2. GENERAL CONSIDERATIONS

2.1 COMPLETENESS OF DATA SUBMISSIONS

The Meeting noted that CCPR relies upon the scientific advice provided by the JMPR when recommending international food standards for pesticide residues. To ensure maximum transparency and acceptability, it is essential that the Meeting provides state-of-the-knowledge evaluations. This requires independent assessment of all the available data.

For several compounds on the agenda for the present meeting, the Meeting became aware at a late stage (during preparation for the present meeting or during the meeting itself) that additional data were available that had not been submitted to the JMPR. Such information could be critical to the completion of the evaluation. At the present meeting, the evaluation of two substances was significantly affected by incomplete data submissions. As a consequence, the toxicological evaluation of one compound had to be deferred to a future meeting, while for the residue evaluation of another compound only a limited number of maximum residue levels could be recommended.

The Meeting emphasized that JMPR is not a regulatory authority that evaluates and registers specific commercial products; JMPR establishes health-based guidance values for pesticides (i.e. ADIs and ARfDs) and recommends maximum residue levels. For toxicological evaluations, the Meeting applies an overall weight-of-evidence approach hence it is critical that all available information be presented for a complete assessment. For residue evaluations, the Meeting considers all aspects of the use and the fate of a pesticide and its residues, which implies that all studies that provide such information are necessary. It is solely for the JMPR to decide which data are relevant and which are not.

2.2 RESPONSE TO CCPR REGARDING CONCERNS RAISED ABOUT THE TOXICOLOGICAL ASSESSMENT OF DELTAMETHRIN AND INDOXACARB

At its Thirty-eighth Session, the CCPR discussed means to speed up the process by which Codex standards for pesticide residues in foods are developed.[2] The Committee confirmed that JMPR is the scientific body supporting the work of CCPR, while noting that the conclusions and recommendations of JMPR may be discussed at CCPR. The Committee agreed that it should recognize the position taken by JMPR as the best available scientific decision (applicable at the international level) until and if a different position is indicated. The Committee stated that should one of its Members have science-based concerns regarding the conclusions and recommendations made by JMPR, these concerns should be substantiated by scientific information, so that they could be considered by JMPR. Guidance for the process by which such concerns should be raised and considered was developed.[2] JMPR would consider these science-based issues as appropriate.

Such concerns relating to the toxicological evaluation of deltamethrin and of indoxacarb were received by the JMPR Secretariat from the EU and were considered at the 2006 JMPR.

2.2.1 Deltamethrin

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[2] Codex Alimentarius Commission. *Report of the Thirty-eighth Session of the Codex Committee on Pesticide Residues, 3–8 April 2006, Fortaleza, Brazil* (ALINORM 06/29/24).

At the Thirty-eighth session of the CCPR, the EU delegation raised concerns regarding the ARfD for deltamethrin established by the JMPR in 2000. The EU questioned the scientific validity of the pivotal study used for setting the ARfD and asked the JMPR to review the basis for the ARfD established.

Evaluation of deltamethrin by the JMPR

In 2000, the Joint Meeting set an ARfD for deltamethrin of 0.05 mg/kg bw on the basis of the NOAEL of 5 mg/kg bw in a study of acute neurotoxicity in rats[3] and with the application of a 100-fold safety factor. Effects noted at the LOAEL of 15 mg/kg bw were salivation, reduced mobility in an open-field test, and soiled fur. The JMPR concluded that microscopic examination of perfused tissues (including sciatic, tibial and peroneal nerves) from animals at 50 mg/kg bw revealed no treatment-related neuropathological lesions.

The EU evaluation of deltamethrin

In August 2002, the EU rapporteur reviewed the study of acute neurotoxicity and concluded that it was not acceptable.[4] The reasons for unacceptability were absence of data on food consumption and primarily no investigations of nervous tissue from the groups at the intermediate and lowest dose. The EU rapporteur considered that there was an increased incidence of digestion chambers in peripheral nerves with or without axonal degeneration in two out of ten animals receiving deltamethrin at a dose of 50 mg/kg bw compared with none in the control group. In October 2002 the EU confirmed an ARfD of 0.01 mg/kg bw.[5, 6]

Comments made by the JMPR

The 2006 JMPR considered a working paper containing details of the findings of the study of acute neurotoxicity, historical control data on lesions in studies of neurotoxicity [2,7] and information on other studies of potential relevance to the derivation of the ARfD. The Meeting also noted recently published findings[8] of an ED_{30} of 2.5 mg/kg bw and a threshold dose of 1 mg/kg bw for reduced motor activity in rats exposed to deltamethrin by gavage. The latter would be a C_{max} effect and a compound-specific assessment factor of 25 would be appropriate. This would give an ARfD of 0.04 mg/kg bw, thus confirming the ARfD set in 2000.

The 2006 JMPR concluded that the absence of data on food consumption and lack of neuropathological investigation for the animals at the intermediate and lowest doses in the study of acute neurotoxicity did not compromise the interpretation of the study. Peripheral nerve oedema was considered to be a phenomenon that occurred only at a high dose, and that other end-points evaluated

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[3] Nemec, M.D. (1998a) An acute neurotoxicity study of deltamethrin in rats. Unpublished report No. A74318 (AgrEvo document C006785), dated 18 March 1998, from WIL Research Laboratories, Inc., Ashland, Ohio, USA. Submitted to WHO by Hoechst Schering AgrEvo, Frankfurt-am-Main, Germany.

[4] The Codex Committee on Pesticide Residues (2006) Concern regarding deltamethrin, from the European Union, as submitted to the JMPR on 27 June 2006.

[5] European Commission (2002) Review report for the active substance deltamethrin (6504/VI/99 final, 17 October 2002).

[6] European Commission (2003) Directive 2003/5/EC, amending Directive 91/414/EEC. Official Journal L8, 14 January 2003.

[7] Nemec, M.D. (1998b) A subchronic (13-week) neurotoxicity study of deltamethrin in rats. Unpublished report No. A74317 (AgrEvo document C0067850), dated 19 March 1998, from WIL Research Laboratories, Inc., Ashland, Ohio, USA. Submitted to WHO by Hoechst Schering AgrEvo, Frankfurt-am-Main, Germany.

[8] Wolansky, M.J., Gennings, C. & Crofton, K.M. (2006) Relative potencies for acute effects of pyrethroids on motor function in rats. *Toxicological Sciences* 89, 271–277.

in the study were judged adequate to identify a NOAEL. The Meeting confirmed that the ARfD of 0.05 mg/kg bw established by the JMPR in 2000 was appropriate for deltamethrin.

2.2.2 Indoxacarb

At the Thirty-eighth Session of the CCPR,[2] the EU delegation raised concerns regarding the ADI for indoxacarb established by the 2005 JMPR. The EU sought clarification as to why the JMPR considered the studies in rats unsuitable to support the ADI.

Evaluation of indoxacarb by the JMPR

The 2005 JMPR considered the establishment of an ADI and ARfD for indoxacarb. The Joint Meeting concluded that the mild haemolysis observed in studies in rats and dogs given repeated doses was characterized by a reduced erythrocyte count, erythrocyte volume fraction, haemoglobin concentration, and a secondary physiological response involving increased haemopoiesis and deposition of haemosiderin in the spleen and liver. While the reductions in erythrocyte numbers through oxidative damage of haemoglobin occurred with a rather shallow dose–response curve, they achieved statistical significance relative to concurrent controls. However, the JMPR considered that these small changes in circulating erythrocyte mass in the absence of a concomitant increase in haematopoeisis were of no toxicological importance. As a consequence, the ADI of 0–0.01 mg/kg bw per day was based on a NOAEL of 1.1 mg/kg bw per day for erythrocyte damage, Heinz body formation and the secondary increase in haematopoeisis in the spleen and liver in a 1-year dietary study in dogs and using a 100-fold safety factor. This NOAEL was supported by a similar value (1.3 mg/kg bw per day) in a two-generation study of reproduction in rats in which reduced body-weight gain and food consumption in dams was observed. At higher doses, the pups had reduced body-weight gain during lactation.

The EU evaluation of indoxacarb

In its consideration of a toxicological database that was similar to that considered by the 2005 JMPR (although it did not contain the new information on the insecticidally inactive enantiomer of indoxacarb that was available to the JMPR), the EU concluded that the dose-related reduction in haematological effects observed in a 2-year study in rats were treatment-related. In the 2-year study, rats were given diets containing indoxacarb at a concentration of 0, 10 (females only) 20, 40, 60, 125 or 250 (males only) ppm. The EU noted that the haematological effects, suggestive of anaemia, were present at the lowest dose tested (10 ppm) in females and therefore no NOAEL could be established. However, because the haematological effects observed in female rats at 10 ppm (0.55 mg/kg bw per day) were marginal, it was considered to be a NOAEL. The ADI of 0–0.006 mg/kg bw per day was based on the NOAEL of 0.55 mg/kg bw per day and a 100-fold safety factor.

Comment made by the JMPR

The 2006 JMPR re-considered the 2-year study in rats and noted that the minor haematological effects observed in females at 10 ppm after 1 year of treatment, which were considered by the EU to be a ‘marginal-adverse’ effect, were only slightly different from the effects observed at the next higher dose of 20 ppm. The dose-response curve for haematological effects in female rats was so shallow that the difference at 10 and 20 ppm (0.55 and 1.04 mg/kg bw per day respectively) was very small (i.e. no significant difference in erythrocyte volume fraction or erythrocytes, and concentration of haemoglobin was reduced by approximately 1%). After 2 years of treatment, mean values for erythrocytes, haemoglobin and erythrocyte volume fraction in males and females at all doses were comparable with or higher than control values.

The 2006 JMPR confirmed that the appearance of Heinz bodies and the secondary increase in haematopoiesis in the spleen and liver as the marker of an adverse effect on erythrocytes was a more robust end-point for the toxicological effects of indoxacarb. Dogs were the most appropriate species

for these effects. The 2006 JMPR confirmed that the ADI for indoxacarb of 0–0.01 mg/kg bw per day, established by the 2005 JMPR, was appropriate.

