codex alimentarius commission

FOOD AND AGRICULTURE ORGANIZATION OF THE UNITED NATIONS

WORLD HEALTH ORGANIZATION

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DISCUSSION PAPER ON PROBABILISTIC MODELLING: MRLS: HEALTH OR TRADE LIMITS?

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Introduction

1. The 34th, 35th, and 36th CCPR discussed probabilistic modelling as a tool in the process of MRL setting, in particular in assessing the acute dietary exposure to pesticide residues (CX/PR 02/3-Add.1 and ALINORM 03/24 para 33-39; CX/PR 03/3 and ALINORM 03/24A para 20-31; CX/PR 04/4 and ALINORM 04/27/24 para 46-59). Although it was recognized by the Committee that the deterministic method currently used to estimate the acute exposure is rather conservative, there was some hesitation in accepting a probabilistic method as a valid alternative. At first, by lack of internationally agreed on software and available consumption databases, probabilistic modelling was considered to be too complex and too time-consuming on the international level. However, the Working Group that was installed at CCPR 35[1] and that presented its findings at CCPR 36[2] made clear that in principle software is available (e.g. the Monte Carlo Risk Assessment (MCRA) software, an internet based programme) and that probabilistic modelling at the international level is possible.

2. The 2004 Committee recognized that there are various ways to perform a probabilistic intake assessment and that there should be international consensus on the preferred way. The WHO Representative informed the Committee of a FAO/WHO workshop on intake assessment planned for November 2004. This workshop is part of the 'Joint FAO/WHO Project to Update the Principles and Methods for Risk Assessment of Chemicals in Food'. Noting this, the Committee decided to establish an *Ad Hoc* Working Group[3] to formulate questions regarding probabilistic intake assessment for this workshop. A list of questions was presented by the Working Group and discussed by the Committee (see ALINORM 04/27/24 para 56-59).

[1] Australia, Canada, Denmark, France, Germany, Sweden, USA, the Netherlands, WHO, EU, International Banana Association, Crop Life International.
[2] CX/PR 04/4 CRD 2 (Report on the probabilistic intake calculations performed for the Codex Committee on Pesticide Residues. P.E. Boon, E. Tjoe Nij, G. van Donkersgoed, J.D. van Klaveren, RIKILT-Institute of Food Safety, Wageningen, January 2004)
[3] the Netherlands (Chair), Australia, Denmark, European Commission, Germany, Ireland, Japan, New Zealand, USA, FAO, WHO, Crop Life International and International Banana Association.

Risk assessment versus risk management

3. The FAO/WHO workshop on intake assessment that was planned for November 2004 was rescheduled for May 2005 and therefore the present CCPR will not be able to discuss the outcome of this workshop. Although most of the questions formulated by the CCPR 36 *Ad Hoc* Working Group are questions to scientists/risk assessors, the first one, '*Advice should be provided on the circumstances under which a "total population approach" versus "consumers only approach" should be used in the probabilistic modelling of acute exposure to pesticide residues'*, should also be discussed by risk managers, since this question requires a decision on who to protect, and a definition on what is safe.

This topic will be discussed below, for more detail see CRD 2[4].

What is the risk manager's question concerning MRL safety?

4. Concerning the establishment of MRLs, the Codex formulated two goals (Codex Alimentarius Vol. 2):

a. Codex MRLs are based on registered or approved usage of a pesticide and are intended to apply in international trade

b. Foods complying with the Codex MRLs should be safe for human consumption

However, tracing unauthorized use of pesticides is a totally different goal from preventing health risks upon exposure. And preventing health risks of consumption of a single food item requires a different approach than the estimation of health risks for a population at actual exposure. A clear definition of the 'question' at stake is important to define the best way how to proceed in the risk assessment process.

5. Concerning food safety two types of questions can be distinguished:

I. Is the MRL safe enough? Suppose that all apples have residue concentrations at the MRL, will there be a health risk? This question is directed to prevent possible health risks of a certain pesticide-commodity combination. This approach is 'commodity-based'.

