codex alimentarius commission

FOOD AND AGRICULTURE ORGANIZATION OF THE UNITED NATIONS

WORLD HEALTH ORGANIZATION

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DIETARY EXPOSURE IN RELATION TO MRL SETTING: DISCUSSIONPAPER ON PROPOSALS FOR IMPROVEMENT METHODOLOGY FOR POINT ESTIMATES OF ACUTE INTAKE OF PESTICIDE RESIDUES

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INTRODUCTION

1. The 34th CCPR (2002) discussed the probabilistic approach to acute dietary exposure analysis and its applicability at the international level (ALINORM 03/24, para 33-39). This matter was extensively elaborated in CX/PR 02/3-Add.1. It was concluded that the probabilistic methodology can lead to a better general assessment of the exposure than deterministic “point estimates” and deserves to be promoted both nationally and internationally. It was ackowledged however that the necessary data to apply Monte Carlo methods on an international basis are not yet available and also that procedural decisions regarding the application of probabilistic methodogy for international purposes need to be taken. Therefore point estimates will for a long time remain to be used in an international context as the primary applicable methodology for international acute exposure assessment and the basis for international risk management decisions. The Committee agreed that there was a need to improve the current methodology used for point estimates and requested the preparation of a paper containing proposals on the improvement of the current methodology and to propose the risk management options for MRLs with acute (short term) intake concerns, for consideration by the next session of the Committee.

2. The 34th CCPR was informed that a FAO/WHO Consultation on intake assessment including considerations related to probabilistic modelling and improving deterministic approaches was planned, as part of its project to up-date the principles and methods for the safety assessment of chemicals in food. This Consultation has not yet taken place. The Committee was also informed that an IUPAC project on acute dietary assessment was close to completion; this would summarize the state of the art for assessment methods and would include proposals for improving the currently employed deterministic approach. The final IUPAC report was not yet published at the time of writing this paper, but we recently received an almost finalised version. Although there was not sufficient time to review this paper fully, proposals contained in the IUPAC document have been used as far as possible and where appropriate in the preparation of this paper.

METHODOLOGY ASPECTS OF ACUTE INTAKE ASSESSMENT METHODS

3. The point estimate methodology as it has been refined in the last years was extensively described in the 2002 JMPR Report. The procedures for calculating the international short-term intake (IESTI) were defined primarily at the Geneva Consultation (WHO, 1997) and were further refined in subsequent JMPR meetings (1999, 2000 and 2001 JMPR Reports). Important contributions for the development of the methodology came from the International Conference on Pesticide residues variability and acute dietary intake assessment, York, December 1998 (published in *Food Additives and Contaminants, 2000, Vol. 17, p. 481-652)* and an ad-hoc Expert meeting on acute dietary intake of pesticide residues in the Hague, April 1999, prior to the 1999 CCPR.

4. The IUPAC is working on the publication of a technical report about acute dietary exposure to pesticide residues. A number of recommendations are given regarding possible refinements of the calculation of the acute dietary exposure. These recommendations are mostly directed towards further refinements in the residue data and the dietary data used for the calculations. The various recommendations are further discussed in the context of the detailed paragraphs on the main parameters used in the short term exposure calculation.

5. The different calculations of the International Estimated Short Term Intake (IESTI) as presented by the 2002 JMPR are used here as a basis. The factors used in the calculations are further discussed in the next chapter. The definitions are as follows:

LP - the highest large portion (defined as the consumption of a commodity during a day by the 97.5th percentile of the eaters), provided by national contributions regarding the consumption of a specific food commodity, in kg of food per day.

HR - the highest residue level found in a composite sample of (the edible portion of) a food commodity, as found in supervised trial data from which the MRL or STMR was derived, in mg/kg.

HR-P - the highest residue in the processed commodity, calculated by multiplying the HR by the processing factor (which defines the relation between the residue content in the raw commodity and that in the processed commodity)

bw - the body weight in kg, provided by the country of which the large portion was used.

U - the unit weight in the edible portion of the food commodity in kg, provided by the country in the region where the trials which gave the highest residue were carried out.

v - the variability factor, describing the unit-to-unit variability between the residues of a pesticide in various units of a lot, and more specifically defined as the residue in the 97.5th percentile unit divided by the mean residue of the lot, or alternatively as the maximum residue level divided by the mean. (This factor v is only used in case 2a and 2b of the IESTI calculation).

STMR - the supervised trials median residue in a commodity, as derived from a data set of results in composite samples of these trials complying with the critical GAP, in mg/kg (in acute dietary intake calculations only used to derive the STMR-P, in case 3).

STMR-P - the STMR in a processed commodity, derived from the STMR by multiplying with a processing factor, describing the effect of processing on the residue content of the commodity (only used in case 3 calculations of the IESTI).

LP, bw and U are derived from national contributions. The database of large portion sizes, body weights and commodity unit weights is available at the GEMS/Food website: http://www.who.int/fsf/chemicalcontaminants/acute_haz_exp_ass.htm .

