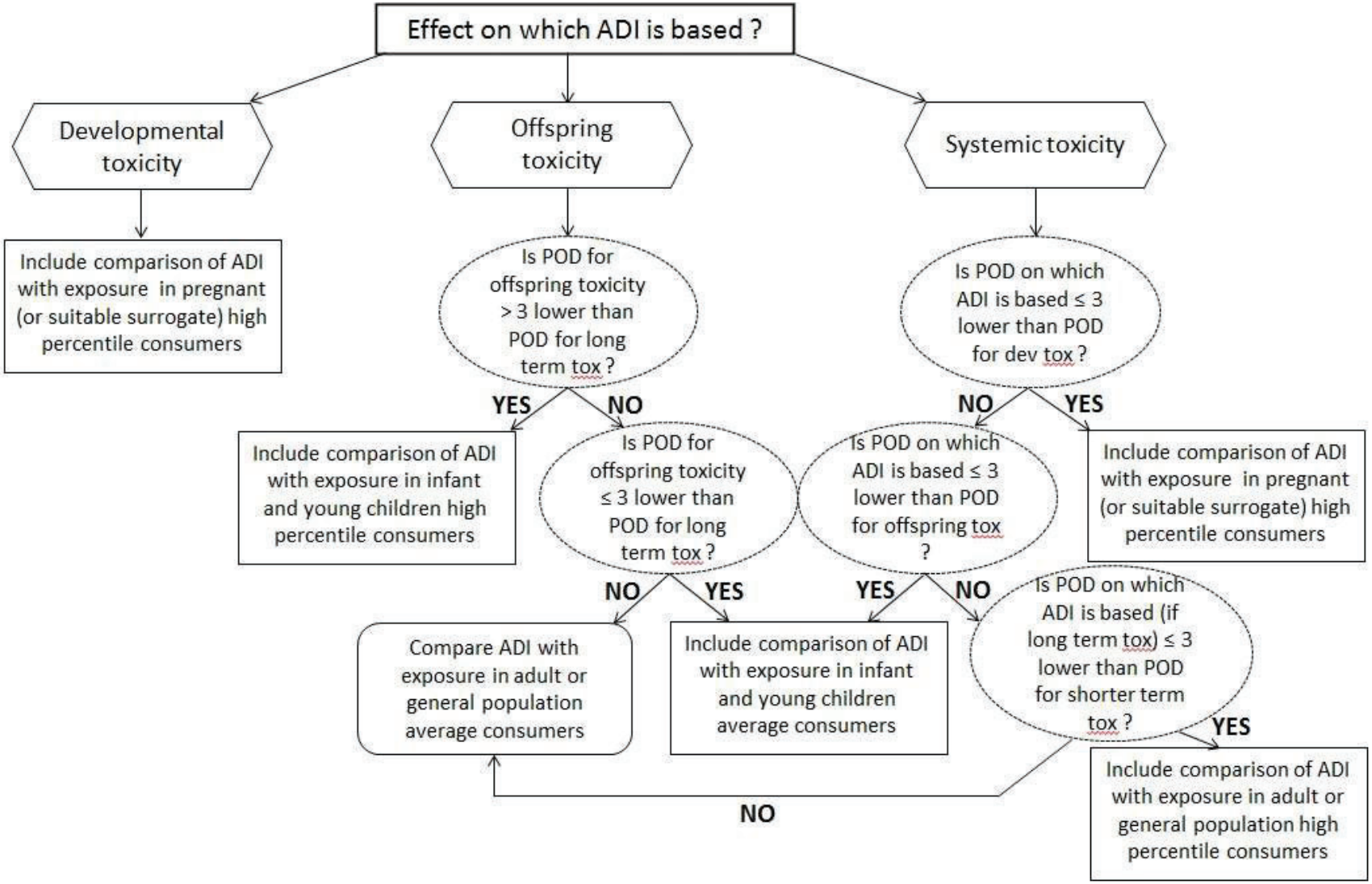
Effect on which ADI is based ?
Developmental toxicity
Offspring toxicity
Systemic toxicity
Include comparison of ADI with exposure in pregnant (or suitable surrogate) high percentile consumers
Is POD for offspring toxicity > 3 lower than POD for long term tox ?
Is POD on which ADI is based ≤ 3 lower than POD for dev tox ?
YES
NO
NO
YES
Include comparison of ADI with exposure in infant and young children high percentile consumers
Is POD for offspring toxicity ≤ 3 lower than POD for long term tox ?
Is POD on which ADI is based ≤ 3 lower than POD for offspring tox ?
Include comparison of ADI with exposure in pregnant (or suitable surrogate) high percentile consumers
NO
YES
YES
NO
Compare ADI with exposure in adult or general population average consumers
Include comparison of ADI with exposure in infant and young children average consumers
Is POD on which ADI is based (if long term tox) ≤ 3 lower than POD for shorter term tox ?
YES
Include comparison of ADI with exposure in adult or general population high percentile consumers
NO

Table 1 Summary of toxicological profiles of compounds not previously evaluated by JMPR, for illustrative purposes only (based on Figure 1)

Pesticide	Study on which the ADI is based	Upper bound of ADI (mg/kg bw)	ARfD (mg/kg bw)	Potential concern in pregnant women	Potential concern in offspring	Potential concern for less-than-lifetime exposure
Ethiprole	Developmental toxicity (rabbit)	0.005	0.005	Appreciable	None	None
Fenpicoxamid	Eighteen-month toxicity (mouse)	0.05	Unnecessary	Moderate	Not applicable	None
Mandestrobin	One-year toxicity (dog)	0.2	3	None	Moderate	None
Norflurazon	Six-month and 1-year toxicity (dog)	0.005	0.3	Moderate	None	None
Pydiflumetofen	Two-year toxicity (rat)	0.1	0.3	None	None	Appreciable
Pyriofenone	Two-year toxicity (rat)	0.09	Unnecessary	None	None	None
Tioxazafen	Two-year toxicity (rat)	0.05	0.5	None	None	Appreciable

ADI: acceptable daily intake; ARfD: acute reference dose; bw: body weight

Table 2 Summary of estimated dietary exposures to pesticide residues (new evaluations only) for populations of interest [a]

Pesticide	Population group assessed	IEDI (µg/kg bw per day)	Mean dietary exposure (CIFOCOss[b]) (µg/kg bw per day)	GECDE (CIFOCOss[b]) (µg/kg bw per day)	Upper bound of ADI[c] (µg/kg bw)	IEDI as % of upper bound of ADI	Mean dietary exposure (CIFOCOss) as % of upper bound of ADI	GECDE (CIFOCOss) as % of upper bound of ADI
Ethiprole	General population	0.05–0.3	0–0.34	0–1.26	5	1–6	0–7	0–25
	Women of childbearing age		0–0.4	0–0.64			0–8	0–13
Fenpicoxamid	General population	0.0009–0.08	0.001–0.004		50	0	0	
	Women of childbearing age		0–0.02	0–0.09			0	0
Norflurazon	General population	0.2–0.9	0–0.79		5	3–20	0–16	
	Women of childbearing age		0–1.12	0–3.2			0–22	0–65
Pydiflumetofen	General population	0.003–0.29	0.01–0.11	0.04–4.1	100	0	0	0–4
	Adults		0.03–0.18	0.35–1.34			0	0–1
Pyriofenone	General population	0.03–0.77	0–0.1	0–3.2	90	0	0	0–4
Tioxazafen	General population	0.01–0.12	0–0.03	0–0.2	50	0	0	0
	Adults		0.02–0.06	0.06–0.15			0	0

ADI: acceptable daily intake; bw: body weight; CIFOCOss: Chronic Individual Food Consumption – summary statistics; GECDE: global estimate of chronic dietary exposure; IEDI: international estimated daily intake

[a] For each national survey in the CIFOCOss database, for the GECDE model for a specified age group, a high percentile dietary exposure was first calculated for each commodity with an assigned supervised trials median residue (STMR): if there were more than 180 consumers of a commodity, a 97.5th percentile dietary exposure for consumers only was derived; if there were more than 60 but fewer than 181 consumers, a 95th percentile dietary exposure was derived; if there were more than 30 but fewer than 61 consumers, a 90th percentile dietary exposure was derived; and if there were more than 10 but fewer than 31 consumers, a median dietary exposure was derived. If there were fewer than 11 consumers, only the mean dietary exposure for the whole population was derived for that Codex commodity code.

