Session 11B

Chemical Residues in Food

Chairman & Session Organiser:	Dr Bernadette Ossendorp *RIVM, Bilthoven, The Netherlands*
Platform Papers:	11B-1 to 11B-4
Poster Presentation:	P11B-5

Review of the EU and NAFTA procedures for MRLs calculation

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Introduction

In recent years, the degree of mathematical sophistication in the regulations of residues of *crop protection products* (CPPs) in foodstuffs has grown. This has been stimulated by increased public attention to food safety and by a desired for harmonization to facilitate international trade. As a result, more advanced statistical and mathematical methods have been introduced for the analysis of residue data.

In this paper, we review in some detail the EU and NAFTA procedures in use or proposed for the calculation of the *maximum residue levels* (MRLs) and discuss their strengths and weaknesses. We also compare their results and provide some recommendations about their application.

Nature of the residue data

The CPP residue populations are usually left-censored (i.e. truncated at the *limit of detection* (LOD) or the *limit of quantification* (LOQ) levels), right skewed (i.e. asymmetric, having a long right tail) and frequently contain suspected outliers (extreme values that appear discrepant from the rest).

There is great diversity in the appearance of residue datasets. Some seem to follow a normal distribution (also called a bell-shaped or Gaussian distribution). Others seem to follow a lognormal distribution (the logarithm of the residue values would follow the normal distribution), which is a right skewed distribution. Others still seem even more right skewed than the lognormal distribution and some residue datasets are so erratic that they do not appear to follow any known distribution at all.

EU existing calculation procedure

The EU guidelines specify the use of two methods. Method I proceeds as if the samples are derived from a normal distribution and sets the MRL at the right-side end-value of the 95% confidence interval of the 95th percentile. That is, the MRL is set so 95% of the time, the 95th percentile of the assumed underlying normal distribution is lower than the MRL.

Method II does not assume that the residue data follow any particular distribution. Instead, the 75th percentile of the sample is computed and then doubled. The percentile is computed using the Weibull procedure, which consistently (and for small datasets, considerably) overestimates the percentile values, representing a somewhat artificial worse case scenario.

Unfortunately, the EU regulations do not provide guidance for when to use Method I or Method II or for what to do when the MRLs produced by the two methods differ. It simply says that the next step consists in the rounding of the MRL value to one of 16 discrete MRL classes listed in the regulations, which significantly distorts the results produced by either method. Another questionable aspect of the EU procedure is the setting of LOD-residues at the LOD value before the start of the calculations, which skews the residue distributions, inflates the estimator of the mean and decreases the estimators of the variability.

NAFTA proposed calculation procedure

The first part of the procedure requires 'filling in' the values of the non-detects (NDs = LODs) by assuming that the samples have been produced from a lognormal distribution. The lognormality of the resulting dataset is checked both by the use of the Shapiro-Francia test as well by a visual inspection. If the dataset is considered not to be lognormal, then the 'California method' is suggested, which sets the tolerance value three standard deviations above the sample mean (for a normal distribution, this would be roughly equivalent to setting the MRL at the 99.9th percentile).

If the dataset is deemed lognormal, then up to three different statistical measurements may be required:

- the 95% upper confidence limit on the 95th percentile;
- the 99th percentile estimate and
- the product of 3.9 times the upper prediction limit of the median.

All these measures are calculated following the rules of the lognormal distribution; so although the first measure looks very similar to the one used in the EU Method I, it is likely to produce a higher result. The third measure is produced under the additional assumption that the *coefficient of variation* CV (the ratio of the standard deviation to the mean) has a value of one.

For large datasets (more than 15 data points), the minimum of the first two measures is taken forward (these two measurements are referred collectively as the '95/99 rule'). For smaller datasets, the minimum of all three measures is required. Whichever option is taken, the result must be rounded. No option for the removal of outliers is provided (the EU allows for the removal of outliers using the Dixon's Q-test, which assumes normality).