6. For the calculation of the acute exposure, various cases can be discerned (JMPR, 2002):

- Case 1, when the concentration of the residue in a composite sample is expected to reflect that in a meal-sized portion; this is applied to commodities with unit weights (of the whole portion) <25 g and to meat, liver, kidney, edible offal and eggs. The main factors involved in the calculation are the LP and the HR or HR-P (mentioned here as HR(-P)).

$$\text{IESTI} = \frac{\text{LP x HR(-P)}}{\text{bw}}$$

- Case 2a, for commodities with unit weights > 25 g, when the unit weight of the whole portion is lower than that of the large portion; the main factors used in the calculation are the U, LP, HR or HR-P and the variability factor v (or a measured highest amount in a single unit).

$$\text{IESTI} = \frac{\text{U} \times \text{HR(-P)} \times \text{v} + (\text{LP-U}) \times \text{HR(-P)}}{\text{bw}}$$

- Case 2b, for commodities with unit weights > 25 g, when the unit weight of the whole portion is higher than that of the large portion; The factors used are as in case 2a, except U.

$$\text{IESTI} = \frac{\text{LP} \times \text{HR(-P)} \times \text{v}}{\text{bw}}$$

- Case 3, for processed commodities which are bulked or blended. In the calculation of the IESTI, the main factors are the LP and the STMR-P.

$$\text{IESTI} = \frac{\text{LP} \times \text{STMR(-P)}}{\text{bw}}$$

DISCUSSION OF THE POSSIBILITIES OF FURTHER REFINING THE FACTORS USED IN CALCULATING THE IESTI

7. The discussion of the possible refinement of the factors used for the IESTI is mainly focussed here on the variability factor and the dietary intake aspects (large portion sizes), because these are the main issues where discussion seems necessary. This does of course not imply that the other factors are of no importance. The unit weight of the commodity and the edible portion of the commodity also deserve attention and are briefly discussed in paragraph 12. Another important aspect is the availability of the effects of processing on the residue content of a food commodity (paragraph 13).

VARIABILITY OF RESIDUES IN UNITS OF FOOD COMMODITIES

8. The unit-to-unit variability of especially medium-sized fruits and vegetables treated with pesticides has received much attention in the last years. The 1997 FAO/WHO Consultation on food consumption and exposure assessment of chemicals recommended that specific variability factors are derived on the basis of individual commodity unit residues data. If these were available, then the 97.5 percentile residue value (in the edible portion) should be used in the acute dietary exposure assment. In the absence of these data, default values were proposed, based on the number of units in a composite sample and the possibility that all the residues would be present in one unit only.

9. The IUPAC-document is an important source of information about variability and provides an extensive discussion of the subject, which is not fully repeated here. The variability as found in analyses of marketplace and of field samples is presented. It is recognized that results of marketplace samples can be confusing because different lots with different pesticide application histories may have been mixed. Therefore information on unit sample testing from crops purchased in the marketplace may only be considered suitable for estimating a variability factor when the sampling has been designed in

such a way that such "mixing" of lots is avoided and the sample is derived from items of a single (common) grower. A number of supervised field trial results are available, which provide reliable information about the variability factor in relation to data from which also the HR and the MRL is derived. This variability factor is now defined as the residue in the 97.5th percentile unit divided by the mean residue for the lot (as suggested by the 1998 UK Conference on Pesticide residues variability and acute dietary risk assessment). The mean residue of a lot is normally measured in a composite sample. IUPAC mentions that the variability between composite samples of the same lot (taken according to accepted sampling procedures) can also be substantial and thus apparently high or low variability factors may be produced. IUPAC therefore recommends a slight change in the definition of the variability factor, as follows: The variability factor for use in deterministic assessments should be defined as the residue level in the 97.5th percentile single unit of a commodity population divided by the mean residue of that population.

10. The reasons for variability in the residue distribution are complex and involve various factors such as the deposition conditions, the degradation rate of the pesticide and growth dilution effects. The form and surface characteristics of the plant and of the commodity will obviously be of influence. No correlation has been found between crop unit size and residue levels in the majority of cases. This implies that the distinction between unit weights > or <250 g may not be justified. The method of application of the pesticide is probably the main factor. In principle this can lead to the use of different factors related to the application method. The IUPAC document recommends on the basis of an analysis of field trial data that a variability factor of 3 should be adopted to give a "likely high-unit residue level" in case 2 deterministic calculations. This would mean a considerable lowering of present IESTI calculations, where the JMPR now uses a default variability factor of 3-10, depending on the unit weight of the whole portion and the treatment situation (a higher variability factor being assigned to residues derived from granular soil treatment). The present default levels of the variability factor as used by the JMPR are as follows:

COMMODITY CHARACTERISTIC	**VARIABILITY FACTOR**
U (whole portion) > 250 g (except head cabbage)	5
U (whole portion) $\leq$ 250 g	7
U (whole portion) $\leq$ 250 g, from granular soil treatment	10
U (whole portion) $\leq$ 250 g, leafy vegetables (except head lettuce)	10
Head lettuce and head cabbage	3

11. The JMPR recognizes that when sufficient data are available on residues in single units, a more realistic variability factor should be used instead of the default value, or analyzed highest residue data in single units can be used in stead of HR x v.

12. In the USA, no variability factor is applied to results obtained form field samples. The reason for this is that it is assumed that composite residue measurements on field trials conducted under the maximum application and minimum pre-harvest interval scenario are sufficiently conservative so as not to underestimate single item concentrations from produce obtained from retail or wholesale establishments. This assumption is well supported by data from the PDP program in which residues obtained from the marketplace rarely even approach those found in supervised field trials. It is obvious that indeed as a rule the results of residues found in monitoring programmes will be much lower than those found in supervised trials, because usually the application will be less than the maximum allowed or recommended rate, the PHI may be longer than the minimum and there often is a delay between harvest and apparition on the marketplace. It may be useful for Codex to investigate this relationship further, on the basis of national contributions on monitoring results. For international acute intake estimates, it will probably be difficult to use such an approach in general, when only supervised field trial data are available. These moderating factors and the fact that a large part of the crop is not treated at all with this specific pesticide (e.g determined nationally as a percentage of crop treated on the basis

of agricultural and/or monitoring information) can be used nationally and will show that actual exposure is usually much lower. There is however no sufficient scientific basis to use these factors in the international context. When it can be substantiated (on a case by case basis) that residues decline very rapidly and would normally not reach consumers with the residue content measured in field trials, this aspect could be mentioned and could contribute to the evaluation as a lower result or alternatively by noting this as an influence on the probability of occurrence of the point estimate result. The other factors mentioned also have an influence on the probability of occurrence of the result, but can not be used to lower the point estimate as such, unless the principle of this calculation as a worst case estimate approach would be abandoned.