[b] The CIFOCOss database has the following numbers of national surveys in the database: whole population, seven surveys; adults, 15 surveys; adult women, two surveys; women of childbearing age, two surveys; children less than 6 years of age, two surveys; and toddlers aged 1–3 years, nine surveys.

[c] For the purposes of this table, the ADI is expressed in µg/kg bw (rather than the usual mg/kg bw).

2.2 Need for sponsors to submit all requested data

In the JMPR call for data, sponsors are requested to submit all data and studies, both published and unpublished, for the toxicological and residue evaluations of the compounds.

For fluazinam, the sponsor did not submit critical information on the levels of a toxicologically relevant impurity in batches used in the toxicity studies. The Meeting was aware that this information had been made available to a number of regulatory authorities. The Meeting was therefore unable to proceed with the evaluation of fluazinam.

For mandestrobin, despite repeated requests prior to the meeting for additional data on environmental fate and other registered labels, the sponsor did not submit this information until well into the meeting. Following a review of the draft appraisal, the sponsor submitted another 18 study reports on environmental fate and field residue studies. This information was deemed necessary for determining the residue definitions for compliance and dietary risk assessment. Considering the amount of new information and its likely impact on the conclusions, the Meeting was unable to process the information in the time remaining and decided to postpone the evaluation of the compound to the 2019 meeting.

Late submissions are leading to additional burdens for experts and ultimately delays in the discussions. For optimal use of the time and resources of the experts and the Joint Secretariat, the Meeting re-emphasized the importance of a complete submission of data on all compounds and their metabolites to enable JMPR to perform a state-of-knowledge risk assessment.

2.3 Hazard characterization in the 21st century: assessing data generated using new mechanism-based approaches for JMPR evaluations

JMPR first discussed the potential contribution of data generated using new mechanism-based approaches ("Tox 21"), often referred to as New Approach Methodologies (NAM), in the risk assessment of dietary exposure to pesticide residues at its meeting in 2012. At that time, JMPR offered to evaluate, without prejudice, data generated using new technologies as they become available, in parallel with the results of traditional toxicity testing, to determine their utility and role in pesticide evaluation. JMPR repeated this offer at the 2013 meeting and agreed that, starting from the 2014 meeting, this offer should be regularly included in the call for data for JMPR evaluations. During the five or so years that this opportunity has been available, JMPR has not received any such information, other than in support of mode of action assessments. In no instance has a sponsor made the case that evaluation of specific effects in vivo would not have been necessary because data from NAM were sufficiently reliable to enable the relevant assessment.

It is unclear why this is the case. In discussions with sponsors, it is evident that such data are being generated to support product development. However, there appears to be great reluctance to subject them to independent comparison with data generated using conventional in vivo tests. Regulatory authorities

such as the USA Environmental Protection Agency (USEPA)[3] and the European Commission[4] envisage the application of NAM in the assessment of pesticides at some point in the future and are investing significant resources to achieve this.

It is therefore important that both the regulated and the regulating communities become familiar with the advantages and limitations of such methods in the hazard characterization of pesticides. It is not envisaged that NAM will provide one-for-one replacements for in vivo tests; rather, NAM will provide an alternative means of assessing the risk of end-points of concern (or their necessary precursors, as verified in method development). The offer made by JMPR would enable practical experience in their assessment to be used in the future development of regulatory guidance by other bodies. Hence, JMPR repeats its offer and urges sponsors to submit at least a few case-studies for consideration at future meetings of JMPR.

2.4 Update on the revision of principles and methods for risk assessment of chemicals in food (EHC 240).

Benchmark dose approach

During the application of the benchmark dose (BMD) approach at several JMPR meetings, Members noted that a number of points have emerged since publication of WHO guidance on this approach (Environmental Health Criteria [EHC] 239[5] and EHC 240[6]) that were not adequately addressed in the current guidance documents. The 2016 Meeting therefore recommended that EHC 240 be updated to reflect experience gained in the application of the BMD approach in dose–response modelling since the guidance was published. The BMD approach is also utilized by JECFA in a number of its evaluations, and an update of the guidance to take new scientific developments into account was also recommended by JECFA.

Hence, the WHO Secretariat has established a working group comprising experts from JECFA and JMPR, together with additional specialists in the area, to revise and update Chapter 5 of EHC 240. This will include not only an update of the BMD approach in dose–response modelling, but also consolidation of the sections on PODs in general and on the establishment of health-based guidance values using these PODs. The revised text will be discussed at an expert meeting in spring 2019, following which the text will be finalized and, after a public comment period, published on the WHO website, to replace the existing chapter of EHC 240.

Evaluation of genotoxicity

At its meeting in May 2016, JMPR assessed the toxicity of glyphosate and malathion. The toxicological database for both compounds was large and comprised studies of diverse quality and design. This was particularly true for genotoxicity. During evaluation of these data, it became apparent that the guidance in section 4.5 of EHC 240 did not cover a number of the key points requiring consideration. Hence, the May 2016 Meeting recommended that a guidance document be developed for the evaluation of genotoxicity studies, taking the experience gained from the meeting into account.

Also following recommendations from JECFA, including the need for guidance to address scenarios where few genotoxicity data are available, the Joint Secretariat convened a working group,

[3] https://www.epa.gov/pesticide-science-and-assessing-pesticide-risks/strategic-vision-adopting-21st-century-science
[4] https://www.sapea.info/wp-content/uploads/SAPEA_PESTICIDES_forJune.pdf
[5] WHO (2009). Principles for modelling dose–response for the risk assessment of chemicals. Geneva: World Health Organization (Environmental Health Criteria 239; http://www.inchem.org/documents/ehc/ehc/ehc239.pdf).
[6] FAO/WHO (2009). Principles and methods for the risk assessment of chemicals in food. A joint publication of the Food and Agriculture Organization of the United Nations and the World Health Organization. Geneva: World Health Organization (Environmental Health Criteria 240; http://www.who.int/foodsafety/publications/chemical-food/en/).

comprising experts from JMPR and JECFA, together with additional specialists in the area, to update and expand section 4.5 of EHC 240. The revised text will be discussed at an expert meeting to be held in October 2018, following which the text will be finalized and, after a public comment period, published on the WHO website, to replace the existing section of EHC 240.