Conclusions

- Both the EU and NAFTA MRL calculation procedures are scientifically based and provide reliable ways of dealing with the great diversity of residue dataset patterns.
- Both methods produce similar results as long as the maximum of the two EU method estimates is taken as the MRL, and the Dixon's Q-test and the MRL classes are not used. When the MRL classes are used, the EU procedure may produce higher MRLs.
- Setting the LOD-residues at a fixed residue value and the use of MRL classes in the EU procedure are unnecessary steps which distort the statistical calculations.

Opportunities for improvement and harmonization

- EU procedure:
  - ❖ better handling of LODs (perhaps in a similar way to NAFTA);
  - ❖ assume lognormality instead of normality in method 1 (again, like NAFTA);
  - ❖ remove the MRL classes and substitute them by a NAFTA-style rounding;
  - ❖ **most importantly**, provide guidance about how the results from method 1 and 2 should be integrated.
- NAFTA procedure:
  - ❖ reduce complexity by using fewer statistical methods (the use of a distributional one and a non-distributional one as done in the EU seems sufficient);
  - ❖ reduce reliance on the lognormality assumption;
  - ❖ **most importantly**, move away from visual estimation which will always be subjective and requires considerable statistical experience.

EFSA model for pesticide exposure assessment of temporary MRLs

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The European Food Safety Authority (EFSA) was established as an independent body to provide scientific advice and to collect and analyse information required to underpin Community decision making.

EFSAs role in the process of setting Maximum Residue Levels (MRLs) has been clearly defined in Regulation (EC) 396/2005, where the specific tasks of risk assessment are allocated to EFSA. This Regulation aims to have a full harmonisation of MRLs, which will be done in a one-off exercise for all active substances that are not yet harmonised. At present, a large number of pesticides are on the market that have not been evaluated at Community level and for which Member States have set national MRLs. The so called 'temporary MRLs' will be set for active substances for which currently no EU MRLs are in place. The temporary MRLs will be included in Annex III of Regulation (EC) No. 396/2005 and EFSA is in charge of the risk assessment for these temporary MRLSs.

The performing of risk assessment and setting of MRLs is hampered by the absence of a European risk assessment model which covers all European population sub-groups. The current risk assessment models are based on limited national food consumption data, representing only a part of the European consumers. As the Community MRLs have to be safe for all European consumers, EFSA decided to take a more comprehensive approach and to develop a European model for risk assessment.

Model design

The model design was driven by the following considerations. The model should:

- apply the principles of the WHO methodology for pesticide exposure assessment;
- allow the assessment of long-term and short term consumer exposure simultaneously;
- include all available European food consumption data to be representative for European consumers (including specific sub groups of the population such as children of different age);
- provide transparent calculations indicating the input parameters used;
- be flexible enough to allow the calculations of alternative scenarios, if necessary, and;
- present the results in a clear and structured form to facilitate risk management decision.

The model should be an easy to use tool for a first screening of the safety of temporary MRL proposals. At the first stage of this specific exercise it was not necessary to have a model which allows a refined risk assessment as no data usually used for refinement were available.

The first step in the model development was the collection of data on food consumption derived from national food surveys. 14 Member States provided data; in total 22 national

diet sets for chronic exposure assessment and 19 data sets for acute exposure were received. EFSA also included the WHO cluster diets B, D and E and the previously used European diet in the chronic risk assessment.

The concept for the chronic risk assessment is comparable with the JMPR approach where the exposure is calculated for all cluster diets in parallel. In an overview report the results of the TMDI calculations are presented for each of the 26 chronic diets. In addition, the three crops which are the main contributors to the total exposure are indicated.

The acute risk assessment is based on the critical European consumer identified for each commodity, i.e. the consumer from the diet set for which the highest exposure is expected. Deviating from the JMPR approach, the IESTI calculations is performed with the MRL instead of the HR or STMR, as these data were not available in the first phase of the temporary MRL exercise.