2.3 APPLICATION OF ALTERNATIVE GOOD AGRICULTURAL PRACTICES (GAP)

The CCPR, at its 37th Session in 2005 drew attention to acute intake concerns arising from proposals for disulfoton, fenamiphos and aldicarb. The 2005 JMPR proposed a *retrospective* approach to deal with requests from CCPR and a *prospective* approach to deal with cases occurring during evaluations of new and periodic review compounds. The aim being to find a GAP, supported by sufficient residue data where short-term dietary intake is not of concern.

The CCPR agreed that both approaches should be applied. The retrospective approach used, in the main, for existing compounds on an as need basis, while the prospective approach would become the routine approach (Thirty-eight ession of CCPR, ALINORM 06/29/24, 2006, paragraph 29).

In the retrospective approach, relevant GAPs are examined sequentially with available supervised residue trials data. The main interest is in the highest residues that occur with each GAP.

The Meeting noted that the number of available trials would be important to ensure that a good estimate of the highest residues was obtained, i.e., the highest residue resulting from a specified GAP or use pattern (label instructions such as application rate, growth-stage timing, pre-harvest interval, etc). If only three or four trials are available, the results could be misleading, e.g., in US trials residues of disulfoton on lettuce (see example below) did not exceed LOQ in four of the eight reported trials. It therefore could be possible, with only three or four trials, to conclude that residues would be less than LOQ.

If the highest residues for a pesticide-commodity combination are in a borderline area for acceptability of short-term intake, probably at least seven or eight relevant trials would be needed for the assessment. In this situation even for a minor crop, at least seven or eight trials would be needed for a good estimate of likely highest residues.

Supporting information for old compounds would include targeted selected monitoring for residues where the use pattern including timing and pre-harvest interval are known.

Example of assessment summary – disulfoton residues in lettuce

Commodity	GAP	Residue data relevant to national GAP	No of trials	Highest residue mg/kg	IESTI Gen pop'n[§] %ARfD	IESTI children %ARfD
Lettuce	Canada, 1.1-2.2 kg ai/ha, soil treatment at seeding	US trials: < 0.03, 0.10, 0.56	3	0.56	180%	280%
Lettuce	US, 2.2 kg ai/ha, PHI 60 days, soil treatment (equiv to Canadian GAP)	US trials: < 0.03, 0.10, 0.56	3	0.56	180%	280%
Lettuce	Mexico, 1.0 kg ai/ha, soil treatment at seeding	US trials: < 0.03, < 0.05, 0.05, < 0.05, 0.22, 0.58, 0.64, 1.1	8	1.1	380%	570%

[§] General population

In this example, none of the residue data, relating to available alternative GAP, suggests a lower maximum residue level to replace the current proposal of 1 mg/kg for disulfoton on head and leaf lettuce.

Example of assessment summary – fenamiphos residues in peppers

Commodity	GAP	Residue data relevant to national GAP	No of trials	Highest residue mg/kg	IESTI Gen pop'n %ARfD	IESTI children %ARfD
Peppers, sweet	Argentina, CS, 3.2-4.0 kg ai/ha, 1 soil application, PHI 90 days	-	0			
Peppers, sweet	Italy, CS, 10 kg ai/ha, 1 application, PHI 60 days, in irrigation water from transplanting to about 10 days later	France, Greece, Italy, Portugal, Spain: < 0.02 (7), 0.02 (2), 0.07, 0.08, 0.11 mg/kg	12	0.11	30%	30%
Peppers, sweet	Spain, CS, 4.8-9.6 kg ai/ha, 1 application[1], PHI 60 days, soil treatment before start of flowering	France, Greece, Italy, Portugal, Spain: < 0.02 (7), 0.02 (2), 0.07, 0.08, 0.11 mg/kg	12	0.11	30%	30%
Peppers, sweet	Iraq, EC, 8 kg ai/ha, 1 soil application	-	0			
Peppers, sweet	Spain, EC, 4.8-10 kg ai/ha, 1 soil application[2], PHI 60 days, before start of flowering	Spain: 0.06, 0.08, 0.26 mg/kg	3	0.26	70%	80%
Peppers, sweet	El Salvador, GR, 1.0 kg ai/ha, 0.6-1.2 kg ai/ha, 1 soil application, PHI 60 days	-	0			
Peppers, sweet	Guatemala, GR, 1.0 kg ai/ha, 0.6-1.2 kg ai/ha, 1 soil application, PHI 60 days	-	0			
Peppers, sweet	Spain, GR, 5-10 ka ai/ha, 1 soil application, PHI 60 days, pre-planting or pre-sowing	Spain: < 0.05, 0.06, 0.35 mg/kg	3	0.35	100%	110%

[1] First application, just before transplanting or sowing or immediately afterwards; and second application, during the rooting period before the start of flowering.

[2] Up to two applications per season can be given, by dividing the dose in half if the duration of the crop makes it possible to observe the safety period. The first application should be before sowing or transplanting or immediately afterwards and the second during the rooting period of the crop before the start of flowering.

For fenamiphos a maximum residue level recommendation, based on Spanish or Italian GAP, for the use of the CS formulation may proceed and appears acceptable because the IESTI does not exceed the ARfD. However, the residue levels arising from the use of three different formulations (CS, EC and GR) were not significantly different and the Meeting decided to use results from all three formulations to estimate a maximum residue level and HR. The highest residue (0.35 mg/kg) was associated with an IESTI that exceeded the ARfD.

In this example, none of the residue data, relating to available alternative GAP, suggests a lower maximum residue level to replace the current proposal of 0.5 mg/kg for fenamiphos in peppers.

Example of assessment summary – pyraclostrobin residues in head lettuce

Commodity	GAP	Residue data relevant to national GAP	No of trials	Highest residue mg/kg	IESTI Gen pop'n %ARfD	IESTI children %ARfD
Head lettuce	USA: 4 applications of 0.117-0.23 kg ai/ha, PHI 0 days	US: 2.0, 3.7, 5.0, 14, 15, 20 mg/kg	6	20	390%	580%
Head lettuce	Greenhouse - Belgium and UK GAP: 2 applications of 0.1 kg ai/ha and PHI 14 days	Greenhouse – Germany, Spain, France, UK, the Netherlands: 0.03, 0.04, 0.13, 0.23, 0.29, 0.33, 0.75, 0.81 mg/kg.	8	0.81	20%	20%

In the prospective assessment for pyraclostrobin residues in head lettuce, residue data relating to US GAP were first examined. When the IESTI calculation from the highest residue exceeded the ARfD, alternative GAP was examined. The next highest residue 0.81 mg/kg of pyraclostrobin in lettuce was associated with Belgian and UK greenhouse GAP from European trials. The IESTI associated with this residue was less than the ARfD. (See report on pyraclostrobin).

Data submissions for alternative GAP evaluation

The Meeting noted that different situations will need different approaches to make the best use of data. Each situation should be considered before a data submission and request is made for an alternative GAP evaluation.

When the MRL in question is set at the limit of quantification (LOQ), unless a new analytical method is developed with lower LOQ and samples are analyzed with this method, the MRL recommendation cannot be lowered regardless of availability of alternative GAP. (In some cases, several methods with different LOQs are used in trials. Regardless of GAP, it may be possible to recommend a maximum residue level on a basis of "lower LOQ" depending on the numbers of trials and feasibility and reliability of the method.)

When the MRL (or rather the supporting HR) in question relates to an IESTI which is just exceeding the ARfD (around 100–200% of ARfD), and there is a viable alternative GAP, i.e., longer PHI or lower rate with a sufficient number of trials, it may be possible to recommend a lower MRL.

When the calculated IESTI is substantially higher than the ARfD, an HR from an alternative GAP should be substantially less than the HR estimated in the previous evaluation, i.e., the alternative GAP should be significantly different. The number of trials matching the alternative GAP must also be sufficient. This may result in a need for new trials matching the alternative GAP.

Information on current GAP is always needed.

2.4 SHORT-TERM DIETARY INTAKE ASSESSMENT: UNCERTAINTIES IN THE INTERNATIONALESTIMATED SHORT-TERM IN TAKE (IESTI) CALCULATION AND ITS INTERPRETATION.

Introduction

The JMPR uses the deterministic method for the International Estimated of Short-Term Intake (IESTI) of a particular pesticide from the consumption of a food commodity. This calculation was

first introduced by a WHO Consultation on exposure assessment in 1997 and further developed by the JMPR in subsequent meetings (Chapter 3; 2005 JMPR Report).

In characterizing the risks associated with the short-term dietary exposure to a pesticide from the consumption of a certain food, the IESTI is compared with the established acute reference dose (ARfD) of the compound, and the intake expressed as a percentage of the ARfD. This value can then be used to make a judgment about the potential risk associated with the consumption of that food commodity.

In a case where an IESTI calculation, for a crop/pesticide combination, results in an intake higher than 100% ARfD, the Meeting will state according to current practice: "The information provided to the JMPR precludes an estimate that the short-term dietary intake would be below the ARfD for the consumption of the commodity". Due to the uncertainties in the assessment, arising from the uncertainties in each of the parameters or assumptions used, an exceedance of the ARfD does not necessarily represent a health risk to the consumers. The establishment of an ARfD which is necessarily conservative and/or a conservative assessment of exposure will lead to an overly conservative estimate of acute dietary risk.

Some governments, regional authorities, the CCPR and the JMPR have discussed the possibilities for improvement in the methodology currently used by the JMPR in assessing the short-term dietary intake of pesticide residues.

International Estimated Short-Term Intake (IESTI)

The equations below show the IESTI calculation used currently by the JMPR for raw agricultural commodities and when post-harvest treatment of the pesticide was used in grains, oil seeds and pulses:

Case 1: U < 25 g $$IESTI = \frac{HR \times LP}{bw}$$

Case 2: U ≥ 25g

Case 2a: LP > U $$IESTI = \frac{HR \times v \times U + (LP - U) \times HR}{bw}$$

Case 2b: LP < U $$IESTI = \frac{HR \times v \times LP}{bw}$$

Where:

HR = highest residue in composite samples from supervised trials conducted according to GAP, in mg/kg

v = variability factor, which gives the relationship between the 97.5th percentile of the residues in crop units and the average residue in the sampled lot of the commodity

LP = highest large portion provided (97.5th percentile of eaters), in kg of food per day

U = median unit size unit weight of the crop unit examined, in kg

Bw = mean body weight, of the selected population, in kg.

