European Community comments on
CODEX CIRCULAR LETTER CL 2009/19-PR:
Request for Comments on the MRL Calculation Method being developed
through the OECD

1. Setting MRLs "high" or "low"?

**Question 1:** Which of these two interests is more important to address when setting MRLs?

Within EC the MRL (fixed at EC level) is set based on the worst case or critical GAP (GAPs are defined at national level). This means that in some cases one out of 27 GAPs of the 27 EC Member States may drive the MRL while 26 MS have a GAP that would lead to a lower MRL. In the case of Import Tolerances or MRLs based on Codex MRLs, the critical GAP is applied outside the EC and the MRL may reflect residues of pesticides that are not even authorised in the EC.

This shows that the MRL is not suitable to enforce correct application of all the nationally authorised GAPs. To enforce the correct GAP, additional measures are taken including controls at the farm gate or on the farm.

Nevertheless, for reasons of consumer protection, the EC MRLs are set low enough that using more product than prescribed in the critical GAP will likely result in an MRL exceedance.

The value proposed is always going to be a compromise between these two key aspects. Whereas an MRL to accommodate GAP is the ultimate aim, there will always need to be a compromise if interest i)(the MRL should be set low enough to discourage misuse, such that using more product than prescribed by the GAP will likely result in an MRL exceedance) is also considered. The current approach taken in the EC is to try to minimise the GAP i.e. set the GAP as low as possible considering all other aspects of the risk assessment and the efficacy of the use rate. If this approach is taken then in theory setting the MRL high enough to accommodate the minimised GAP should also meet the criteria of interest i).

One aspect that is critical to the approach of setting the MRL high enough such that use according to GAP is unlikely to result in an MRL exceedance is to quantify the term “unlikely”.

In the EC it is agreed that such an exceedance should not be more than 5%. Interestingly, the results of the EU monitoring programme show that since 1996 the violation rate fluctuates between 3 and 5%, but part of this.

Neither of the two aspects prevail in the EC; they are in a tight balance. To be able to strike the right balance the EC requires a large enough dataset.
**Question 2:** Is it acceptable for the MRL to be lower than one or more residues found in a set of supervised field trials when there are many data? Alternatively, should other non-statistical procedures be implemented to ensure that the recommended MRL is always higher than the HR?

From a statistical point of view, setting of an MRL at a level lower than the respective HR is acceptable in case of large datasets. In fact, up to 5% of the overall number of samples in one dataset may exceed the MRL because of the present methodology.

Nevertheless, it must be kept in mind that in many cases datasets which are available for the estimation of MRLs include 8 or less uncensored data points depending on the importance of the crop (in Europe a data set of 8 (major crop) or 4 (minor crop) trials per region within the EU is defined as a MINIMUM). These rather small datasets normally result in an underestimation of the high percentiles used for MRL setting (compared to the underlying parent population). Under practical conditions the usage of MRLs being lower than the highest residues found in field trials which match the critical GAP should be considered carefully on a case by case basis.

**2. Minimum dataset needed for a statistical technique for MRL setting**

**Question 3:** In order to determine the minimum dataset size appropriate for calculating MRLs, how much variability is acceptable in an MRL estimate?

The accuracy of MRL estimates should be higher for commodities that are major contributors to dietary intakes (chronic and acute). In addition, when the MRL is closer to the highest toxicologically acceptable level, less variability is acceptable.

To assure that above goal is met the target percentile should not be less than 95th percentile. However, the overall goal should be that MRL exceeding should be well below 5%.

The acceptable variability of the residue data strongly depends on the use being evaluated and is therefore difficult to generalise. For “normal” applications like foliar spray applications on cereals or fruits, a variability of 2-3 orders of magnitude is normally accepted within the residue data. In special cases like granular applications, an even higher range of results is acceptable, since normally a nil-residue situation occurs with a few exceptions of very high residues. No real “distribution” is present in these cases.

The variation in MRL estimations should still allow determining which MRL class is most appropriate to cover residues from the intended use. Normally comparable datasets should result in the same or a closely related (next highest or next lowest) MRL class. In general, high residues found in field trials should have a higher impact on the estimation of the appropriate MRL class than low residues detected near the LOQ.

