Evaluating MRLs for Veterinary Drugs and Pesticide Residues

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The Codex Alimentarius is a collection of internationally adopted food standards and related texts presented in a uniform manner.

- They are aimed at protecting consumers’ health and ensuring fair practices in the food trade.

The publication of the Codex Alimentarius is intended:

- to guide and promote the elaboration and establishment of definitions and requirements for foods to assist in their harmonization and
- to facilitate international trade.
Scope of the Codex Alimentarius

They include

• standards for all the principal foods, whether processed, semi-processed or raw, for distribution to the consumer.
• materials for further processing into foods should be included to the extent necessary to achieve the purposes of the Codex Alimentarius as defined.
• provisions in respect of food hygiene, food additives, residues of pesticides and veterinary drugs, contaminants, labelling and presentation, methods of analysis and sampling, and import and export inspection and certification.
Nature of Codex Standards

• the standards and related texts are not a substitute for, or alternative to national legislation.
• Every country’s laws and administrative procedures contain provisions with which it is essential to comply.
• they contain requirements for food aimed at ensuring for the consumer a safe, wholesome food product free from adulteration, correctly labelled and presented.
• the standard for any food or foods should be drawn up in accordance with the Format for Codex Commodity Standards and contain as appropriate.
CAC Definitions

- **Food** means any substance, whether processed, semi-processed or raw, which is intended for human consumption, and includes drink, chewing gum and any substance which has been used in the manufacture, preparation or treatment of “food” but does not include cosmetics or tobacco or substances used only as drugs.

- **Food Hygiene** comprises conditions and measures necessary for the production processing, storage and distribution of food designed to ensure a safe, sound, wholesome product fit for human consumption.
Pesticides

- **Pesticide** means any substance including unwanted species of plants or animals during the production, storage, transport, distribution and processing of food, agricultural commodities, or animal feeds or which may be administered to animals for the control of ectoparasites intended for
  - preventing,
  - destroying,
  - attracting,
  - repelling, or
  - controlling any pest

- Includes substances intended for use
  - as a plant growth regulator,
  - defoliant, desiccant,
  - fruit thinning agent,
  - or sprouting inhibitor and substances applied to crops either before or after harvest to protect the commodity from deterioration during storage and transport.

- It normally excludes fertilizers, plant and animal nutrients, food additives, and animal drugs.
Pesticide Residues

• Pesticide Residue
  – any specified substance in food, agricultural commodities, or animal feed resulting from the use of a pesticide.

It includes any derivatives of a pesticide, such as conversion products, metabolites, reaction products, and impurities considered to be of toxicological significance.
Good Agricultural Practice in the Use of Pesticides (GAP)

- **Good Agricultural Practice in the Use of Pesticides (GAP)**
  - includes the nationally authorized safe uses of pesticides under actual conditions necessary for effective and reliable pest control.

  - encompasses a range of levels of pesticide applications up to the highest authorised use, applied in a manner which leaves a residue which is the smallest amount practicable.

- **Authorized safe uses are determined**
  - at the national level and include nationally registered or recommended uses, which take into account public and occupational health and environmental safety considerations.

  - actual conditions include any stage in the production, storage, transport, distribution and processing of food commodities and animal feed.
Codex Maximum Limit for Pesticide Residues (MRL)

- It is the maximum concentration of a pesticide residue (expressed as mg/kg), recommended by the Codex Alimentarius Commission to be legally permitted in or on food commodities and animal feeds.

- MRLs are based on GAP data and foods derived from commodities that comply with the respective MRLs are intended to be toxicologically acceptable.

- They are primarily intended to apply in international trade and are derived from estimations made by the JMPR following:
  
  (a) toxicological assessment of the pesticide and its residue; and

  (b) review of residue data from supervised trials and supervised uses including those reflecting national good agricultural practices.
Data Sources for Evaluating MRLs for Pesticide Residues

• Data from
  – supervised trials conducted at the highest nationally recommended, authorized or registered uses are included in the review.
  – to accommodate variations in national pest control requirements, Codex MRLs take into account the higher levels shown to arise in such supervised trials, which are considered to represent effective pest control practices.
Veterinary Drugs & Residues

• Veterinary Drug
  – any substance applied or administered to any food producing animal, such as meat or milk producing animals, poultry, fish or bees, whether used for therapeutic, prophylactic or diagnostic purposes or for modification of physiological functions or behaviour.

• Residues of Veterinary Drugs
  – include the parent compounds and/or their metabolites in any edible portion of the animal product, and include residues of associated impurities of the veterinary drug concerned.
Antimicrobials

• Antimicrobials are classified functionally according to the manner in which they adversely kill microorganisms or suppress their multiplication or growth and include antibacterial drugs, antiviral agents, antifungal agents, and antiparasitic drugs.
Antimicrobials

– Some interfere with the synthesis of the bacterial cell wall.

– Some interfere with the synthesis of nucleic acids.

– Some change the permeability of the cell membrane, causing a leakage of metabolic substrates essential to the life of the microorganism.

– Some interfere with metabolic processes within the microorganism.

– Some interfere with the translation of proteins by the ribosome.
Antibiotics

Are drugs such as penicillin or erythromycin, produced by or derived from certain microorganisms, including fungi and bacteria, that can destroy or inhibit the growth of other microorganisms, especially bacteria.
Good Practice in the Use of Veterinary Drugs (GVP)

• It is the official recommended or authorized usage including withdrawal periods, approved by national authorities, of veterinary drugs under practical conditions.
Codex MRLs for Veterinary Drugs

• **MRL**
  – is the maximum concentration of residue resulting from the use of a veterinary drug (expressed in mg/kg or μg/kg on a fresh weight basis) that is recommended by the Codex Alimentarius Commission to be legally permitted or recognized as acceptable in or on a food.

  – It is based on the type and amount of residue considered to be without any toxicological hazard for human health as expressed by the Acceptable Daily Intake (ADI), or

  – on the basis of a temporary ADI that utilizes an additional safety factor. It also takes into account other relevant public health risks as well as food technological aspects.
Codex Criterion for Safe Food

Consideration of the various dietary residue intake estimates and determinations both at the national and international level in comparison with the ADI, should indicate that foods complying with Codex MRLs are safe for human consumption.
RISK ANALYSIS AT THE
CODEX ALIMENTARIUS COMMISSION
Risk Analysis

CODEX ALIMENTARIUS COMMISSION

CCRVDF

RISK MANAGERS
1. Identification of food safety problem (hazard)
2. Establishment of risk profile
3. Ranking of the hazard for RA & RM priority
4. Establishment of RA policy for RA
5. Commissioning the RA
6. Consideration of the result of the RA
7. Communicating the RM recommendations

CCPR

JECFA

RISK ASSESSORS

JMPR

19
Role of JECFA & JMPR meetings

• establish and further elaborate principles for evaluating the safety of veterinary drugs and pesticide residues in foods;
• determine acceptable safe levels of such residues when the drugs are administered to food producing animals in accordance with GAP and GVP;
• Determine criteria for appropriate methods of analysis for quantifying residues in foods;
• evaluate or re-evaluate the safety of residues of certain veterinary drugs and pesticides;
• discuss and provide advice on matters of interest arising from reports of the CCRVDF and CCPR.
RISK ANALYSIS

Risk Assessment (RA)

Risk Management (RM)

Risk Communication (RC)
Risk Analysis

• **Risk Analysis** - A process consisting of three components:
  – risk assessment,
  – risk management, and
  – risk communication.

• **Risk** - A function of
  – the probability of an adverse health effect and the severity of that effect, consequential to a hazard(s) in food.

• **Hazard** - A biological, chemical or physical agent in, or condition of, food with the potential to cause an adverse health effect.
Risk Analysis

• The three components of risk analysis should be applied within an overarching framework for management of food related risks to human health.