2.5 Microbiological effects

The use of pesticides, particularly fungicides, in agriculture to control plant pathogens in crops could result in residues in food, which, on ingestion, may interact with the microbiome in the human gastrointestinal tract. The intestinal microbiome is a diverse microbial community consisting of bacteria, fungi, viruses and protozoa.[7,8] Disruption in the composition of the intestinal microbiome, including the fungal communities, by residues of fungicides or by other pesticides could have an impact on intestinal homeostasis and systemic immunity. In 2017, JMPR therefore recommended that studies of the effects of pesticides on the intestinal microbiota should be routinely considered, following the step-wise decision-tree approach used by JECFA when establishing a microbiological ADI and ARfD for veterinary drugs.[9]

Therefore, the fungicides fenpicoxamid, fluazinam, mandestrobin, pydiflumetofen and pyriofenone were evaluated for JMPR 2018 to determine their impact on the microbiota in the gastrointestinal tract. As no data were submitted by the sponsors, a literature search was performed using a number of search engines. These included Google Scholar[10], Google search engine[11], PubMed[12], Web of Science[13], BioOne[14] and ScienceDirect[15].

The search strategy used included the input keywords of the fungicide chemical name (fenpicoxamid, fluazinam, mandestrobin, pydiflumetofen and pyriofenone), chemical structure, antimicrobial mode of action, antimicrobial spectrum of activity, antimicrobial resistance, resistance mechanisms and genetics, microbiome, microbiota, gut microbiota, gut microbiome, gastrointestinal microbiota, gastrointestinal microbiome, etc., and the Boolean operators AND, OR and NOT.

The extensive search and review of the scientific literature did not find any reports on the effects of the fungicides evaluated by JMPR 2018 on the intestinal microbiome to include in the toxicological risk assessments. This is an important information gap, as recent literature has reported on the critical role of the microbiota in maintaining intestinal health.

2.6 Transparency of JMPR procedures

JMPR is a scientific body producing two types of documents: namely, JMPR reports and JMPR monographs.

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[7] Paterson MJ, Oh S, Underhill DM (2017). Host–microbe interactions: commensal fungi in the gut. Curr Opin Microbiol.40:131–7. doi:10.1016/j.mib.2017.11.012.

[8] Gilbert JA, Blaser MJ, Caporaso JG, Jansson JK, Lynch SV, Knight R (2018). Current understanding of the human microbiome. Nat Med.24(4):392–400. doi:10.1038/nm.4517.

[9] Boobis A, Cerniglia CE, Chicoine A, Fattori V, Lipp M, Reuss R et al. (2017). Characterizing chronic and acute health risks of residues of veterinary drugs in food: latest methodological developments by the Joint FAO/WHO Expert Committee on Food Additives. Crit Rev Toxicol.47(10):889–903. doi:10.1080/10408444.2017.1340259.

[10] http://scholar.google.com/

[11] https://www.google.com/

[12] http://www.ncbi.nlm.nih.gov/pubmed

[13] https://apps.webofknowledge.com

[14] http://www.bioone.org/

[15] http://www.sciencedirect.com/

Each JMPR monograph is prepared by the experts assigned to the compound prior to the Meeting based on the original studies and the toxicological and residue dossiers submitted by the sponsor(s) (i.e. industry or Codex members), on the relevant published scientific literature and on data provided by Codex members. The monographs describe and evaluate in detail the design and the results of the studies performed to assess the toxicological effects and the residue aspects of the pesticides and include tables summarising the data submitted. The experts carefully check the study descriptions, data and the submitted tables for completeness, accuracy and consistency.

The JMPR report is prepared by the experts during the Meeting and adopted by the whole group. The report consists of an evaluation and interpretation of the data compiled in the monograph and concludes on the possible risk of the chemical from dietary exposure.

The Meeting noted that while the JMPR reports constitute original publications, the JMPR monographs may contain study descriptions and tables based on those in the dossier submitted by the sponsors. The Meeting considers this to be an appropriate use of the submitted materials.

The Meeting agreed that a disclaimer will be prepared by the Joint Secretariat to be included in future JMPR monographs.

2.7 Review of the large portion data used for the IESTI equation

FAO and WHO regularly collect so-called “large food portions” to be used by JMPR, JECFA and other international scientific bodies for acute dietary exposure assessments. These large portions are based on the 97.5th percentile consumption for consumers only on a single day or eating occasion.

The last data call was launched in 2012, and a new call should be posted in 2019. In order to obtain fully comparable data between countries, this call should describe suitable procedures for deriving the 97.5th percentile, for establishing the number of consumers necessary to derive statistically robust percentiles as well as for disaggregating food as consumed into its component ingredients (processed and raw commodities), when needed.

JMPR encourages Member States and relevant institutions to update their data by responding to the upcoming call.

2.8 Update of the iedi and iesti models used for the calculation of dietary exposure: commodity grouping according to the revised codex classification and new large portion data

The 2003 Meeting agreed to adopt automated spreadsheet applications for the calculation of dietary exposure in order to facilitate the process. The IEDI model for long-term dietary exposure and the IESTI model for acute dietary exposure were constructed by RIVM (National Institute for Public Health and the Environment) of the Netherlands in cooperation with WHO/GEMS/Food. The IEDI model had last been updated by the 2014 JMPR, while the IESTI model had last been updated by the 2017 JMPR.

The 2017 Codex Alimentarius Commission (CAC) had adopted the revision of the Classification of Food and Feed for Vegetable Commodity Groups and the Group of Grasses and Cereal Grains. To enable dietary exposure assessments for commodity groups and subgroups as presented in this revised classification, the food consumption data in the IEDI and IESTI models were regrouped according to this revised classification. Furthermore, the amendments to the Fruit Commodity Groups adopted by the 2017 CAC were implemented in the IEDI and IESTI models.

In addition, since dual uses from pesticides and veterinary drugs can be expected in the future, available food consumption data for fish have been added to both models.

Furthermore, the IESTI model has been updated for the present Meeting to contain the more recent large portion data from Finland and the EFSA PRIMo rev 3 model. The large portion data for Finland, France, Germany, the Netherlands and the United Kingdom that were submitted to WHO/GEMS/Food, are also taken into account in the EFSA PRIMo rev 3 model. To avoid any discrepancies between the PRIMO rev 3 model and the JMPR IESTI model, any large portion data from these individual European countries were replaced by the large portion data for equivalent commodities in the PRIMO rev 3 model. When no equivalent commodities were present in the PRIMO rev 3 model, the large portion data from these individual European countries were kept. The current model now contains large portion data for Australia, Brazil, Canada, China, 13 European countries (BE, CZ, DE, DK, ES, FI, FR, IE, IT, NL, PL, LT, UK), Japan, Thailand and the USA.

The IEDI model, the IESTI large portion data overview and the IESTI model, as used by the JMPR 2018, are available on the WHO[16] and FAO[17] websites.

2.9 Recommendations for (sub) group maximum residue levels for fruiting vegetables, other than cucurbits revisited.

Some delegations at the Fiftieth Session of the CCPR expressed concern that the 2017 JMPR had not recommended (sub) group maximum residue levels for the tomato and pepper groups for a number of pesticides. The JMPR secretariat agreed that, based on information to be supplied by the EU and Canada, the 2018 JMPR would revisit those recommendations for the subgroup peppers that were made with exceptions for martynia, okra and roselle.

The Meeting did not receive any data relating to the relative residues in the various crops, rather the information supplied comprised national and regional policy and guidance documents.

From the EU the current meeting received:

- the EU guidance document relating to extrapolations and crop groupings (Guidelines on comparability, extrapolation, group tolerances and data requirements for setting MRLs, SANCO 7525/VI/95 Rev.10.3 13 June 2017)
- a listing of crop grouping used in the EU (COMMISSION REGULATION (EU) 2018/62 of 17 January 2018 replacing Annex I to Regulation (EC) No 396/2005 of the European Parliament and of the Council).

