

English Only

**DRAFT WORKING DOCUMENT FOR THE RISK ASSESSMENT WORKING
GROUP OF THE CODEX *AD HOC* INTERGOVERNMENTAL TASK FORCE
ON ANTIMICROBIAL RESISTANCE**

FOR CONSULTATION ONLY

Prepared by

Delegation of Canada

with the Consideration of Comments from Codex Members and Observers

February 29, 2008

**PROPOSED DRAFT GUIDELINES FOR THE RISK ASSESSMENT OF
FOODBORNE ANTIMICROBIAL RESISTANT MICROORGANISMS
RELATED TO NON-HUMAN USE OF ANTIMICROBIALS**

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SECTION 1. INTRODUCTION

Antimicrobial resistance (AMR) is a major global public health concern and a food safety issue with significant social and economic burdens. When pathogens become resistant to antimicrobial agents, they can pose a greater health risk as a result of potential treatment failure and increased likelihood and severity of illness. AMR is inherently related to antimicrobial use in any environment including human and non-human uses. Food is generally considered to be the most important vehicle for spread of resistant microorganisms from animals to humans.

In accordance with the Codex principles, risk assessment is an essential tool in assessing the overall risk to human health from foodborne antimicrobial resistant microorganisms. In this context, AMR risk assessment (AMR-RA) described in this document characterizes the adverse effects to human health resulting from exposure via food to antimicrobial resistant microorganisms or resistance determinants in animal feed, food animals (including aquaculture), food production/processing and retail foods, arising from the non-human use of antimicrobials.

Over the past decade, there have been significant developments with respect to AMR-RA. A series of FAO/OIE/WHO expert consultations on AMR have identified that antimicrobial resistant foodborne microorganisms are possible microbiological food safety hazards. Consequently, the need for the development of a structured and coordinated approach for AMR risk analysis has been emphasized (FAO/OIE/WHO, 2003, 2004 and 2008). The OIE guideline on risk analysis of AMR is a major development in addressing the potential public health impact of antimicrobial resistant microorganisms of animal origin (OIE, 2007). However, it is necessary to capture the multidisciplinary aspects of AMR within the entire farm to table continuum. In order to address the existing gaps and controversies in the methodologies and approaches, there is a need to develop a consolidated guidance document specific to AMR-RA.

The objective of this guidance document is to provide a structured risk assessment framework to assess the risk to human health associated with the presence in food and animal feed (including aquaculture), and the transmission through food and animal feed, of antimicrobial resistant microorganisms or resistance determinants linked to non-human use of antimicrobial agents. This document should be read in conjunction with the Working Principles for Risk Analysis for Food Safety for Application by Governments (CAC/GL 62-2007) (FAO/WHO, 2007), the Principles and Guidelines for the Conduct of Microbiological Risk Assessment (CAC/GL 30-1999) (FAO/WHO, 1999) and the proposed guidelines on AMR risk profile and AMR risk management (currently under development).

SECTION 2. SCOPE

The scope of this guidance document encompasses risk assessment of foodborne antimicrobial resistant microorganisms¹ and resistance determinants derived predominantly from food-producing animals and their products as well as those associated with plant produce. This document is also designed to address the microbial food safety impact of non-human use of antimicrobials used in animals, plant production and food processing. It can be adapted to conduct a pre- or post-market risk assessment of an antimicrobial intended for non-human use (either therapeutic or non-therapeutic), or to conduct a risk assessment of food products (including imported food products). The food safety assessment of the use of AMR marker genes in recombinant-DNA plants² or microorganisms³ or of certain food ingredients which could potentially carry AMR genes such as probiotics⁴ are outside the scope of this document.

Essentially, this AMR-RA guidance document provides a transparent science-based approach to identify and assess a chain of events that affect the frequency and amount of antimicrobial resistant microorganisms to which humans are exposed and to describe the magnitude and severity of the adverse effects of that exposure. The extent of the farm-to-table pathway covered by the AMR-RA should fit its intended purpose. A schematic presentation in Figure 1 shows the scope and relationship of the components of AMR-RA.

Intended users of this document include food safety authorities of member countries or international organizations. Industries/organizations involved in food production, and/or manufacture, distribution and use of antimicrobials may find it useful in assessing the AMR risks.