• There should be a functional separation of risk assessment and risk management to,
  – ensure the scientific integrity of the risk assessment,
  – avoid confusion over the functions to be performed by risk assessors and risk managers, and
  – reduce any conflict of interest.
Precaution is an inherent element of risk analysis.

- Many sources of uncertainty exist in the process of risk assessment and risk management of food related hazards to human health.

- Where there is sufficient scientific evidence to allow Codex to proceed to elaborate a standard or related text, the assumptions used for the risk assessment and the risk management options selected should reflect the degree of uncertainty and the characteristics of the hazard.

- The needs and situations of developing countries should be specifically identified and taken into account by the responsible bodies in the different stages of the risk analysis.
RISK ASSESSMENT (RA)
Risk Assessment and Risk Assessment Policy

Risk Assessment
A scientifically based process consisting of the following steps:
– (i) hazard identification,
– (ii) hazard characterization,
– (iii) exposure assessment, and
– (iv) risk characterization.

Risk Assessment Policy
Documented guidelines on
– the choice of options and associated judgements for their application at appropriate decision points in the risk assessment such that the scientific integrity of the process is maintained.
Risk Profile and Characterization

Risk Profile
– The description of the food safety problem and its context.

Risk Characterization
The qualitative and/or quantitative estimation, including attendant uncertainties, of the probability of occurrence and severity of known or potential adverse health effects in a given population based on
– hazard identification,
– hazard characterization, and
– exposure assessment.
Risk Assessment

The scope and purpose of the particular risk assessment being carried out should be clearly stated and in accordance with risk assessment policy.

- The output from and possible alternative outputs of the risk assessment should be defined.

- Experts responsible for risk assessment should be selected in a transparent manner on the basis of their expertise, experience, and their independence with regard to the interests involved.
Risk Assessment

Should be conducted

– in accordance with the Statements of Principle Relating to the Role of Food Safety Risk Assessment;
– incorporate the four steps of the risk assessment, i.e.
  • hazard identification,
  • hazard characterization,
  • exposure assessment, and
  • risk characterization.
– be based on all available scientific data.
– use available quantitative information to the greatest extent possible
– may also take into account qualitative information.
Risk Assessment

– take into account relevant production, storage and handling practices used throughout the food chain including traditional practices, methods of analysis, sampling and inspection and the prevalence of specific adverse health effects.

– seek and incorporate relevant data from different parts of the world, including that from developing countries that should particularly include epidemiological surveillance data, analytical and exposure data

– be based on realistic exposure scenarios, with consideration of different situations being defined by risk assessment policy.
Risk Assessment

• Should include consideration of
  – susceptible and high-risk population groups.
  – acute, chronic (including long-term), cumulative and/or
  – combined adverse health effects should be taken into account in carrying out risk assessment, where relevant.

• The conclusion of the risk assessment including a risk estimate, if available, should be presented in a readily understandable and useful form to risk managers and made available to other risk assessors and interested parties so that they can review the assessment.
Risk Assessment

Constraints, uncertainties and assumptions having an impact on the risk assessment should be explicitly considered at each step in the risk assessment and documented in a transparent manner.
RISK MANAGEMENT (RM)
Risk Management

The process, distinct from risk assessment, of weighing policy alternatives, in consultation with all interested parties, considering risk assessment and other factors relevant for the health protection of consumers and for the promotion of fair trade practices, and, if needed, selecting appropriate prevention and control options.
Risk Management

The dual purposes of the CAC are:

• to protect the health of consumers, and
• ensure fair practices in the food trade

Codex decisions and recommendations on risk management have as their primary objective the protection of the health of consumers.
Risk Management

• RM
  – should follow a structured approach including preliminary risk management activities,
  – evaluation of risk management options,
  – monitoring and review of the decision taken.

• In achieving agreed outcomes, RM
  – should take into account relevant production, storage and handling practices used throughout the food chain including traditional practices, methods of analysis, sampling and inspection, feasibility of enforcement and compliance, and the prevalence of specific adverse health effects.
Risk Management

• should be transparent, consistent and fully documented.

• The outcome of the preliminary RM activities and the RA should be combined with the evaluation of available RM options in order to reach a decision on management of the risk.

• RM options should be assessed in terms of the scope and purpose of risk analysis and the level of consumer health protection they achieve.

• The option of not taking any action should also be considered.

• To avoid unjustified trade barriers, risk management should ensure transparency and consistency in the decision-making process in all cases.
RISK COMMUNICATION (RC)
Risk Communication

The interactive exchange of information and opinions throughout the risk analysis process concerning risk, risk-related factors and risk perceptions, among risk assessors, risk managers, consumers, industry, the academic community and other interested parties, including the explanation of risk assessment findings and the basis of risk management decisions.
Risk Communication

Risk communication should:

– (i) promote awareness and understanding of the specific issues under consideration during the risk analysis;

– (ii) promote consistency and transparency in formulating risk management options/recommendations;

– (iii) provide a sound basis for understanding the risk management decisions proposed;

– (iv) improve the overall effectiveness and efficiency of the risk analysis;
Risk Communication

Risk communication should:

– (v) strengthen the working relationships among participants;
– (vi) foster public understanding of the process, so as to enhance trust and confidence in the safety of the food supply;
– (vii) promote the appropriate involvement of all interested parties; and
– (viii) exchange information in relation to the concerns of interested parties about the risks associated with food.
METHODS OF ANALYSIS
Types of Methods of Analysis

• **Type I Methods** - A method which determines a value that can only be arrived at in terms of the method per se and serves by definition as the only method for establishing the accepted value of the item measured.
  – *Examples*: Howard Mould Count, Reichert-Meissl value, loss on drying, salt in brine by density.

• **Reference Methods (Type II)** - A Type II method is the one designated Reference Method where Type I methods do not apply. It should be selected from Type III methods (as defined below). It should be recommended for use in cases of dispute and for calibration purposes.
  – *Example*: Potentiometric method for halides.
Types of Methods of Analysis

• Alternative Approved Methods (Type III) - A Type III Method is one which meets the criteria required by the Committee on Methods of Analysis and Sampling for methods that may be used for control, inspection or regulatory purposes.
  – Example: Volhard Method or Mohr Method for chlorides

• Tentative Method (Type IV) – This is a method which has been used traditionally or else has been recently introduced but for which the criteria required for acceptance by the Committee on Methods of Analysis and Sampling have not yet been determined.
  – Examples: chlorine by X-ray fluorescence, estimation of synthetic colours in foods.
General Criteria for the Selection of Methods of Analysis

• Official methods of analysis elaborated by international organizations occupying themselves with a food or group of foods should be preferred.

• Preference should be given to methods of analysis the reliability of which have been established in respect of the following criteria, selected as appropriate:

• (i) selectivity
• (ii) accuracy
General Criteria for the Selection of Methods of Analysis

- (iii) precision; repeatability intra-laboratory (within laboratory), reproducibility inter-laboratory (within laboratory and between laboratories)
- (iv) limit of detection, limit of quantification
- (v) sensitivity
- (vi) practicability and applicability under normal laboratory conditions
- (vii) other criteria which may be selected as required.
General Criteria for the Selection of Methods of Analysis

• The method selected should be chosen on the basis of practicability and preference should be given to methods which have applicability for routine use.

• All proposed methods of analysis must have direct pertinence to the Codex Standard to which they are directed.

• Methods of analysis which are applicable uniformly to various groups of commodities should be given preference over methods which apply only to individual commodities.
Single-Laboratory Validated (SLV) Methods of Analysis

• Inter-laboratory validated methods are not always available or applicable, especially in the case of multi-analyte/multi substrate methods and new analytes.

• The criteria to be used to select a method are included in the General Criteria for the Selection of Methods of Analysis.