The information on each of these parameters and the limitations attached to the data provided to the Meeting are described below.

Highest residue

The highest residue (HR) is estimated from supervised trials evaluated by the Meeting that have been conducted according to GAP. The uncertainties in these values are mainly associated with the residue dataset available to the JMPR. For major commodities moving in trade, a minimum of eight residue trials are necessary for recommendations to be made, but for minor or specialty crops, as low as three trials could be acceptable. When only limited residue data is available, and the distribution of the residue population is not known, the resulting MRL recommendation can be substantially higher than the HR.

The HR used in the IESTI calculation refers to the residues of toxicological concern present in the edible portion of the crop, while the MRL refers to a residue definition relevant for enforcement purposes related to the commodity in trade. There is a concern that conducting the assessment using the HR value instead of the MRL might not assure the safety of consumers, mainly when the MRL is much larger than the HR. The incorporation of statistical calculation in the recommendation process in 2006 (General Consideration 2.10), will improve the consistency in the estimations of the MRL made by the JMPR based on the available data.

Variability factor

For crops with unit weight > 25 g (Case 2), a variability factor of 3 applied to the HR value will represent a unit with the highest residue value. The variability factor reflects the variability of residues in individual units and is defined as the 97.5^{th} percentile of residue data within a lot divided by the mean of the lot. The factor of 3 represents the mean of variability factors estimated from a dataset of residue data from over 22000 crop units in single plots from 13 countries representing 13 crops and 25 pesticides (2005 JMPR Report). Further improvement on this estimation may be made based on new data or new approaches.

Large portion, unit weight and body weight

Data on the consumption of large portions (LP), unit weight (U) and body weight used currently by the JMPR were provided by the governments of Australia, France, The Netherlands, Japan, Sweden, South Africa, the UK and the USA and compiled by GEMS/Food. The large portion value from each country represents the 97.5^{th} percentiles of consumers; however, the information provided to GEMS/Food does not include the method used to collect the data neither the size of the dataset which was the base of the estimated LP. Consequently, the uncertainty behind the consumption data is unknown.

In the IESTI calculation, the unit weight value (U) will determine whether a variability factor is to be applied to the HR and whether the LP will be composed by more than one crop unit (Case 2a) or will be a portion of the unit (Case 2b). The Meeting does not know whether the U values provided represent the median of units consumed in a country or a different estimation. Also, it is not clear in all cases whether that value refers to the whole commodity or the edible portion.

The body weight (bw) data provided represent the mean body weight for children and for the general population in each country. However, the correlation between the large portion and body weight of each population should be established.

The IESTI was primarily developed to assess the short-term exposure arising from the consumption of food containing residues at levels found in supervised residue trials conducted according to GAP. Some countries have been applying the IESTI equations to assess the safety of food containing residues at levels found in monitoring and/or enforcement programs. The adequacy of such an approach needs to be discussed further.

The acute reference dose (ARfD)

When setting ARfDs, the WHO panel of the JMPR uses the most appropriate data from the available toxicology database. For some compounds such as those which have specific investigations of acute toxic endpoints the ARfD that is set will have a relatively low level of uncertainty associated with it. For other compounds such as those with ARfDs based on repeat dose studies with large margins between NOAELs and LOAELs the degree of uncertainty will be large and the resulting ARfD will be conservative.

Further uncertainty and potential conservatism can occur in the ARfD if the default safety/uncertainty factor of 100 (10× for interspecies extrapolation, 10× for variability of responses in the human population) is used in the absence of specific data which support the application of chemical specific adjustment factors (CSAFs).

Attention is drawn to the fact that when the ARfD is conservative, because of a lack of appropriate toxicological data, this will be clearly stated in the relevant section of the JMPR report, together with an indication of the types of data needed to refine the estimate. The Meeting notes that since the introduction of the acute reference dose concept at the national and international level in the late 1990s, a number of conservative ARfDs which were set initially have subsequently been amended on the basis of recently generated acute toxicity data and improved guidance on the establishment of ARfDs.

Conclusions

It is recognized that the IESTI and the ARfD values are not absolute numbers but are associated with uncertainty and variability. While it is possible to reduce uncertainty, biological variability[9,10] can only be characterized. Both are set conservatively and the degree of conservatism reflects the level of uncertainty and variability in the data The IESTI calculation should assist the decision making process rather than be the sole determinant of acceptable or unacceptable risk. The calculation takes into account only the parameters presented to it. At present, the decision making process does not take into account important qualitative influences, e.g. the nature of the toxicological endpoint.

In order to improve the estimation process the uncertainty of the individual components of the estimation should be examined and possible ways of improvements be identified.

The Meeting recommended that FAO and WHO address the issues identified in this document, with the participation of all relevant stakeholders. The main objectives would be the improvement of the estimation of the short-term dietary intake of pesticides and of the interpretation of the outcome of the short-term assessment conducted by the JMPR. The discussion should include *inter alia* the following specific issues:

- Uncertainty and variability of the parameters used in the estimation;
- Ways to improve the consumption, unit weight and body weight data provided to the JMPR;
- Identification of additional subgroups of the population for which the assessment should be conducted, e.g., toddlers;

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[9] Uncertainty: Imperfect knowledge concerning the present or future state of an organism, system, or (sub) population under consideration. (IPCS Risk Assessment Terminology, WHO Geneva 2004).

[10] Variability: Heterogeneity of values over time, space, or different members of a population, including stochastic variability and controllable variability. Variability implies real differences among members of that population. National Resource Council, Science and Judgement in Risk Assessment (National Academy Press, Washington, DC, 1994).

- The adequacy of the IESTI equations when residues from monitoring/enforcement data are used or the need of a specific methodology for this application;
- How to improve communication between the JMPR and the risk managers and the public on the output of the risk assessment conducted by the Meeting

2.5 UPDATE OF THE AUTOMATED SPREADSHEET APPLICATIONS FOR THE CALCULATION OF DIETARY INTAKE: INTRODUCTION OF THE 13 GEMS/FOOD CONSUMPTION CLUSTER DIETS.

The 2003 Meeting agreed to adopt automated spreadsheet applications for the calculation of dietary intake in order to harmonize and facilitate the process. The spreadsheet applications were constructed by RIVM[11], of The Netherlands, in cooperation with WHO/GEMS/Food incorporating all available consumption data in Excel spreadsheets and, where possible, linking this consumption data to the Codex Commodities for which MRLs, HR(-P)s and STMR(-P)s are estimated. The spreadsheets are used to calculate the IEDI and IESTI using the formulas as described in Chapter 3 of the 2003 Report. To use the spreadsheets, estimates made by JMPR (ADI, acute RfD, STMR (-P), HR (-P), and when necessary MRL values) are entered according to the manual attached to the templates. Then calculations and generation of a final table are performed automatically.

Until now, the long-term dietary exposure (IEDI) was calculated based on the five GEMS/Food Regional Diets. At the Thirty-eighth Session of the CCPR (April 2006), WHO presented more accurate and representative diets. Using a cluster analysis approach, thirteen GEMS/Food Consumption Cluster Diets were developed based on average FAO Food Balance Sheet data for the period 1997-2001 (CX/PR 06/38/3). In cooperation with The French Food Safety Agency and GEMS/Food, these Consumption Cluster Diets have now been incorporated by RIVM in the JMPR IEDI spreadsheet. The main difficulty in this process was, that FAO Food Balance Sheet data do not match one-to-one with the Codex Classification of Foods and Animal Feeds, which are also used in the Cluster Diets. These two classification systems have some incompatibilities in the definition of the commodity and also in the numbering. The spreadsheets contain a number of footnotes to explain how these discrepancies were dealt with.

The main impact of having thirteen diets instead of five will be, that the consumption of a food important to a certain region will no longer be averaged with regions that do not consume the food so much. For that specific region there will be an increased intake of such a food when compared with the five Regional Diets. Furthermore, because in certain clusters the average total food consumption in grams has substantially increased since the previous diets were developed, the impact on dietary intake of pesticide residues is also expected to increase in a similar fashion. The Meeting noted that despite the increase in total food consumption, the mean body weights used in the IEDI spreadsheet are still 55 kg for the Asian clusters (G and L) and 60 kg for all others. GEMS/Food will update these numbers in a future project.

The Meeting noted that in the spreadsheet, the main entry for a commodity would take into account major processed commodities, e.g., in 'FP 0226 Apple', apple juice is included. If an STMR-P is available for apple juice, the consumption of the juice has to be subtracted from the total apple consumption to yield the consumption of apple as raw agricultural commodity, and the two items can be calculated separately. Therefore, in such cases the consumption figures in the final tables in Annex 3 will be somewhat modified when compared to the figures in the spreadsheet itself.

The Consumption Cluster diets are available on the following address: (http://www.who.int/foodsafety/chem/gems/en/index1.html). The spreadsheet applications will be

[11] Dutch National Institute for Public Health and the Environment (RIVM)

available on http://www.who.int/foodsafety/chem/ClusterDietsAug06.xls and will be updated when necessary.

2.6 A TIERED TOXICITY-TESTING STRATEGY FOR PESTICIDES

The Meeting received a brief presentation outlining the results of the ILSI Health and Environmental Sciences Institute (HESI) ACSA (Agrochemical Safety Assessment) project, the results of which have been published in a series of four manuscripts.[12] ACSA involves participants from academia, industry and regulatory/government agencies from a range of countries. The objective of the ACSA project was to review and revise, as appropriate, the data requirements for evaluating the safety of pesticides. The outcome was a proposal for an integrated, tiered testing strategy, with emphasis on the incorporation of information on metabolism and kinetics at all stages, adequate characterization of sensitivity at all life stages, and the provision of information that better suited the needs of risk assessment with respect to duration and pattern of exposure. Other elements were the improved incorporation of physicochemical data into the testing strategy, maximizing the information obtained from a study, the reduction, refinement and replacement of animal use where possible, flexibility and the use of 'trigger' effects to signal the need for higher-tier testing, in a similar manner to that currently used for neurotoxicity testing.