¹ The term “microorganisms” in this document refers to pathogenic and commensal bacteria derived from animals, animal feed, plants and food, i.e., those occurring at various stages along the farm-to-table continuum or animal and plant production. Other foodborne microorganisms (i.e., fungi, protozoa and viruses) are outside the scope of this document. The guidelines established in this document could be, in general, applicable to other resistant microorganisms if they are considered of human health concern.

² The food safety assessment on the use of antimicrobial resistance marker genes in recombinant-DNA plants is addressed in the Guideline for the Conduct of Food Safety Assessment of Foods Derived from Recombinant-DNA Plants (CAC/GL 45-2003) (FAO/WHO, 2003b).

³ The food safety assessment on the use of antimicrobial resistance marker genes in recombinant-DNA microorganisms is addressed in the Guideline for the Conduct of Food Safety Assessment of Foods Produced Using Recombinant-DNA Microorganisms (CAC/GL 46-2003) (FAO/WHO, 2003c).

⁴ The food safety assessment on the use of probiotics in foods is addressed in a Report of a Joint FAO/WHO Working Group on Drafting Guidelines for the Evaluation of Probiotics in Foods (FAO/WHO, 2002).

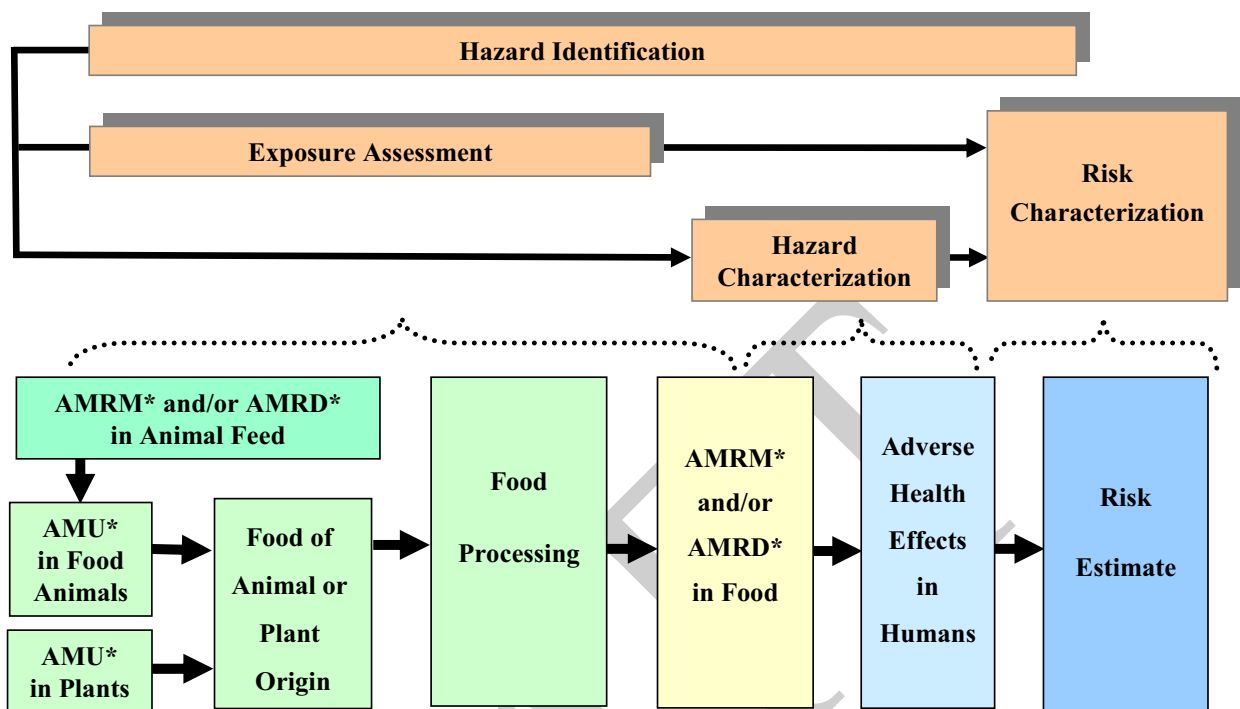


Figure 1. Schematic showing the scope and relationship of the components of AMR-RA

(*: AMU, antimicrobial use; AMRM, antimicrobial resistant microorganism; AMRD, antimicrobial resistance determinant)

SECTION 3. DEFINITIONS

The following definitions are included to establish a common understanding of the terms used in this document. The definitions presented in the Principles and Guidelines for the Conduct of Microbiological Risk Assessment (CAC/GL 30-1999) (FAO/WHO, 1999) are applicable to this document. Where necessary, some established Codex definitions have been modified for the purpose of this document (existing definitions are cited in *italics*).