• In addition the single-laboratory validated methods must fulfil the following criteria:
  – (i) the method is validated according to an internationally recognized protocol (e.g. those referenced in the harmonized IUPAC Guidelines for Single-Laboratory Validation of Methods of Analysis)
  – (ii) the use of the method is embedded in a quality system in compliance with the ISO/IEC 17025: 1999 Standard or Principles of Good Laboratory Practice;
Single-Laboratory Validated (SLV) Methods of Analysis

– the method should be complemented with information on accuracy demonstrated for instance with regular participation in proficiency schemes, where available;

– calibration using certified reference materials, where applicable;

– recovery studies performed at the expected concentration of the analytes;

– verification of result with other validated method where available.
TOXICOLOGY EVALUATIONS
RESIDUE EVALUATIONS
DIETARY EXPOSURE ASSESSMENTS
Residue evaluation data requirements

- Residue depletion studies
  - Bound residues
  - Injection site residues
Compound Identity

• Under this heading, nomenclature for the substance which is the subject of the risk assessment is presented.

• The nomenclature used for the substance must be clearly presented, so that there can be no misunderstanding as to the identity of the substance which has been evaluated by JECFA.

• Include the following information, using these sub-headings and in this order, to identify the compound:
  • International Non-proprietary Name (INN)
  • Synonyms (common and trade names)
  • IUPAC name(s)
  • Chemical Abstract Service Number
  • Structural formula of main component(s)
  • Molecular formula
  • Molecular weight
provide additional information on the physical and chemical properties of the substance. It typically includes the following sub-headings, as appropriate:

- Pure active ingredient
- Appearance
- Impurities
- Melting point
- Solubility
- Log $K_{ow}$ or Partition Coefficient
- pH
- Optical rotation
- $UV_{\text{max}}$
- Stability (particularly important to indicate if exposure to light, acidic or basic conditions can cause degradation, as this may be critical in residue analysis for the substance)
Conditions of use

- The MRLs recommended by JECFA are based on the conditions of use (GVP) approved by member states of the Codex Alimentarius and therefore it is critical that these not only be well established, but also that the studies evaluated are carried out under conditions reflecting the GVP, including the species and classes of animals used in the studies.

- Provide information on the approved conditions of use in member states of the Codex Alimentarius Commission.
  
  - General information on the nature of the substance should be included, such as the activity of the substance (i.e., state whether the substance is used as an anti-bacterial, a coccidiostat, etc.) and the species against which the substance is active or the condition for which it is used as a therapeutic treatment.

- For agents approved for other uses, such as use as a production aid, state the nature of such approved use. The information in this section should include the species and class of food-producing animals for which the substance is approved and may also include withdrawal periods imposed by national authorities.

- Any restrictions on the use should be noted.
Dosage

• Provide information on the approved formulation(s), approved route(s) of administration and dosage(s) and the food-producing animals to which they apply. This information, along with the conditions of use given under the previous sub-heading, constitutes the Good Veterinary Practiced for the substance and MRL recommendations are made based only on usage consistent with the GVP information provided to the Committee for review.

• When a substance has approved uses in multiple species and information on GVP is available for a number of countries, a summary table may be included to present this information.
Pharmacokinetics and Metabolism

• This provides information on the pharmacokinetic behaviour of the substance in both laboratory and food producing animals, such as the rates of absorption and elimination, half-life in plasma and tissue, elimination pathways and metabolism.

• The pharmacokinetic data provide the first indication of the potential for persistent residues and the tissues in which they may occur.

• These may be important factors in Committee decisions on MRLs for minor species when limited depletion data are available for those species.
Pharmacokinetics and Metabolism

• When it is demonstrated that metabolism is similar across all species for which data are available, this can be a key factor in decisions on MRLs for minor species.

• Metabolic data also typically are used to identify the marker residue and target tissues.

• Any additional information which may have had an impact on the study results.

• For pharmacokinetic studies, the results, including any pharmacokinetic data calculated or percentage of bound residues in tissues should be provided.
Pharmacokinetics in Laboratory Animals (Toxicology)

• This information is also typically reviewed by the Toxicology group, so discussion should focus on key information of relevance to the behaviour of residues and the recommendation of MRLs.

• Typically, information is provided on one or more species, most commonly rats and/or mice, with other species used in these studies most commonly being dogs.

• When a substance has hormonal activity, studies using monkeys may also be provided.

• The usual order of presentation is rat, then mice, dog, monkey and any other laboratory species.
Pharmacokinetics in Food Producing Animals (Residues)

• The focus of the residue evaluation and discussion should be on the absorption and elimination of the drug in food producing animal species and the associated pharmacokinetic parameters.

• Issues related to residues at injection or application sites should be noted if observed, and similarities or differences in absorption or elimination between species should be discussed.
Metabolism in Food Producing Animals

• Studies should be provided which define the metabolites found in any major food producing animal species for which MRLs are to be established
  – cattle (bovine),
  – pig (porcine),
  – sheep (ovine) and
  – Chicken

• This information may be derived from \textit{in vivo} studies conducted with representative animals of the target species or with suitable \textit{in vitro} systems, such as liver microsomes.

• For major species, dossiers should typically include studies conducted with radiolabelled drug to ensure that all administered product is accounted for and to aid in the separation and identification of the metabolites
Comparative Metabolism

• When metabolic data are provided for a number of food producing animals and laboratory animals, the experts may find it useful to include all of this data in the metabolism section titled: “Comparative Metabolism”.

• This should include a paragraph summarizing the findings from the studies reported in various species, plus paragraphs summarizing any in vitro or other comparative metabolism studies.

• The availability of comparative metabolism information may be of particular importance when determining if MRLs can be harmonized across multiple species or in considering the extension or extrapolation of MRLs from major species to minor species.
Identification of Marker Residue and Target Tissues

• From the metabolic information provided, a marker residue should be identified and this identification should be clearly stated.

• The MRL is usually expressed in terms of the marker residue, which is the target compound for analysis of residue of the substance. The marker residue is defined as follows:

• A residue whose concentration decreases in a known relationship to the level of total residues in tissues, eggs, milk or other animal tissues. A specific quantitative analytical method for measuring the concentration of the residue with the required sensitivity must be available.
Identification of Marker Residue and Target Tissues

• A marker residue may be:
  • the parent compound;
  • a major metabolite;
  • the sum of the parent compound and/or a metabolite or metabolites; or
  • a derivative formed during analysis by chemical reaction of the parent drug and/or metabolites.
Guidance on experimental design and representative species

• See VICH GL46 (MRK), *Metabolism and Residue Kinetics - Studies to evaluate the metabolism and residue kinetics of veterinary drugs in food-producing animals: metabolism study to determine the quantity and identify the nature of residues*. 
  – provides similar guidance on the criteria which should be applied in the evaluation of metabolic studies with laboratory animals.
  – discusses suitable test formulations, criteria for *in vitro* and *in vivo* experiments, sampling and analytical requirements, particularly for comparative metabolism studies.
Tissue Residue Depletion Studies

- These studies provide the necessary data/information on residue depletion in food-producing animals upon which MRL recommendations will be based.

- The first study (used to be called: Hot studies) generates depletion data using formulations containing radiolabelled substance, and

- The second study (used to be called: Cold Studies) generate depletion data with the unlabelled drug, usually the commercial formulation.

- For guidance on acceptable study design, consult VICH GL 48 (MRK), Metabolism and Residue Kinetics – Studies to evaluate the metabolism and residue kinetics of veterinary drugs in food-producing animals: Marker residue depletion studies to establish product withdrawal periods.
Tissue Residue Depletion Studies

- Each study should include the following information:
- The objective of the study, the GLP status of the study and the study reference.
- The breed and number of animals used in the study, their sex, age and weight.
- The duration of the study, the sampling times and the number of animals sacrificed at each sampling time.
- The nature of the formulation used in the study, the route of administration and the frequency of administration (preferably consistent with GVP for the commercial product).
- Any additional information which may have had an impact on the study results, including stability of analyte during storage.
Tissue Residue Depletion Studies

• The results must include which residues were identified in specific tissues, urine and faeces.