The Meeting welcomed the initiative to undertake a science-based review of the data requirements and to develop an up-to-date testing strategy. The Meeting endorsed the basic approach and encouraged agencies and other stakeholders to continue efforts to validate ACSA proposals and to implement those that were scientficially justified, with due consideration of other issues such animal reduction, refinement and replacement. The Meeting would welcome the opportunity to review progress in this area at a future date.

This proposal receives international attention from various regulatory authorities and organizations. For example, the ILSI-HESI tiered-testing proposal on ACSA is consistent with the US Office of Pesticide Program's vision of a more efficient and reliable science-based paradigm. Thus, OPP views the ACSA as an important springboard to its next generation of data requirements because it incorporates existing knowledge, reduces/refines/replaces animal usage, and takes into account exposure characteristics. Some plans are under way in order to build a foundation and consensus for this new hypothesis-driven toxicology testing paradigm, including an extensive retrospective analysis of the pesticide database.

2.7 GUIDANCE ON THE INTERPRETATION OF HEPATOCELLULAR HYPERTROPHY

Introduction

This document is focused on the histological observation of hepatocellular hypertrophy, a change to the liver that is commonly observed in toxicological studies, particularly in rodents. The purpose of this document to provide general guidance for determining whether the observation of hepatocellular

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[12] Barton et al. (2006). The acquisition and application of absorption, distribution, metabolism, and excretion (ADME) data in agricultural chemical safety assessments. *Critical Reviews in Toxicology,* 36:9–35; Carmichael et al. (2006). Agricultural chemical safety assessment: a multisector approach to the modernization of human safety requirements. *Critical Reviews in Toxicology,* 36:1–7; Cooper et al. (2006). A tiered approach to life stages testing for agricultural chemical safety assessment. *Critical Reviews in Toxicology,* 36:69–98; and Doe et al. (2006). A tiered approach to systemic toxicity testing for agricultural chemical safety assessment. *Critical Reviews in Toxicology,* 36:37–68.

hypertrophy in different laboratory species is indicative of an adaptive or an adverse event,[13] so that the most appropriate reference dose can be identified for the establishment of health-based guidance values. This document is intended to facilitate consistent and transparent decisions in pesticide evaluations, and to promote international harmonization in human risk assessment. This guidance should not be regarded as prescriptive; as with any assessment, scientific judgment and consideration of all pertinent information should be used. Because findings of liver effects can encompass a wide range of observations, reported effects should be considered individually and in combination in an overall weight-of-evidence assessment. This guidance places attention on the description of effects that are not adverse and therefore should not contribute towards the selection of a NOAEL; and on those effects that are typically considered to represent evidence of biologically significant toxicity and can contribute towards a selection of a lowest-observed-adverse-effect level (LOAEL).

Hepatocellular hypertrophy

Hepatocellular hypertrophy is a general increase in the size of the liver because of cell enlargement and accumulation of fluids. It is not attributable to tumour formation or to an increase in the number of cells (hyperplasia). An indication that hypertrophy is occurring in hepatocytes is usually an increase in the size and weight of the liver. At the cellular level, the response is a proliferation of the smooth endoplasmic reticulum (SER) that would be evident microscopically at an early stage at the tissue level as an increase in acidophilia (e.g. eosinophilia). Proliferation of SER would be confirmed by electron microscopy.

Hepatocellular hypertrophy is typically related to increased functional capacity. To maintain homeostasis in the whole organism, the hepatocyte frequently responds to xenobiotic exposure by increasing its metabolic capacity via induction of xenobiotic metabolizing enzymes. Such hepatic adaptive responses usually result from chemical interaction with cellular regulatory pathways (often receptor-mediated), leading to changes in gene expression and protein synthesis, and eventually cell growth and alteration of microsomal enzyme activities. Adaptive responses are potentially beneficial in that they enhance the capacity of the organism to respond to chemical-induced stress, and are reversible. However, there are limits to these homeostatic responses and it is important to recognize when these limits have been exceeded. Because toxicity is an exposure-related phenomenon, there are lower exposures that produce effects within the control of homeostatic mechanisms and higher exposures that result in effects that exceed the capacity of these mechanisms to return the organism to its previous condition once exposure has ceased.

Weight-of-evidence approach: factors to consider

No single effect is generally sufficient to support a determination that liver hypertrophy is adaptive or adverse. Determination of hepatotoxicity involves a detailed consideration of clinical chemistry and histopathology (or other relevant information such as histochemistry, morphometry and electron microscopy). The type, severity or magnitude, and dose–response relationship of observed effects, as well as the progression of observed lesions with duration of dosing, should be considered. It is important to evaluate whether the observed effects present a biologically plausible and consistent pattern of changes in clinical chemistry and histopathology indicative of hepatotoxicity. Sustained effects should be given more weight than transient effects. The key questions that should be addressed in the analysis are listed below.

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[13] *Adverse effects* are considered to be functional impairments or pathological lesions that may affect the performance of the whole organism or that reduce an organism's ability to cope with an additional challenge (USEPA, 2002; see footnote 19). On the other hand, an adaptive effect is an initial response of the organism to maintain homeostasis, and can be defined as those biological effects that do not cause biochemical, physiological, and morphological changes that affect the general well being, growth development or lifespan of the organism (Williams & Iatropoulos, 2002; see footnote 20).

Does the histological evidence support the hypothesis that the hepatocellular hypertrophy is an adaptive effect? Hypertrophy as an adaptive response should not be accompanied by other hepatic responses identifiable by histology, such as necrosis, apoptosis, pigment deposition, or hyperplasia (an increase in the number of cells, as a result of tissue regeneration or mitogenic stimulation). In rodents, hypertrophy and hyperplasia may occur together following exposure to microsomal enzyme inducers. Thus, it is important that the hyperplasia is histologically distinguished from the hypertrophy and characterized for its relevance for human risk assessment. Care should be exercised to ensure that eosinophilia is not attributable to the presence of eosinophilic foci of altered hepatocytes. In general terms, it has been stated that, "To the best of our knowledge there is neither any hepatocarcinogenic agent which does not elicit FAH [foci of altered hepatocytes], nor is there any model of hepatocarcinogenesis without formation of these lesions prior to the manifestation of benign or malignant hepatocellular neoplasms."[14] Thus, although neoplasia is not an inevitable outcome of FAHs, the possibility should be considered. Lesion type, distribution, and grade of severity should also be considered in determining whether and to what extent a liver finding is adverse. Differentiation of the zone of damage (e.g. periportal, centrilobular) may provide insight into the mode of action of hepatotoxicity. Also, it should be considered whether the liver hypertrophy occurred secondary to damage in another organ system (e.g. as a result of exposure to haemolytic or nephrotoxic agents).[15]

Does the clinical chemistry support the hypothesis that the hepatocellular hypertrophy is an adaptive effect? If there is no evidence of histopathological change, do the clinical chemistry findings exclude a conclusion of hepatotoxicity? The following changes in clinical chemistry can be considered to be indicators of liver damage, their extent and relevance depending on the species: decreased concentration of plasma albumin, increased activities of alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP) and gamma-glutamyltransferase (GGT), and increased concentration of free or total bilirubin and cholesterol. Increases in ALT and AST activity indicate damage to the hepatocyte, in particular cellular membrane leakage. On the other hand, hepatocellular hypertrophy alone can be associated with some increase in ALT or AST activity owing to membrane leakage, with no other evidence of significant hepatic injury. An increase in total bilirubin, cholesterol, and ALP and GGT activities can be indicators of damage to the biliary system (changes in free bilirubin indicate hepatocellular damage). A dose-dependent response and a statistically significant change would lend weight to the interpretation of the significance of these changes. However, statistical significance alone is not a reliable indicator of hepatic toxicity, particularly in a single parameter. Marginal changes in blood chemistry that show a biologically plausible and consistent pattern of effects might be considered to be indicative of liver toxicity. However, the values should be outside the normal range for control animals of the species (depending on strain, breeder, testing laboratory, etc.) being examined and not only different from those for the concurrent controls. Therefore, robust databases on consistent trends in the data, group means, the number of animals examined and the number affected are necessary for the important considerations in the clinical chemistry analysis.

Are the liver changes transient or sustained? Is there a progression of the effect? The results from studies of shorter duration should be compared with those from studies of longer duration or long-term tests to determine the progression of effects with duration of dosing and whether they are transient and reversible. Thus, recovery studies are very useful. It is sometimes difficult to use short-term studies to determine whether hepatocellular hypertrophy or liver size/weight is associated with adverse effects. If long-term studies of toxicity are available and show no progression of liver toxicity

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[14] Bannasch P, Haertel T, Su Q (2003) Significance of hepatic preneoplasia in risk identification and early detection of neoplasia. *Toxicologic Pathology,* 31:134–139.

[15] Andrew, D. (2005) PSD guidance document: interpretation of liver enlargement in regulatory toxicity studies. York, England, Pesticides Safety Directorate, dated May 26, 2005. Available from http://www.pesticides.gov.uk/uploadedfiles/Liver%20paper%20post%20ACP(1).doc

(e.g. neoplasia, hyperplasia, degeneration, necrosis), then the observed cellular hypertrophy and/or increase in liver size/weight observed in short-term studies is not likely to be adverse.

Is liver hypertrophy accompanied by the induction of P450 or other xenobiotic metabolizing enzymes? Are there any toxicological effects consequent to that induction? Chemicals may induce enzymes responsible for rate-limiting steps in the metabolism or elimination of other xenobiotic or endogenous compounds. Such interactions can potentially lead to clinically relevant outcomes (e.g. reducing the efficacy of a drug, increasing the toxicity of another chemical, or altering hormonal homeostasis). To assess the adequacy of the margin between the dose that causes enzyme induction and the established health-based guidance value (e.g. ADI), the following factors should be considered:

- Is the extent of induction minimal or substantial?
- In the absence of data on enzyme induction, are there data to suggest the hypertrophy is due to factors unlikely to be associated with enzyme induction (e.g. chlorinated hydrocarbon-induced lipid accumulation)?
- Are there data characterizing the induction (e.g. which receptors are activated or which isoenzymes are induced) and its human relevance?
- Are there interspecies comparative data (e.g. from studies with human and animal hepatocytes in vitro) characterizing chemical interactions (both induction and inhibition)?
- Can the evaluation of microsomal enzyme induction help to interpret the basis of effects found in other organs or tissues?