Adverse Health Effect - An undesirable or unwanted outcome in humans. In this document, this refers to the human infections caused by antimicrobial resistant microorganisms of food and animal feed or of animal/plant origin as well as the increased frequency of treatment failures and increased severity of infections. Increased severity of infection includes prolonged duration of illness, increased frequency of bloodstream infections, increased hospitalization, and increased mortality.

Antimicrobials (Antimicrobial Agents) - Substances (natural, semi-synthetic or synthetic) that kill or inhibit the growth of microorganisms such as bacteria.

Antimicrobial Resistance - The ability of a microorganism to withstand the effects of an antimicrobial. In this document, it refers to acquired resistance.

Exposure Assessment - *The qualitative and/or quantitative evaluation of the likely intake of biological, chemical, and physical agents via food as well as exposures from other sources if relevant.* In this document, it is the evaluation of the amount and frequency of exposure of humans to antimicrobial-resistant microorganisms and resistance determinants.

Hazard - *A biological, chemical or physical agent in, or condition of, food with the potential to cause an adverse health effect.* In this document, hazard includes antimicrobial resistant microorganisms and their resistance determinants (derived from food, animal feed, animals and plants).

Hazard Characterization - *The qualitative and/or quantitative evaluation of the nature of the adverse health effects associated with the hazard.*

Hazard Identification - *The identification of biological, chemical, and physical agents capable of causing adverse health effects and which may be present in a particular food or groups of food.*

Multiple Antimicrobial Resistance (Multidrug Resistance) - The ability of a microorganism to withstand the effects of more than one structurally-unrelated antimicrobials.

Resistance Determinant – The genetic element(s) encoding for the ability of microorganisms to withstand the effects of an antimicrobial. They are located in a chromosome or a plasmid, and may be associated with transmissible genetic elements such as integrons or transposons.

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

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 Estimate - *Output from Risk Characterization.*

Weight of Evidence - A measure that takes into account the nature and quality of scientific studies intended to examine the risk of an agent. Uncertainties that result from the incompleteness and unavailability of scientific data frequently require scientists to make inferences, assumptions, and judgments in order to characterize a risk.

SECTION 4. GENERAL PRINCIPLES

AMR-RA is considered a specific form of microbiological risk assessment. The approach of AMR-RA should be consistent with the Working Principles for Risk analysis for Food Safety for Application by Governments (FAO/WHO, 2007) and the Principles and Guidelines for the Conduct of Microbiological Risk Assessment (FAO/WHO, 1999). Additional principles more specific to AMR-RA are highlighted below:

- AMR-RA should address the risk question taking into account the whole farm-to-table continuum approach, where appropriate, encompassing the food pathway of production, processing, storage, distribution and consumption.
- AMR-RA should essentially consider the principal contributing factors, such as non-human antimicrobial use (including both therapeutic and non-therapeutic uses in animals), to the emergence and dissemination of AMR among pathogenic and commensal microorganisms that have food reservoirs.
- AMR-RA should consider the impact of AMR on the effectiveness of the available antimicrobial agents in human medicine which are needed to treat related and unrelated human infections.
- AMR-RA should consider the dynamics of genetic resistance determinants within microbial populations (e.g., in animal feeds, aquaculture or environment) as well as their persistence and spread within humans and animals.

SECTION 5. GENERAL CONSIDERATIONS

In accordance with the Working Principles for Risk Analysis for Food Safety for Application by Governments (FAO/WHO, 2007), AMR-RA should clearly document the scope and purpose as well as the output format assessed, which are generally defined by the risk manager commissioning the work. Scientific evidence related to AMR risks originates from studies of diverse sources, which often may not have been designed for the purpose of an AMR-RA.

Given the complexity of AMR issues, AMR-RA will require the expertise that spans multiple scientific disciplines and a multidisciplinary team with effective interaction is important to the endeavour. Involvement of appropriate experts will help select the data of high quality, and identify their strengths and limitations. AMR-RA should consider the weight of evidence and uncertainty of scientific data used, and should transparently record the sources of data and the data selection process. AMR-RA should particularly demonstrate how the risk estimates are reached. Appropriate selection of the presentation formats or the order of data presentation may facilitate transparency. Similarly, AMR-RA should be reassessed when new evidence emerges, either through identification of new risk factors or changes in risk levels, e.g., through risk management interventions.