• The LOD and/or LOQ of the method(s) used in the study and method recoveries, where appropriate.

• The analytical recovery, where appropriate.

• The recovery of methods using radiolabel detection is usually assumed to be 100%, so recovery information should focus on methods for parent compound and/or metabolites using other methods of detection.
  – Recovery information may not be provided when analytical methods use an internal standard and results are assumed to be recovery corrected by the internal standard.

• An assessment of the extent of method validation information provided for review.
Radiolabelled Residue Depletion Studies

• The radiolabel depletion study data provide key information on the total residues found in various tissues and excreta and should also provide data on concentrations of the marker residue.

• Critical information on the proportion of residues which are present as parent, metabolites or bound residues is obtained from these studies and is used in the risk assessment formulating MRL recommendations and determining potential dietary exposure.

• The studies using radiolabelled drug in food-producing animals are evaluated, with a primary focus on residues in the four tissues for which MRLs are typically established,
  
  – fat, kidney, liver and muscle, plus milk when the product is used in dairy animals or eggs if the product is used in egg-laying poultry.
Radiolabelled Residue Depletion Studies

• For many compounds under evaluation, the marker residue (MR) may only represent a portion of the total residue of toxic concern (TR).

• A primary purpose of the review of the data should be to determine if marker-to-total residue (MR:TR) ratios can be established for the edible tissues and milk or eggs, when these are required for the dietary intake calculation.

• The data also provide information on the relative distribution of the drug residues in the various edible tissues and Maximum Residue Limit (MRL) recommendations should reflect the relative distribution of the residues in the edible tissues (muscle, M; liver, L; kidney, K; fat, F).
Dietary Intake Calculations

• Determination of the MR:TR ratio for use in the dietary intake calculation is a key element of the review for many substances reviewed by JECFA.

• It is critical that the MR:TR ratio is determined at the time point which coincides with the concentrations used as a basis for the MRLs and the dietary intake calculations.

• The MR:TR ratios typically vary over time, usually becoming larger as the marker residue depletes and bound residues remain unchanged in the tissues.

• Ideally, these data are provided from a radiolabel depletion study where both total residues and marker residue are determined at each sampling time in each tissue.

• In the review of derquantel, the 78th JECFA stated in the residue monograph that “the Committee concluded that determining the MR:TR ratio from a radiolabel study was the customary and preferred practice.”
Marker-to-Total Residue Conversion Factors

- The “Radiolabelled Residue Depletion Studies” section should include a clear statement of the factors for conversion of marker to total residues (MR:TR) for each species when these can be determined.
- These should be determined at the withdrawal time corresponding to the MRL for use in the dietary intake calculation.
- When the data are insufficient to make such a determination, a statement should be made that they could not be determined or the process used to derive the factors from the available data should be clearly explained (e.g., MR:TR ratios from another major species were used as surrogates, with the scientific justification for this decision).
- When the conversion factors are not deemed relevant to the dietary exposure calculation, this should also be stated.
Residues at the Injection Site

• Depending on routes of administration used in the pharmacokinetic and metabolism studies, there may be information suggesting that persistent residues at the injection site require consideration.

• The definitive information on this issue will typically come from the depletion studies with labelled drug carried out with a route of administration and dose typical of those used in treatment of animals with the commercial product.
Residue Depletion Studies with Unlabelled Drug

- This section should include only data from studies in food-producing animals starting with the major species designated by JECFA (cattle, pig, sheep and chicken) and then progressing to minor (additional) species.

- These studies provide data on residues of the marker residue in the edible tissues, eggs and milk (or honey) and are therefore critical for the recommendation of MRLs.

- Since MRLs are established based on an assumption of 100% recovery of the marker residue, it is critical to state whether the residue concentrations reported in the studies under review have been corrected for recovery and whether this has been taken into account in the MRL recommendation.

- Before conducting the depletion studies, the company or individuals conducting the study should have demonstrated that the analytical method used in the study was suitably validated [see VICH GL 49 (MRK), Method used in residue depletion studies: Guidelines for the validation of analytical methods used in residue depletion studies for guidance on appropriate validation criteria] and that the stability of residues in the tissues (or eggs, milk or honey) during storage pending analysis has been demonstrated.
Relationship of data from unlabelled drug studies to MRL recommendations

• The data from the studies with unlabelled drug are usually the basis for MRL recommendations.

• In assessing the available data, the experts should determine if these data are sufficient to support MRL recommendations and whether the dietary intake calculation used will be the Estimated Daily Intake, EDI, or the Theoretical Maximum Daily Intake, TMDI.

• In the EDI approach, the median concentration and the MRL are determined for the same time point from the depletion curve using the JECFA Statistical Tool or an equivalent method of calculation.

• Since the EDI calculation is based on median concentrations, there should be quantifiable residues present in the majority of tissues or other matrices (eggs, milk, honey) from which median residues for the EDI calculation may be determined and from which an MRL can be assigned.
Relationship of data from unlabelled drug studies to MRL recommendations

• When data are insufficient to calculate median concentrations, the Committee uses the TMDI calculation to assess potential dietary intake of residues.

• MRL recommendations by JECFA for tissues (or eggs, milk or honey) containing no quantifiable residues (or no detectable residues) are typically based on 2 x LOQ of a suitable analytical method.

• This approach was first used by the 43rd JECFA in recommending MRLs for spiramycin and has been used at subsequent meetings of the Committee.
Bound Residues and Bioavailability

- The bioavailability of the residues in food to consumers may be a factor in the intake calculation.

- A section on bioavailability of bound residues is only included in the monograph when data are provided and it usually appears after the section dealing with depletion studies with unlabelled drug. A dossier may include studies where laboratory animals received a diet of edible tissues from a food producing animal containing residues of radiolabelled drug.

- The use of the term “bioavailability” used with respect to the bioavailability of incurred residues in tissues (residues resulting from administration of the drug to the animal) should not been confused with the use of the term with respect to the portion of a dose of the formulated product that is “bioavailable” to the treated animals.

- The term has been used in both contexts in monographs, so it must be clearly stated in the monograph which type of study is being described.

- A bioavailability correction factor is not applied in the dietary intake calculations based on the bioavailability of the formulated product to treated animals. It has only been applied in a limited number of cases where there were data for the bioavailability of incurred residues in edible tissues and where this bioavailability was not included in the establishment of the ADI.
Methods of Analysis for Residues in Tissues

• The analytical methods used for the studies are reviewed for acceptability using the analytical method validation criteria established by the CCRVDF in CAC/GL 71-2009.

• The objective of the review is to identify a method or methods suitable for use in national regulatory testing programmes to support the MRLs recommended for residues of the substance in animal derived foods.

• In addition to the typical method validation criteria (method range, recovery, selectivity, measurement uncertainty, etc.), criteria for method suitability include the availability of necessary reagents and equipment and the accessibility of the method for a routine regulatory laboratory.

• Methods using reagents that are not commercially available, unless these can be prepared in a routine laboratory, or methods using prototype (or obsolete) instruments are not considered suitable.

