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Methodology of setting limits on antibiotic residues in Milk

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Why the need ?

Chemical residues which could contaminate milk are pesticides, herbicides, fungicides, anthelmintic drugs, antibiotics, hormones, detergents and disinfectants, nitrites, dioxins, mycotoxins, heavy metals and somatotropin hormone.

Antibiotic residues may lead to :

- allergic reactions
- antibiotic resistant bacteriaVIDEO-AMR-2019-03-08-21-25-56.mp4
- teratogenicity risk to the foetus
- hypoplasia in developing teeth
- aplasia of bone marrow
- cancer risk
- disruption of body's reproductive, immune, endocrine and nervous system.

Since dairy products are widely consumed by infants, children and many adults throughout the world. Governments have responsibility for making regulations to protect consumers against harm arising from chemicals in food.

Drug Residues – how these travel to humans

- Antibiotics are mainly used :
  - for therapeutic uses
  - prophylactic purposes
  - used as feed additives to promote growth and improve feed efficiency.

- However, the antibiotic residues may get transferred to milk due to :
  - extra label administration of drug
  - failure to observe withdrawal period after treatment.

- Many of the administered drugs are not completely absorbed from gut and excreted through faeces and urine as either parent compound or its toxic metabolites. The application of manure or farm effluents in agricultural land leads to selection of resistant bacteria, development and transmission of antibiotic resistance genes in the microbes.

- Implications: AMR leads to poor response to treatment during illness.
  Antibiotic residues in animal product causes harmful effect on health
  Interferes with the processing of milk and milk products.

Methodology for fixing MRLs:

Some definitions:

- **Veterinary Drug** means 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 behavior.

- **Residues** of veterinary drugs include the parent compounds and/or their metabolites in any edible portion of the animal product, and include associated impurities of the veterinary drug concerned.

- **ADI -** An estimate by the Joint FAO/WHO Expert Committee on Food Additives (JECFA) of the amount of a veterinary drug, expressed on a body weight basis, that can be ingested daily over a lifetime without appreciable health risk.

- **MRL** - is defined as the maximum concentration of a residue, resulting from regulated use of a veterinary chemical that is recommended to be legally permitted or recognized as acceptable in 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.

- When establishing an MRL, consideration is also given to residues that occur in food of plant origin and/or the environment. Furthermore, the MRL may be reduced to be consistent with good practices in the use of veterinary drugs and to the extent that practical analytical methods are available.

- When setting ADIs and MRLs for antibiotics, the safety evaluation is carried out in accordance with international guidelines and should include

  - effects on the human intestinal flora
  - toxicological effect
  - pharmacological effect

An acceptable daily intake (ADI) and a maximum residue limit (MRL) for milk should be established for each antimicrobial agent.

- MRLs are necessary in order that officially recognized control laboratories can monitor that the antibiotics are being used as approved.
- Withdrawal periods should be established for each antibiotic, which make it possible to produce food in compliance with the MRLs.
- The extra-label use of these antimicrobial treatments, insufficient withdrawal period and lack of records are the most common causes of these residues in milk, which lead to the increase of these residues in milk above the acceptable maximum residue limits (MRLs).

In the U.S.

The FDA Center for Veterinary Medicine (CVM) is a consumer protection organization is responsible for ensuring that all animal drugs and medicated feeds are safe and effective for their intended uses.

- It is the responsibility of the drug sponsor to conduct the necessary tests.
- Must also must develop analytical methods to detect and measure drug residues in edible animal products.
- Shall submit complete dossier in the CVM Office of New Animal Drug Evaluation (ONADE) for review and approval by CVM.
- Drug must be clinically tested for effectiveness and safety in the target animal, as also in human consumers.

Only then a new animal drug receives FDA approval

In the E.U.