The IPCS document on chemical-specific adjustment factors provides useful guidance for evaluating toxicokinetic and toxicodynamic data to address interspecies and interindividual differences.[16]

General principles

The following principles should be followed in the final assessment of liver hypertrophy:

- In the absence of histopathological damage and relevant clinical chemistry changes, at the dose that induces only hepatocellular hypertrophy and/or liver size/weight changes, hypertrophy should not be identified as an adverse effect or used for establishing health-based guidance values. This dose should be identified as a lowest-observed-effect level (LOEL).
- If hepatotoxicity, as characterized by toxicologically significant changes in histopathology and/or clinical chemistry, occurs at doses higher than those causing liver hypertrophy, then the LOAEL for the study should be the dose that elicits hepatotoxicity (or some other relevant toxicity found in the study).
- If there is insufficient information to determine whether the observed liver hypertrophy is an adaptive or an adverse response, then the default is to assume that the effect is adverse.
- If other organ responses are observed that may be the secondary consequence of enhanced hepatic metabolism (e.g. increased hepatic clearance of thyroid hormones), these effects should be

[16] IPCS (2005) Chemical-specific adjustment factors for interspecies differences and human variability: guidance document for use of data in dose–concentration response assessment. Harmonization Project Document No. 2. Geneva, WHO.

evaluated for their relevance to the establishment of health-based guidance values.

- The lowest-observed-effect level (LOEL) for the induction of xenobiotic metabolizing enzymes should not be lower than the established health-based guidance value (e.g. ADI).

- The observation of hyperplasia or neoplasia would result in consideration of a mode-of-action analysis. Liver hypertrophy and a range of other morphological changes can result from chemically-mediated effects on different nuclear receptors, but not all these mechanisms are necessarily relevant to humans. The IPCS Framework for analysing the mode of action of an agent in causing hepatic effects in animals and its relevance for humans[17] should be followed.

In summary, a weight-of-evidence approach should be used to interpret findings of hepatotocellular hypertrophy. Hepatocellular hypertrophy and the associated increase in liver size and weight are morphological descriptions and do not necessarily characterize nor indicate liver damage. The principles of this guidance (including the weight-of-evidence approach) were especially applied by the 2006 JMPR in its evaluation of liver effects caused by boscalid, haloxyfop, quinoxyfen and thiacloprid.[18] For additional information, the evaluator is referred to the USEPA[19] and the UK PSD[3] documents, as well as a paper by William & Iatropoulos.[20] For the interpretation of histopathology, the evaluator is further referred to standard text books of pathology.[21]

Recommendation

The consistent interpretation of findings from studies of toxicity to determine whether they have significance for human health safety assessments is a critical aspect of the evaluation. Thus the Meeting recommended that the interpretation of effects other than hepatocellular hypertrophy that may be modest or adaptive (e.g. reductions in body weight, changes in some organ weights), that may not be associated with any functional impairment or structural damage, should be considered in the IPCS Harmonization Project.

2.8 UPDATING THE PRINCIPLES AND METHODS OF RISK ASSESSMENT: MRLS FOR PESTICIDESAND VETERINARY DRUGS.

The Meeting welcomed the report[22] of a workshop hosted by FAO, WHO and The Dutch National Institute for Public Health and the Environment (RIVM) at Bilthoven in The Netherlands in November 2005. The workshop was organized within the framework of the *Project to Update the Principles and Methods for the Risk Assessment of Chemicals in Food.*

The main aim of the workshop was to harmonize, to the extent possible, risk assessment procedures for pesticide residues and veterinary drug residues. The workshop issued 14

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[17] Boobis A, Cohen SM, Dellarco V et al. (2006) IPCS Framework For Analysing the Relevance of a Cancer Mode of Action for Humans. *Critical Reviews in Toxicology* (in press).

[18] See section 4. Full toxicological evaluations to be published as *Pesticide residues in food—2006 evaluations. Part II. Toxicological.* Geneva, World Health Organization.

[19] USEPA (2002) Hepatocellular hypertrophy. HED Guidance Document # G2002.01, October 21, 2002. Office of Pesticide Programs, Health Effects Division (HED), USEPA. Available on request.

[20] Williams GM, Iatropoulos MJ (2002) Alteration of liver cell function and proliferation: differentiation between adaptation and toxicity. *Toxicologic Pathology*, 30:41–53.

[21] For example: Cheville NF (1994) *Ultrastructural pathology—an introduction to interpretation*. Iowa State Press; and Haschek WM, Rousseaux CG (1998) *Handbook of toxicologic pathology*. New York, NY, Academic Press, Inc.

22 FAO/WHO. 2006. Updating the Principles and Methods of Risk Assessment: MRLs for Pesticides and Veterinary Drugs. http://www.fao.org/ag/AGP/AGPP/Pesticid/JMPR/DOWNLOAD/bilthoven_2005.pdf

recommendations, some of which were directed to JECFA, some to JMPR and some to both. This report provides a response to the recommendations relevant to JMPR. The numbering is preserved from the workshop report.

Recommendation 5. Partitioning of residues in milk into the fat is influenced by the molecular structure of the compound. Furthermore, the fat content of milk is variable. JECFA proposes MRLs for whole milk. JMPR now recommends two MRLs for fat-soluble compounds, one on whole milk and one on milk fat. This is necessary to estimate residues in processed dairy commodities. The workshop recommended that JECFA and JMPR consider harmonizing this practice.

The partition of fat-soluble compounds between the fat and non-fat phases of milk has been the subject of recent JMPR Reports[23] [24].

The convention had been adopted, that milks contain 4% fat and that fat-soluble compounds partition exclusively into the fat. Until 2004 the JMPR followed the Codex convention of expressing the MRL for fat-soluble compounds in milk on the basis of the calculated whole product, assuming that all milks contain 4% fat[24]. The main purpose of this convention was to allow a calculation of an MRL for fat-soluble compounds in dairy products containing fat concentrations different from that of milk.

The 2004 JMPR noted that some pesticides have intermediate solubility in fat; even if they are regarded as fat-soluble they can be distributed equally between the fat and non-fat portions of milk.

The 2004 JMPR decided that, for fat-soluble pesticides, two maximum residue levels would be estimated where the data permit: one for whole milk and one for milk fat. For enforcement purposes, a comparison could be made either of the residues in milk fat with the MRL for milk (fat) or of the residue in whole milk with the MRL for milk. When needed, maximum residue levels for milk products could then be calculated from the two values, by taking into account the fat content of the milk product and the contributions from the fat and non-fat fractions[24].

The MRL for milk estimated by JMPR should be equivalent to the MRL for whole milk estimated by JECFA.

Recommendation 6. For dual-use substances the evaluation of the application as a pesticide/drug to animals should be undertaken using the same principles. This can be achieved by several means that require coordination between JECFA and JMPR and also CCRVDF and CCPR (risk assessment policy) and will involve the adoption of mutual notification and co-ordination of procedures.

Recommendation 7. JMPR and JECFA should carry out a comprehensive review of all commodity and tissue definitions. As appropriate: harmonizing meat and muscle tissue definitions, combining definitions of poultry and poultry meat, avoid subdivision into specific commodities for milk and eggs, harmonize definition of animal fat to be equivalent and to exclude dairy milk, harmonize definitions for aquatic species, and consider whether JECFA MRLs for liver and kidney should include other offal. Subsequently, amending instructions on the portion of commodity to which the MRL applies is recommended.

The Meeting agreed that recommendations 6, 7 and 11 (see below) requiring coordination and harmonization should progress through a process involving a joint task group from JMPR and JECFA.

Recommendation 8. National governments are encouraged to submit GAP information particularly on 'minor crops' during the data and information call-in process for JMPR.

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23 FAO. 2003. 2.6 Expression of MRLs for fat-soluble pesticides in milk and milk products. Pesticide Residues in Food – Report 2003. FAO Plant Production and Protection Paper, 176:7-8.
24 FAO. 2004. 2.7 Revisited: MRLs for fat-soluble pesticides in milk and milk products. Pesticide Residues in Food – Report 2004. FAO Plant Production and Protection Paper, 178:24-25.

The Meeting encouraged the submission of GAP information on minor or specialty crops especially where it was the same or very similar to a registered use on a major crop of the same crop group. Such information would facilitate extrapolation to the minor crop.

Tables of summary GAP information are not generally adequate to convey the nuances of the use pattern necessary for evaluation. For example, it is not always clear from summary tables if the label specifies the maximum number of applications or maximum application amount per season or if there is such a limitation. Sometimes information other than label information is included in summary tables. A copy of the label directions or an English translation of the relevant label directions should be provided.

Recommendation 9. JMPR should continue to evaluate extrapolation of pesticide residues data between geographic zones.

JMPR extrapolates supervised residue trial data between geographic zones when the use pattern (label instructions such as application rate, timing, etc) is the same and when the cultural practices for producing the crop are similar. For example, at this meeting, residue data for aminopyralid on wheat and wheat straw from different geographic zones were combined because the use patterns were similar and the cultural practices for wheat production are known to be similar.

Recommendation 11. Procedures for extrapolation from one species of animal having a full data set and recommended MRLs to another species need to be agreed upon and harmonized guidance documents prepared. This should be based on past experience with specific cases.

When pesticide residues occur in crops and feeds, those residues may readily transfer to food-producing livestock. It is not practical to control the species of livestock that might have access to feeds with various pesticide treatment histories and in such situations MRLs are preferably recommended for the range of livestock commodities that might contain the residues.

In 2002[25] the JMPR decided that the results of cattle feeding studies would be used to support MRLs for mammalian meat and offal and milks. Similarly, the results of studies in chickens or laying hens would be extrapolated to poultry meat, offal and eggs.

The JMPR will maintain this practice of setting broad group MRLs for animal commodities where residues occur via the animal feed.

The situation is different for direct application to an animal. Residues should occur only where there is a registered use for that species. The Meeting agreed that extrapolation to a second species would be considered where the uses were similar and where past experience suggests sufficient comparability between species.

Recommendation 12. A general principle on recommending Group MRLs in wider circumstances should be considered in an attempt to cover more uses where national authorizations exist.

