



European Medicines Agency
Veterinary Medicines and Inspections

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**COMMITTEE FOR MEDICINAL PRODUCTS FOR VETERINARY USE
(CVMP)**

**REFLECTION PAPER ON THE NEW APPROACH DEVELOPED BY JECFA FOR
EXPOSURE AND MRL ASSESSMENT OF RESIDUES OF VMP**

INTRODUCTORY NOTE

Since the initial publication of the reflection paper in June 2008 the CVMP has had its understanding of how JECFA intends to use the EDI questioned. Experts familiar with JECFA methodology have indicated that they consider that the EDI will be used ONLY at the end of the process of establishing MRLs, as a final check to ensure that exposure to a veterinary drug does not exceed the ADI. The CVMP understanding is that JECFA also intends to use the EDI earlier in the process of deriving MRLs; specifically that the point at or beyond which the predicted median intake (EDI) equals the ADI will be used as the point of departure for the derivation of MRLs, as set out in section 4 of this reflection paper. The following text, extracted from p16-17 of the report of the 66th JECFA meeting, appears to support the CVMP understanding of how JECFA intends to use the EDI:

“The calculated intake of residues is compared with the ADI, and the time point of depletion below the ADI is selected to determine the MRLs”

If it is not the case that the first step in proposing MRLs consists of comparing the calculated intake (using the EDI) to the ADI at different time points on the residue depletion curve, then it is unclear how JECFA intends to derive MRLs and clarification should be provided.

REFLECTION PAPER ON THE NEW APPROACH DEVELOPED BY JECFA FOR EXPOSURE AND MRL ASSESSMENT OF RESIDUES OF VMP

Executive summary

At its 2006 meeting the Joint FAO/WHO Expert Committee on Food Additives (JECFA) agreed upon a new approach for the estimation of chronic dietary intake for use in MRL assessments for veterinary drugs¹. The new approach uses median residue levels in animal derived food for the calculation of a so-called Estimated Daily Intake (EDI) from a model daily food basket. Previously exposure was estimated using the Theoretical Maximum Daily Intake (TMDI) and a model daily food basket. The TMDI represents a 'worst case' assumption in which residue levels are at the maximum permitted level (i.e. the MRL) in each food commodity consumed.

JECFA considered the EDI to be the most reliable and accurate estimate of the actual long-term exposure to residues and therefore a more appropriate tool in determining whether residues pose any chronic (lifetime) risks.

The CVMP, having thoroughly examined the new JECFA approach, agreed that median residue values would be an appropriate model for estimating chronic dietary exposure. However, the CVMP concluded that a change of the 'chronic' model would automatically imply consideration of a complementary approach to address 'acute' scenarios based on the assumption of short-term 'high residue exposure'. As this necessary second element of the model has not yet been developed, the CVMP considered the new JECFA proposal to be unfinished. A full evaluation of the EDI approach and its use in MRL assessments is not possible until information is available on how the acute exposure assessment will be made.

The new JECFA approach of estimating the MRL involves an apparent disconnection of the link between the MRL derivation and ADI (i.e., the proposed MRL will no longer need to lead to exposure below the ADI when exposure is calculated using the TMDI). The CVMP considered that this approach can only be accepted when the ADI is based on chronic exposure data AND data has been provided to demonstrate that acute exposure scenarios do not represent a safety concern.

A further serious concern raised by the CVMP was that with the new approach the size of the MRL would be very sensitive to variability and extreme values in the data, which in turn, are to a considerable degree dependent on the design and quality of the residue study performed. It was noted that weak data (i.e. few data points or data showing high variability) would be rewarded with higher MRLs and that the spread between median and extreme values in a single residue trial could determine the size of the MRL, which could represent a concern for consumer safety.

Alternative approaches need to be investigated to overcome this issue and to reward the production of robust data. One way this might be achieved would be to use the lower confidence limit of a percentile instead of the upper confidence limit of a percentile as the point of departure in the MRL calculation (see figure 4).

The CVMP also noted that it is likely that an increased number of animals would be required in order to use the new approach compared to those given in current international guidelines. Other parameters such as the number of time points and the frequency of time points may also need to be adjusted.

Another point of concern was that the presented approach relies to a great degree on the applicability of a specific statistical model of linear regression and tolerance limit determination.