From Canada the meeting received an explanation of the Canadian policy regarding extrapolation for the commodities under consideration. The document from Canada also noted that a comparison of EU MRLs for okra, sweet peppers/bell peppers, and hibiscus/roselle indicated that when quantifiable residues were observed in these crops, in almost all cases (except 3 of over 400 MRLs) the MRLs were the same. However, the EU reported that for martynia and roselle, that they have no experience of the residue situation in these crops. In addition, the Meeting noted MRLs in the EU for okra are likely extrapolations from peppers and so offer no insight into the relative residue potential for the different commodities.

The Meeting recalled the guiding principles and the criteria for crop group of the Classification (CL 2017/22-PR) and that the characteristics for crop grouping are:

[16] http://www.who.int/foodsafety/areas_work/chemical-risks/gems-food/en/
[17] http://www.fao.org/agriculture/crops/thematic-sitemap/theme/pests/jmpr/jmpr-docs/en/

1. Commodities' similar potential for pesticide residues;
2. Similar morphology;
3. Similar production practices, growth habits, etc;
4. Edible portion;
5. Similar GAP for pesticide uses;
6. Similar residue behaviour;
7. To provide flexibility for setting (sub) group tolerances.

To provide an evidence-based justification for extrapolation within subgroups, a review was conducted of the residue potential of the crops in the tomato and pepper subgroups. Residues of foliar applied pesticides are to a large extent governed by the initial spray deposits which in turn depend on a number of plant parameters including the relative surface area of the fruit compared to leaves and stems, the wettability of the fruit and leaf surfaces (waxy surface versus hairy surface etc.) as well as crop morphology.

Residues on the day of application of foliar sprays provide a good indication of relative residue potential for different commodities, with the ranking of residue potential largely preserved with increasing time after application even with relative differences in growth dilution within a group or subgroup and the potential impact on residues at longer post-application intervals.

A measure of the initial spray deposits can be gained by collating residue levels in the commodities on the day of application following a single spray. To expand the database, the Meeting considered that data from trials where more than one spray had been applied could be used provided there was sufficient evidence to conclude the earlier spray did not contribute more than 25% to the observed residue. The Meeting utilised JMPR evaluations in the period 1993 to 2017 and supplemented these with other publicly available information such as published scientific papers and EU draft Assessment Reports to assemble a database of initial residue levels normalised to an application rate of 1 kg ai/ha.

A summary of the initial residue deposits for the different commodities is shown in Figure 2 in the form of box-plots. The boxes cover 50% of values (25^{th} to 75^{th} percentiles) while the whiskers cover 95% of values with the median represented by the dark horizontal lines.

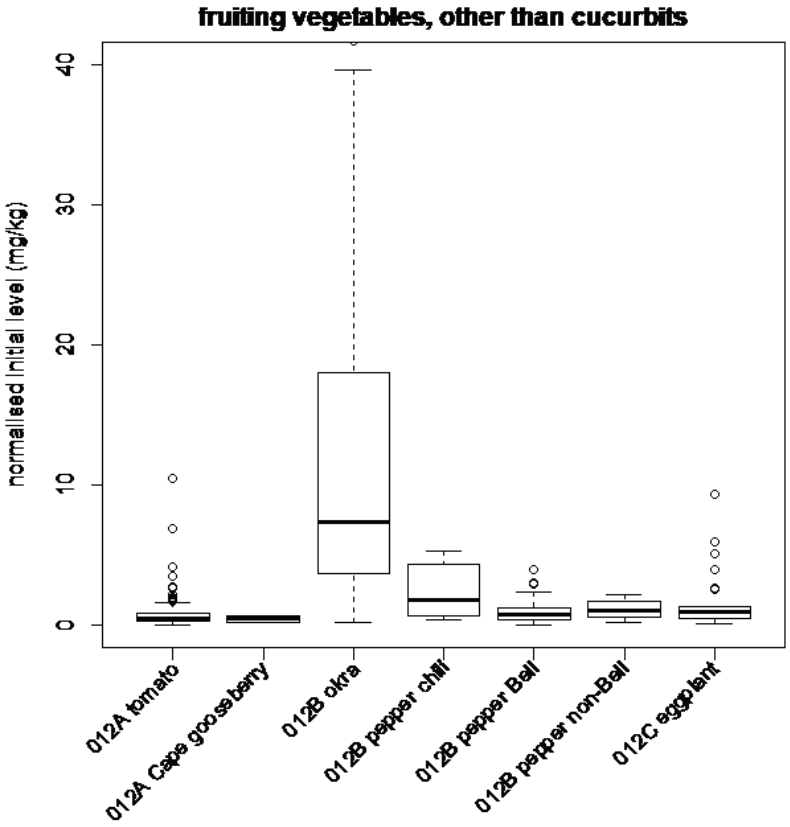

Figure 2 Initial residue (normalised to application rate 1 kg ai/ha) for fruiting vegetables, other than cucurbits

Subgroup Tomatoes

Data for tomato were not separated into cherry and other tomatoes due to the difficulty in assigning the size classification based on the crop variety information available. The data for Cape gooseberries were obtained from the Australian Pesticides and Veterinary Medicines Authority with permission of the data owner. For members of the subgroup tomato (012A), median normalised initial residues are 0.52 mg/kg (n = 213) for tomato and 0.47 mg/kg (n = 2) for Cape gooseberry (including husk). The limited data resolve the concerns expressed by the 2017 JMPR and support the extrapolation of residue data on tomatoes to the whole subgroup.

Subgroup Peppers

In the case of subgroup peppers (012B), median normalised initial residues for okra 7.4 mg/kg (n = 108) are much higher than for peppers chili 1.8 mg/kg (n = 9), peppers Bell 0.74 mg/kg (n = 40) and peppers non-Bell 1.1 mg/kg (n = 4). The data suggest that peppers are unlikely to reflect the residues present in okra when treated according to the same cGAP. Using the principles and criteria for crop grouping, this finding is explained by differences in size and shape of okra fruit (ridged and slight hairy surface) when compared to pepper (smooth-skinned surface) and their relative residue potentials due to fruit morphology.

The Meeting confirmed the conclusion of the 2017 JMPR for the subgroup of peppers - available information suggests residues in okra differ from those in peppers. While the JMPR is not aware of trials comparing residues in peppers, roselle and martynia, differences in crop growth habit, commodity size and shape lead the Meeting to suspect that residues in Bell and non-Bell peppers may not be representative of residues in the other commodities, i.e. okra, martynia and roselle. In the absence of data on relative residues

in these crops, the Meeting decided when data are available for Bell and non-Bell peppers to recommend maximum residue level for:

VO 0051 Subgroup of Peppers (except okra, martynia and roselle).

Subgroup Eggplants

It is current practice of the JMPR to extrapolate recommendations for tomatoes to eggplants when the crops share a common use pattern (GAP) and no residue data is available for eggplants. As noted earlier, residues on the day of application of foliar sprays provides a good indication of the relative residue potential of different crops. The median normalised initial level for eggplant was 0.97 mg/kg (n = 28) whereas the levels for tomato were 0.52 mg/kg (n = 213) (Figure 2). Extrapolation of recommendations for tomato to eggplant may result in maximum residue level recommendations that are too low for eggplant. The Meeting observed that normalised levels in peppers are closer to eggplant (peppers Bell 0.74 mg/kg, n = 40; peppers non-Bell 1.1 mg/kg, n = 4) suggesting peppers is a better representative commodity for extrapolation to eggplants.