The model was validated with a fictitious example where the results gained were compared with the results of the national models. Basically, there was a good correspondence. The differences are mainly due to the fact that the French and the UK chronic model deviate from the JMPR approach: in these models for the two main contributing food commodities the intake calculations are based on the 97.5th percentile intake instead of the mean consumption figures. Therefore the national models give a higher exposure.

The EFSA model is published on the EFSA website, where the Excel-spreadsheet and the instructions for use can be downloaded[1]. Experiences with Member States experts showed that the model is easy to handle for people which are familiar with risk assessment.

The limitations of the model

As mentioned, the user should be aware that the results in the chronic risk assessment do not exactly correspond to the results obtained with the national UK or French model. Another drawback of the first version of the model is that refined calculations are not possible: both, the acute risk assessment are calculated with the MRL.

Further developments

As in the further discussions on the temporary MRLs data for refinements were made available, it became evident that there is a need for a model which allows incorporation of these refinement data. For this reason EFSA introduced new features for this purpose in a second revised version of the model.

In addition, revision two comprises additional diets, such as the cluster diet F, representing Romania and Bulgaria. As the update of the diets is a crucial point with regard to the acceptance of the model, Member States are encouraged to submit new consumption data if available.

As the development of the EFSA model is considered to be a European project, Member States are invited to make proposals how to improve the model taking into account the experiences gained in practice.

[1] http://www.efsa.europa.eu/en/science/praper/maximum_residue_levels/mrl_opinion.html

Acute dietary intake assessment of pesticide residues in fruit and vegetables

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Acute dietary intake is one of the factors considered by Member States, the European Commission and international authorities when setting Maximum Residue Levels (MRLs) for pesticides. The MRL is the maximum concentration of a pesticide residue (expressed as mg/kg) that is legally permitted in or on a food or agricultural commodity or animal feedstuff. The measure of acute dietary exposure that is used in MRL-setting is the International Estimate of Short Term Intake (IESTI). The IESTI is calculated using one of four standard equations, depending on the type of commodity involved. An MRL above the limit of detection is set for a commodity only if its IESTI does not exceed the Acute Reference Dose (ARfD) of the pesticide concerned.

There are discussions at international level about whether to change the way that IESTI equations are calculated. Therefore the European Commission asked the EFSA PPR Panel for an Opinion on how conservative the IESTI equation is, with respect to the percentage of the total European population protected from intakes above the ARfD, and how much this would be altered by changes to the way the IESTI is calculated. However, the Panel is aware that risk managers are also interested in the special case of people who consume a commodity containing residues at the MRL. Therefore the Panel undertook two types of assessment: 'total population assessments', estimating the level of protection for the total population based on the levels of pesticides observed in monitoring programs, and 'MRL-level assessments' for the special case of people who consume one commodity containing residues at the MRL and other commodities at monitoring levels.

The Panel estimated acute dietary intakes by probabilistic modelling. This used data on food consumption and body weight from national surveys, and took account of unit-to-unit variability of residues using variability factors. It was not possible to conduct probabilistic modelling for the entire population of the EU, or for all pesticides. The Panel conducted total population assessments for a number of scenarios representing different combinations of 13 pesticides, eight countries and a range of age groups from babies to seniors. For practical reasons, the MRL–level assessments were based on a reduced range of scenarios, representing only two countries (Germany and the Netherlands) and 11 pesticides.

For the total population, the Panel's estimates suggested that the level of protection (LoP) provided by the IESTI equation as currently used in the EU (including variability factors of five and seven) varies quite widely between different countries, age groups and pesticides. For some pesticide/country/age group scenarios the estimated LoP was between 99 and 99.9%, i.e. between 99% and 99.9% of the population had estimated intakes below the

ARfD. None of the estimated LoPs for the total population were below 99%, and for most scenarios they were above 99.9% and often above 99.99%. The estimates are very uncertain but probably conservative, i.e. probably underestimate the true LoPs.