- THE EUROPEAN union adopts a similar approach
- Based on generally recognized principles of safety assessment, i.e. toxicological risks, environmental contamination, and the microbiological & pharmacological effects of residues.
- Also considers the Scientific assessments which may have been undertaken by international organisations or scientific bodies established within the EU.
- MRLs shall be in accordance with Directive 2001/82/EC, which sets out EU rules on the authorisation, manufacturing, supervision, sale, distribution and use of veterinary medicinal products
- provides that veterinary medicinal products may be used in animals only if pharmacologically active substances contained therein have been assessed as safe according to Regulation (EEC) No 2377/90.
- The person responsible for marketing shall submit an application to the Commission along with a fee, who sends it to Committee for Veterinary Medicinal Products for further processing. The process will be completed within 210 days.

Regulatory Authorities Involved in Assessment of the Effects of Antimicrobial Drug Residues from Food of Animal Origin

Antimicrobial residues are evaluated internationally by:

- Food and Drug Administration (FDA)
- Joint Expert Committee on Food Additives (JECFA)
- European Medicines Evaluation Agency (EMA/CVMP)
- Codex Alimentarius Commission (CAC)
- Other National Regulatory Authorities (Health Canada)

CODEX - RISK ANALYSIS FRAMEWORK FOR MRLs

- It is a structured, systematic process that examines the potential adverse effect consequential to a hazard or condition of a food and exposure to the hazard and that develops options for mitigating the risk.

- Risk analysis includes interactive communication amongst all interested parties involved in the process.

Risk analysis

Figure 1: Relationship between the Three Components of Risk Analysis

Risk Analysis

- 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 Management : It is 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 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 Assessor - JECFA

- The Joint FAO/WHO Expert Committee on Food Additives (JECFA) is an international expert scientific committee that is administered jointly by the Food and Agriculture Organization of the United Nations (FAO) and the World Health Organization (WHO).
- Jointly, FAO and WHO convene international expert meetings to address emerging or emergency issues and provide independent risk assessments. The recommendations from these meetings feed directly into the Commission's standard-setting process.
- Set up in 1956, initially to evaluate the safety of food additives. Their scope has now been extended for Risk assessment/safety evaluation of Processing aids, Flavoring agents, Residues of veterinary drugs in animal products, Contaminants, Natural toxins etc.
- JECFA is the Risk accessor who provides expert scientific advice to codex committee.
- The scientific advice developed by JECFA aims to provide maximum residue levels for individual animal products, based on the results of scientific studies, so that these levels can be used by the relevant Codex committee to develop the draft MRLs, which may be adopted by the CAC.
- MRLs are set by the CAC, acting as the risk manager.

Codex Alimentarius Commission

Executive Committee

Horizontal / General Committees

- General Principles (France)
- Food Labelling (Canada)
- Import and Export Inspection and Certification Systems (Australia)
- Residues of Veterinary Drugs in Foods (United States)
- Food Additives (China)
- Pesticide Residues (China)
- Contaminants in Foods (Netherlands)
- Food Hygiene (United States)
- Methods of Analysis and Sampling (Hungary)
- Nutrition and Foods for Special Dietary Uses (Germany)

Vertical / Commodity Committees

Active

- Processed Fruits and Vegetables (United States)
- Fresh Fruits and Vegetables (Mexico)
- Fats and Oils (Malaysia)
- Spices and Culinary Herbs (India)
- * Sugars (Colombia)
- * Cereals, Pulses and Legumes (United States)

Adjourned sine die

- Natural Mineral Waters (Switzerland)
- Vegetable Proteins (Canada)
- Meat Hygiene (New Zealand)
- Cocoa Products and Chocolate (Switzerland)
- Fish and Fishery Products (Norway)
- * Milk and Milk Products (New Zealand)

Ad-hoc Intergovernmental Task Forces

Active

- Antimicrobial Resistance (Republic of Korea)

Dissolved

- Animal Feeding (Switzerland)
- Foods Derived from Biotechnology (Japan)
- Fruit Juices (Brazil)
- Processing and Handling of Quick Frozen Foods (Thailand)

* Working by correspondence

FAO/WHO Regional Coordinating Committees

- Africa (Kenya)
- Asia (India)
- Europe (Kazakhstan)
- Latin America and the Caribbean (Chile)
- North America and South West Pacific (Vanuatu)
- Near East (Iran)