The Meeting agreed that when GAPs allow for extrapolation to the subgroup Eggplant, the extrapolation would be based on peppers

The Meeting agreed to use the dataset for peppers or tomatoes that would lead to the higher maximum residue level recommendation.

2.10 Preliminary results for probabilistic modelling of acute dietary exposure to evaluate the IESTI equations

As part of the process to review the international estimate of short-term dietary intake (IESTI) equations, the acute dietary exposure assessment for 47 pesticide residues in food for different populations/countries should be performed by WHO based on a probabilistic approach and combining results from national food consumption surveys and reported concentrations of pesticide residues from official monitoring programmes.

The data submitted by countries, the protocol for probabilistic assessment and preliminary results for Australia and the USA of America (USA) were presented to the meeting by the WHO Secretariat for information only. No further comments were made. A final report, including additional results for Brazil, Canada and four European countries (Czech Republic, France, Italy and the Netherlands), should be presented to the Meeting in 2019.

3. Responses to specific concerns raised by the codex committee on pesticide residues (CCPR)

3.1 BENZOVINDIFLUPYR (261)

Background

The 2016 JMPR estimated a maximum residue level of 0.15 mg/kg for benzovindiflupyr in beans (dry) and a maximum residue level of 0.2 mg/kg in peas (dry). However, many specific species of dry pulses, including but not limited to fava bean, chick-pea and lentils, have no CXL. This has resulted in difficulties within the Canadian export market for dry beans and peas. The current Meeting received a request from the manufacturer to expand the maximum residue levels for beans, dry (VD 0071) and peas, dry (VD 0072) to Subgroup 15A, Dry beans (VD 2065) and Subgroup 15B, Dry peas (VD 2066), respectively.

Comments by JMPR

The 2016 JMPR estimated a maximum residue level of 0.15 mg/kg and a STMR of 0.011 mg/kg for benzovindiflupyr in beans (dry) based on the critical GAP for Canada in pulses (not including soya beans). In addition, the 2016 JMPR estimated a maximum residue level of 0.08 mg/kg and a STMR of 0.01 mg/kg in soya beans (dry) based on the critical GAP of Paraguay.

The GAPs for Canada and Paraguay are different: 2 × 0.075 kg ai/ha with a 7 day interval and a 15 day PHI for Canada and 3× 0.045 kg ai/ha with 14 day intervals and a PHI of 21 days for Paraguay. Since the GAPs were different, the maximum residue level recommendation for dry beans cannot be expanded to the whole subgroup of dry beans. The current Meeting decided to expand the current maximum residue level recommendation of 0.15 mg/kg for beans, dry (VD 0071) to the Subgroup 15A, Dry beans (VD 2065), excluding soya beans, and to withdraw its previous recommendation of 0.15 mg/kg for beans, dry (VD 0071).

The 2016 JMPR estimated a maximum residue level of 0.2 mg/kg, a STMR of 0.014 mg/kg for benzovindiflupyr in peas (dry) based on the critical GAP for Canada in pulses (not including soya beans).

The current Meeting decided to expand the maximum residue level recommendation of 0.2 mg/kg for peas, dry (VD 0072) to the Subgroup 15B, Dry peas (VD 2066), and to withdraw its previous recommendation of 0.2 mg/kg for peas, dry (VD 0072).

Dietary burden

The expansion to the subgroup of dry beans and dry peas does not affect the dietary burden calculation and therefore the previously recommended maximum residue levels for animal commodities are not affected.

Recommendation

Definition of the residue for compliance with the MRL and for dietary risk assessment for plant and animal commodities: *benzovindiflupyr*

3.2 BROMOPROPYLATE (070)

A public health concern was raised by the European Union (EU) about the acute toxicity of bromopropylate, and therefore this compound was listed by WHO in the call for data for periodic review by JMPR in 2018. This compound is not supported by industry, and no data were submitted. According to a communication from the European Food Safety Authority (EFSA), the concern form was triggered not by new toxicological studies that would require a revision of the health-based guidance values, but because the JMPR assessments are outdated.

A review of the last JMPR monograph on bromopropylate (1993) shows that the lowest NOAEL for a possible acute effect (body weight deficit) was 20 mg/kg body weight (bw) per day (pregnant rabbits in a developmental toxicity study), indicating that any ARfD would be significantly higher than the upper bound of the ADI of 0–0.03 mg/kg bw. The acute oral median lethal dose (LD_{50}) is greater than 5000 mg/kg bw, and there are no indications of any other toxicological effects that would be likely to be elicited by a single dose.

The Meeting recognized that the existing JMPR assessment is outdated and, in the absence of data, was not able to re-evaluate bromopropylate according to current JMPR requirements. However, based on the 1993 JMPR monograph, the Meeting also concluded that the critical driver identified for a potential ARfD, reduced body weight, was unlikely to represent a major, acute public health concern from dietary exposure to bromopropylate.

3.3 Crop groups – Reconsideration of maximum residue estimations made by the 2017 JMPR for FENPYROXIMATE (193), FLUOPYRAM (243), OXAMYL (126) AND SPINETORAM (233)

The meeting reconsidered its policy for extrapolation in the subgroups of tomatoes and peppers (see item 2.9 of this Summary Report) and subsequently agreed to reconsider maximum residue level estimations made by the 2017 JMPR for these subgroups. Specifically, the estimations made for four pesticides (fenpyroximate, fluopyram, oxamyl and spinetoram) were revisited following concerns raised by the EU and Canada. The resulting maximum residue level estimations are summarised below.

Fenpyroximate

The critical GAP in the USA is for fruiting vegetables (US crop group 8-10 which includes all commodities in the Codex subgroups tomatoes, peppers and eggplants) and is 2×117 g ai/ha with a PHI of 1 day.

Tomato

The Meeting agreed to extrapolate its previous maximum residue level estimation of 0.3 mg/kg for tomato to the subgroup of tomatoes. The Meeting agreed to withdraw its previous maximum residue level estimations for tomato and for cherry tomato of 0.3 mg/kg.

Further to the dietary exposure conclusions in 2017, a recently amended consumption figure resulted in the meeting concluding that residues of fenpyroximate in dried tomatoes were unlikely to exceed the ARfD.

The International Estimated Short-Term Intake (IESTI) for fenpyroximate was calculated for all the food commodities in the Subgroup of Tomatoes (and their processed fractions) for which maximum residue levels were estimated and for which consumption data were available. The results are shown in Annex 4 in the 2018 JMPR Report.

For tomatoes (including dried tomatoes), the IESTI represented 2–20% of the ARfD for the general population and 5–60% for children. The Meeting concluded that the acute dietary exposure to residues of

fenpyroximate in food commodities in the Subgroup of Tomatoes, when used in ways that have been considered by the JMPR, is unlikely to present a public health concern.

Fluopyram

The critical GAP in the USA for fruiting vegetables is 2× 0.25 kg ai/ha with a PHI of 0 days.

Tomato

The Meeting agreed to extrapolate its previous maximum residue level recommendation of 0.5 mg/kg for tomato to the subgroup of tomatoes to replace the previous recommendations of 0.5 mg/kg for tomato and 0.4 mg/kg for cherry tomato.

Oxamyl

The GAP available to the 2017 JMPR was for tomato and peppers only. As a GAP is not available for the other members of the subgroup of tomatoes and the subgroup of peppers the Meeting confirmed its previous maximum residue level estimations.

Spinetoram

The 2017 JMPR only considered peppers. No change required.