II. Is there a health risk at actual exposure levels? This question is directed to estimate the health consequences of real-life exposure of a certain pesticide (or group of pesticides with the same mode of action) that may be present on several commodities. This approach is 'population-based'.

Up until now, the risk managers question in the CCPR and in most national registrations has been the first one: 'if one would eat a commodity with a residue level at the MRL, would this present a health risk?' Currently, to address this question the acute intake is calculated by multiplying the highest residue found in supervised residue trials, with the highest large portion (LP, 97.5th percentile of non-zero consumption-days) provided, and compared to the acute reference dose (ARfD).[5]

6. In the slip-stream of the discussion on introducing probabilistic methods in the acute intake assessments, the risk managers question has implicitly been changed to: 'what is the probability that a residue intake presenting health risks actually is encountered, and is that probability acceptable?'.

This change of policy was already made in the USA, where it is accepted that in some cases the MRL/tolerance may not necessarily be reflective of a safe level of dietary intake according to Codex risk assessment procedures, because the MRL is not regarded to represent what is on the food commodity as

[4] RIVM report 320011001 (2005) Probabilistic modeling of dietary intake of substances. What are the benefits for policy managers? Pieters, M.N., Ossendorp, B.C., Bakker, M, Slob, W. (see http://www.rivm.nl/bibliotheek/index-en.html)

[5] The present risk assessment procedure considers both long-term ('chronic') and short-term ('acute') exposures, to be compared to the acceptable daily intake (ADI) and the ARfD respectively. Although the risk managers question should be clear for both types of assessment, this paper is focussed on the acute exposure since it is this part of the assessment that is the most strict and stops MRLs from finishing the Codex step-procedure.

eaten[6]. The USA applies a risk assessment methodology which attempts to include all relevant factors which affect the residue in the food as eaten in a probabilistic total population intake assessment, using as a cut-off value the 99.9th percentile. This total population approach allows MRLs that would not pass the current JMPR point estimate test to be accepted.

7. However, Codex MRLs are trade limits. For trade purposes monitoring occurs at the border/port-of-entry, on a commodity-by-commodity basis. A country needs to know that a lot containing residues at the MRL is safe for human consumption. It has to be decided whether the lot at hand can be accepted, or not. The fact that if accepted the residues will be diluted over the total population of the country is irrelevant. In other words, because Codex is concerned with the safety of commodities in trade, there could be an argument that foods should be treated on a commodity-by-commodity basis and not aggregated into a total diet, and that the residue level of which to assess the safety should be the level of the MRL, using information on peeling and processing to obtain the residues in the items as consumed, but not mixing residue data from treated and untreated commodities (see also para 11).

'Total population' versus 'consumers only'[7]

8. It follows that to answer question I (para 5) one should consider actual consumption events ('consumers only'), while to answer question II all consumption data, including the zero intakes, should be considered ('total population'). In the following paragraphs the differences between these approaches are elaborated.

9. First, it should be recognized that the discussion 'total population' versus 'consumers only' does not equal the discussion 'point estimate' versus 'probabilistic approach'. Although the misconception of 'point estimate means using 'consumers only'' and 'probabilistic approach means using 'total population'' is understandable, since at present this is the way these calculations usually are performed, probabilistic intake calculations *can* be performed based on 'consumers only', and point estimates *can* be made based on the 'total population'.