13. The scientific aspects of this issue should be discussed by the JMPR and/or in further expert consultations. At the same time it should be recognized that there is a risk management aspect associated with the choice of this variability factor. It is evident that the variability is difficult to assess precisely and therefore it is defendable that available data on single units of supervised trials or (in the absence of this) default values (a variability factor) are used. Nationally, other approaches are possible in trying to assess the occurrence of high exposures in practice, based on supervised trial results, as mentioned in paragraph 10. In the international context, it seems inevitable that a default value is used in the absence of more specific data. The question remains whether this default value should be the highest factor found in the literature or whether a "typical" variability factor may be used, as suggested by IUPAC. The use of a default variability factor which aims to represent the high end (97.5th percentile) of residue levels found in practice is defendable but evidently will not lead to the highest residue level which could occur in practice. On the other hand, it may be questioned whether choosing the highest possible level is needed in this approach, because the scientific uncertainties about the highest possible residue level in a single food unit will always be large and aiming at the highest level may not be needed for sound decision making. The choice of a cut-off level of 97.5% for the determination of the variability factor probably is not entirely scientific in nature, but is arbitrarily chosen, generally based on the limited amount of data usually available and the amount of units in a composite sample and the resulting variability pattern still thought to be sufficiently reliable. Also HR values found in supervised trials should not be seen as exact figures representing the real HR which could be found. When the database from which the HR is derived is larger, the HR will probably be higher, but the chance of finding this HR in practice will be lower. The assignment of a probability aspect to the specific figures for the factors used in an acute exposure assessment could be helpful in deciding which principle and which figure should be used. Various figures could all be valid as such, e.g. in the choice between a typical default value or a high end default value for the variability factor, the difference between these two figures is that both could occur, but the probability of occurrence of the high default value will be lower than that for a typical default factor.

14. The conclusion can be that the risk assessors should further discuss the choice of the parameters used for deriving a HR or a variability factor and should document the statistical aspects of the factor used in the IESTI calculation. The adoption of the variability factor of 3 as proposed by IUPAC for case 2 assessments should be considered (and has already been adopted by the 2002 JMPR for head lettuce and head cabbage). Further scientific research regarding the variability and the occurrence of high residues in practice should be encouraged. Contributions based on sound research could contribute to further refinement of the residue variability aspect. Risk managers should request more transparency about the statistical aspects of the parameters used and should consider the risk management consequences of these probability aspects.

UNIT WEIGHTS AND EDIBLE PART OF PRODUCT

15. The data base of unit weights and the edible part of the commodity unit as it is now assembled by GEMS/Food consists of contributions from four countries (France, Japan, UK and USA). The 1999 JMPR decided to use in point estimate calculations the unit weight from a country in the region with the relevant supervised residue trials. The definition of a unit probably deserves further discussion in a number of cases and the figures as they are now may need to be scrutinised by experts, e.g. the unit weight of a bunch of grapes is now estimated to be rather low (125 g) in the GEMS-Food data-base, it

must be clarified that bananas are usually bought in hands (which are parts of bunches) with the same pesticide history and thus must be treated as units with the same high residue figure, the unit weight of celery (stalk) seems rather low (being often sold as the stalks of a complete plant), etc. Many commodities still lack a figure for unit weight. In some occasions it is not clear whether the unit weights which are mentioned in the database are defined in the same way as the CCPR definition for the commodity which should be analyzed and to which the MRL applies.

16. It will be obvious that the database on this subject is still very limited and needs further contributions from countries in order to be valid world-wide. It would also be useful when this subject is further evaluated by experts in order to give guidance towards further improvement of the database.

PROCESSING EFFECTS

17. The effects of processing on the residue concentration may only be used in a point estimate of acute intake when the food is always eaten after processing, because in principle a worst case is being assessed. Borderline cases for deciding about such a situation may need to be further evaluated. It might also be useful to check the database of large portions on the possibility that the consumption of processed products has been added to the consumption figure for the raw agricultural commodity (especially for fruits); this would mean that the intake estimate result is too high. A problem with processing effects is often also the limited availability of the necessary data for assessing these effects on the residues, especially for older substances; this again may be a cause of unnecessary high estimates. The risk management aspects of having to base decisions on IESTI calculations which could not incorporate the effects of processing for products that are always eaten in a processed form (e.g. cereals and oilseeds) may need further scrutiny. For new compounds usually sufficient information is available on the effects of processing.

18. Information on food processing in general was asked in 1999 and again in 2000 by means of a circular letter, but met unsatisfactory response (ALINORM 01/24A, para 57-62). The JMPR noted that information on important processed foods, such as fruit juices, barley beer, maize meal and bran of rye and wheat was currently not available for use in dietary risk assessment. Further attention is desirable to fill data gaps here.

19. In principle there is a possibility of taking account in point estimates of situations in which most of the product is eaten in processed form (e.g. washing and or peeling an apple), by noting this aspect as a factor in the probability of occurrence of the worst case estimate.