Changing the variability factors of five and seven to three would decrease the calculated IESTIs for some commodities. This would result in additional MRLs being set, potentially increasing intakes and decreasing LoPs. Changing the variability factor to three increased the number of commodities qualifying for MRLs in 25 of 78 pesticide/country/age group scenarios in the Panel's total population assessments. The resulting reductions in LoPs were: generally much smaller than the existing range of variation in LoPs between the pesticide/country scenarios modelled by the Panel; smaller than the effect on LoPs of reducing the margin between maximum IESTI and the ARfD in the scenarios modelled by the Panel; and for most but not all scenarios, within the range of quantified and unquantified uncertainties affecting the assessment.

The Panel's results suggest that the IESTI is a poor indicator of the LoP for the total population (a purpose for which it was not designed), and of the contribution of individual commodities to the aggregate intake of a pesticide. This is because it considers each commodity separately, and does not take account of key factors such as the frequency of consumption and residues.

For consumers of a single commodity at the MRL and others at monitoring levels (MRL-level assessments), the LoP provided by the current IESTI equation again varied widely between different countries and pesticides, and also between commodities. The Panel estimated LoPs for a total of 92 pesticide/country/commodity scenarios relating to in the Netherlands and Germany, mainly for young children. Eighty-one of these scenarios would qualify for MRLs with the current IESTI equations. For some of these scenarios, the estimated LoP was between 90 and 99%, but most scenarios were above 99% and many above 99.9%. Again, the estimates are very uncertain but probably conservative, i.e. probably underestimate the true LoPs.

The Panel's results suggest that the IESTI is a much better indicator of the LoP for consumers of commodities at the MRL (the purpose for which it was designed) than for the total population. On average, the commodity at the MRL contributed over 90% of the intake in these scenarios. Changing the variability factor from five and seven to three increased the number of pesticide/country/commodities qualifying for MRLs from 81 to 86. Because the proportion of scenarios added was small it did not markedly change the overall distribution of LoPs, although four of the five added scenarios had estimated LoPs at or below 99%.

There is a need for risk managers to decide which measure(s) of the level of protection they consider relevant for which purposes (e.g. in MRL-setting versus post-authorisation assessment of monitoring data). The Panel's results suggest that the current IESTI equations are better indicators of the LoP for consumers of commodities at the MRL, for which they were designed, than of the LoP for the total population at monitoring levels. If measures of the LoP for the total population are required, then consideration should be given to modifying the IESTI equations or developing alternatives for this purpose. Based on the Panel's experience, this would require substantial research. For full opinion, refer to: http://www.efsa.europa.eu/en/science/ppr/ppr_opinions.html

Cumulative exposure assessment – input data

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Cumulative risk assessment is the assessment of risk from exposure to more than one pesticide. The risk assessment may include dietary exposure from food and/or water and may also include residential exposure. The choices of input data are crucial when estimating cumulative exposure. Focusing mainly on dietary exposure from food, there are decisions needed on both residue data and consumption data. These decisions may be driven by the objective of the cumulative risk assessment (e.g. for MRL setting or for post-registration exposure assessment) and/or the toxicological properties of the pesticides (e.g. short-term and/or long-term effects).

Residue data may be available as supervised residue trials, trade enforcement monitoring and monitoring at the consumer level (e.g. distribution centers, grocery stores). Oftentimes residue data are available on many, but not all, commodities leading to decisions on the translation of residue data from one commodity to another. These residue data sources are, most often, analyses of composite residue samples so decisions on how to deal with single-unit commodity residues (e.g. one apple) are required. Decisions must also be made on how to handle non-detectable or non-quantifiable residues. To refine the assessment, data on residues following industrial and home processing (e.g. peeling, juicing, baking) may be used. These data may be available for the compound of interest or may be default calculations. The decisions just described are crucial for dietary exposure assessment whether cumulative or not. An additional complexity for cumulative dietary exposure assessment is the co-occurrence of residues.