The report[22] explains the current situation:

The current JMPR approach to the estimation of group maximum residue levels is explained in the FAO Manual26. Group tolerances may be proposed where data are available on a number of crops within that crop group or at least two species are included in products of animal origin.

Commodity groupings described in the Codex Classification of Foods and Feeds are the basis for group maximum residue levels. Generally, for a group limit to be proposed, residue levels in the main commodities of the group should not be too divergent and registered uses should be similar. In

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25 FAO. 2002. 2.11 Maximum residue levels for animal commodities – group MRLs. Pesticide Residues in Food – Report 2002. FAO Plant Production and Protection Paper, 172:20-23.

[26] FAO 2002. Submission and evaluation of pesticide residues data for the estimation of maximum residue levels in food and feed. FAO Plant Production and Protection Paper, 170.
http://www.fao.org/ag/agp/agpp/pesticid/p.htm.

some cases where the residues on one or a few commodities in the group are quite different from the rest, it may be possible to recommend a limit for "group, except …..".

MRLs for pesticide residues in food commodities are needed for control-of-use and as trade standards.

Registered uses may vary widely from place to place because of the climate, the variation in pests to be controlled and the cultural practices employed to produce the crop, so control-of-use MRLs are also likely to vary from place to place. Such MRLs are useful for checking if the pesticide has been correctly used, but are problematic for international trade.

MRLs for control-of-use are parochial, while MRLs for trade purposes should be global.

Codex MRLs are used as trade standards. For many commodities, including commodities from minor or specialty crops, MRLs as trade standards are now the predominant need.

From a trade perspective, it is better to have an MRL than no MRL if residues are likely to arise in that food commodity. Even if the MRL is set too low (say 20–50% of what it should be) because of the inadequate data it is better than no MRL.

The Meeting agreed that a more liberal extrapolation to group MRLs was needed.

The Meeting recommended that CCPR consider the following scientific assessment policy for group MRLs.

After dietary intake assessment, commodity group MRLs may be proposed on the following minimum conditions:

(1) The pesticide is registered or authorized for use on the crop group; and

(2) Relevant and adequate residue data are available for at least one major commodity of the group. (However, all relevant data for the commodities of the group should be taken into account.)

If the recommended group MRL is subsequently found to be inadequate for some commodities and their registered uses, there would be no impediment to submission of further data to amend the group MRL or to propose specific commodity MRLs.

In line with the alternative GAP proposal, if the IESTI calculations suggested that short-term intake would exceed the ARfD of the compound for one or more commodities in the group, the JMPR would examine and recommend alternative proposals including alternative GAP and single commodity MRLs.

2.9 RESIDUES IN ROTATIONAL CROPS

The JMPR regularly reviews residues in follow up or rotational crops as part of its evaluation of residues in food. The residues in follow up crops are usually composed of various metabolites in low concentrations and the compounds included in the residue definition are generally below the LOQ and do not require any further action.

Boscalid evaluated by the 2006 JMPR represents a special case because it persists in soil for a relatively long period of time (estimated half lives ranged between 108 days and over one year under aerobic soil conditions) and can be taken up extensively by crops grown in treated areas. It is estimated that following repeated application of the compound at recommended rates the residues in soil would vary approximately in the range of 0.5 and 2 mg/kg.

The Meeting was initially provided with only three confined rotational crop studies, indicating that residues of boscalid in radish leaves and wheat forage were relatively high following the application of boscalid on bare soil at 2.1 kg/ha (typically 2–3 times higher than the maximum recommended rate). Based on a special request additional rotational field studies were submitted.

These studies indicated that, following the use, according to GAP, high residues could occasionally occur, i.e., up to 15 mg/kg in mustard green leaves, 7 mg/kg in straw of wheat and hay, 1 mg/kg in cantaloupe and summer squash. Whereas lower residues may occur in a large variety of crops planted in fields previously treated with boscalid.

The occurrence of such residues has the potential to cause trade disruptions and an under estimation of the dietary intake, particularly for crops in which the compound is not registered.

The Meeting emphasized that in cases where the residues in follow-up and rotational crops may occur at levels above the LOQ, in addition to the minimum data requirement as specified in the *FAO Manual*, the data submitters should automatically provide information on:

Metabolism in root or tuber vegetables;

results of field studies on follow-up and rotational crops carried out at various times after the application of the pesticide;

environmental fate studies, and

any other relevant information, which may assist the comprehensive evaluation of residues in food.

The Meeting recommended to CCPR to request member countries to provide information on how residues in follow up crops, including the special case of boscalid, are regulated at the national level. This information will be taken into account in making recommendations based on the evaluation of residues in follow-up and rotational crops at a future meeting.

2.10 USE OF STATISTICAL METHODS IN THE EVALUATION OF SUPERVISED FIELD TRIAL DATA FOR THE ESTIMATION OF MAXIMUM RESIDUE LEVELS

The Meeting utilized the NAFTA spreadsheet for assistance in evaluating field trial data in the estimation process for maximum residue levels. The spreadsheet was evaluated in 2004 and 2005 (Report 2004, Report 2005) and adopted as a tool to be used by JMPR reviewers.

The Meeting also tested a binomial spreadsheet first described by Hamilton at IUPAC (2006)[27]. To estimate an MRL from a set of residue data, the residue evaluator first uses a binomial (non-parametric) procedure to calculate the highest percentile value possible on the limited data with a 95% confidence limit, e.g. for 8 data points, the 68.8th percentile may be calculated. Next, that value is multiplied by factors from the empirical data distribution to produce the 95th and 99th percentile values. An empirical data distribution was obtained from approximately 75 sets of residue trials. The minimum number of data points required is 5.

The two spreadsheets usually provided comparable estimates. The 95th percent upper confidence limit on the 95th percentile or the point estimate of the 99th percentile value from the NAFTA spreadsheet typically fell at or between the 95th percentile and 99.5th percentile point value estimates from the binomial spreadsheet. The two methods were judged to be mutually compatible, and it was agreed that both provide valuable information to the evaluator. It was also confirmed that the spreadsheet results are only suggested values and that the Meeting must always use best scientific judgment in the assignment of the maximum residue level.

The following is a typical calculation result from use of the spreadsheets. There were 51 field trials for the foliar application of the fungicide quinoxyfen to grapes: 0.01, 0.02 (2), 0.04 (3), 0.05 (2), 0.06 (4), 0.07, 0.08 (3), 0.09 (4), 0.10, 0.13 (3), 0.15 (5), 0.16, 0.17 (2), 0.18 (3), 0.21, 0.22 (3), 0.23, 0.24 (2), 0.29, 0.30, 0.41, 0.44, 0.45, 0.49, 0.54, 0.82 and 1.1 mg/kg.

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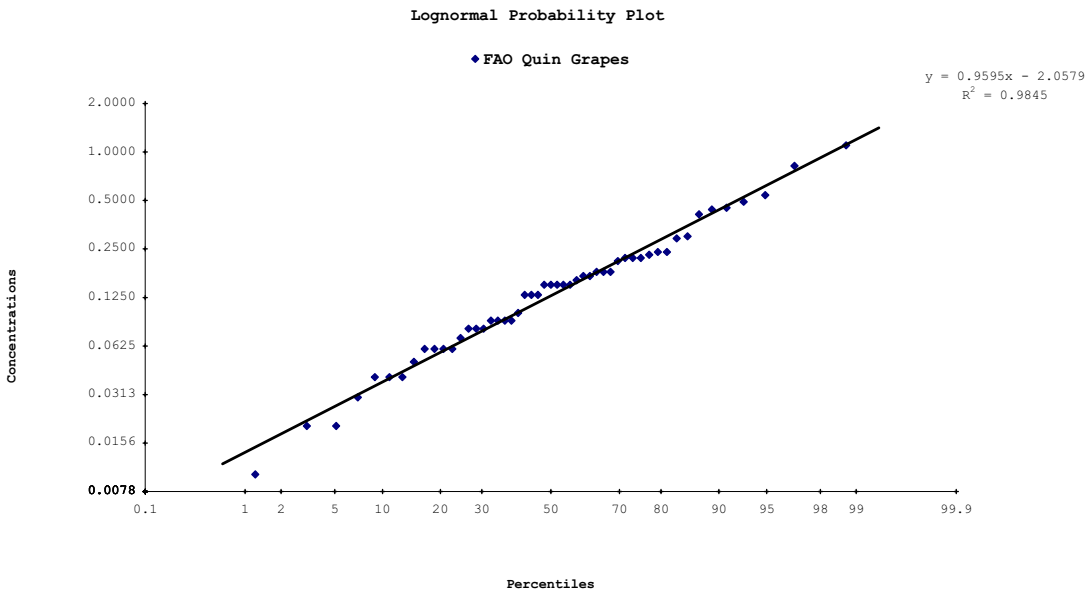
[27] Hamilton, D. 2006. Statistical calculation of MRLs. 11th IUPAC International Congress of Pesticide Chemistry. 6-11 August, Kobe, Japan. Abstract III-4-09B

The NAFTA calculation indicates the 95% percent upper confidence limit of the 95th percentile is 0.91 mg/kg and that the 99th percentile is 1.16 mg/kg for a log normal distribution. The binomial calculation yields a 95th percentile of 0.712 mg/kg and a 99.5th percentile of 1.425 mg/kg. The Meeting considered the 99th percentile value of 1.16 mg/kg as a good estimate and rounded it up to 2 mg/kg. The Meeting recognized that the recommended value provided by the NAFTA spreadsheet represents a regional policy decision and therefore elected to consider all outputs from use of the spreadsheet. For log normal situations, attentions will focus on the 99th percentile.