¹ Joint FAO/WHO Expert Committee on Food Additives (JECFA), 66th meeting (Residues of veterinary drugs), Rome, 22 - 28 February 2006, Evaluation of certain veterinary drug residues in food. WHO TRS 939 http://whqlibdoc.who.int/publications/2006/9241209399_eng.pdf; Summary and Conclusions ftp://ftp.fao.org/ag/agn/jecfa/jecfa66_final.pdf

Practical experience has shown that the statistical assumptions underlying this model are not met for a considerable number of data sets.

To deal with data that cannot be assessed using the proposed statistical approach, a robust alternative approach will probably need to be developed to allow application and extension of the EDI concept to a wider range of substances.

A further concern of the CVMP is that JECFA reports that before an MRL recommendation is made the candidate value is checked against Good Veterinary Practice (GVP) data, and is altered to make it consistent with this data. However, GVP is a poorly defined term and the effect of incorporating GVP data into the approach may be enormously variable. The use of GVP data is not considered to be scientifically robust and its incorporation into a method that is argued to be scientifically superior is inappropriate.

The CVMP agreed that practical experience with this approach is very limited (only very few substances have been assessed with the new approach) and that the methodological and statistical questions raised in this paper need to be addressed before any definitive conclusions can be drawn.

In addition, the CVMP strongly suggests that a strategy should be agreed upon that addresses the objectives of the approach, its scope of application, and the implementation of the new approach. This should take into account current limitations of the approach, the major impact it has on the setting of MRLs, and the fact that it is significantly different to the approach used over the last decades. This could be addressed by both JECFA (in respect to scientific) as well as CCRVDF (regarding risk management issues).

1. Background

The Joint FAO/WHO Expert Committee on Food Additives (JECFA) agreed at its 66th meeting (2006)¹ a new approach for the estimation of chronic dietary intakes for use in MRL assessments for veterinary drugs. The elaboration of this new approach followed up recommendations from the FAO/RIVM/WHO Workshop in Bilthoven (2005)². The CVMP reviewed the new approach developed by JECFA in 2007. The comments of the European Community at the 17th Session of the Codex Committee on Residues of Veterinary Drugs in Foods in September 2007 presented under point 3a, Report of the 66th JECFA meeting (see CRD 13 of 17th CCRVDF meeting), which were based on the CVMP considerations, summarized the first findings and concerns regarding this approach.

In the meantime a further in depth review has been undertaken by the CVMP and its Safety Working Party (SWP-V). In this review the SWP-V held a dedicated workshop in February 2008 to discuss the approach with Dr Dieter Arnold (Vice-Chairman of the 66th JECFA meeting on residues of veterinary drugs) and Dr Annika Wennberg (JECFA Secretariat). The workshop aimed to clarify commonalities and differences between the CVMP and JECFA approaches for assessing the safety of residues, and to evaluate possible implications that would arise from the new JECFA principle for estimating exposure if it were endorsed by the EC.

Having completed the review the CVMP supported by the SWP-V prepared this document detailing their findings. In this document the JECFA approach is described followed by the discussion and conclusions of the CVMP.

2. Exposure scenarios

2.1 Chronic exposure

At its 66th meeting the JECFA Committee¹ modified its procedure for estimating chronic exposure to residues of veterinary drugs. The new concept is to use median residue levels in animal derived food for the calculation of a so-called Estimated Daily Intake (EDI) from a model daily food basket. JECFA considered the EDI to be the most reliable and accurate estimate of the actual long-term exposure to residues and therefore a more appropriate tool in determining whether residues pose any chronic (lifetime) risks.

In the past, exposure was estimated using the Theoretical Maximum Daily Intake (TMDI) which represents the 'worst case' assumption of maximum permitted residue levels (i.e. at the MRL) in each food commodity consumed. This important change of model was initiated because the TMDI approach was thought to grossly overestimate the true chronic level of exposure of the population. JECFA considered that, if good veterinary practice is observed, there is a relatively low statistical probability that residues in edible tissues will approach the MRL.

The calculation of the EDI is based on the same equation as used previously for the calculation of the TMDI (including use of standard consumption figures and corrections for ratios of marker/total residues) with the one exception of using median residues instead of the MRLs as the point estimate of the residue concentration in animal derived food.