The US EPA has completed a cumulative risk assessment for organophosphates and is scheduled to complete the *N*-methyl carbamate cumulative risk assessment in August 2007. The *N*-methyl carbamate cumulative risk assessment is a post-registration exposure assessment focused on short-term exposure since the mechanism of toxicity for *N*-methyl carbamates is rapidly reversible acetylcholinesterase inhibition.

For the *N*-methyl carbamate cumulative risk assessments, the following preliminary decisions were made on residue input data.

- The base residue data are taken from the USDA Pesticide Data Program (PDP). The PDP is a consumer-level monitoring program sampling commodities at food distribution centers and preparing the commodities for consumption (e.g. washing, peeling) prior to analysis.
- The analyses are conducted using multi-residue methods. The co-occurrence of residues in each sample is recorded and maintained in the PDP database and is available for use when estimating the cumulative exposure. For the *N*-methyl carbamate cumulative, it is assumed that the co-occurrence of residues in US food mirrors the co-occurrence measured in the PDP. Co-occurrence data are reflected during the exposure assessment by calculating, for each sample, an index equivalent residue. In other words, the residue for each individual carbamate quantified on the

commodity is multiplied by the specific carbamate's relative potency index and all resulting individual residues are summed to provide a single total index equivalent residue for the sample.

- Residue data for commodities monitored in the PDP are translated to additional commodities according to the US EPA's SOP for Translation of Monitoring Data based on similar crop morphologies and cultural practices. For example, residue monitoring data on head lettuce was used also for cabbage.
- Residues from composite samples are assumed to adequately reflect single-unit residues.
- Samples with non-detectable residues are assumed to be 'zero' values. A sensitivity analysis performed during the organophosphate cumulative risk assessment assuming all <LOD values were alternatively '0' or '½ LOD' verified the assumption of zero values for all non-detects did not significantly impact the results at the higher end of the exposure distributions.
- Processing information, including processing factors for dried and cooked foods and juices, provided by registrants, publicly available, or calculated for loss of water during drying, were incorporated into the assessment for foods forms not directly measured in the PDP.

Similarly, consumption data are available from a variety of sources (e.g. daily surveys, food balance sheets). These consumption data might be representative of the general population and/or subpopulations determined by, for example, age, gender, ethnicity, region, or socioeconomic status. Data are also required on the co-occurrence of consumption (e.g. apple and pear consumption on the same day) to provide a realistic assessment of exposure. For the N-methyl carbamate cumulative risk assessments, the following decisions were made with regard to consumption input data.

The consumption data are taken from the USDA Continuing Survey of Food Intakes by Individuals (CSFII), 1994-1998. This survey was designed to represent multiple subpopulations including those for which the US EPA generates acute dietary food exposure distributions as well as seasonal and weekly eating patterns. The consumption data are recorded per day per participant maintaining the consumption co-occurrence between commodities.

The *N*-methyl carbamate dietary exposure from food is considered uniform across seasons and regions. However, when considering exposure from drinking water and residential exposure, seasonal and regional exposures are modeled to identify the regions with the highest potential for exposure. These regional exposures are combined with the uniform dietary exposure from food in time-course models to provide the final estimates of cumulative exposure.

False positives in dithiocarbamate analysis: a review of the literature

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Dithiocarbamate fungicides are commonly used in agriculture, however the determination of the associated residues in foodstuffs can be problematic due to their lack of stability during storage and extraction and poor solubility in both organic and aqueous solvents. There are three classes of dithiocarbamates; dimethyldithiocarbamates (e.g. ziram, thiram), ethylenebisdithioarbamates (e.g. mancozeb, zineb) and propylenebisdithiocarbamates (e.g. propineb). For compliance with both national and international MRLs, the current residue definition of dithiocarbamates is 'the total residues arising from the use of any dithiocarbamate fungicide, determined as CS_2'. Although methods specific to individual dithiocarbamates are under development, the method that is commonly used to determine dithiocarbamate residues by monitoring laboratories involves the acid digestion of the sample which evolves carbon disulfide (CS_2), which is then measured by either headspace gas chromatography or spectrophotometry.