LARGE PORTION SIZE OF FOOD COMMODITY CONSUMPTION

20. The present point estimate calculation by JMPR depends regarding the dietary input used on the database of large portion sizes set up by WHO (GEMS/Food). The present database is still rather limited, being based on the contributions of only six countries. The data include large portion consumption data at the 97.5th percentile for eaters only, for the general population and for children aged 6 years and under. Additional necessary information, such as body weights and ages of the population in question, is available from these contributions.

21. For short-term intake calculations, usually the daily recorded food intake figures of 97.5% of the eaters only are used. Obviously, it will make a big difference for the probability of occurrence of the outcome, whether foods are assessed which are eaten regularly or only occasionally. Especially in the last case, it may be possible that when these foods are eaten only occasionally in large portions, the result of the IESTI calculation may be high, but the likelihood that such a high intake would occur will be extremely low, whereas other short-term residue intake estimates could have a much higher probability of occurrence. The question may arise whether it is necessary to know the probability aspect of the short term estimate. This is further discussed in paragraph 17 and also later on. The probability aspects of the consumption are routinely recorded in food consumption assessments. The percentage of the eaters, which often is a small part only of the general population size for which the daily

consumption was recorded, is known in principle by the contributing countries, but is not recorded (and possibly not available) in the WHO database. The CCPR might consider requesting contributing countries to supply this data to WHO.

22. The fact that the highest reported national LP is selected for the calculation of the IESTI again introduces the effect that the reported result will be a worst case on a global scale, but the probability of occurrence of that result globally is much smaller than the percentage of the eaters from the contributing country. It might be useful to place also this aspect in perspective by trying to assign a more world-wide probability factor to such an LP. Evidently, this is difficult to do and the databases available now are limited, but in priciple the databases could be mixed in a weighed relation to the population they represent, to form a "global LP database" and a more truly global 97.5th percentile could be extracted from such a database. Alternatively, it might be possible that the highest national LP could be assigned a probability of occurrence in that global database, so that the probability of occurrence of the resulting exposure estimate would become lower.

23. IUPAC recommends that the diets used in the exposure estimates should be valid for the population being assessed and account should be taken of seasonal consumption. Using the 97.5th percentile daily consumption of a food for the eaters only in the IESTI calculation is supported. No arguments have been found in the literature against this practice. It can be argued indeed that also such a high intake should be safe, so that the high point estimate approach for eaters only is justified. When we accept the last argument to be valid, it will be necessary to always take these point estimate results into account for risk management decisions. The point could then be raised however if this would mean that risk management decisions have to be taken without any regard to the probability of occurrence of the scientific assessment which is available. This matter is further discussed in the chapter on risk management. It is concluded here that in order to bring more transparency in IESTI results, it seems possible and desirable to introduce an evaluation of the probability aspect for the IESTI, because this may be rather different for the various reported results, based on the eaters only percentage, which can be either near to 100 % or very low.

DISCUSSION AND CONCLUSIONS REGARDING POSSIBLE REFINEMENTS IN THE POINT ESTIMATE METHODOLOGY AS SUCH

24. It is clear that the database of the factors used for the IESTI calculations still needs further national contributions in the form of more information on large portion sizes, corresponding consumer weights, unit weights and the edible fraction of units, etc. Also, in many cases information on highest residues and variability factors is far from adequate. Using a lower default residue variability factor (based on an analysis of available data) as suggested by IUPAC could lead to lower outcomes of IESTI calculations. Also contributions on processing effects for foods that are always eaten after processing could have that result. It is evident that further contributions to the dietary intake data base are desirable and could contribute to further refined estimates of the possibly occurring highest residue intake. It is not to be expected however that further refinements on food consumption aspects will lead to very different results in the IESTI; probably other national contributions regarding food consumption will even lead to higher large portion sizes used in the point estimate, because it is standard procedure that the highest reported LP is chosen for the calculation of the IESTI.

25. A general remark which often is made about deterministic (point) estimates is that they indicate a possible but highly unrealistic residue intake. Often worst-case scenarios and extreme values are used, so that the realistic value of the approach can be questioned. The question is however if the lack of realism is such that the results of point estimates can be disregarded. A detailed evaluation does not reveal any major flaws in the method which is used. A discussion could arise on the validity of the figures that are used now in the calculations of the JMPR, and on the principle on which they are based: e.g. is the 97.5% of the distribution of consumption figures the best cut-off point, or might 95% or 99% be a better choice? Is it right to base an international intake assessment on the highest consumption level occurring in one country, when the probability of occurrence of such a high consumption level in other countries is much lower? Comparable remarks could be made on the residue and other aspects of

the point estimate calculation. Do we have to strive to the highest residue possible regarding the HR, or is a HR from a small data set as considered adequate for registration purposes enough? Do we have to use the highest variability factor found in the literature or is an average variability factor sufficient? All these questions are related to probability aspects of the occurrence of the intake assessment. These aspects however can not lead to the conclusion that the result of an IESTI calculation is not a truly possible exposure level; the methodology of calculating the IESTI as such seems to be undisputed regarding its scientific validity as such. All of the parameters used in the calculation would benefit from further scientific contributions regarding their validity and further (national) data regarding high food intake etc. No specific suggestions have been found to improve on the equations and concepts as such in the short term intake estimations. The 2002 JMPR does not mention further possibilities or desirabilities for refinement of the methodology. The suggestion from IUPAC to consider a somewhat lower default value for the variability factor deserves further scientific attention, but this also has a statistical aspect which should be looked at in a risk management context. In general it can be concluded that the probability aspect of the IESTI needs further clarification and seems to be the only new factor which needs to be taken into account in order to be able to make better judgments on the degree of realism of the point estimates.