10. In theory, when the *same assumptions* are used for both deterministic and probabilistic calculations, the outcome of the point estimate should be at the high end of the intake distribution as calculated by the probabilistic method. When probabilistic calculations were performed for one commodity at a time and using only the consumption-days where the commodity was actually eaten ('consumers only') this was shown to be more or less correct (CX/PR 04/4 para 11, and CRD2 (2004)). Discrepancies observed can be attributed to the fact that one assumption was different: in the probabilistic assessment the actual bodyweights of each person eating the commodity was used in the calculation, while in the point estimate a default bodyweight was used. And since there is a correlation between the size of the large portion and the bodyweight of the person eating this large portion, this leads to an overestimation of the large portion per kg bw in the point estimate. Another reason may be that the number of consumption-days used to estimate the Large Portion

[6] The rationale behind this is, that the residues on what one eats are usually a small fraction of the MRL (except in cases of gross misuse of the pesticide or uses close to or after harvest). This is due to the amount of time in storage and transport, where residues usually will decline, and to the admixing of treated (at various rates) and untreated commodity. Monitoring data from the food distribution and local market levels are thus considered a more realistic estimate of consumer exposure. Dietary intake calculations with MRL level residues are only a first tier calculation, and although they may indicate potential intake concern it is not automatically taken to mean that the use-pattern that was used to derive the MRL is 'not safe'.

[7] It should be recognized that the used terminology may easily lead to confusion about the *meaning* of the consumption data (see CRD ..). The phrase 'consumers only' incorrectly suggests that the data allow for the identification of individuals that eat or do not eat a certain food item. However, the consumption data only show zero and non-zero consumption days! Or, in other words, individuals classified as non-consumer in a two-day food consumption survey may turn out to be classified as consumer in a survey with longer study duration.
A participant in a food consumption survey may thus have contributed to the observed non-zero data and to the observed zero-data. It would therefore be better to regard the data as 'observed non-zeros' and the 'total of observed zeros and non-zeros' and to keep in mind that real non-consumers will be a very rare phenomenon.

(LP) for the point estimate may have been less than required to obtain a useful 'non-zero' estimate of the 97.5th percentile intake.

11. In CRD 2 (2004) it was shown that when probabilistic intake assessments are performed on a 'total population' basis, in general the observed exposures are (much) lower than those calculated for 'consumers only'. This can be explained as follows. A consumption database is a distribution of zero and non-zero intakes. Since there are only data on a few consumption days available, there will be many zero's when the food is only incidentally eaten. Including the zero intakes in the calculation will lead to a lower exposure at the same cut-off value. In parallel, when comparing these results with a point estimate made on a 'total population' basis, this may lead to the LP, being the 97.5th percentile of the total distribution, being zero. Multiplying a zero LP with a residue concentration will only indicate that **not eating** the food commodity is safe. Therefore the current point estimate procedure is based on the non-zero intakes, the 'consumers only'.

12. From the above it follows that when the interest lies in assessing the safety of actually eating a commodity, the 'consumers only' approach should be used. However, if one is interested in the probability of eating the commodity and thus in the probability of being at risk, one should take into account that the commodity is only incidentally eaten, and therefore would use the total database, including the zero intakes. One should be aware that in the case of infrequently eaten commodities the latter approach may result in setting an MRL for a food item, e.g. papaya, while accepting that every time someone eats a papaya with a residue at the MRL he/she is at risk. However, since only a small percentage of the total population will eat papaya, the methodology may lead to the conclusion that the risk is acceptable. Although scientifically this is a valid conclusion, this observation is often referred to as 'diluting the risk'.

13. In a population-based approach, and especially when assessing monitoring survey results, a relevant question is: 'is the exposure from multiple foods acceptable?' This question has also been considered in the commodity-based approach that is in use now for MRL-setting. The 1997 FAO/WHO Consultation[8] already stated that '*the consumption of two different commodities in large portion weights by an individual consumer in a short period of time is not likely. Furthermore, the presence on those commodities of the same pesticide at its MRLs is considered even less likely*.'

Although it was observed that sometimes there are significant contributions from more than one food item in the upper part of the exposure distribution, e.g. when the residue has been measured in commonly eaten foods like wheat, potatoes, rice, the CCPR 36 Working Group concluded that '*high exposures resulting from multiple high commodity exposures occur seldom, usually the contribution from one commodity dominates the outcome*' (CX/PR 04/4 para 13). It should be noted that the Working Group used supervised field trial data for all food items. Since it is known that supervised field trial data do not represent actual exposure (see para 6) it may be argued that only the food item under consideration should be modeled at the level of field trial data, while the remaining food items should be modeled at monitoring residue levels. This consolidates further the conclusion of the 1997 FAO/WHO Consultation.