NAFTA (log normal)



	Regulator: FAO **Chemical:** Quin **Crop:** Grapes **PHI:** **App. Rate:** **Submitter:** **n:** 51 **min:** 0.01 **max:** 1.10 **median;** 0.15 **average:** 0.19		
	95th Percentile	**99th Percentile**	**99.9th Percentile**
EU Method I Normal	0.53 (0.61)	0.66 (0.77)	0.82 (--)
EU Method I Log Normal	0.61 **(0.91)**	**1.16** (1.92)	2.40 (--)
EU Method II Distribution-Free		0.44	
California Method μ + 3σ		**0.80**	
UPLMedian95th		**0.77**	
Approximate Shapiro-Francia Normality Test		0.9845 p-value > 0.05 : Do not reject lognormality assumption	

Binomial

Mean =	0.19	94.3	value =	0.673	
n=	51	0.057		95th percentile=	0.712
		0.95		99.5th percentile =	1.425
1	1.100	0.155		0.170	
2	0.820	0.234		0.191	
3	0.540	0.231		0.124	
4	0.490	0.167		0.082	
5	0.450	0.095		0.043	
6	0.440	0.044		0.019	
7	0.410	0.017		0.007	
8	0.300	0.006		0.002	
9	0.290	0.002		0.000	
10	0.240	0.000		0.000	
11	0.240	0.000		0.000	
12	0.230	0.000		0.000	
13	0.220	0.000		0.000	
14	0.220	0.000		0.000	
15	0.220	0.000		0.000	
16	0.210	0.000		0.000	
17	0.180	0.000		0.000	
18	0.180	0.000		0.000	
19	0.180	0.000		0.000	
20	0.170	0.000		0.000	
21	0.170	0.000		0.000	
22	0.160	0.000		0.000	
23	0.150	0.000		0.000	
24	0.150	0.000		0.000	
25	0.150	0.000		0.000	
26	0.150	0.000		0.000	
27	0.150	0.000		0.000	
28	0.130	0.000		0.000	
29	0.130	0.000		0.000	
30	0.130	0.000		0.000	
31	0.100	0.000		0.000	
32	0.090	0.000		0.000	
33	0.090	0.000		0.000	
34	0.090	0.000		0.000	
35	0.090	0.000		0.000	
36	0.080	0.000		0.000	
37	0.080	0.000		0.000	
38	0.080	0.000		0.000	
39	0.070	0.000		0.000	
40	0.060	0.000		0.000	
41	0.060	0.000		0.000	
42	0.060	0.000		0.000	
43	0.060	0.000		0.000	
44	0.050	0.000		0.000	
45	0.040	0.000		0.000	
46	0.040	0.000		0.000	
47	0.040	0.000		0.000	
48	0.030	0.000		0.000	
49	0.020	0.000		0.000	
50	0.020	0.000		0.000	
51	0.010	0.000		0.000	

Values above the estimate ("Outliers")

With a sufficient number of residue data points, it is likely that the spreadsheet estimate of the maximum residue level will be *less than* the highest residue value. An increasing number of data points are accompanied by an increasing probability that one or more of those points will exceed the 95th or 99th percentile estimate of the MRL. The Meeting concluded that such apparent "outliers" will

not be routinely excluded from the data set and that the maximum residue estimate will include the highest value. The Meeting will consider such situations on a case-by-case basis. The exclusion of one or more high values at the 99th or 99.5th percentiles will alert the evaluator to look very carefully at the particular field trial and analysis to ascertain if there is an error in the study that would justify deletion of the result from consideration.

Scaling (rounding)

The use of the statistical spreadsheets provides information on the 95th and 99th/99.5th percentile of residue distributions. The relationship of a selected value to all values can be approximated. For example, selection of the 99th percentile value gives a measure of confidence that about 1 residue value in each 100 may exceed the selected value. This is a benchmark not previously available. It was previously judged necessary to "round up" considerably on the value selected for the maximum residue level. This is no longer the situation where the statistical estimation tools are utilized.

In order to more fully reflect the impact of this new tool, the Meeting concluded that the scaling steps last presented in the 2001 JMPR Report (General Consideration 2.3), would be abandoned in those situations where the statistical tools are successfully used. For example, using the scaling approach, a value of 7.2 is raised to 10. If the 7.2 value is shown to be the 99th percentile of a log normal distribution or the 99.5th percentile distribution from the non-parametric binomial procedure, it would be possible to estimate the maximum residue level at 8. Of course, expert judgment must be used in estimating the value. If only a few data points were in the distribution or if a significant fraction of the points were near the highest value, then thought might be given to using a value greater than 8.

The Meeting further concluded that estimations should continue to be expressed as one significant figure, with exceptions on a case-by-case basis. This recognizes the inherent uncertainties in sampling and in analysis and in the frequent practice of compositing sample sets, where data sets from countries are combined when they appear not to be from different populations.

Conclusions

The Meeting concluded that:

The statistical spreadsheets described above are to be used by the evaluators as a tool to assist in the estimation of maximum residue levels, and the spreadsheets will be included in the next revision of the FAO Manual.

The widespread use of such statistical procedures will be useful in the promotion of harmonized maximum residue limit estimations among the various national and regional authorities.

Statistical tools are an aid to the reviewer and are not a substitute for sound scientific judgment. Thus, values falling above the spreadsheet maximum residue level estimate are not routinely discarded.

The statistical procedures provide a good estimate of the 95th to 99th percentile range where there are sufficient data points. In such situations the scaling system is not needed.

2.11 OECD GUIDANCE AND GUIDELINES FOR RESIDUE CHEMISTRY

Under the auspices of the OECD Working Group on Pesticides (WGP), an OECD Pesticide Residue Chemistry Group has been given the task of writing harmonized guidelines and associated guidance documents for the various topics of residue chemistry for pesticides in foods/feeds. The Pesticide Residue Chemistry Group is composed of experts from numerous OECD member countries from around the globe and includes the FAO as well as pesticide industry experts. Several members of the FAO Panel of JMPR also participate in the Group. During the drafting of the various documents, the

writers have consulted national and regional guidelines and the *FAO Manual.*

A primary goal of the project is to provide standardized procedures/methods for the various residue chemistry requirements, so that industry may submit one set of studies to the various OECD member countries for registration. This will facilitate work sharing among national and regional authorities.

The Group has finalized and obtained approval for guidelines covering Plant Metabolism, Livestock Metabolism, Rotational Crop Metabolism, Rotational Crop Field Trials, and Residues in Livestock. Additionally, a Residue Definition guidance document and an Overview document were prepared. The guidelines were accompanied by templates designed to be standardized summary documents for industry submission as part of a registration package. These documents were presented in draft form to the experts of the FAO Panel of the 2005 JMPR, for comments. Numerous comments were submitted via the FAO to the Group and were incorporated in the final documents.

Work has now progressed on the writing of the second set of documents: Analytical Method Guidance, Nature of the Residue in Processing Guideline, and Storage Stability Guideline are in an advanced draft stage. Final drafts will be available for comment by the JMPR. Initial drafting of the Magnitude of the Residue in Processed Commodities Guideline and Guidance has commenced, and planning continues for the Crop Field Trial Guideline.

Implications for the JMPR

The Guidelines and Guidance documents will impact the FAO Panel's methods and procedures for the review of residue chemistry. For example, the new OECD livestock feed tables provide information on livestock diets in three regions and will allow the JMPR to make a more inclusive and improved calculation of the livestock dietary exposure for livestock commodity maximum residue levels (see General Item 2.13).

Conclusions

The JMPR welcomes the publication of the OECD residue chemistry guidelines and guidance documents, with a view to improving the work of the JMPR. The documents will be utilized in the preparation of future versions of the *FAO Manual* with the aims of maximum harmonization and future opportunities for work share.

The JMPR looks forward to reviewing and commenting on the guidelines and guidance documents currently under preparation.

2.12 OECD TEMPLATES FOR RESIDUE SUPERVISED TRIALS DATA

The Meeting was informed that the OECD, through its "Residue Chemistry Expert Group", has initiated the development of guidelines and templates for supervised residue trials on plants as part of its test guideline development program. Under this programme certain draft templates (e. g., for livestock metabolism, livestock feeding, crop metabolism and rotational crops) have already been prepared. This process is welcomed as it provides a foundation for further work-sharing and strengthens harmonization.

The FAO/OECD Workshop "Electronic field trial data for pesticides" (Rome, February 2006) has shown that manufacturers use their data from residue trials, which are present in an electronic format, to print individual study reports and also to generate other required data summary sheets. One main conclusion of the workshop was that the submission of residue supervised trials data in electronic format could support and facilitate the evaluation of pesticide residues submitted to the JMPR as well as to national authorities for pesticide registration. It would also reduce the probability of errors in data entry and transfer.

However, the structure of the existing draft OECD templates allows only that data are reported in free text fields in so-called "rich text areas".

The Meeting stressed the fact that the templates for residue supervised trials on plants need a more detailed structure due to the huge amount of residues data which have to be handled by the manufacturer, by the national authorities and by the JMPR. Less structured templates would require a considerable manual data entry which should be avoided. The more detailed structure would mean that a number of prompts that are now included in free text fields become distinct data entry fields or numeric fields which would also allow a standardised electronic exchange of relevant data between databases.

National authorities and JMPR would benefit from such structured templates allowing for the electronic import of detailed residue data. Hence it would be possible to improve further existing working procedures of the data evaluation by national and regional authorities and by JMPR.

2.13 OECD LIVESTOCK FEED TABLES AND POSSIBLE IMPLICATIONS FOR THE WORK OF JMPR

As part of the ongoing development of harmonised guidelines and guidance documents for registration of pesticide products, the OECD Pesticide Residue Chemistry Group has developed a set of livestock feed tables. These tables were initially developed as part of the OECD test guideline for Residues in Livestock. The purpose of the tables is to enable chemical manufacturers to determine appropriate livestock dietary burden for a number of regions for the conduct of livestock feeding studies or transfer studies. The conduct of livestock feeding studies is a costly exercise and the tables are a way of ensuring that a single feeding study will be acceptable to all regulators, thereby avoiding the need for other studies if the dietary burden does not adequately account for all regions.

During the development phase of the feed tables, a working group considered livestock production practices in various countries (extensive vs intensive), the different types of feeds used, typical percentages of feed intakes and also nutritionally based information used by livestock production industries. The regions in the feed tables include US & Canada, the EU, Australia and New Zealand, which represent both intensive and extensive livestock production practices.