26. The point estimate is an exposure assessment method which only considers single values for single food commodities. It is not able to provide results for the variability of foods in general as they are consumed and the resulting variability of the dietary intake of residues; for this probabilistic assessment methods are necessary. The point estimate has the advantage however that it is relatively simple and provides a clear result for the possible exposure related to a specific pesticide use. Therefore it is in principle well suited for taking risk management decisions about this specific use. In order to have a good view of the risks involved with a specific use and to make the right judgments in this situation, it will be necessary however to know the probability aspects of this type of risk assessment, because this is an essential aspect of risk management in general.

27. It is concluded that the IESTI as such can be improved technically regarding the factors used in the calculation, but is undisputed in principle as a valid estimation of a possible high exposure and therefore should continue to be used in exposure estimations until better alternatives are available. The development of probabilistic calculations, as more refined sources of information on the exposure distribution, remains important, but point estimates can not be ignored until an assessment methodology is available which integrates all necessary aspects needed for sound decision making. Further possible refinements in the IESTI calculation as such have not been identified. Further refinement in the factors used for the calculation are possible and desirable, and are likely to bring changes in the calculated results of the present IESTI methods, but these changes could both bring higher or lower results, depending on the factor and the nature of the change. A change in the variability factor as suggested by IUPAC could be considered. Further discussion seems however possible and necessary about the essential goal and the scope of the IESTI calculation, especially with a view on probability aspects and the risk management regarding the evaluation of IESTI results.

DISCUSSION OF SOME METHODOLOGICAL ASPECTS OF PROBABILISTIC ASSESSMENTS

28. Until now, only some countries have developed probabilistic intake estimations. This method, which was extensively described in CX/PR 02/3-Add.1, allows both chronic and acute exposure calculations. It is an integrated approach in which all relevant parameters (e.g. all uses of a pesticide on food plants) can be used to compute the exposure distribution of the population to chemicals in foodstuffs. The parameters used are of great importance for the result. CX/PR 02/3-Add.1, para 18 mentions a number of issues about which further procedural agreement may be needed. A full discussion about these questions deserves further scientific attention and is not necessary here because it was not asked to be elaborated by the 34th CCPR. The possibility of a tiered approach in acute intake assessment has been proposed in an ECPA Workshop in 2002, using point estimates in the first tier and probabilistic assessment and more refined data in the higher tiers. In the interest of a better evaluation of deterministic acute intake calculations, results of probabilistic calculations could indeed be useful. It may be necessary however to specify clearly what parameters should be used in such calculations. Also

the practical implications for JMPR and CCPR of such a tiered approach, which might need several years to yield results in the Codex context, need to be considered.

29. Probabilistic intake estimations could in the long run be used as international higher tier or replacement methods for deterministic acute risk assessment methods. It is necessary that probabilistic results which are provided for comparison with international point estimates are calculated on the same basis regarding the residues input (meaning that the same set of supervised trials residue data are used on which the MRL assessment is based). When the calculation is done with the same assumed or available residues in the one commodity for which the point estimate is calculated and no other residues, the result wil provide information on the probability pattern of high exposures for the diet which was used. Whole national or regional or when possible "mixed global" consumption patterns should be used, because what is needed is the international estimate of the probability aspect of high exposures derived from one commodity. For this reason it would be desirable to report not only the 99.9th percentile but also higher percentiles, as far as scientifically justified and requested by the CCPR. It should be noted however that results of probabilistic assessments at a higher percentile level will be less accurate. It will be obvious that the result will also be an overestimate of actual risk, but in the international context for regulatory recommendations no further mitigating factors seem to be possible than already was agreed upon. The effect of processing and a percentage of products eaten processed could be used, as far as available, but applying a percentage of pesticide usage would not be possible in the international context. Because of the present absence of international food consumption statistics about complete short term consumption patterns of relevant regional populations, such contributions can also for the time being not be more than examples of national evaluations with specific residue parameters, for comparison with the international point estimates. National more realistic probabilistic evaluations with residue monitoring results could further illustrate the difference between theory and practice.

30. It would be possible in principle that not only one set of trial residue figures for one commodity is used in a probabilistic assessment, but the whole set of residue figures used for MRL proposals for one substance; this would yield a kind of probabilistic TMDI and TMESTI for a compound based on data submitted for registration. The results would be interesting and could be useful as a first step in evaluating the capabilities of using probabilistic methodology, but would obviously be gross overestimations of the exposure which can be expected in practice. Further discussions may follow on what is possible here, but for the time being it does not seem useful to speculate further on the possibilities because this type of calculation can not yet be performed in an international context.

DISCUSSION OF THE DIFFERENCES AND THE COMPARABILITY OF RESULTS OF IESTI CALCULATIONS AND PROBABILISTIC SHORT INTAKE ASSESSMENTS

31. Usually, probabilistic results are reported as the 99.9th percentile lev el of the calculated intakes of the chemical in question. This result is mostly much lower than a point estimate calculation for the same chemical for one specific commodity, even when essentially no different data are used. The reason for this is that the point estimates are generally calculated for an outcome with a much lower probability of occurrence, when the 97.5th percentile of the consumption figure of the population and the 97.5th percentile of a residue distribution are used in a point estimate, the result would have an occurrence probability of about 0.06% and would thus be more or less comparable with a Monte Carlo calculation result (based also on supervised trial residue data only) at the 99.9th percentile of the distribution. The probability of occurrence of the IESTI could easily become much lower for products which are usually, but not always, eaten in a processed form. Also the probability of occurrence of a HR with the highest variability factor could be lower than the 97.5th percentile from a residue distribution, so the point estimate will based on the residue aspects usually have a very low probability of occurrence.