• The method should use equipment that is expected to be found in a laboratory that does routine testing for veterinary drug residues in foods.
JECAF RESIDUE EVALUATION PROCESS

- Metabolism & Distribution Studies
- Field Trials & GVP
- ADI; ARfD

Marker Residue

Depletion Curves & Confidence Intervals

Total Residue

MRL

Median Residue

Intake Assessment (Model Food Basket)

Intake ≤ ADI
- Accept MRL

Intake > ADI
- Adjust MRL or MRL not Recommended

Exposure Assessments GECDE or GEADE
JMPR RESIDUE EVALUATION

Metabolism & Distribution Studies

Field Trials & GAP

ADI; ARfD

Intake Assessment (Regional/National Diets)

Intake ≤ ADI; ARfD

Recommend MRL

Intake > ADI; ARfD

Do Not Recommend MRL; state if ADI or ARfD is exceeded

STMR; HR

Marker (enforcement) Residue

MRL

Residues for Risk Assessment

Exposure Assessments GECDE or GEADE
• The “Appraisal” is where the key facts which have been established from the evaluation of the dossier, with the assessments on the quality and completeness of the studies summarized.

• Also in the Appraisal is found all the considerations cited in formulating the MRL recommendations and supporting information used in the assessment.
Basis for MRL recommendations

• The Appraisal section must clearly state the following:
  • The species and matrices for which data were provided and for which MRLs have been requested by the CCRVDF;
  • The adequacy of the pharmacokinetic data provided;
  • The adequacy of metabolic information provided and whether a marker residue was identified;
  • The adequacy of radiolabelled depletion studies and whether data were sufficient to calculate ratios of marker to total residues if these are required for the dietary intake calculations;
Basis for MRL recommendations

- The adequacy of depletion data to enable the Committee to formulate MRL recommendations; and
- The availability of suitably validated analytical methods to support the MRL recommendations;
- Any other issues, such as bound residues, bioavailability of residues or persistent residues at injection sites, which may be relevant to the MRL recommendations and/or dietary intake calculations.
- The dietary intake model to be used in the assessment and the reasons for use of this model.
Maximum Residue Limits

- The MRL recommendations are developed from an evaluation of the depletion data associated with use according to Good Veterinary Practice for the substance and should result in a dietary intake calculation that is consistent with the ADI.

- The basic consideration is that whichever dietary exposure calculation is used for a particular substance, that calculation should not yield a result which exceeds the upper limit of the ADI.

- The ADI is expressed as a range, from 0 to an upper limit, such as 0 – 2 µg/kg, with the upper limit of the ADI in this example for a 60 kg individual being 120 µg.
Importance of GVP as basis for MRL recommendations

- CCRVDF and CCPR have requested that JECFA and JMPR to provide recommendations for MRLs that are consistent with the approved use of a substance in Codex member states, referred to as the Good Veterinary Practice, or GVP or Good Agricultural Practices (GAP).

- Factors which should be considered as part of the GVP and GAP when recommending MRLs include the species and class of animals for which the substance is approved, the dose and route of administration, any limitations on use, plus the MRLs and withdrawal periods which have been established by the competent authorities in the member states.

- When the studies submitted use different dosages than those which have been approved or animals in the studies are not representative of the typical animals receiving treatment, this must be noted and should be a major factor when the Committee considers MRL recommendation.
Exposure assessments
Chronic and Acute
Chronic Exposure Endpoint – The ADI

- The ADI must be based on a chronic exposure toxicological endpoint.

- There must be sufficient data points to calculate the median, mean and UTL 95/95 concentrations for most of the matrices for which MRLs are recommended.

- When the ADI is based on an acute exposure toxicological endpoint or data are insufficient to allow the calculation of median concentrations for the residues, the TMDI is calculated.
Chronic Dietary Exposure Assessments

• Chronic dietary exposure assessments are conducted for food chemicals that have toxicological effects from exposure over a long period. Because exposure over a long time is being assessed, it is not usually appropriate to select extremes of food chemical concentration data.

• Mean (TMDI) or median (EDI) concentration data are most often used as, over a lifetime, people are most likely to consume an average concentration of a chemical in a food rather than continually be exposed to high levels of a chemical (FAO/WHO, 2009b).
Chronic dietary exposure assessments

- There may be assessments involving a subset of a population who have unusual eating patterns and who may select foods with persistent high chemical levels. For example, recreational fishers or indigenous peoples who regularly eat fish caught in a single area may have long-term high exposures to chemicals present in waters in that area.

- For chronic dietary exposure assessment, it would be beneficial for long-term food consumption data to be used. Considerable care must be taken to use data that represent long-term food consumption patterns.
Exposure Assessment

• It is an essential step in the risk assessment

• The MRLs recommended by JECFA and JMPR are based
  
  – on “estimates of long-term (chronic) dietary exposures to residues of veterinary drugs in which point estimates of both the amounts of food commodities consumed and the residue concentrations are used”.

• The numerical result of the exposure estimate
  
  – is “then compared with the type and amount of residue considered to be without toxicological, pharmacological or microbiological hazard for human health, as expressed by the ADI”.

  – This comparison is reported in each drug residue for the information of the risk managers, the CCRVDF, and other interested parties.

• Based on the results of the exposure assessment provided by the JECFA or JMPR, CCRVDF and CCPR can then determine that the MRLs recommended by JECFA or JMPR are consistent with the mission statement of the Codex Alimentarius Commission, “to ensure safe, good food for everyone, everywhere”.
TMDI IS CALCULATED WHEN RESIDUE DATA ARE INSUFFICIENT
Theoretical Maximum Daily Intake (TMDI) approach

• The 34th Meeting of JECFA (1989) adopted the
  – Theoretical Maximum Daily Intake, or TMDI, as the standard dietary
    exposure calculation to be used by the Committee.

• The TMDI for all types of food items assigned an MRL is then
  summed, using the highest MRL for each individual food item.

• For example, if there are MRLs for a substance in beef, pork and
  sheep muscle, with the highest MRL being for pork muscle, the
  MRL for pork muscle is used in the calculation.

• The resultant TMDI for all food items must not exceed the upper
  limit of the ADI.
Theoretical Maximum Daily Intake (TMDI)

- Using this approach, the quantity of residues of toxic concern is currently calculated for a food basket that includes
  - 300 g of muscle,
  - 100 g of liver,
  - 50 g of kidney,
  - 50 g of fat,
  - 1.5 kg of milk,
  - 100 g of eggs and
  - 50 g of honey.

- The concentration of residues is calculated using the MRL, expressed as the marker residue, with inclusion of a factor (when required) to convert the marker residue concentration to total residues.
## TMDI Calculation for Colistin

<table>
<thead>
<tr>
<th>Food Item</th>
<th>MRL (μg/kg)</th>
<th>Standard Food Basket (kg)</th>
<th>MR:TR (microbiological activity)</th>
<th>Daily Intake (μg/person/day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Muscle</td>
<td>150</td>
<td>0.3</td>
<td>0.8</td>
<td>56</td>
</tr>
<tr>
<td>Liver</td>
<td>150</td>
<td>0.1</td>
<td>0.8</td>
<td>19</td>
</tr>
<tr>
<td>Kidney</td>
<td>200</td>
<td>0.05</td>
<td>0.8</td>
<td>13</td>
</tr>
<tr>
<td>Fat</td>
<td>150</td>
<td>0.05</td>
<td>0.8</td>
<td>9</td>
</tr>
<tr>
<td>Milk</td>
<td>50</td>
<td>1.5</td>
<td>0.8</td>
<td>94</td>
</tr>
<tr>
<td>Eggs</td>
<td>300</td>
<td>0.1</td>
<td>0.8</td>
<td>38</td>
</tr>
<tr>
<td><strong>TMDI</strong></td>
<td><strong>229</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**ADI for Colistin 0-7 μg/kg**

**ADI (Upper Bound)** 420

TMDI is 55% of the Upper Bound Limit of the Microbiological ADI
Daily Intake = MRL (μg/kg) x Food basket item (kg)/MR:TR

Daily Intake for Muscle for Colistin

\[ = (150\mu g/kg \times 0.3 \text{ kg}) = 56 \]

\[ 0.8 \]