14. An area under development is the assessment of cumulative and aggregate exposure to chemicals. 'Cumulative exposure' is referring to different chemicals with the same mode of action, while 'aggregate exposure' refers to exposure to a chemical from different sources, e.g. a chemical that is used as a pesticide (exposure through food), but which also is included in shampoo (exposure through skin). It is clear that assessments like these can only be done on a total population basis, using probabilistic methods.

Food consumption data requirements

15. Irrespective of the calculation method chosen, detailed information on the food consumption data is needed for realistic intake calculations. Not only a list of 97.5 percentiles of consumption figures should be available, but also the number of person-days behind this percentile and more information on the distribution (e.g. geometric mean and geometric standard deviation, or list of percentiles, or, preferably, all individual data). If a national survey does not contain enough data on a particular commodity to discriminate the 97.5 percentile of consumption, this should be noted and the geometric mean or perhaps the highest consumption

[8] FAO/WHO (1997). Food consumption and exposure assessment of chemicals. Report of FAO/WHO Consultation, Geneva, Switzerland, 10-14 February 1997 (WHO/FSF/FOS/97.5). Geneva: World Health Organization.

figure should be used instead. Note that the CCPR 36 Working Group was able to access the complete consumption distributions of Denmark, Sweden, the Netherlands, the US, Australia and New Zealand by using the total consumption databases of these countries[9], while JMPR only has available the 97.5 percentiles of consumption ('large portions') from Australia, France, the Netherlands, South Africa, the UK and the USA, without further information.

16. In the context of SAFE FOODS[10], an European project financed by the EC, more consumption databases will be coupled to the MCRA programme via internet. A multi-database approach will be developed in which national food consumption databases from the Netherlands, Sweden, Denmark, Czech Republic, Italy and China located on local websites (e.g. of food safety authorities or institutes involved in risk assessments) will be linked to the MCRA-software. Together with databases of other countries, e.g. Australia / New Zealand, South Africa, and US, a whole range of food habits across the world can be covered when addressing the safety of pesticides at an international level. Although it is recognized that it will take a lot of work to harmonize food consumption coding and to solve compatibility issues, it would be an enormous step forward if JMPR could access these databases through this electronic platform, and if possible comparable platforms from other parts of the world.

Toxicological considerations: what does the ARfD represent?

17. In the process of MRL setting, the final risk assessment consists of comparing the calculated exposure to the toxicological safety limit. In the case of acute exposure this limit is the ARfD. Therefore, a discussion on risk assessment approaches would be incomplete without discussing the difficulties encountered in establishing ARfDs.

18. The concept of the ARfD[11] was developed by JMPR[12] as a health safety limit aiming to prevent health risks. It is set to ensure that when the intake stays below this value no health risk is anticipated from acute exposures. However, the ARfD is also used by enforcement authorities, where the limit is more or less regarded as an intervention value. In this case, the limit should predict the level above which health effects may start to occur. Ideally, the concept of the ARfD should be able to cover both needs.

19. The process of deriving ARfDs involves the determination of the most appropriate 'no observed adverse effect level' (NOAEL) from a set of animal studies and a safety factor (also called an uncertainty or assessment factor). These factors are used to extrapolate from data in animals to the average human and to allow for interindividual variation within the human population. Usually, a 100-fold (10×10) or 10-fold (e.g. when based on human data) default safety factor is used. It should be realized that many dossiers do not contain the most adequate (acute) data for setting an ARfD. In those cases an ARfD is derived from studies in which animals were exposed for longer time frames, providing a 'conservative estimate' of the ARfD. In other cases, acute effects have not been properly addressed within the toxicological dossier. This may be handled by using an additional safety factor in the estimation of the ARfD. Together these considerations are sometimes taken to suggest that the ARfD may be exceeded to some extent. Although from a scientific point of view this may be correct for some substances it does not hold true for all situations. When an ARfD is set e.g. on human data, default only an assessment factor of 10 is used. In other cases, the acute toxicity takes place at the same level as chronic toxicity, leaving much less room for conservatism. Therefore, exceeding an ARfD should not be tolerated. However, conservative ARfDs may be refined on a case-by-case basis based on additional data.