5.1. PURPOSE

The purpose of AMR-RA is to determine the human health risk associated with specific antimicrobial resistant foodborne microorganism(s) and/or specific resistance determinant(s).

5.2. QUALITATIVE AND QUANTITATIVE AMR-RA

The principles of AMR-RA apply equally to both qualitative and quantitative risk assessment. While the design differences may yield different forms of output, both approaches are complementary. Based on the purpose or the type of questions to be answered and data availability for a specific AMR-RA, the decision on selection of a qualitative or quantitative approach should be made. In accordance with CAC/GL 62-2007 (FAO/WHO, 2007), quantitative data should be used to the greatest extent possible without discounting the utility of available qualitative information.

5.3. SOURCES OF DATA OR EVIDENCE

Given the fact that multiple data sources are likely required for an AMR-RA and that these data can be limited, their strengths, limitations, discrepancies, and data gaps should be clearly presented using a weight of evidence approach (e.g., JETACAR, 1999).

Data and possible sources of information:

- Non-human antimicrobial use data such as daily dosage, route of administration, and duration.
- Field animal trials addressing the linkage of antimicrobial usage and resistance.
- Research on properties of antimicrobials including their resistance selection (in-vitro and in-vivo) potential.
- Investigations of the characteristics of resistant microorganisms and resistance determinants (in-vitro and in-vivo studies).
- Studies on interaction between microorganisms and their environment through the farm-to-table continuum.
- Clinical studies including case reports on the relevant foodborne-related infectious disease prevalence, primary and secondary transmission, and antimicrobial therapy.
- Epidemiological investigations of outbreaks and endemic cases associated with resistant microorganisms.
- Monitoring and surveillance programs including active and passive surveillance (phenotypic and if applicable genotypic information) for AMR derived from humans, food, animal feed, animals, or plants.

SECTION 6. PROCESS OF AMR-RA

According to the established working principles for risk analysis for food safety (FAO/WHO, 2007), the process of an AMR-RA is composed of **Hazard Identification, Exposure Assessment, Hazard Characterization, and Risk Characterization**⁵ (Exposure Assessment and Hazard Characterization can be conducted in parallel). This proposed process utilizes the microbiological risk assessment (FAO/WHO, 1999) and integrates the structured approach described in the OIE guideline (i.e., hazard identification, release assessment, exposure assessment, consequence assessment and risk estimation) (OIE, 2007).

6.1. HAZARD IDENTIFICATION

The process of hazard identification recognizes that the hazards, foodborne resistant pathogenic and commensal microorganisms and/or resistance determinants of food, animal feed, and/or of animal/plant origin, have an inherent capacity to cause an adverse human health effect⁶. The resistance determinants from resistant microorganisms (e.g., commensals) can be transferred horizontally to other microbial species. The conditions under which the hazard produces adverse health effects include any scenarios through which humans could become exposed to a pathogen which contains the resistance determinant. The hazards and outcomes are presented in Table 1 (EAGAR, 2007; EMEA, 1999; FAO/OIE/WHO, 2003, 2004 and 2008, FDA, 2003; OIE, 2007). The adverse human health effect endpoints have been previously described (FAO/OIE/WHO, 2003 and 2004; OIE, 2003 and 2007).

Data in the hazard identification step may include: description of the microorganisms and their genotypic and phenotypic characteristics including molecular characterization of resistance determinants, virulence and pathogenicity, in-vivo studies in laboratory animals, surveillance or epidemiological studies of resistant infections or resistance determinants, and clinical studies. Additionally, interaction of resistant microorganisms or resistance determinants with the environment (e.g., interactions in animal feeds or aquaculture environment as well as in food matrices), and information on the susceptible strains of the same organisms or related resistant microorganisms (or resistance determinants) will be useful.

⁵ Recent practical guidelines from the Joint FAO/WHO Meeting on Microbiological Risk Assessment (JEMRA) are available, respectively, with respect to the food safety risk analysis (FAO/WHO, 2006a), the use of microbial risk assessment outputs to develop practical risk management strategies (FAO/WHO, 2006b), the assessment for hazard characterization (FAO/WHO, 2003a), exposure assessment (in press), and risk characterization (in press).