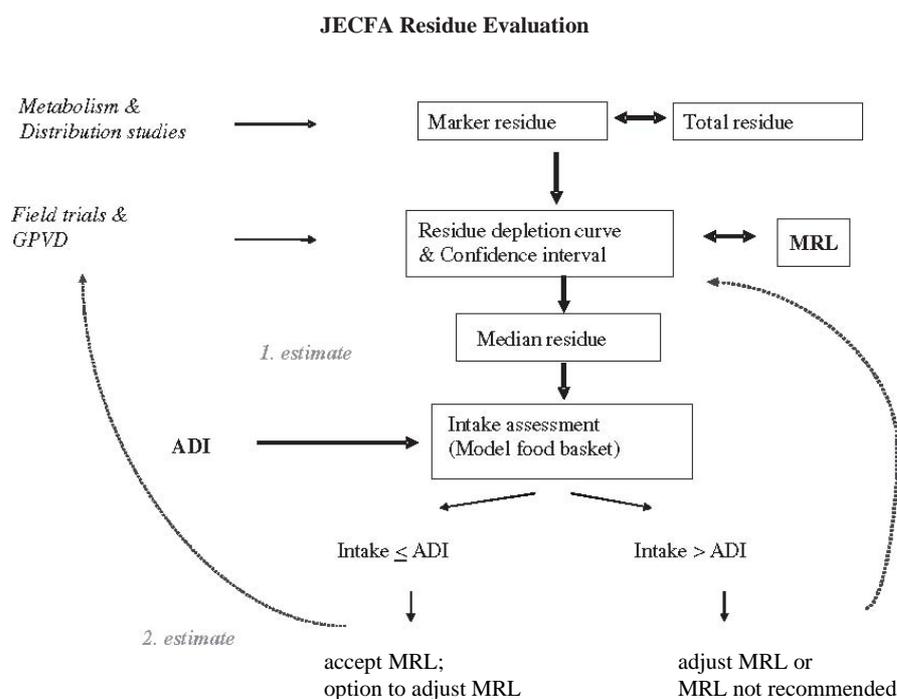
The modified chronic model proposed by JECFA is consistent with the approach already used by JMPR in the assessment of chronic exposure to pesticide residues. In this area the TMDI concept was reviewed in 1997 and it was proposed to use supervised trials median residue (STMR) levels

² FAO/RIVM/WHO Workshop: "Updating the Principles and Methods of Risk Assessment: Maximum Residue Levels (MRLs) for Pesticides and Veterinary Drugs (2005)
http://www.fao.org/ag/AGP/AGPP/Pesticid/JMPR/DOWNLOAD/bilthoven_2005.pdf

instead of the MRL to estimate a chronic intake³. Thus, the new JECFA proposal contributes to a better harmonization of Codex residue assessment procedures for chemicals in food. The CVMP is currently using TMDI estimates in relation to chronic exposure.

The new JECFA proposal is schematically shown in Figure 1, taken from the report of the 66th JECFA meeting¹.

Figure 1: The JECFA residue evaluation process



CVMP conclusion

The CVMP was in agreement with JECFA that median residue values would be an appropriate model for estimating chronic dietary exposure.

2.2 Acute (short-term) exposure

Replacement of the ‘worst case concept’ by ‘median values’ can be expected to considerably lower exposure estimates and, consequently, the estimates of risk. This inevitably raises the question of whether the EDI approach would provide a sufficient degree of protection for consumers exposed to residue levels higher than the median, on occasions when food baskets containing higher than average residues are consumed (e.g. residues at MRL levels in a single meal/over the course of day). While the likelihood of this happening on a regular basis was considered relatively low, there was consensus that the EDI does not cover the scenario of a ‘short-term/high-concentration’ exposure.

³ WHO 1997: Guidelines for predicting dietary intake of pesticide residues (revised); Prepared by the Global Environment Monitoring System - food contamination monitoring and assessment programme (GEMS/Food) in collaboration with the Codex Committee on Pesticide Residues, WHO/FSF/FOS/97.7., WHO, Geneva, Switzerland.
http://www.who.int/foodsafety/publications/chem/en/pesticide_en.pdf

In addition, acute exposure scenarios are of particular interest for pharmacologically active substances which, in many cases, present a relevant acute hazard (i.e., ADI/NOEL is based on an acute effect). In relation to acute effects a separate exposure assessment would be needed to ensure that there is no relevant acute risk at the MRLs established.

JECFA has currently no established procedures for addressing acute intake scenarios. JECFA recognized, however, that further work is necessary to adequately address concerns related to short term hazard and exposure assessment²:

“[...] JECFA should consider the use of the concept of the acute reference dose (ARfD) in addition to the ADI, when a veterinary drug being considered exhibits acute toxicity. JECFA should develop procedures to discriminate between ADI and ARfD for cases where it would be appropriate to estimate short-term (acute) intakes.”