[9] In several other projects the MCRA programme was also succesfully linked with, among others, food consumption databases of the UK, Germany, France, South Africa and Brasil.
[10] http://www.safefoods.nl
[11] The following definition of the ARfD was adopted by the 2002 JMPR: "The ARfD of a chemical is an estimate of the amount of a substance in food and/or drinking-water, normally expressed on a body-weight basis, that can be ingested in a period of 24 h or less, without appreciable health risk to the consumer, on the basis of all the known facts at the time of the evaluation".
[12] For current procedures see Item 2.1 of the General Considerations in the JMPR Report 2004 'Guidance On The Establishment Of Acute Reference Doses'. This item summarizes a document drafted by a Working Group of the JMPR WHO Core Assessment Group which will be published elsewhere.

20. It is proposed to further strengthen the criteria for setting ARfDs and to support the generation of additional (acute) data where needed. In this way potential conservatism in the ARfD values can be limited. In addition, the use of new methodologies (such as the Bench Mark Dose approach and the use of probabilistic assessment factors) can improve the the quality of the ARfD and provide insight in its uncertainty. Taken together, such developments should lead to setting an ARfD that covers both the safety evaluation (for authorization purposes) as well as the intervention approach (for enforcement purposes).

Summarizing discussion

21. Three scenarios in which residue intake has to be calculated can be envisaged: MRL setting, evaluation of enforcement measurements on single lots in trade, and evaluation of monitoring measurements. These scenarios may call for different types of calculations. The method used should follow the risk manager's question, not determine it. It could for example be argued that the first two scenarios should be commodity-based ('consumers only'), while the last one should be population-based ('total population'). It is emphasized that in all cases one could make use of consumption distributions and residue distributions (supervised field trial/enforcement/monitoring data) thus performing a probabilistic calculation.

22. The commodity-based approach will allow decisions on single lots in trade, while the population-based approach will allow the comparison of pesticide risks with risks from other chemicals, and in future will allow the assessment of cumulative and aggregate exposures. The question at stake is not whether risk assessment methods should use deterministic or probabilistic techniques, the question is whether CCPR wants to define safety based on the commodity under consideration, based on the total population, or both. Once this question is answered, the FAO/WHO workshop on intake assessment can bring progress on improving the intake assessment methodology.

Conclusions and recommendations.

23. It is imperative that Codex risk assessments are such that they are acceptable world-wide. This does not preclude changes in the risk assessment methods as they are now, but it implies that any change in methodology must be seriously discussed and accepted before it is generally applied. Most important, the methodology used should address the right question.

Therefore, CCPR should decide whether it wants to define MRL safety based on the commodity at hand, or based on the population of interest. More specifically, does CCPR want an answer to question I or II (or both):

I. If one would eat a commodity with a residue level at the MRL, would this cause health risks?

II. What is the probability that a residue intake presenting health risks is actually encountered?

Question I represents the present situation. It should be noted that the FAO/WHO workshop on intake assessment most probably will find ways to refine the current intake assessments while addressing the current risk managers question. Question II represents a changed risk managers question and will allow many MRLs that would not pass the present JMPR point estimate test to be accepted. If CCPR should choose question II, such a change of policy would mean a fundamental change for CCPR that should be endorsed by the CAC and be very well explained to the public.

24.It is recommended that GEMS Food will investigate the possibilities to use the electronic platform on consumption databases as set up by SAFE FOODS (and any comparable initiatives) as a tool for JMPR intake assessments.

25. It is recommended that the WHO Core Assessment Group of JMPR will continue to refine the methodology used to set the ARfD.