3.4 CYPRODINIL (207) AND PROPICONAZOLE (160) – POST-HARVEST USES

Background

Cyprodinil and propiconazole were evaluated for new maximum residue levels by the 2017 JMPR. At the 50th Session of the CCPR the EU submitted a concern over the decision of the 2017 JMPR to use the CF*3 Mean to recommend maximum residue levels for post-harvest uses.

The EU also raised a concern that for both cyprodinil and propiconazole the plant metabolism data were generated using foliar applications only and there were no specific metabolism data generated via post-harvest applications.

Comments by the current Meeting

The 3*mean is used to ensure the coefficient of variance is at least 0.5, given small data sets can underestimate the standard deviation (SD). The SD of the data sets for the post-harvest uses of cyprodinil and propiconazole were low (for cyprodinil/pomegranate it was 0.37, propiconazole/ cherry it was 0.34, for propiconazole/peach it was 0.032 and propiconazole/plum it was 0.049). However, the Meeting considered that as more homogenous residues are expected for post-harvest uses it is not appropriate to account for the low SD when estimating the maximum residue level and therefore base it on the CF*3 Mean. The Meeting agreed that more refined maximum residue levels are possible for the post-harvest uses considered by the 2017 JMPR using the mean + 4SD.

With respect to plant metabolism, data are available for each active to cover the metabolism following foliar applications in three crop categories. The plant metabolism data for both actives also included data where applications where made with the mature commodities present and therefore exposed to the applications. For both actives the metabolic profiles observed in the different crop groups were similar and therefore residue definitions for estimating both maximum residue levels and dietary exposure cover all crop categories.

The Meeting concluded that it was unlikely a post-harvest application would result in more extensive metabolism than that observed from the foliar applications. The residue definitions for both actives include the parent compound and therefore there are no concerns with respect to determining the residue levels of the parent if less extensive metabolism occurs in the post-harvest treated crops. In addition, the data for both actives show that there are no concerns with respect to degradation of the total residue on storage.

The Meeting concluded that the residue definitions for cyprodinil and propiconazole will cover post-harvest uses. The residues data assessed by the 2017 JMPR for post-harvest uses are suitable for estimating maximum residue levels, and for estimating STMR and HR for long-term and acute dietary exposure assessments.

The Meeting recommended the following maximum residue levels based on the mean + 4SD for the post-harvest uses of cyprodinil and propiconazole on the crops considered in the 2017 Meeting.

CNN	Commodity	Number of trials	2017 JMPR		2018 JMPR	
			CF*3 Mean	Maximum residue level (mg/kg)	Mean+4SD	Maximum residue level (mg/kg)
	Cyprodinil					
FI 0355	Pomegranate	4	9.450	10 Po	4.629	5 Po
	Propiconazole					
FC 0004	Subgroup of Oranges, Sweet, Sour (including orange-like hybrids)	16 (combined)	11.213	15 Po	9.026	10 Po
FC 0003	Subgroup of Mandarins (including Mandarin-like hybrids)	16 (combine)	11.213	15 Po	9.026	10 Po
FC 0002	Subgroup of Lemons and Limes (including Citron)	16 (combined)	11.213	15 Po	9.026	10 Po
FC 0005	Subgroup of Pumelo and grapefruit (including Shaddock-like hybrids)	4	5.775	6 Po	3.435	4 Po
FS 0247	Peach	3	1.430	1.5 Po	0.605	0.7 Po
FS 0013	Subgroup of Cherries (including all commodities	4	2.970	3 Po	2.337	3 Po

CNN	Commodity	Number of trials	2017 JMPR		2018 JMPR	
			CF*3 Mean	Maximum residue level (mg/kg)	Mean+4SD	Maximum residue level (mg/kg)
	in this subgroup)					
FS 0014	Subgroup of Plums (includes all commodities in this subgroup)	5	0.480 (error) (correct, 0.390)	0.5 Po (error) (correct, 0.4))	0.326	0.4 Po
FS 0353	Pineapple	4	3.143	4 Po	1.555	2 Po
OR 0001	Orange oil			2800 (MRL ,15 × Pf, 185)		1850 (MRL, 10×Pf, 185)

3.5 2, 4-D (020)

Background

The 2017 JMPR evaluated residues arising from the use of 2,4-D on a genetically modified cotton crop (AAD-12), in which expression of the aryloxyalkonoate dioxygenase-12 confers tolerance to 2,4-D and an associated increase in the metabolism of 2,4-D. No maximum residue level had been recommended by JMPR for cotton seed.

The residue definition established by the 1998 JMPR is 2,4-D for enforcement of MRLs and for dietary risk assessment.

The USA submitted a concern form at the 50th Session of the CCPR. The USA requested clarification on the conclusion of the 2017 JMPR regarding the lack of stability of residues in cotton seed in frozen storage noting that a storage stability study on soya beans indicated stability of 2,4-D in soya beans under frozen condition.

Comments by the current Meeting

The 2017 JMPR was aware of the evaluation and conclusion of the 1998 JMPR on frozen storage stability studies. The 1998 JMPR reviewed studies on soya bean (high oil matrix) as well as maize and rice bran, and concluded that 2,4-D was stable in soya bean matrices for at least 365 days.

A new storage stability study on 2,4-D in AAD-12 cotton seeds and related matrices at -20 °C was reviewed by the 2017 JMPR. During frozen storage at the fortification level of 0.10 mg/kg, 2,4-D was stable in undelinted cotton seed for up to one month, with the percentage remaining becoming lower than 70% thereafter. The 2017 Meeting considered that the results of the stability study in cotton seed were of higher relevance to the interpretation of the submitted supervised trial data. The periods of frozen storage of samples in the supervised trials were in a range of 84–118 days, much longer than the period of demonstrated stability.

Therefore, the 2017 Meeting concluded that due to the questionable storage stability of 2,4-D in cotton seed, the residue data were inadequate for estimating a maximum residue level.

The current Meeting confirmed the conclusion of the 2017 Meeting.

3.6 FLUOPYRAM (243)

Fluopyram was evaluated by the 2017 JMPR for a number of additional uses, including rice. Based on the available data, the Meeting recommended a maximum residue level of 4 mg/kg and a STMR of 0.615 mg/kg for fluopyram on rice grain.

The Fiftieth Session of the CCPR noted that processing factor data were available, and that it might also be possible to derive maximum residue level recommendations for husked and polished rice.

Based on the processing factor of 0.29 estimated by the 2017 JMPR for husked (brown) rice, and applying this to the maximum residue level of 4 mg/kg and the STMR of 0.615 mg/kg for rice grain, the Meeting estimated a maximum residue level of 1.5 mg/kg and a STMR of 0.18 mg/kg for fluopyram on rice, husked.

Based on the processing factor of 0.11 estimated by the 2017 JMPR for polished rice, and applying this to the maximum residue level of 4 mg/kg and the STMR of 0.615 mg/kg for rice grain the Meeting estimated a maximum residue level of 0.5 mg/kg and a STMR of 0.068 mg/kg for fluopyram on rice, polished.

On the basis of the data from supervised trials the Meeting concluded that the residue levels listed below are suitable for establishing maximum residue limits and for IEDI assessment.

	Commodity	Recommended maximum residue level (mg/kg)		STMR or STMR-P (mg/kg)	HR or HR-P (mg/kg)
CCN	Name	New	Previous		
CM 0649	Rice, husked	1.5	-	0.18	-
CM 1205	Rice, polished	0.5	-	0.068	-

3.7 PHOSPHONIC ACID (301) / FOSETYL-ALUMINIUM (302)

Phosphonic acid, as the major metabolite of fosetyl-aluminium and fosetyl, is toxicologically similar to fosetyl-aluminium and is covered by the ADI for fosetyl-aluminium. In response to a request for clarification from CCPR, the Meeting confirmed that the ADI of 0–1 mg/kg bw established in 2017 for fosetyl-aluminium (302), while derived from toxicological studies on fosetyl-aluminium, also applies directly to phosphonic acid.