The feed tables (Annex 6) include four categories of feed items: forages and fodders, roots and tubers, grains and seeds and processed by-products. The various percentages of each feed item in the four categories are tabulated for typical diets of cattle (beef and dairy), sheep (lambs and rams/ewes), pigs/swine (breeding & finishing) and poultry including hens (layers and broilers) and turkeys. For simplicity and ease of use, the OECD tables include information on percentage Dry Matter (DM) for each feed item as well as whether the STMR or highest residue (HR) should be used in the maximum dietary burden calculations.

The Meeting noted the work of the OECD Pesticide Residue Chemistry Group in relation to livestock feed items and estimates of dietary burden. In relation to the current practices of JMPR for the estimation of maximum dietary burden, it was highlighted that the OECD tables indicate a change from use of highest residue for grains and seeds to use of STMR for pre-harvest treatments[28]. This change was proposed by the OECD group on the basis that for many grains and seeds, the forage and/or fodder components of grain and seed crops would contribute to a larger proportion of the residue in the dietary burden than the grain itself. The exception to this is for post-harvest grain and/or seed treatments where the highest residue must be used. All other current JMPR practices and methods in relation to livestock burden remain the same.

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[28] Pesticide Residues in Food, 2004, 178, p. 26 – 29, General Considerations Item 2.28.

The Meeting considered this difference between current JMPR practice and the OECD proposal and decided that the current JMPR practice is still appropriate as there may be situations where a feedlot or user of a pesticide product on-farm may use grain from a single source and therefore the STMR may not always be appropriate. However, the Meeting agreed that the OECD feed table be adopted, noting that in most cases, the forage and/or fodder components of a grain or seed crop would dominate the livestock burden and would therefore still provide a realistic and conservative estimate of livestock exposure to residues in feed items.

The Meeting noted that the current livestock feed table used by JMPR is not as extensive or as detailed as the OECD table, as it was originally based on US feed levels. It was considered that the current feed table (Appendix IX in the *FAO Manual* 2002) should be replaced with the OECD feed tables for the estimation of dietary burden for recommending maximum residue levels in animal commodities.

Use of the modified tables would be an improvement in the work of JMPR in terms of accounting for appropriate percentages of typical feeds used in different regions and the inclusion of feeds that had not previously been considered by JMPR due to lack of appropriate information. Examples of feeds not previously considered by JMPR include various pulse grains, a range of root and tuber crops, grape pomace and limited forage intake by poultry.

The Meeting agreed to replace Appendix IX of the *FAO Manual* 2002 with the OECD livestock feed tables and in addition to use the new tables in the 2007 Meeting of the JMPR. The full tables with definitions of commodities will be included in the next update of the FAO Manual.

2.14 PILOT PROJECT ON WORK SHARING FOR QUINOXYFEN

Quinoxyfen was selected by the CCPR as a candidate compound for a work-share exercise (ALINORM 05/28/24, 37th Session of the CCPR, 2005, paragraph 257). The first exercise was conducted with trifloxystrobin (JMPR Report 2004, General Consideration 2.4). The experience gained from that work was incorporated into a plan for the current exercise (JMPR Report 2005, General Consideration 2.1). The JMPR Report 2005 indicated that workshare in the context of JMPR was defined as an independent expert peer review of existing evaluations and incorporation of text, tables, and figures from existing national/regional evaluations into the JMPR assessments. It was emphasized that validated information could be incorporated into the JMPR evaluations but the final assessment must be a totally independent.

WHO procedure and result

There were three evaluations available from the United States (US) EPA, Australia and the United Kingdom/European Union (UK/EU). There was also a comparison of the US and UK evaluations, performed by Bob Tomerlin of the US EPA. The style, level of detail and content of the documents indicated that the three evaluations had been performed independently.

The first step was to prepare a table by which to compare the no-observed-adverse-effect levels (NOAELs)/effects identified for each study by the company, the US, EU and Australia. This showed that although there were some minor differences in the effects noted at the lowest-observed-adverse-effect level (LOAEL), there was only one study for which the actual NOAEL value differed, but this did not have any impact on the ADIs proposed. There was also agreement on the absence of genotoxicity, carcinogenicity and reproductive toxicity.

Using the EU draft as the basis for the JMPR working paper, the following changes were made:

Minor editing;

Reorganization of the study order; preparation of a summary, tables for results of studies of acute toxicity and genotoxicity etc, to suit the JMPR format;

Addition of details of five extra studies completed after the EU evaluation. Some were in the Australian review and use was made of appropriate texts/tables.

Checking of critical details with study reports and addition of some extra detail and tables to permit independent evaluation by the JMPR Meeting of key findings—making some use of tabulation from the text from Australia.

FAO procedure and result

Quinoxyfen residue chemistry evaluation packages were received from Australia, the EU (UK), and the USA. The documents provided varied from a single composite report of the residue chemistry to individual reports for specific residue chemistry topics. None of the authorities provided detailed reviews of studies of environmental fate beyond the confined rotational crop study evaluation from the UK. Quinoxyfen was not a workshare compound for any group of national governments, and thus the national review packages received were prepared independently by each authority.

A methodical but practical approach was taken to the use of the national evaluations. First, a comparison was made of the studies submitted to Australia, the EU (UK), the USA, and the JMPR. The study submitted to the JMPR was also the study submitted to at least two of the three authorities for:

metabolism in goats;

metabolism in wheat;

metabolism in grapes;

metabolism in cucumbers;

analytical methods—livestock;

livestock feeding—ruminant.

As might be expected, the field trial reports were country-specific with no overlap, except for inclusion of European field trials in the studies in grapes reported by Australia and some Australian studies in grapes in the UK report.

The residue definitions of the three authorities were compared as a measure of agreement of findings. *The residue definitions of Australia, the EU, and the USA are harmonized*. All define the residue in plant commodities for both monitoring and risk assessment as quinoxyfen. Australia and the EU define the residue in livestock commodities for both monitoring and risk assessment as quinoxyfen, while the US has not considered the issue.

The national evaluations for the six areas listed above were *compared* to see if they were consistent with one another. For example, the reviews of studies of metabolism in goats for Australia and the EU were compared to see if similar metabolic pathways were listed with similar distributions of metabolites. The following national evaluations were then adapted with slight modifications into the JMPR evaluation:

metabolism in goats from Australia;

metabolism in wheat from the UK;

metabolism in grapes from the USA;

metabolism in cucumber from the USA.

Additionally, tables and limited text were incorporated from the US evaluations of the metabolism in tomato and metabolism in sugar beets. Data on these crops were reported from the US only. In this case, the original studies provided by the manufacturer were consulted.

The analytical methods for cattle commodities submitted to JMPR were the same as those provided by Australia and the UK. Both national reports lacked sufficient details. Moreover, the method for poultry (eggs) was provided only to the JMPR.

Although the ruminant feeding study was reviewed by both Australia and the UK, the format and table utilized were not particularly appropriate for JMPR purposes. It was judged more efficient to consider the manufacturer's study submissions.

Some effort was made to incorporate field trial summary information (tables) from the various national sources, but this was not generally effective. For example, some tables were taken from the US evaluation for cherries, but the rather extensive modifications required negated any savings in time.

Conclusions and considerations

WHO

1. The total time taken to complete the final draft working paper was about 70–100 hours. Performing this evaluation using only the sponsor's submission would probably require in the region of 200–250 hours. Therefore a significant saving in time (50–70%) was achieved. The two main contributors to time taken were reviewing the new studies and putting into JMPR style. The former is unavoidable when using a 10-year-old evaluation; the latter leaves some scope for further time savings.

2. Quinoxyfen was a straightforward workshare example, with no severe toxicity, good agreement on NOAELs, and a reasonable draft text available. It probably represents the optimum in time savings. More complex compounds are not likely to yield such significant savings in time.

FAO

1. It is estimated that the incorporation of sections from national evaluations saved approximately 15–20% of the preparation time needed by a reviewer in creating an evaluation and appraisal for the JMPR Meeting. This is based on time distribution of 70% for the evaluation and 30% for the appraisal and dietary intake calculations. Total time typically required to perform an evaluation and appraisal for a new chemical using only the manufacturer's data submissions is about 240–300 hours. The use of the national evaluations for metabolism and the incorporation of some tables elsewhere saved about 25% of the time needed for the evaluation, or about 15–20% overall, i.e. about 48–60 hours were saved.

2. Quinoxyfen represents the optimum case for workshare in that its metabolism is not complex, the analytical methods are straightforward, and its uses are limited to foliar applications only on a few crops. If residue definitions differ among the national/regional reviews, workshare becomes problematic.

3. The greatest obstacles to worksharing for residue chemistry in FAO JMPR continue to be the different formats used by the various national authorities and different studies reviewed by the national authorities. This situation will improve as more workshare reviews are conducted by an expanded number of national authorities. Multi-national workshare should directly benefit JMPR.

Recommendations of the JMPR

The evaluations conducted by national and regional authorities are useful to JMPR in the preparation of compound evaluations. Appropriate use of materials from these evaluations can save significant preparation time for the JMPR experts preparing the draft evaluation for the Meeting.

The JMPR recommends that:

A mechanism is needed to identify national and regional evaluations (toxicology and residue chemistry) available for those compounds scheduled for evaluation at a subsequent JMPR meeting. The JMPR Joint Secretaries are requested to explore means for securing such information and for acquiring evaluations identified. Likewise, sponsors and government organizations should take steps to permit formal exchange of documents with JMPR.

Where several independent evaluations on a pesticide are available in a given subject area, and where the JMPR expert is able to validate the information either by comparing national reviews (e.g. end-point comparisons for the toxicology), or by limited referral to the original studies, text and tables from the national/regional evaluations may be incorporated directly into the JMPR evaluation, taking care to include sufficient detail for an independent assessment by the JMPR.

With the dossier submitted to the JMPR, sponsors should include copies of available evaluations performed by regional or national authorities. This recommendation in no manner negates the requirement for the manufacturer(s) to provide *all* relevant original studies, as these will continue to be the primary source.

International, regional and national organizations should look to further harmonize the style and format of documents describing the assessment of risk of chemicals to human health. Efforts to develop a common format for the evaluation of pesticide data should be pursued and encouraged. A common format acceptable to national and regional authorities and to JMPR is critical to the efficient use of work sharing.

The pilot workshare exercises had been shown to be of benefit to toxicology and residue chemistry evaluations and there was no need to perform further pilot studies.