Codex Committee on Residues of Veterinary Drugs in Foods (CCRVDF)
Host Government: United States

- Established in 1985 by CAC
- Primarily responsible for recommending risk management proposals for adoption by the CAC, based on JECFA's risk assessments of veterinary drugs.
- Recommend extrapolation of MRLs to one or more other species, where JECFA has identified that is scientifically justifiable and the uncertainties have been clearly defined
- Modify the MRLs in consideration of other legitimate factors relevant to the health protection of consumers and for the promotion of fair practices in food trade;
- Develop risk management guidance, as appropriate, for veterinary drugs for which JECFA has not been able to establish an ADI and/or to recommended a MRL, including those with specific human health concern.

ESTABLISHING MRLs : RISK ASSESSMENT

- RISK : f (Hazard x Exposure)

Risk assessment is the scientific evaluation of known or potential adverse effects resulting from human exposure to food borne hazards.

- Risk Assessment consists of four steps:
  - Hazard identification
  - Hazard characterization
  - Exposure assessment
  - Risk characterization

Assessment process

- Hazard Identification: Information required is huge -well designed animal-based toxicity studies with internationally recognized protocols. Covering all possible adverse effects. Hazard identification is not a static science. Methods are constantly being re-assessed and improved and complemented by validated alternative methods.

- Hazard Characterization: Evaluation of the nature of the adverse health effects associated with the drug residues present in food. Focus is on dose -response relationship for critical adverse effects

- Exposure Assessment: Minimum information required:
  - drug concentration present in the edible parts/ products of the treated animals
  - How withdrawal periods affect the residue concentration
  - Information on the amounts of these foods eaten daily by consumers

- Risk Characterization: Here the results of hazard characterisation and exposure assessment are integrated and transformed into advice to risk managers.

Assessment process - Data required

- Chemical identity and properties
- Use and dosage forms
- Description of the analytical procedures for detection and determination of residues
- Detailed pharmacology data, e.g, drug metabolism to identify the specific molecules for toxicological evaluation. Typical toxicology requests include :
    - short-term and long-term carcinogenicity
    - Reproduction and developmental studies in experimental animals
    - Genotoxicity, neurotoxicity
    - Pharmacological effects and evaluation of microbial risk.

Assessment Process

- Study conducted in target animal species using approved formulation at maximum label dose and duration under typical field conditions.
- Residue depletion studies

  i. with radio-labelled drug in target animals (to provide information on total residues and major residue components)

  ii. with non-radio-labelled drug in target animals at appropriate times of withdrawal

- Measure residues in muscle, fat, liver and kidney, whole milk and eggs.
- Residue data used by the expert body is derived from animal studies submitted by sponsors.
- Based on toxicological data, JECFA would establish Acceptable daily Intake (ADI) for chemicals that are safe to be associated with foods
- ADI forms the basis for deciding on maximum residue limits (MRLs) for chemicals, considering the exposure to humans through different foods

- There are a number of veterinary drugs for which Codex has not adopted an MRL.
    - Particular drug might not have been evaluated by JECFA
    - Toxicological data did not support an ADI
    - Insufficient residue data
    - suitable validated method not identified

- In the absence of ADI/MRL, national authorities commonly resort to zero tolerance regulatory approaches, with the prevalence of residues of concern potentially changing as analytical method detection capabilities improve.

- Additional tools are needed to evaluate risk when the existing approach of establishing an ADI and MRL cannot be applied.

Indian perspective

- FSSAI had recently published a Gazette Notification related to Pharmacologically active substances and Veterinary Drug Residues, wherein 94 drugs were prescribed with MRLs of most of them set at 10 ppb.
- The legislation, effective from 1st Jan 2019, was deferred till 31st March 2019 pending a review.
- Now FSSAI has come up with a revised list of 28 drugs including antibiotics, effective 1st April 2019
- This covers 11 drugs at MRL levels of CODEX, and where CODEX norms are not available, mostly it is fixed at 10 ppb
- FSSAI has also stated that compliance to other antibiotics is extended till further order, and will work further for their deletion or changes in tolerance limits.

Thank You