During the 1993 JMPR evaluation of maneb it was observed that CS_2 was evolved from control samples of onions, broccoli and cabbage (FAO, 1993). The phenomenon of high CS_2 residue levels and the occurrence of false positives were investigated by Ahmad *et al.* between 1993 and 1995. Ahmad *et al.* (1996) modified the standard headspace gas chromatography method by incorporating thiophene as an internal standard to measure method performance; this improved sensitivity and resolution of the method. They also developed an improved method for measuring levels of ethylenethiourea (ETU), a degradation product of the ethylenebisdithiocarbamates (EBDC), in order to confirm the origin of positive results.

Their data showed that CS_2 was detectable in a wide range of fruit and vegetable samples (samples were bought fresh from a local market). ETU analysis confirmed that EBDC was the source of these residues in kiwi fruit (this had been denied by the growers). The confirmatory data for other fruit and vegetables were not presented, however, the authors claimed that EBDC residues had been confirmed in matrices reported to contain endogenous compounds that contain CS_2.

Work carried out at the UK's Central Science Laboratory (Harrington *et al.*, 1997) determined the CS_2 levels in a variety of vegetables that were members of the *Cruciferaceae* family. For each vegetable type, CSL-grown samples, samples obtained from suppliers approved by the Soil Association and samples labeled as organic and purchased at retail outlets were tested for CS_2 on the day of purchase or after storage for 5/10 days. The primary detection of CS_2 was carried out using GC-FPD and quantitatively confirmed using GC-MS (m/z ion 76). It should be noted that the GC-FPD analytical method employed could not differentiate between CS_2 and dimethyl sulfide, thereby rendering it unsuitable for analysis of CS_2 levels on its own. The data produced showed that fresh or stored spinach and asparagus gave no significant levels of CS_2 (none >0.01mg/kg). However, broccoli samples showed low levels of CS_2 (0.01 – 0.04mg/kg) in both the CSL-grown and retail outlet samples, although this level was not affected by storage.

Samples from the cabbage types tested (red, green and white) showed levels of CS_2 between 0.02 and 0.10mg/kg, although inconclusive data was obtained regarding whether storage increased the levels of CS_2.

Perz *et al.* (2000) analysed CS_2 levels in *Brassiaceae* family members grown without any pesticide application. The results showed that CS_2 levels determined using the acid digestion method in crops rich in sulfur compounds, such as mustard oil glycosides, have to be interpreted with caution. In the study, they demonstrated that freezing samples resulted in the levels of CS_2 increasing from 0.098 mg/kg to 1.41 mg/kg in healthy unprocessed red cabbage samples. Cooking (20 minutes) or blanching (3 minutes at 80°C) of the red cabbage prior to freezing reduced the detected CS_2 levels to 0.083 mg/kg or 0.30 mg/kg, respectively. The same pattern was seen for the Savoy cabbage, turnip-rooted cabbage and cauliflower samples. The hypothesis presented by the authors for this increase is that when tissue compartments are destroyed by the freezing process enzymatic reactions cause the liberation of isothiocyanates from glucosinolates; these are then converted to CS_2 during the acid digestion step.

To try to overcome the problems of false positives, de Kok & van Bodegraven (2000) developed a new method involving the extraction of CS_2 in iso-octane followed by analysis of the organic extract by GC-ECD. Data obtained using this method gave blank values for papaya samples; a crop which gave false positives using the acid digestion method. However, it did not prevent the occurrence of false positives from the analysis of cabbage-type crops.

Improved methodologies for the detection of the individual dithiocarbamate compounds are currently under development. As recently as May 2007 the Republic of Korea has presented an amended method for the determination of dithiocarbamate residues to the Codex Committee on Pesticide Residues (CCPR). This method uses HPLC-UV detection to determine the three separate groups of dithiocarbamates. In conclusion, it is likely that further consideration will be required when setting MRLs for dithiocarbamate residues in crops which potentially contain endogenous sources of CS_2.

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