⁶ Depending on the purpose of the AMR-RA, antimicrobials may also be considered hazards since their use in animals or plants can lead to the development and persistence of resistant microorganisms in food.

Table 1. Description of the Hazard and Adverse Health Effect in AMR-RA

Element	Description
Hazard	<ul style="list-style-type: none">• Antimicrobial resistant microorganisms (i.e., bacteria) of food, animal feed, or of animal or plant origin including pathogenic and commensal microorganisms• Antimicrobial resistance determinants of food, animal feed, or of animal or plant origin
Adverse health effect	<ul style="list-style-type: none">• Human infection/illness caused by antimicrobial-resistant microorganisms of food, animal feed, or of animal or plant origin.• Increased frequency of treatment failures and additional days of illness• Increased severity of infection including prolonged duration of illness, increased frequency of bloodstream infections, increased hospitalization, and increased mortality

6.2. EXPOSURE ASSESSMENT

The exposure assessment will address all the modular pathways resulting from non-human uses of antimicrobials and leading to the emergence and dissemination of resistant microorganisms and resistance determinants to humans via the food chain. This step covers the release and exposure assessments of the OIE guideline (OIE, 2007). The fundamental preliminary activities in this step should therefore include: (a) clear depiction or drawing of the exposure pathway; (b) detailing the necessary data requirements based on this pathway; and (c) summarizing the data. Data requirements are linked to the specific risk question posed, and reflect points that may alter the level of resistant microorganisms or resistance determinants (microbial load) and the likelihood of their occurrence in food at the time of consumption. Accordingly, there will be exposure assessment for different scenarios such as for AMR-RA of food or animal feed or for the purpose of AMR-RA of non-human use of antimicrobials.

The exposure assessment for food involves pre-harvest and post-harvest considerations, which are, respectively, equivalent or similar to the release and exposure assessment of the OIE guideline (OIE, 2007). The pre-harvest considerations should focus mainly on risk factors for emergence and spread of resistant microorganisms and resistance determinants, while the post-harvest considerations should place an emphasis on prevalence of the hazards as well as the food consumption factors in humans. The possible data requirements are presented in Tables 2 and 3, which are a consolidation of recommendations from Principles and Guidelines for the Conduct of Microbiological Risk Assessment (FAO/WHO, 1999) and OIE guideline (OIE, 2007) as well as with information available from literature (EAGAR, 2007; FAO/WHO, 2003a and 2006a ; FAO/OIE/WHO, 2008; FDA, 2003; JETACAR, 1999; OIE, 2003 and Salisbury et al, 2002).

An AMR-RA of the overall risk to the general population will examine the load and

likelihood of contamination of all foods (domestic and imported) by resistant microorganisms/resistance determinants and the factors that increase their prevalence in food, while AMR-RA of the imported food products will limit exposure assessment to the load and level of contamination in the food and take into consideration antimicrobial use practices in exporting countries. Similarly, assessing the risk from on-farm antimicrobial use may consider potential increases in pre-harvest contamination by resistant microorganisms/resistance determinants.

When the hazard of interest is the resistance determinant, then exposure assessment should consider whether they can be transferred to human pathogens that subsequently become resistant and cause human illness, i.e., adverse health effect. Assessing the exposure through animal feed should also consider potential in-vitro resistance selection in microorganisms in animal feed due to exposure to in-feed antimicrobials and their transmission to food animals including aquaculture species. There is a potential for environmental microorganisms to be a reservoir of resistance determinants for subsequent transfer to pathogens/commensals that have human health implications. When resistance clones are established, they can disseminate both vertically and horizontally. Intra- or inter-species transfer occurs for mobile resistance determinants from both pathogenic and commensal microorganisms. Hybrid virulence-resistance plasmids also occur in foodborne microorganisms, and AMR-RA should consider all these factors while assessing the potential routes of exposure or increased disease severity associated with resistant microorganisms.