**Question 4:** Are there any recommendations concerning how to set MRLs when there is concern about excessively high MRL proposals for small datasets?

The value of an MRL derived from field data will in any procedure depend on the number of available data.

A simple procedure like rounding-up the largest residual has the disadvantage that it is very sensitive for single data points (possibly outliers).
A statistical procedure where the upper bound of a given high percentile is taken has the advantage of being less sensitive to single data points, but it has a very serious drawback: the smaller the sample size, the higher the upper bound of that percentile.

This problem is “solved” in the MRL calculator by proposing the 95/99 rule. This is an *ad hoc* solution, which undermines the starting point of trying to quantify the uncertainties (limitations) in the data. Besides, it might be quite advantageous for the manufacturer. The manufacturer may just start with the lowest number of data required, hoping that the upper bound of the 95th percentile will be higher than the point estimate of the 99th percentile. In addition, there is a fifty percent probability that even the 99th percentile is overestimated. The point estimate of the 99th percentile might even be smaller than the (real) 95th percentile in a particular case.

Instead, it could be considered to establish the MRL based on the lower bound of a given percentile. To compensate for the expected lower values of that criterion, a higher percentile could be chosen. E.g., instead of taking the upper bound of the 95th percentile, take the lower bound of the 99th percentile. Or it might be considered to use a lower confidence level, if needed. This procedure will “punish” for a situation where few data are available. At least, it is a straightforward procedure, which avoids difficult discussions on “special” cases, and temptations to delete single observations that make the 95/99 procedure more profitable. In addition, the use of lower confidence bounds makes the issue of the “cut-off” sample size less critical.

**3. Introduction of an upper limit for the MRL (Regulatory ceiling)**

**Question 5: Is the use of a regulatory ceiling appropriate? If so, is the currently defined ceiling of the maximum of 2 x HR or 3 x STMR appropriate?**

In the EC a regulatory ceiling is not applied. The experience shows that MRLs are hardly ever higher than two times the HR or three times the STMR (the last point can be estimated from the EC method I when taking into account that the mean is in the same order of magnitude than the standard deviation.)

We feel it would be more appropriate if the calculator would give a warning that this ceiling of 2x HR or 3x STMR is exceeded. It would than be up to the risk managers to decide whether to use the statistical value from the MRL calculator or another value. But it is important that the MRL calculator is based on sound statistical calculations and not on arbitrary criteria.

The EC believes that the basis for an MRL proposal should be statistical analysis of the data available. A certain amount of expert judgment can be applied if the value seems unreasonable high based on the data set available, however if there is a significant amount of variability within the results of a data set then this would indicate good reason to set the MRL at a higher value (it is more likely that variable residues occur and so the MRL needs to be higher to accommodate this).
4. Transparency of expert judgement in MRL setting

**Question 6:** Is it acceptable that a fully automated procedure be used for selecting the most appropriate statistical distribution?

A fully automated procedure is acceptable if the calculator is used as a first step in decision making. This would be better for transparency because when in later steps case by case decisions are taken based upon expert judgement this needs clear justification.

However, a prerequisite for a fully automated procedure is the transparency on the modules used and a transparent evaluation of the procedure, i.e. to guarantee that the calculation method used gives correct results (Application of “Good Computer Practice”).

It will also depend on how the statistical fit is determined. The EC has some concerns over the approach of choosing the “best fit” from a selection of distributions given that the data sets used are quite small. The uncertainties around the different possibilities for the fit need to be clear (perhaps by some sort of weighting for each one –this would of course require expert judgment to interpret the data and reach a logical conclusion) so that the overall approach used is transparent.

The methodology used in the statistical calculators needs to be clearly and transparently explained so those using the calculator can clearly explain the uncertainly around the results to risk managers.

5. How to treat outliers in residue data set

**Question 7:** Considering the differing views of OECD member countries regarding the use of outlier tests, is it acceptable to reject outliers based solely on statistical tests?