32. Point estimates are based on the 97.5%-ile of the eaters only, which is for many commodities only a small part of the population based on the use of daily reported consumption data, and regularly calculations are presented of specific groups of the population (especially children), so the probability of

occurrence of a high consumption is again much lower and the IESTI calculated for these parameters will have a probability much lower than 0.1%. Indeed, the probability of the occurrence of an intake at the level of the point estimate will (calculated on the basis of supervised residue trial data) often be in the region of $10^{-4} – 10^{-5}$; in practice the probability of such an event will obviously be even much lower, because it is not usual that pesticide residues occur in practice at a level of supervised residue trials, and other mitigating factors (such as processing and percentage of pesticide use) further contribute to lower probabilities of such high intake levels.

33. When the probability of occurrence of the IESTI calculation result becomes much lower than 0.1%, e.g. in the order of 0.01% or less, the specific probabilistic calculations as mentioned before would probably need a higher reported percentile level of the assesment, e.g. the 99.99th percentile or even higher, in order to reach comparability with the point estimate result.

34. The question of the percentile level which should be used as a reporting level for probabilistic assessments is extensively discussed in a US-document (Choosing a percentile of acute dietary exposure as a threshold of regulatory concern, EPA, March 2000), in which the choice of the 99.9th percentile is defended. With a view on the large difference which often is found between (inter)national point estimates and Monte Carlo calculations reported at the 99.9th percentile level, it could be argued that the main issue is in fact the probability of occurrence of a critical result (e.g. exceeding the ARfD) and the risk management conclusions based on these results. A point estimate calculation which has been performed using all known accepted mitigating factors has an outcome which as such is scientifically valid. The outcome of other valid risk assessment methods however also has to be taken into account.

35. It is generally undesirable that various risk assessment methodologies cannot be seriously compared and yield different outcomes. Especially for Codex this issue is important, because the risk management decisions for acutely toxic compounds depend on the outcome of the point estimates, and there is a danger that national evaluations based on probabilistic assessments lead to other decisions, so that international harmonisation becomes problematic. The superiority of a probabilistic approach for exposure assessment is generally ackowledged, and efforts should be aimed at enabling the JMPR to make use of this type of assessment in the future. In order to gain wide acceptance about the scientific basis for acute intake decisions and to be able to reach credible intake assessment results it is necessary to be transparent in the scientific basis of the assessment and to define exactly what the relevant parameters are on which the calculation results are based. Therefore it is desirable that the probability aspects of point estimate method results are clarified and that probabilistic assessment methods, when used in conjunction with point estimates, also provide results at the probability level of these point estimates, as far as scientifically possible. There obviously is also a need for reaching agreement about the risk management aspects of dealing with calculation results with various probabilities of occurrence; these aspects are further discussed in the chapter on risk management (paragraph 30), but in order to start this discussion it is necessary to pay attention to the hazard characterisation, which is the other main factor in the risk assessment.

ESTABLISHMENT OF THE ACUTE REFERENCE DOSE (ARFD)

36. The scientific basis for the establishment of the ARfD is specifically elaborated in the 2002 JMPR Report. This is essentially a toxicological issue which is not discussed as such here. It is obvious that this subject is also a difficult field of science, in which often conclusions have to be drawn on the basis of data which leave room for considerable uncertainty. The uncertainty factors used in deriving the ARfD from an appropriate NOAEL have a.o. the function of protecting the population against possible harm because parts of the population could be more susceptible than others. Because acute toxicological aspects have only recently gained recognition as an important aspect for public health protection and residue regulation, it is understandable that especially regarding acute intake effects, the toxicological data base of a compound will often be deficient according to modern standards and the registration requirements are still in the process of being further discussed and developed. The 2002 JMPR has made substantial progress on this road. Strengthening the scientific basis for establishing appropriate acute toxicological hazard assessment should be further encouraged.

37. An important aspect of the ARfD in the context of risk management is that discussion may be needed on how to deal with probability aspects in relation to the possibility of exceeding the ARfD. This is a sensitive issue which requires a dialogue between risk assessors and risk managers, but which can not be completely avoided, because the subject of acute risk assessment has to deal with elusive endpoints and extremely low probabilities of the exposure assessment. Therefore some kind of clarification is necessary about the risks involved with low probabilities of exceedings of the acute RfD. It is desirable that the JMPR provides further advice about this matter.

RISK MANAGEMENT ABOUT ACUTE INTAKE CONCERNS

38. In CX/PR 01/5, the chairman of the CCPR presented the risk analysis principles and methodologies so far applied in the work of the CCPR. Regarding acute dietary intake assessments, especially in CX/PR 00/3 the chairman discussed the principles to be used in relation to various cases of acute risk assessment situations. It is noted that there are cases where the JMPR has indicated that an acute RfD may be necessary, but is pending waiting further review. The CCPR is then reluctant to advance MRLs on chronic dietary intake assessment only. When an acute RfD is established, it is still a problem that the consumption database is so preliminary that it is difficult to reach solid decisions based on the exposure estimates. As an interim procedure, the chairman stated that when the IESTI (general population or children aged 6 years and under) exceeds the acute RfD, the MRL will not be advanced and when no further refinement of the calculation seems possible, the MRL will be considered for deletion. Several delegates supported this position, but no firm conclusion was recorded (ALINORM 01/24, para 27-31 and ALINORM 01/24A, para 44-51). The question is in principle still undecided, on how to proceed regarding acute intake concerns, especially in those cases where the JMPR has indicated that the information provided to the JMPR precludes an estimate that the short-term dietary intake in this commodity would be below the acute RfD. The CCPR is obviously reluctant to accept MRLs for which the IESTI as calculated by the JMPR is exceeded, but further discussion seems possible on this issue. The present situation leads to problems because the risk assessment by JMPR represents the worst international case and is not allowed to take mitigating factors into account which are used nationally, with the consequence that the work of Codex regarding harmonising MRLs internationally is hampered.