TMDI = \[ \sum \text{ Daily Intakes for All Tissues} \]
Daily Intake for Muscle for Colistin

\[= \left(150 \, \mu g/kg \times 0.3 \, \text{kg}\right) = 56\]

\[0.8\]

TMDI \[= \sum \text{ Daily Intakes for all Food Basket Items} \]

\[= 56 + 19 + 13 + 9 + 94 + 38 \]

\[= 229\]

\(< 420\)
## TMDI Calculation for Tylosin

<table>
<thead>
<tr>
<th>Food Item</th>
<th>MRL (μg/kg)</th>
<th>Standard Food Basket (kg)</th>
<th>MR:TR (microbiological activity)</th>
<th>Daily Intake (μg/person/day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Muscle</td>
<td>100</td>
<td>0.3</td>
<td>1.0</td>
<td>30</td>
</tr>
<tr>
<td>Liver</td>
<td>100</td>
<td>0.1</td>
<td>1.0</td>
<td>10</td>
</tr>
<tr>
<td>Kidney</td>
<td>100</td>
<td>0.05</td>
<td>1.0</td>
<td>5</td>
</tr>
<tr>
<td>Fat</td>
<td>100</td>
<td>0.05</td>
<td>1.0</td>
<td>5</td>
</tr>
<tr>
<td>Milk</td>
<td>100</td>
<td>1.5</td>
<td>1.0</td>
<td>150</td>
</tr>
<tr>
<td>Eggs</td>
<td>300</td>
<td>0.1</td>
<td>1.0</td>
<td>30</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>TMDI 230</td>
</tr>
<tr>
<td>ADI for Tylosin: 0-30 μg/kg</td>
<td>ADI (Upper Bound)</td>
<td>1800</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

TMDI is 12.8% of the Upper Bound Limit of the Microbiological ADI
ESTIMATED DAILY INTAKE (EDI) IS CALCULATED WHEN THERE ARE SUFFICIENT RESIDUE DATA
Estimated Daily Intake (EDI) approach

- The Estimated Daily Intake, or EDI, was adopted by the 66th Meeting of JECFA (2006) to be used when the ADI is based on chronic exposure.

- The calculation is essentially the same as that used for the TMDI, except that the median residue concentration associated with the MRL is used in the calculation instead of the MRL.

- JECFA considers that the median residue is more representative of potential exposure than the upper limit represented by the MRL, a view accepted by the CCRVDF at its 18th Session in 2009.

- However, the EDI can only be used when there are sufficient residue data for all food basket items at the time point associated with the MRL to provide median concentrations to use in the calculation.

- When the residue data are insufficient to calculate the EDI, The TMDI calculation is used instead.
Estimated Daily Intake (EDI)

- The use of an extreme value of the distribution (the MRL) is not realistic in a scenario describing chronic exposure. Instead, all concentrations of the distribution of residues should be considered.

- The median concentration is selected as representing the best point estimate of a central tendency over a prolonged period.

- Hence the EDI, calculated using the same factors as the TMDI, but using the median residue concentration instead of the MRL.

- An example of the EDI calculation for colistin is provided.

- As noted by the 66th JECFA (2006), the EDI should not be applied when there is concern for acute toxicity or acute exposure (JECFA, 2006 [TRS 939]).

- The use of the EDI is currently applicable only to the evaluation of chronic toxicity of, and chronic exposure to, residues as reflected by the ADI.
EDI (Median Concentrations)

The **median** of a column of numbers is found by sorting the data, from smallest to highest, and finding the middle value in the list. If the sorted list has an odd number of elements, then the median is uniquely defined.

If the sorted list has an even number of elements, the median is the **mean of the two middle values**.

If the sorted list has an odd number of elements, the median is the value of the concentration that is mid-way between the elements.
## Estimated Daily Intake (EDI) Calculation for Colistin

<table>
<thead>
<tr>
<th>Food Item</th>
<th>Median Residue (μg/kg)</th>
<th>Standard Food Basket (kg)</th>
<th>MR/TR (microbiological activity)</th>
<th>Estimated Daily Intake (μg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Muscle (Turkey)</td>
<td>38</td>
<td>0.3</td>
<td>0.8</td>
<td>14.3</td>
</tr>
<tr>
<td>Liver (Pig)</td>
<td>38</td>
<td>0.1</td>
<td>0.8</td>
<td>4.8</td>
</tr>
<tr>
<td>Kidney (Rabbits)</td>
<td>145</td>
<td>0.05</td>
<td>0.8</td>
<td>9.1</td>
</tr>
<tr>
<td>Fat (Rabbits)</td>
<td>82</td>
<td>0.05</td>
<td>0.8</td>
<td>5.1</td>
</tr>
<tr>
<td>Milk (Cattle)</td>
<td>11</td>
<td>1.5</td>
<td>0.8</td>
<td>20.6</td>
</tr>
<tr>
<td>Eggs (Chicken)</td>
<td>24</td>
<td>0.1</td>
<td>0.8</td>
<td>3.0</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>EDI</th>
<th>ADI for Colistin 0-7 μg/kg</th>
<th>ADI (Upper Bound)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>56.9</td>
<td>ADI for Colistin 0-7 μg/kg</td>
<td>420</td>
</tr>
</tbody>
</table>

EDI is 13.5 % of the Upper Bound Limit of the microbiological ADI
Estimated Daily Intake for each food basket item

\[
= \left[ \text{Median residue (\(\mu g/kg\))} \times \text{food basket item (kg)} \right] \times \text{MR:TR}
\]

\[\text{EDI} = \sum \text{Estimated Daily Intakes for all food basket items}\]
Estimated Daily Intake for Muscle for Colistin

\[
\text{EDI} = \sum \text{Estimated Daily Intakes for all Food Basket Items}
\]

\[
= (38\mu g/kg \times 0.3 \text{ kg}) = 14.3
\]

\[
= 0.8
\]

\[
\leq 420
\]
Example Calculation of EDI knowing the BIOAVAILABILITY (bioav) FACTOR

$$\text{EDI} = \text{Median residue (µg/kg)} \times \text{food basket item (kg)} \times \text{bioav factor}$$

$$\text{MR:TR}$$

For Triclabendazole, with a bioav factor of 0.13 and MR:TR of 0.18

EDI for liver = $$(423.1 \times 0.1 \times 0.185)/0.13 = 29.7$$

$$\text{EDI} = 19.4 + 29.7 + 4.7 + 1.6$$

$$= 55.4 \, \mu g$$
## EDI for Triclabendazole including Bioavailability Factor

<table>
<thead>
<tr>
<th>Food Item</th>
<th>Median Residue ($\mu$g/kg)</th>
<th>Standard Food Basket (kg)</th>
<th>MR:TR</th>
<th>Bioavailability Factor</th>
<th>EDI ($\mu$g)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Muscle</td>
<td>423.1</td>
<td>0.1</td>
<td>0.185</td>
<td>0.13</td>
<td>29.7</td>
</tr>
<tr>
<td>Liver</td>
<td>172.5</td>
<td>0.05</td>
<td>0.24</td>
<td>0.13</td>
<td>4.7</td>
</tr>
<tr>
<td>Kidney</td>
<td>160.6</td>
<td>0.3</td>
<td>0.32</td>
<td>0.13</td>
<td>19.4</td>
</tr>
<tr>
<td>Fat</td>
<td>100</td>
<td>0.05</td>
<td>0.40</td>
<td>0.13</td>
<td>1.6</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>EDI</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>55.4</td>
</tr>
</tbody>
</table>

**ADI (Upper bound)**

180

EDI is 30.8 % of the Upper Bound Limit of the ADI
Example calculation of EDI with Molecular Weight Correction Factor (MWCF) from Marker Residue to Parent Compound

Monepantel molecular weight of 473.4 was measured as monepantel sulfone with a molecular weight of 444.9.

Thus a correction factor of 0.94 (444.9/473.4) is applied to the daily intake value to convert the data to monepantel equivalents.