**Table 2. Points for Consideration of Pre-Harvest Factors
in the Exposure Assessment**

Element	Description or scope of data
Selection pressure	<p>Extent of antimicrobial use or proposed use</p> <ul style="list-style-type: none"> • Number of hosts exposed to the antimicrobial (i.e., farms, animals, and plant crops) • Geographical distribution of use and/or hosts <hr/> <p>Intensity of non-human use of antimicrobials</p> <ul style="list-style-type: none"> • How much is used per host (defined daily dose), sales data • Methods and routes of administration of the antimicrobial (individual/mass medication) • Dosing regimen and duration of use • Cumulative effects of use of other antimicrobials
Host and microbial factors affecting resistance development and spread	<ul style="list-style-type: none"> • Seasonal changes in microorganism prevalence • Rate of resistance development and resistant population decline in commensal and zoonotic microorganisms after antimicrobial administration • Resistance mechanisms, location of resistance determinants, occurrence and rate of transfer of resistance between microorganism species • Cross-resistance and/or co-selection for resistance to other antimicrobials (phenotypic or genotypic description) • Existing prevalence of commensals and zoonotic microorganisms in hosts and proportion resistant to the antimicrobial (and minimal inhibitory concentration levels) • Primary and secondary transmission among hosts • Animal management factors affecting immunity
Other possible sources of resistant microorganisms for the host	<ul style="list-style-type: none"> • Prevalence of other hosts carrying microorganisms of interest; fraction that are resistant to antimicrobial in question • Prevalence of animal feed contaminated with resistant microorganisms • Prevalence of resistant microorganisms in soil or water, animal and human waste products
Possible output	<p>Estimate or probability of the prevalence of host species carrying resistant commensal and/or resistant zoonotic microorganisms presented for food harvest that is attributable to the intended use of the antimicrobial, and the level of contamination</p>

**Table 3. Points for Consideration of Post-Harvest Factors
in the Exposure Assessment**

Element	Description or scope of data
Primary contamination of the food product	Prevalence of commensals and zoonotic microorganisms present in the host at slaughter or time of food harvest and proportion resistant to the antimicrobial
Food production factors	Factors affecting the frequency and level of microorganism contamination: <ul style="list-style-type: none"> • Sanitation and process controls • Methods of processing • Points for cross-contamination • Packaging • Distribution, and storage • Regional or seasonal differences in quantity of food products produced
Consumer behaviour	<ul style="list-style-type: none"> • Storage and cooking • Cross-contamination • Role of food handler as a source of contamination • Human-to-human transmission of the microorganisms • Overall per capita consumption • Patterns of consumption and socio-economic, cultural, ethnic and regional differences
Microbial factors	Capacity of food-derived resistant microorganisms to transfer resistance to human commensal and/or pathogenic microorganisms
Possible output	Estimate of the likelihood and level of contamination of the food product at the time of consumption with resistant microorganisms and attendant uncertainty

6.3. HAZARD CHARACTERIZATION

The hazard characterization step considers the characteristics of the pathogen, matrix and host in order to determine the probability of illness upon exposure to the pathogen (FAO/WHO, 2003a and 2006a). AMR-RA also includes the characteristics of the acquired resistance so as to estimate the additional consequences that can occur as a result of illness attributed to a resistant pathogen (OIE, 2003 and 2007). The overall structure of the consolidated hazard characterization step in the AMR-RA is presented in Figure 2 (FAO/WHO, 2003a and 2006a; OIE, 2007) and the hazard characterization step has incorporated the consequence assessment of the OIE guideline that considers the relationship between the exposure and the adverse effect with the emphasis on the severity of the adverse health consequence (FDA, 2003; OIE, 2007).