39. It is generally accepted that in the case of chronic risk assessment, occasional limited exceedings of the ADI may be considered acceptable because the ADI is directed at lifetime exposure and in most cases the risk of a short term intake is much less than that of prolonged intakes. For this reason, the intake assessment in the international context on the basis of average (regional) diets is generally seen as acceptable, although it is evident that short term or also medium term intakes could sometimes exceed the ADI. The principle used for decision making in the international context is that when in the most refined exposure estimate the ADI is calculated to be exceeded, the MRLs should not be advanced, unless this matter can be resolved by further information about mitigating factors or by withdrawal of risk-driving MRLs. The use of some factors which may be used at the national level for more realistic exposure estimates (e.g. a percentage of crop treated) is not well possible in the international context, implying that the international assessment is usually an overestimate of the exposure.

40. In the case of short term intake assessment, in comparison with the approach for chronic intake concerns it seems logical that the principle for decision making in Codex should again be that the toxicological reference dose, in this case the ARfD, may not be exceeded in short term intake assessments. This has led to problems in accepting MRLs for acutely toxic compounds, because the parameters used for the calculation of the IESTI lead to much higher intakes than the average exposure. The use of probabilistic exposure assessment methods seems interesting in this respect, because there are statistical reasons for not expanding the calculations to the last digit, and the 99.9th percentile generally seems conservative enough as approach and often yields results which lead to the conclusion that in fact there are no appreciable risks involved with the MRLs in question. Risk managers have to deal with this situation. In a national context, it is possible to use probabilistic calculations only for decision making. In the EPA document about choosing the threshold of regulatory concern the idea is defended that small exceedances of the acute RfD which could occur above the chosen threshold

reporting level could be accepted. The reasoning for this is that these cases would occur with a low probability, and the expectation is that such small exceedances will not cause any harm, in view of the conservative uncertainty factors used in the assessment of the acute RfD. In Codex, this can not be done in the same manner because probabilistic assessments are not yet possible. The best way forward is probably to aim at an approach which tries to make the best of both methodologies, thus assuring that future developments can be integrated without too many changes and problems. Suggestions for a possible approach are elaborated in the next paragraphs.

41. In the previous paragraphs, it was pointed out that the main reason for large differences in exposure assessment results between deterministic and probabilistic methods is that the probability aspects of a deterministic calculation are not taken into account. The concept of basing decisions on probabilistic method results implies usually that the calculation is stopped at a specific high percentile. The scientific reason for this is that further calculations at higher percentiles become rather uncertain and higher percentile level results might be driven by questionable inputs at the tail end of the databases. The risk management reason for doing this is that the chosen percentile reporting level is considered adequate as a threshold of regulatory concern. The consequence of such an approach is that possible higher exposures are ignored. Also the concept of a point estimate calculation, although it is an approach aiming at assessing a kind of maximum exposure, is not the ultimate exposure possible. The result of a point estimate is as such valid and should not be ignored. The results of different point estimates can be quite different regarding their probability aspects, depending on the percentage of the eaters and other relevant factors. The only possibility of reconciling these different concepts and situations, while maintaining scientific transparency and risk management consistency, is to continue using different valid concepts of exposure assessment, but to accept the idea that it may be necessary to base risk management decisions on the probability of occurrence of the exposure.

42. Risk managers should not interfere with toxicological considerations and evaluations. It is a responsibility of risk managers to aim at integrating the risk management of acute risks of pesticide residues in a general risk analysis approach. It is a matter of risk management to decide what should be done about the possibility of exceeding a toxicological advice about a level of intake which is considered safe. The question can be raised if exceeding the ARfD in a point estimate should always lead to the conclusion that this is unacceptable. It is proposed here to consider the possibility that some limited exceeding might be accepted, when the probability of occurrence is very low. Regarding this difficult issue, it should be borne in mind that the principles used for the calculation of point estimates already imply that higher intakes could occur. It is better to be transparent about this issue than to ignore it. Exceeding the ARfD does not imply as such that actual health effects will occur. Accepted public health policies often use a probability of 10^{-6} for acceptance of serious risks such as tumor formation in relation to inevitable intake of tumorigenic compounds. In the case of pesticides we are dealing with situations which can be regulated and which therefore can be avoided, so we must be far more strict and leave no room for serious public health effects. Nevertheless, for pesticides a comparable policy could be established, as long as it can be maintained that there will be no consequences for public health. Therefore it is conceivable that for far smaller risks related to seldom occurring higher exposure to pesticides, some controlled level of exceeding the ARfD could be seen as acceptable.

43. The options for risk management in the CCPR regarding deterministic acute intake assessments (point estimates) are in principle as follows:

1. Maintain the ARfD as a figure which may not be exceeded and use the available international point estimate results. The consequence is that many MRLs will have to be deleted, possibly unnecessarily, causing crop protection problems and international harmonisation problems because national evaluations may conclude that the use is acceptable.

2. Idem, but change the assessment in such a way that higher levels are discarded from the evaluation (e.g. by choosing lower percentile levels for the consumption figures and/or for

the variation factor in the point estimate). A more consistent approach would be aiming at a specific probability level for reporting results, e.g. the levels 10^{-3} and/or 10^{-4}.