**Daily Intake = Median Residue x Food basket item x MWCF**

\[
\text{MR:TR}
\]
### EDI Calculation with Molecular Weight Correction Factor

<table>
<thead>
<tr>
<th>Tissue</th>
<th>Median Residue Concentration (μg/kg)</th>
<th>Standard Food basket (kg)</th>
<th>MR:TR</th>
<th>MWCF</th>
<th>Estimated Daily Intake (μg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Muscle</td>
<td>152</td>
<td>0.3</td>
<td>1</td>
<td>0.94</td>
<td>43</td>
</tr>
<tr>
<td>Kidney</td>
<td>1295</td>
<td>0.05</td>
<td>0.66</td>
<td>0.94</td>
<td>184</td>
</tr>
<tr>
<td>Liver</td>
<td>406</td>
<td>0.1</td>
<td>0.66</td>
<td>0.94</td>
<td>29</td>
</tr>
<tr>
<td>Fat</td>
<td>2620</td>
<td>0.05</td>
<td>0.66</td>
<td>0.94</td>
<td>187</td>
</tr>
<tr>
<td></td>
<td><strong>EDI</strong></td>
<td></td>
<td></td>
<td></td>
<td><strong>443</strong></td>
</tr>
<tr>
<td></td>
<td><strong>ADI (Upper Bound)</strong></td>
<td></td>
<td></td>
<td></td>
<td><strong>1200</strong></td>
</tr>
</tbody>
</table>

The EDI is 36.9 % of the Upper Bound Limit of the ADI
The 66th Meeting of the Committee (2006) concluded that the TMDI was no longer the most suitable estimate of chronic exposure, because the MRL was a single concentration representing the estimated upper limit of a high percentile of the distribution of marker residue present in a given tissue of the treated animals (JECFA, 2006 [TRS 939]).

Therefore, the Committee decided to use the median of the residue distribution to substitute for the MRL in the exposure estimate.

The new estimate of exposure is the EDI.

Further considerations are in the report of the 70th Meeting of the Committee (2009) in reply to comments submitted by the Committee for Medicinal Products for Veterinary Use (CVMP), European Medicines Agency (JECFA, 2009 [TRS 954]).
Review – TMDI/EDI

• Currently, for estimating chronic dietary exposures to veterinary drug residues in foods, JECFA uses the median of the residue depletion, when available, to derive the EDI.

• These calculations have been carried out as part of the standard work of the 78th JECFA as well as for this pilot study to compare with the GECDE.

• Where a median residue cannot be derived, the MRL may be substituted for the median residue to calculate the TMDI, as was the case with derquantel at the 78th JECFA meeting (2013).

• Both the EDI and TMDI assume that the food consumption applies to a standard human with a bodyweight of 60 kg. This weight represents the average bodyweight of the whole population including adults, children, male and female. The model diet is also intended to also cover the consumption of all processed foods with these foods as ingredients. All muscle tissues are equivalent, so meat and fish consumed are considered as equivalent in the calculations.
Global Estimated Chronic Dietary Exposure (GECDE) Calculations
New approaches for estimating drug residues: GEADE and GECDE

• The Joint FAO/WHO Expert Meeting on Dietary Exposure Assessment Methodologies for Residues of Veterinary Drugs developed two new approaches for the calculation of potential dietary exposure to residues of veterinary drugs in foods (FAO/WHO, 2012b).

• The same general equation applies for both acute and chronic dietary exposure estimates, represented as:

\[
\text{Dietary Exposure} = \sum \frac{\text{Concentration of chemical in food} \times \text{Food consumption (g)}}{\text{Body weight (kg)}}
\]
A New Approach to Dietary Exposure Calculations

- The 78th Meeting of JECFA, held in 2013, investigated two new approaches to dietary exposure calculation which were proposed by the Joint FAO/WHO Expert Meeting on Dietary Exposure Assessment Methodologies for Residues of Veterinary Drugs in 2011.

- The Global Estimate of Chronic Dietary Exposure, or GECDE, which is defined as “the highest exposure calculated using the 97.5th percentile consumption figure for a single food selected from all the foods plus the mean dietary exposure from all the other relevant foods” is the alternative method proposed for calculations involving a chronic exposure risk.
Global Estimated Chronic Dietary Exposure (GECDE)

• In assessment of chronic exposure, consumption reflects the ongoing average (mean) and habitual high consumption of a food.

• In contrast, consumption derived for acute exposure reflects consumption at a single eating occasion.

• In addition to the general population, exposure is also estimated for children and infants using this method.
Global Estimated Chronic Dietary Exposure (GECDE)

The Global Estimated Chronic Dietary Exposure (GECDE) uses median residues combined with two different types of consumption data to estimate chronic dietary exposure.

- Firstly, the highest exposure at the 97.5\(^{th}\) percentile of consumption is selected from all the foods relevant to exposure. This value is derived from chronic consumers of the food; that is, the percentile consumption is calculated from consumers of the food only.

- Secondly, the mean dietary exposures from all the other relevant foods are then added to estimate total exposure.

- The mean dietary exposure is derived from the total population; in other words, non-consumers of the food are included in the mean calculation.

\[
\text{GECDE} = \text{Highest exposure from one animal product} + \text{Total mean exposure from all other products}
\]
The GECDE assumes that, in the longer term, an individual would be a high-level consumer of only one category of food and that their consumption of other foods containing the residue would remain at the population average (total population).

Therefore, the 97.5\textsuperscript{th} percentile food consumption amount for consumers only should be used, to be derived from surveys with individual records of two or more days’ duration by first calculating the average food consumption amount per day per person, preferably expressed on a per kilogram bodyweight basis for each individual.

The choice of a high percentile, such as the 97.5\textsuperscript{th}, is justified by its application for a single commodity (instead of two, as applied for other food chemicals).
GECDE

• The 97.5\textsuperscript{th} percentile is used because it was more commonly reported in the data submitted. It is essential to document information on the number of consumers on which the percentile is based to demonstrate that the data are truly representative of the population of interest.

• In summary, the GECDE is the highest exposure calculated using the 97.5\textsuperscript{th} percentile consumption figure for a single food selected from all the foods, plus the mean dietary exposure from all the other relevant foods, and is calculated as:

• In most cases, the food with the highest estimate of exposure using the 97.5\textsuperscript{th} percentile consumption value drives the resulting dietary exposure estimate. In the rare case where two foods have similar 97.5\textsuperscript{th} percentile exposure values, the calculation is undertaken for each one to determine the higher GECDE.
Global Estimated Acute Dietary Exposure (GEADE) Calculations
Another Approach to Dietary Exposure Calculation

• The 78th Meeting of JECFA, held in 2013, investigated two new approaches to dietary exposure calculation which were proposed by the Joint FAO/WHO Expert Meeting on Dietary Exposure Assessment Methodologies for Residues of Veterinary Drugs in 2011.

• A similar calculation, the **Global Estimate of Acute Dietary Exposure, or GEADE**, is used when there is concern that an acute exposure may occur for a consumer. The GEADE is calculated based on a selected high residue concentration in each food to which a consumer...
It is an “estimate of the amount of a substance in food or drinking water, expressed on a bodyweight basis, that can be ingested over a short period of time, usually during one meal or one day, without appreciable health risk to the consumer on the basis of all the known facts at the time of the evaluation” (FAO, 1967)
Acute dietary exposure assessments

- An estimate of acute dietary exposure is required for each food or commodity for which an MRL is proposed for those agricultural and veterinary chemicals where an ARfD has been established.

- Acute dietary exposure assessments are conducted for food chemicals that have toxic effects from short-term exposure (from one meal or over one day).