3.8 PICOXYSTROBIN (258)

Background

Picoxystrobin was reviewed for the first time by the JMPR in 2012. The 2017 JMPR recommended a maximum residue level for picoxystrobin in rape seed.

The USA of America submitted a concern form at the Fiftieth Session of the CCPR. The USA noted that "the JMPR review concluded that there were an insufficient number of field trials at the GAP to estimate

an maximum residue level for oilseed rape. We note that eighteen residue trials were conducted and summarised in the 2012 JMPR Evaluation document with the correct application use pattern and additional GAP or near-GAP trials are listed in the 2017 JMPR report (Table 29). " The USA sought "a clear explanation of why the JMPR concluded that there were an inadequate number of MOR [magnitude of residue] trials available for review to recommend a maximum residue level for picoxystrobin on oilseed rape".

Comment by the JMPR

The 2017 JMPR identified the critical GAP for rape in the USA is 2× 0.22 kg ai/ha with a 28 day PHI. Three trials, two from Canada and one from the USA, matched cGAP and residues of picoxystrobin in rapeseed were < 0.01, 0.012 and 0.031 mg/kg. In another 14 trials on rape seed two applications were made at 0.22 kg ai/ha with seed harvested at a PHI of 19 to 21 days.

In assessing whether trials that deviate from cGAP can be considered to approximate cGAP, the JMPR considers tolerances on the parameters should be those that would result in ±25% change in the residue concentration, not ±25% changes in the parameters themselves. The JMPR considered whether there was sufficient information available to conclude residues in seed harvested at 21 days and residues at 28 days would be the same, or within ±25%.

Residues at 21 days ranged from < 0.01 to 0.047 mg/kg with most samples having residues above the LOQ.

Two residue decline trials in rape were available and were inconclusive. Residues in seed at 21 and 28 days were <LOQ in the first study, while in the second study residues at 21 and 28 days were similar at 0.013 and 0.012 mg/kg. Additionally, the 2017 JMPR also considered information on the decline of residues in rape pods with seeds that occurred with half-lives of two to four days. The limited information available was inadequate to enable the JMPR to conclude with confidence that residues in rape seed at 21 days would be within ±25% of residues at 28 days. Therefore the 14 trials where seeds were harvested at 19 to 21 days were not considered as approximating cGAP.

Consequently, the number of trials available to the 2017 JMPR approximating cGAP was three, which was inadequate for the purposes of estimating a maximum residue level for rape seed.

The current Meeting confirmed its previous decision.

3.9 QUINCLORAC (287)

Background

Quinclorac was reviewed for the first time by the JMPR in 2015. The 2015 JMPR determined that the definition of the residue for plant commodities for compliance with the MRL was quinclorac plus quinclorac conjugates.

At the Forty-ninth Session of the CCPR in 2017, the European Union submitted a concern form that the residue definition should be reconsidered because quinclorac methyl ester, which is ten times more toxic than quinclorac, was not included in the residue definition for enforcement.

The 2017 JMPR reconfirmed the residue definition established by the 2015 JMPR.

At the 50th Session of the CCPR, the European Union reserved their position on the advancement of the maximum residue level recommendation for rape seed due to the exclusion of the more toxic quinclorac methyl ester from the residue definition for enforcement.

The 2017 JMPR received an analytical method D1607/01 developed for more precise accounting of quinclorac and quinclorac methyl ester in rape seed, and also received a multi-residue analytical method D1502/1 for quinclorac in plant matrices and for quinclorac methyl ester in rape seed. Those methods are suitable for the analysis of quinclorac and quinclorac methyl ester residues in rape seed.

The residue data using the analytical method D160701 from supervised field trials on oilseed rape were submitted to the 2017 JMPR.

The Meeting noted that monitoring quinclorac and its conjugates is an adequate residue definition for determining compliance with cGAP as residues may be found in treated crops above the LOQ. The residue definition for dietary risk assessment is the appropriate location for compounds that contribute to the toxicological burden and are required for assessing consumer risk. The Meeting also noted that even though the methyl ester has a toxicological potency that is 10 times that of quinclorac, residues (including the methyl ester) are low as rape seed oil is a blended commodity resulting in negligible consumer risk. As reported by the 2015 JMPR, the IESTI associated with rape seed oil is less than 1% of the ARfD.

The Meeting confirmed its previous conclusions regarding the residue definitions for plant commodities:

Plant commodities:

Definition of the residue for compliance with the MRL for plant commodities:

Quinclorac plus quinclorac conjugates

Definition of the residue for dietary risk assessment for plant commodities:

Quinclorac plus quinclorac conjugates plus quinclorac methyl ester expressed as quinclorac.

4. Dietary risk assessment for pesticide residues in food

4.1 Long-term dietary exposure

At the present Meeting, an international estimated daily intake (IEDI) was calculated for each compound for which an acceptable daily intake (ADI) was established. The IEDI was calculated by multiplying the median concentrations of residues (supervised trials median residues [STMRs] and/or supervised trials median residues in a processed commodity [STMR-Ps]) for each commodity, for which maximum residue levels were recommended, by the average daily per capita consumption, estimated on the basis of the 17 Global Environment Monitoring System – Food Contamination Monitoring and Assessment Programme (GEMS/Food) consumption cluster diets. A detailed description of the method is included in the Environmental Health Criteria 240 (EHC 240) monograph. [18]

Fluazinam was not evaluated for toxicology because of missing critical information. No chronic dietary risk assessment was conducted.

Mandestrobin was evaluated for toxicology, and an ADI was established. It was not possible to complete the evaluation for residues at the current Meeting due to late submission of critical information. Chronic dietary risk assessments will be conducted when the compound is evaluated for residues.

These IEDIs are expressed as a percentage of the upper bound of the ADIs for a 55 kg or 60 kg person, depending on the cluster diet (Table 1). The spreadsheet application is available from the WHO website[19].

The detailed calculations of the chronic dietary exposure assessments are given in Annex 3.

Table 1 Summary of long-term dietary exposure assessments (IEDI)

CCPR code	Compound name	ADI (mg/kg bw)	Range of IEDI, as % of the upper bound of the ADI
177	Abamectin	0–0.001	1–6
172	Bentazone	0–0.09	0–1
254	Chlorfenapyr	0–0.03	1–6
263	Cyantraniliprole	0–0.3	4–40
281	Cyazofamid	0–0.2	0–5
031	Diquat	0–0.006	2–30
304	Ethiprole	0–0.005	1–6
305	Fenpicoxamid	0–0.05	0
211	Fludioxonil	0–0.4	1–6
256	Fluxapyroxad	0–0.02	6–20
110	Imazalil	0–0.03	2–40
290	Isofetamid	0–0.05	0–6
199	Kresoxim-methyl	0–0.3	0–0.5
286	Lufenuron	0–0.02	2–10

[18] FAO/WHO (2009). Principles and methods for the risk assessment of chemicals in food. A joint publication of the Food and Agriculture Organization of the United Nations and the World Health Organization. Geneva: World Health Organization (Environmental Health Criteria 240; http://www.who.int/foodsafety/publications/chemical-food/en/).