3. As an alternative for case 2, the use of a simple probabilistic type of assessment (as mentioned in paragraph 24, for trial data only) with a not too high reporting level (e.g. 10^{-3} and/or 10^{-4}) could be envisaged in the future, as a higher and more refined tier of the exposure estimate. This would require then that higher point estimate results are overruled by the more refined approach.

4. Accept some controlled exceedance of the point estimate result in relation to low probability levels, assuring that still a sufficient safety margin is upheld between the possible high exposure and the acute RfD.

44. It is important to define the principles which should be upheld for responsible risk management. This will need some time for dialogue between risk assessors and risk managers. It will be evident that continuing in the present situation (option 1) will lead to problems in harmonising MRLs. An alternative can be that the point estimate is limited to a specific probability level and that possible exceeding of the ARfD above this level is not taken into account (option 2). This could lead to accusations however that these possible exceedings are ignored, so what is necessary is an evaluation of the risk of this situation.

45. A comparable approach could be to adopt simple probabilistic approaches as a higher tier calculation of exposure for point estimates (option 3), but this will require further international dietary modelling. This tiered approach would have the same problem, that point estimates leading to higher exposure are not taken into account. The problem would become "invisible" when the probabilistic approach would be adopted as the only calculation which needs to be presented, but before accepting such an approach the inherent risks and the parameters used would need further discussion. In situations where the ARfD would still be exceeded using the agreed parameters and approach, point estimates might still be useful to signal the pesticide uses which lead to these exceedances and for which risk management action has to be considered.

46. In option 4 it is suggested that the degree of acceptable exceeding of the ARfD is limited in relation to the probability of occurrence of that situation.

47. The conclusion is that the CCPR should discuss if and how far and how often exceeding an ARfD could be acceptable on the basis of sound scientific advice. This could be in the form of a conclusion about a probability limit which is considered sufficient for evaluating a worst case exposure estimate. It could also come in the form of a more specific advice.

48. A preliminary proposal for a more specific advice is mentioned here for the sake of discussion; a prerequisite is that it is only applicable for IESTI calculations with supervised trials residue levels and using only the relevant factors agreed for the international assessment (so no percentage of crop treated), implying that actual probabilities of occurrence will always be smaller:

- Based on specific CCPR discussion and sufficient argumentation that actual occurrence will be lower than 10^{-4}, until 2-fold exceeding of the ARfD in the best available point estimate results could be acceptable for the establishment of Codex MRLs.
- Based on occurrence and toxicological data from the JMPR, until 3-fold exceeding of the ARfD could be seen as acceptable when the occurrence probability is lower than 10^{-5} and the uncertainty factor used for establishing the ARfD is 100 or more.
- Idem, [5-10]-fold exceedance might be acceptable for an occurrence probability lower than 10^{-6}.

CONCLUSIONS AND RECOMMENDATIONS

- Further refining of point estimates is possible to a limited extent by refining the factors used. The IUPAC recommendations (especially regarding the variability factor) deserve consideration. Countries are encouraged to send in their data which add to the scientific validity of the factors used in point estimate calculations (including probability aspects). This should at least also include the percentage of the eaters of a commodity for which large portions are reported, and also the percentage of this commodity which is eaten in processed form. A continuous update of the consumption and residue databases used for acute exposure assessment is desirable.
- No suggestions have been raised regarding refinements to the international acute exposure methodology itself, except for the fact that probabilistic assessments could bring further clarification regarding the distribution of the possible exposures. The possibilities of introducing simple international probabilistic calculations should be investigated.
- The validity of point estimates as performed by the JMPR should not be questioned as such; it is a problem however that the probability of occurrence of the calculated IESTI may be extremely low. It is therefore questionable whether this warrants strict risk management decisions based on these results, whereas in other risk management cases a different public health policy is followed, taking account of the probability of occurrence of critical events.
- In order to make progress with Codex decisions on acute intake concerns, a way forward might be in the first place to achieve transparency about the occurrence probability of acute intake calculation results and about the toxicological and risk management aspects of exceeding the ARfD in low probabilities of occurrence. The JMPR should be asked to mention the probability aspects of their point estimates, when the results exceed the ARfD. The absence of possible mitigating factors should be clearly mentioned and the conservative elements in the international exposure assessment in comparison to reported national approaches should be pointed out. Also, in relation to the ARfD, the uncertainty factors used should be mentioned, the toxicological effects on which the ARfD is based, the effects occurring at the acute LOAEL and a statement on the risk of exceeding the ARfD at a low probability of occurrence.
- Countries which can make probabilistic assessments are invited to make available to the JMPR probabilistic calculations of the intake based on the JMPR residue figures and their national consumption data bases, for cases where the international point estimate calculation indicates exceedance of the acute RfD. This would particularly be relevant for the country from which the LP was derived.
- The CCPR is invited to discuss the possibility of accepting limited exceedance of the acute RfD in point estimate calculations, under specified circumstances. Alternatively, it is conceivable to limit also deterministic acute exposure assessments to a specified probability of occurrence. In the future, when probabilistic approaches would be possible on an international level, a tiered approach using probabilistic calculations in a higher tier could be considered, or the adoption of a specified probabilistic approach as the primary exposure assessment method.
- Further toxicological advice is desirable on the issue of possible limited exceeding of an acute RfD in cases with extremely low probability of occurrence.
- The guidance on the derivation of the acute RfD by the 2002 JMPR is welcomed. Further strengthening of the toxicological data and of the procedures and considerations necessary for developing acute RfDs deserves recommendation.