Statistical tests for outliers should be used very carefully. Rejection of a value as being an outlier on the basis of a statistical test solely is not appropriate. A concerned residue study should be examined carefully and if there are doubts that the study was conducted correctly the value could be discarded.

In the EC outlier tests are used only at the upper end of the distribution denying that outliers could also occur at the lower end of the distribution.

Rejecting the outliers is only acceptable when justification (biological or experimental) is provided and not only on the basis of statistical tests. The number of results generally available from the residue trials is not large enough for robust statistics, without any justification the EC does not know really the difference between an extreme value or an outlier. One could ask up to which percentile (99%, 95%) we can consider the extreme values for the evaluation.

6. Rounding and MRL classes

**Question 8:** Is the system of MRL classes proposed in the draft calculator an appropriate compromise?

Results from one set of trials according to GAP have a quite high variability; furthermore measurement uncertainty is not yet defined. Too narrow classes give a false impression of precision.
MRLs should be rounded to one figure (0.01, 0.02, ..., 0.1, 0.2, ..., 1, 2, ..., 10, 20, ..., 100, 200, ...). Note one figure is not one decimal! Therefore the 0.015, 0.15 and 1.5 values are not appropriate. The variability of the residue data does not allow such tight limits and rounding to one figure is appropriate. If you look only at analytical variability than an RSD of 20% is allowed RSD means 1x standard deviation and generally a value of 2 stdev is considered appropriate to indicate the confidence interval around the mean. This means that the value that you measure, e.g. 1.1 could as well be 0.66 (1.1-2x20%) or 1.5 (1.1+2x 20%) or anywhere in-between. But if you also want to take in homogeneity of sampling into account than the confidence intervals become even larger. So there is no point in setting an MRL at more than one figure.

Although a statistical calculation is used to estimate an MRL from the selected residue values, the variability around these selected values is not taken into account. You do not gain precision from statistical calculations, if this variability is not taken into account. The MRL calculator should be used to get a minimum MRL value.

Too small classes may lead to problems due to analytical uncertainty. Under practical conditions a difference in residue levels of less than 25% can not be distinguished due to analytical uncertainty. Taking also into account intra-laboratory variation, a difference in residue levels of less than 50% can not be distinguished. Nevertheless, with 25% level in uncertainty the proposed classes are barely acceptable.

**Question 9: Is the Calculator Workgroup's proposal to round down MRL calculations in these cases acceptable?**

It is not clear why the conventional (international) approach to rounding could not be used in this instance i.e. for the example given calculations of 0.449 and below would be rounded down to 0.4 and calculations of 0.450 and above would be rounded up to 0.5. Going back to the first question if the aim is to set the MRL high enough such that use according to GAP is unlikely to result in an MRL exceedance the rounding up should always be employed. Either way it should be made clear what approach is being taken to ensure consistency.

**Question 10: Should lower MRL classes such as 0.001, 0.002, and 0.005 mg/kg be included as demonstrated by limit of quantitation (LOQ) of the enforcement analytical method?**

There will always be need to be a balance between setting the lowest class to reflect current analytical capabilities and allowing for quicker (and cheaper) monitoring of residues in food. The EC is aware of these issues in relation to the implication of the current EU MRL Regulation which has in place a “default” LOQ value of 0.01mg/kg for all MRLs/uses not notified. This is proving challenging for our monitoring laboratories given that historically higher levels were considered suitable LOQs for monitoring purposes. Consideration should only be given to lower MRL values where the toxicity of the compound requires it, or where there are specific risk issues requiring lower levels.

For legal certainty it is good to indicate when an MRL coincides with the generally agreed LOQ for routine laboratory analysis for a particular combination.
Question 11: Would an adjustable case-by-case lowest MRL class be acceptable or should we consider other specific guidelines for establishing low MRL classes?

MRL should be set as low as necessary from a toxicological point of view. If necessary even lower than 0.01 mg/kg, but if there is no toxicological necessity the MRLs should be as low as feasible but not below the value of 0.01 mg/kg if the consumer risk is acceptable.