[19] http://www. who. int/foodsafety/areas_work/chemical-risks/gems-food/en/

CCPR code	Compound name	ADI (mg/kg bw)	Range of IEDI, as % of the upper bound of the ADI
231	Mandipropamid	0–0.2	0–6
308	Norflurazon	0–0.005	0–20
291	Oxathiapiprolin	0–4	0
171	Profenofos	0–0.03	0–20
148	Propamocarb	0–0.4	0–2
309	Pydiflumetofen	0–0.1	0
210	Pyraclostrobin	0–0.03	1–7
310	Pyriofenone	0–0.09	0
200	Pyriproxyfen	0–0.1	0–1
252	Sulfoxaflor	0–0.05	2–9
311	Tioxazafen	0–0.05	0

ADI: acceptable daily intake; bw: body weight; CCPR: Codex Committee on Pesticide Residues; IEDI: international estimated daily intake

4.2 Acute dietary exposure

At the present Meeting, an international estimate of short-term intake (IESTI) was calculated for compounds for which an acute reference dose (ARfD) was established. For each relevant food commodity, the highest expected residue (highest residue in the edible portion of a commodity [HR] or highest residue in a processed commodity [HR-P]) and the highest large portion data for the general population (all ages) and children (6 years and under) were used for the calculation of the IESTI. In the case where a separate ARfD was established for women of childbearing age, the IESTI was calculated for this population group only. A detailed description of the method is included in EHC 240.

These IESTI results are expressed as a percentage of the ARfD (Table 2). The spreadsheet application is available from the WHO website[20].

Fluazinam was not evaluated for toxicology due to missing critical information. No acute dietary risk assessment was conducted.

No acute dietary risk assessment was conducted for mandestrobin, as the evaluation for residues could not be completed at the current Meeting due to late submission of critical information. Acute dietary risk assessments will be conducted when the compound is evaluated for residues.

The present or previous Meetings agreed that ARfDs for cyantraniliprole, fenpicoxamid, fludioxinil, kresoxim-methyl, lufenuron, mandipropamid, oxathiapiprolin, pyriofenone, pyriproxyfen and sulfoxaflor were unnecessary. For these compounds, an acute dietary exposure assessment was not conducted.

The detailed calculations of acute dietary exposure are given in Annex 4.

Table 2 Summary of acute dietary exposure assessments (IESTI)

CCPR code	Compound name	ARfD (mg/kg bw)	Commodity (maximum % of ARfD)	Exceeding: population, (country)
177	Abamectin	0.003	40	
172	Bentazone	0.5	0	
254	Chlorfenapyr	0.03	60	

[20] http://www. who. int/foodsafety/areas_work/chemical-risks/gems-food/en/

CCPR code	Compound name	ARfD (mg/kg bw)	Commodity (maximum % of ARfD)	Exceeding: population, (country)
281	Cyazofamid	0.2 (CCIM)	90	
031	Diquat	0.8	10	
304	Ethiprole	0.005	80	
256	Fluxapyroxad	0.3	10	
110	Imazalil	0.05	90	
290	Isofetamid	3	3	
308	Norflurazon	0.3	10	
171	Profenofos	1	0	
148	Propamocarb	2	1	
309	Pydiflumetofen	0.3	20	
210	Pyraclostrobin	0.7	60	
311	Tioxazafen	0.5	0	

ARfD: acute reference dose; bw: body weight; CCIM: 4-chloro-5-*p*-tolylimidazole-2-carbonitrile (metabolite); CCPR: Codex Committee on Pesticide Residues; IESTI: international estimate of short-term intake

Possible refinement when the IESTI exceeds the ARfD

None of the compounds evaluated at the meeting had acute dietary exposures that exceeded the relevant ARfD.

6 Future work

The items listed below are tentatively scheduled to be considered by the Meetings in 2020. The compounds listed include those recommended as priorities by the CCPR at its Fiftieth and earlier Sessions and compounds scheduled for re-evaluation within the CCPR periodic review programme.

Updated calls for data are available at least ten months before each JMPR meeting from the web pages of the Joint Secretariat[27].

NEW COMPOUNDS

TOXICOLOGY EVALUATIONS	RESIDUE EVALUATIONS
Broflanilide (Insecticide) USA	Broflanilide
Ethalfluralin (Herbicide) Canada	Ethalfluralin
Fluoxapiprolin/BCS-CS55621 (fungicide)	Fluoxapiprolin/BCS-CS55621
Inpyrfluxam (fungicide)	Inpyrfluxam
Isoflucypram/BCS-CN88460 (Fungicide) Germany	Isoflucypram/BCS-CN88460
Mefentrifluconazole/BAS 750 F(Fungicide) USA	Mefentrifluconazole/BAS 750 F
Pyraziflumid (fungicide) Japan	Pyraziflumid
Pyrasulfutole (Herbicide) Canada	Pyrasulfutole
Tetraniliprole (Insecticide) Germany	Tetraniliprole

PERIODIC RE-EVALUATIONS	
TOXICOLOGY	RESIDUE
Aldicarb (117)	Aldicarb (117)
Diazinon (022)	Diazinon (022)
Ethoxyquin (035)	Ethoxyquin (035)
Fipronil (202)	Fipronil (202)
Methidathion (51)	Methidathion (51)
Pirimicarb (101)	Pirimicarb (101)
Prochloraz (142)	Prochloraz (142)
Quintozene (064)	Quintozene (064)

NEW USES AND OTHER EVALUATIONS	
TOXICOLOGY EVALUATIONS	RESIDUE EVALUATIONS
	Chlorfenapyr (254)
	Clofentezine (156)
	Clothianidin (238)
	Cypermethrin (118)
	Deltamethrin (35)
	Diazinon (22)
	Dicofol (26)
	Dimethoate (27)
	Fenpropathrin (185)

[27] http://www.fao.org/agriculture/crops/core-themes/theme/pests/jmpr/en/

NEW USES AND OTHER EVALUATIONS	
TOXICOLOGY EVALUATIONS	**RESIDUE EVALUATIONS**
	Fenpyroximate (193)
	Fluensulfone (265)
	Fluopyram (243)
	Flupyradifurone (285)
	indoxacarb (216)
	Isoprothiolane
	Isoxaflutole (268)
	Lambda-cyhalothrin (146)
	Metalaxyl (138)
	Metalaxyl-M (212)
	Methomyl (94)
	Parathion (59)
	Phorate (112)
	Phosalone (60)
	Profenofos (171)
	Propiconazole (160)
	Prothioconazole (232)
	Pydiflumetofen (309)
	Pyraclostrobin (210)
	Spiromesifen (294)
	Sulfoxaflor (252)
	Tebuconazole (189)
	Thiamethoxam (245)
	Triazophos (143)
	Trifloxystrobin (213)

The annual 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 was held in Berlin, Germany, from 18 to 27 September 2018. The FAO Panel of Experts had met in preparatory sessions from 13 to 17 September 2018. 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 pesticide residues in foods. During the meeting the FAO Panel of Experts was responsible for reviewing pesticide use patterns (use of good agricultural practices), data on the chemistry and composition of the pesticides and methods of analysis for pesticide residues and for estimating the maximum residue levels that might occur as a result of the use of the pesticides according to good agricultural use practices. The WHO Core Assessment Group was responsible for reviewing toxicological and related data and for estimating, where possible and appropriate, acceptable daily intakes (ADIs) and acute reference doses (ARfDs) of the pesticides for humans. This report contains information on ADIs, ARfDs, maximum residue levels, and general principles for the evaluation of pesticides. The recommendations of the Joint Meeting, including further research and information, are proposed for use by Member governments of the respective agencies and other interested parties.

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