CVMP conclusion

While the logic for using the EDI in relation to chronic exposure was clearly understood, the CVMP reconfirmed its previous conclusion that a change of the ‘chronic’ model would automatically imply consideration of a complementary approach to address ‘acute’ scenarios based on the assumption of a short-term ‘high residue exposure’. As this necessary second element of the model has not yet been developed, the CVMP considered the new JECFA proposal to be unfinished. A full evaluation of the EDI approach and its use in MRL assessments is not possible until information is available on how the acute exposure assessment will be made.

3. Previous JECFA and current CVMP approaches

The previous JECFA approach was based on the concept that the TMDI calculated using the MRLs does not exceed the ADI. This principle has also been and is still applied in the EU.

4. New JECFA approach

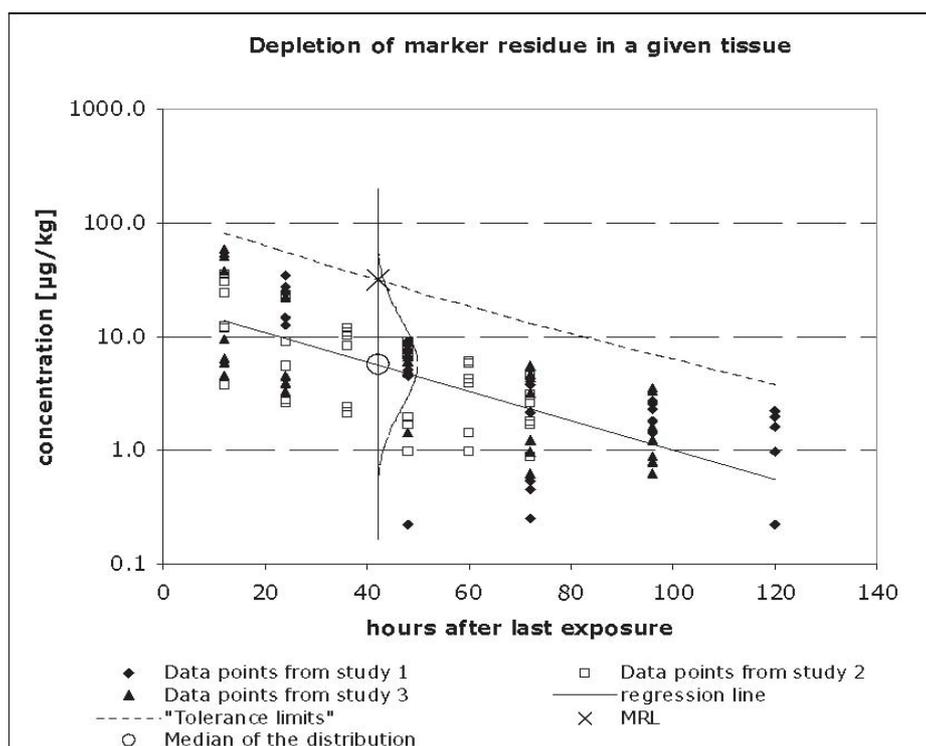
The new approach described in the 2006 JECFA report for the 66th meeting defines the link between MRL and daily residue intake (as expressed through the EDI) as follows¹:

“The MRL and the median concentration are derived from the same time point of the depletion data of the marker residue. The MRL is a point on the curve describing the upper one-sided 95% confidence limit over the 95th percentile. The median is the corresponding point on the regression line for the same time point. Both figures are obtained from a statistical evaluation of the data”

This relationship between MRL and EDI is illustrated in Figure 2 (taken from the JECFA report¹). The point at or beyond which the predicted median intake (EDI) equals the ADI is used as the point of departure (POD) for the derivation of MRLs. In this first approximation the MRL represents the upper tolerance limit for the marker residue concentration in the edible tissue at $t_{\text{EDI/ADI}}$ ⁴.