- In estimating acute dietary exposure, the aim is to generate a ‘worst case’ assessment that takes into account the potential occurrence of someone who eats a large amount of a food happening to also select food that has a high concentration of the chemical in question.
Acute dietary exposure assessments

• Therefore, in a deterministic acute exposure assessment, a high consumption amount (typically the 97.5th percentile) is multiplied by a high chemical concentration amount, where a distribution of chemical concentrations is known.

• In some circumstances, a factor is also included to account for variability in the chemical concentration data set arising from lack of homogeneity in foods or due to small data sets being use.

• Although acute dietary exposure assessments generally focus on exposure from a single food, exposure from a range of dietary sources can be taken into account if this is relevant.

\[
GEADE = \frac{97.5^{th} \text{ percentile food consumption (1 person day)} \times \text{High residue tissue}}{\text{Body weight (kg)}}
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Acute Reference Dose (ARfD) and Exposure Calculation

- JECFA has not typically dealt with compounds for which it has been deemed necessary to establish an acute reference dose, or ARfD, but does apply ARfD on case-by-case basis.

- The first time JECFA applied ARfDs occurred during the 52nd JECFA, where JECFA did establish an ARfD for carazolol based on the potential that residues at the injection site could exceed the ARfD for several hours post-injection in pigs.

- The Committee, in recommending MRLs for carazolol in pig tissues, also stated that “unless appropriate measures can be taken to ensure that the concentrations of residues at the injection site do not result in intake exceeding the acute ARfD, use of carazolol during the transport of animals to slaughter is not consistent with the safe use of the drug”.

- The ARfD, in this case, was set as the upper limit of the ADI.

- The exposure calculation was made using consumption of 300 g of muscle (injection site muscle) and the actual concentrations of carazolol residues found 2 hours post-treatment in the injection site muscle of pigs injected with the approved dose of carazolol.
Global Estimated Acute Dietary Exposure (GEADE)

- The current approach to estimating exposure does not explicitly estimate acute exposure. However, the proposed new acute dietary exposure model, the Global Estimated Acute Dietary Exposure (GEADE), is an explicit estimate of acute exposure.

- The GEADE considers high-level exposure from each relevant food of animal origin individually. The concurrent occurrence of the selected high residue concentration in each food to which a consumer might be exposed (e.g. an MRL or high residue concentration derived from depletion studies, such as the upper one-sided 95% confidence limit over the 95th percentile residue concentration) is combined with a high daily consumption (97.5th percentile) of that food (meat, offal, milk, others).

- The 97.5\textsuperscript{th} percentile food consumption amount (consumers only) was selected as being a more statistically robust value than the maximum food consumption amount because it represents an actual distribution of values. The GEADE is calculated as follows:

- Unlike the EDI, estimates are derived for the children as well as for the general population, following the principle that dietary exposure assessments should cover the whole population and should include children. When calculating the GEADE, instead of the amounts of food consumed set out in the model diet, more detailed estimates of consumption are used to calculate exposure.
GEADE

• For an acute dietary exposure assessment, an Acute Reference Dose (ARfD) must first be established. The GEADE is used to calculate the percentage exposure of the ARfD it represents for each population. JECFA has made limited use of an approach to acute exposure based on an ARfD.

• The Committee has considered this approach primarily when:
  – there is a concern that residues of an injectable drug may remain in excess of the MRL at the injection site after the residues in normal muscle tissue are below the MRL; and
  – the residue concentrations at the injection site could pose a serious risk to consumers (JECFA, 2000 [TRS 893]).

• For example, in the case of the β-adrenoreceptor blocking agent carazolol, which is used as a sedative for transport of pigs, the Committee noted that at 2 h following treatment, residues at the injection site could result in an exposure of 18 μg of parent carazolol, which is three times the ARfD.

• The Committee therefore advised that, unless appropriate measures could be taken to ensure that residues at the injection site do not result in residues exceeding the ARfD, use of carazolol prior to transport for slaughter is not consistent with the safe use of this drug (JECFA, 2000 [TRS 893]).
Dietary Consumption Factors

- The basic dietary intake factors (food basket items) which are used in the dietary intake calculations based on a standard food basket (EDI or TMDI) are:
  - 300 g of muscle
  - 100 g of liver
  - 50 g of kidney
  - 50 g of tissue fat
  - 100 g of eggs
  - 1500 g of milk
  - 50 g of honey

- The intake factors for tissues, milk and eggs were first used by the 34th JECFA, based on dietary survey and food balanced sheet information, and the approach was confirmed
Acute and Chronic Dietary Exposure Assessments

• The 70th Meeting of the Committee confirmed that the median residue level from depletion studies with a correction for marker residue to total residue (the Estimated Dietary Intake, or EDI) would continue to be used in chronic exposure assessments for long-term dietary exposure estimates, when supported by the available data (JECFA, 2009 [TRS 954]).

• Only when median residue data are not available may the chronic exposure estimate be based on a calculation using the MRL with a correction for marker residue to total residue to calculate a Theoretical Maximum Daily Intake, or TMDI.

• It should also be noted that when data on bio-availability are available, a correction for bio-availability might also be used in the dietary exposure calculation (JECFA, 1989 [TRS 788]).
Acute and Chronic Dietary Exposure Assessments

- The report of the Joint FAO/WHO Expert Meeting on Dietary Exposure Assessment Methodologies for Residues of Veterinary Drugs (FAO/WHO, 2011b) proposed models to estimate both acute and chronic exposure to residues of veterinary drugs in food:
  - the Global Estimate of Acute Dietary Exposure (GEADE) and
  - the Global Estimate of Chronic Dietary Exposure (GECDE).
- The 75th JECFA noted that the proposed models use more detailed consumption data than the EDI.
- It also noted that comments on the draft report of the expert meeting would be sought from participants of the 75th Meeting of the Committee soon after the meeting and that, following consideration of these comments, a revised draft report would be prepared for public comments.
- The final report was discussed at the 20th Session of the CCRVDF. The expert report and comments from the CCRVDF would then be discussed at a future meeting of the Committee, at which time additional worked examples would be prepared using the GECDE and GEADE to provide more experience with their application.
Advantages and Disadvantages of the Model Diet Approach

• The advantages of the model diet approach are that it:
  • is cost effective;
  • can take different population sub-groups into account;
  • can take different chemical levels into account; and
  • is useful when limited data are available.

• The disadvantages of the model diet approach are that:
  • it is subject to error when many foods are involved;
  • the outcome is very dependent on assumptions made; and
  • it does not account for individual variation in consumption.
Advantages and Disadvantages of the Model Diet Approach

• The best data for conducting dietary exposure estimates are food consumption data collected from individuals, as is used in the new approach. Dietary exposure assessments using food consumption data for individuals may be necessary if the results of exposure assessments, using screening methods or model diets, are not conclusive or indicate that potential dietary exposure to a food chemical is likely to approach or exceed a HBGV.

• Alternatively, they may be used in the first instance if the data are available and an accurate estimate of dietary exposure is likely to be required. The usual dietary modelling approach involves the use of individual dietary records derived from national nutrition surveys. These individual consumption records may be used in a deterministic assessment, as typically occurs for agricultural and veterinary chemicals, or they can be used as inputs in semi or fully probabilistic techniques.
Advantages

The advantages of using individual food consumption data are:

- dietary exposure for a wide range of food chemicals can be estimated if the consumption data are representative and comprehensive;
- a range of consumption amounts for each food or food group can be taken into account;
- dietary exposures for different population sub-groups can be estimated;
- dietary exposure of consumers at low and high points of the distribution can be assessed to represent low or high consumers; and

  - scenarios of food chemical concentrations can be modelled to predict exposure under different risk management options.
  - The disadvantages of using individual food consumption data include:
    - data collection is resource intensive;
    - their use is more time consuming than use of data from screening techniques and requires more technical expertise; and
    - some critical groups may not be adequately represented (e.g. very young children).