⁴ $t_{\text{EDI/ADI}}$ = time point when the EDI reached the level of the ADI

Figure 2: Statistical approach to determine MRL based on the EDI concept

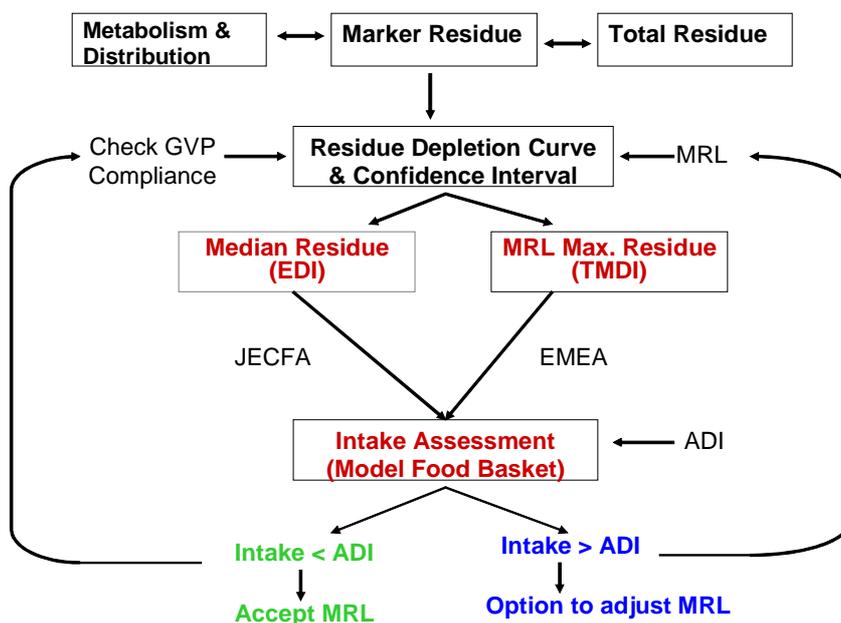


Explanation of the relationship between MRL and the median concentration used for the calculation of the estimated daily intake (EDI)

JECFA also considers the likely level of residue that can be expected in edible tissues after use of the veterinary product under field conditions (i.e. in accordance with the principles of Good Veterinary Practice) and the MRL may be further reduced if suitable analytical methods are available that allow for routine monitoring at lower levels. After taking account of such factors, the resultant MRLs would usually be lower than the maximum value (first approximation) that can be estimated solely on the basis of an acceptable dietary exposure.

Figure 3 provides a comparison of the new JECFA method and the CVMP method.

Figure 3: Comparison of new JECFA and CVMP method (Figure taken from JECFA report¹ and modified)



CVMP conclusions

Apart from open questions related to the selection of appropriate exposure scenarios (chronic versus acute), the new approach of estimating the MRL involves an apparent disconnection of the link between the MRL derivation and ADI (i.e. the proposed MRL will no longer need to lead to exposure below the ADI when exposure is calculated using the TMDI). This approach can only be accepted when the ADI is based on chronic exposure data AND data has been provided to demonstrate that acute exposure scenarios do not represent a safety concern.

A main concern was that with the new approach the size of the MRL would be very sensitive to variability and extreme values in the data, which in turn, are to a considerable degree dependent on the design and quality of the residue study performed. It was noted that weak data (i.e. few data points or data showing high variability) would be rewarded with higher MRLs and that the spread between median and extreme values in a single residue trial could determine the size of the MRL, which could represent a concern for consumer safety.

Alternative approaches need to be investigated to overcome this issue and to reward the production of robust data. One way this might be achieved would be to use the lower confidence limit of a percentile instead of the upper confidence limit of a percentile as the point of departure in the MRL calculation (see figure 4).

It was also noted that it is likely that an increased number of animals would be required in order to use the new approach compared to those given in current international guidelines. Other parameters such as the number of time points and the frequency of time points may also need to be adjusted.

Another point of concern was that the presented approach relies to a great degree on the applicability of a specific statistical model of linear regression and tolerance limit determination. Practical experience has shown that the statistical assumptions underlying this model are not met for a considerable number of data sets.

To deal with data that cannot be assessed using the proposed statistical approach, a robust alternative approach will probably need to be developed to allow application and extension of the EDI concept to a wider range of substances.

JECFA reports that before an MRL recommendation is made the candidate value is checked against Good Veterinary Practice (GVP) data, and is altered to make it consistent with this data. However, GVP is a poorly defined term and the effect of incorporating GVP data into the approach may be enormously variable. The use of GVP data is not considered to be scientifically robust and its incorporation into a method that is argued to be scientifically superior is inappropriate.

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Figure 4: Ways to overcome the problem of variation should be explored. One way could be to use a lower confidence limit of the selected percentile instead of the upper confidence limit. In this way, the resulting MRL will become lower in case of weak data and become higher with strong data. If there is a concern that the MRLs will become too low, then a higher percentile could be selected (e.g. P99 instead of P95).