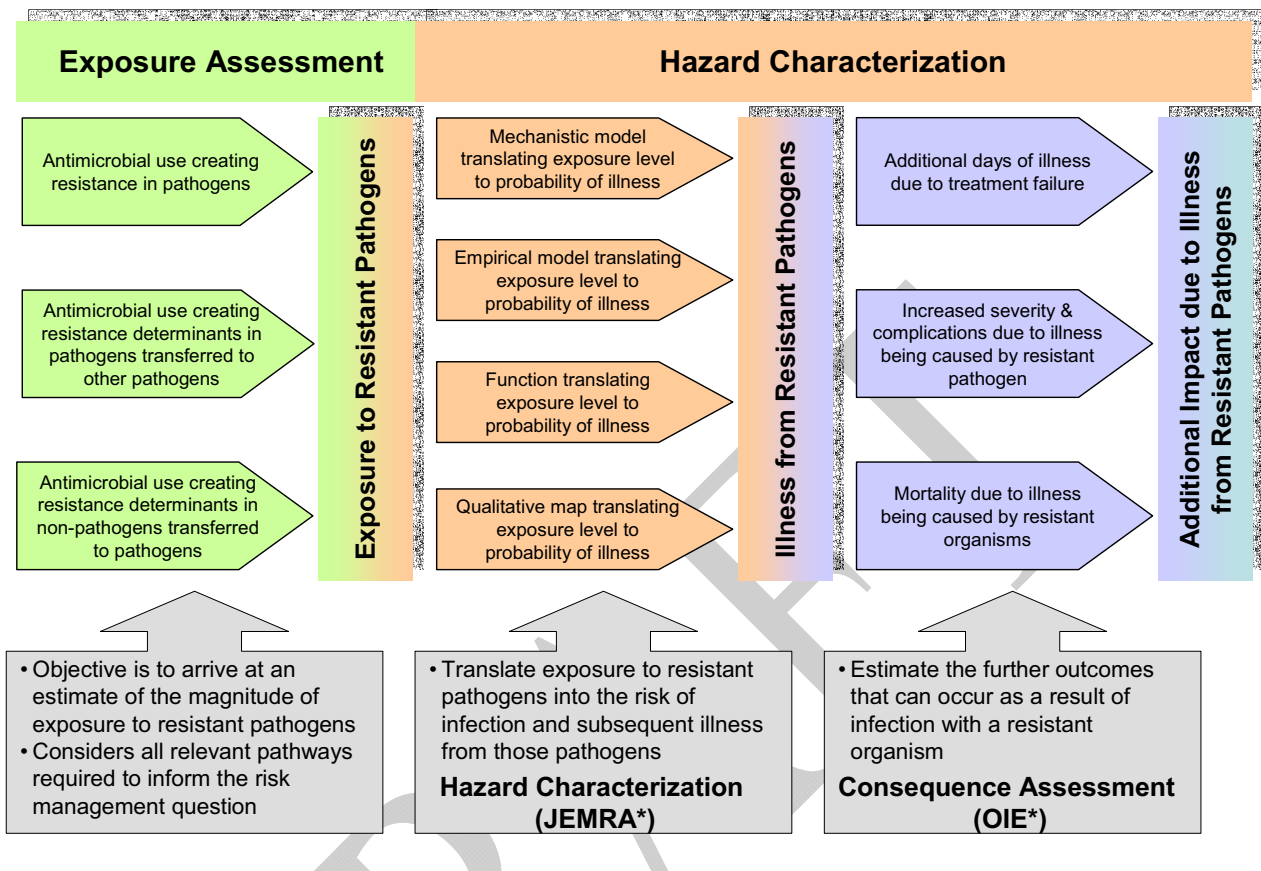


Figure 2. Scheme for the consolidated Hazard Characterization in AMR-RA
 (*: JEMRA, Joint FAO/WHO Expert Meetings on Microbiological Risk Assessment [FAO/WHO, 2003a and 2006a]; OIE, World Organisation for Animal Health [OIE, 2007])

The hazard characterization step translates exposure levels to risk levels (i.e., dose-response) using a number of potential tools. However, paramount to this is that the exposure assessment step provides an estimate of the level of exposure of the human population to resistant pathogens or resistance determinants. In order to translate this exposure to risk, the appropriate models can potentially be employed. A comprehensive model with high quality data will have a higher degree of confidence on the estimates of adverse health effects. Consideration will need to be given to how exposures are converted into risks as well as the scales used.

In the situation where the resistant microorganisms are assessed and they do not exhibit increased adverse health effects compared to the non-resistant microorganisms, then the AMR-RA is similar to non-AMR microbiological risk assessments. The risk outcome in AMR-RA, like microbiological risk assessments, will focus on illness, except in this case the focus is specifically on illness attributed to resistant pathogens. It also considers the

subsequent risk of treatment failure or other complications as a result of infection from microorganisms that have acquired resistance. It is important to recognize that, compared to non-AMR-RA, these outcomes are just a series of additional consequences that can occur following the initiating infection event. The hazard characterization step estimates the probability of infection, and then conditional to this event, estimates the probability of illness. The other consequences that occur because infection is from a resistant microorganism are additional conditional probabilities, as illness is conditional on infection.

Further assessment of the severity of the adverse human health effects attributed to and/or associated with different categories of antimicrobials, as previously defined (FAO/OIE/WHO, 2008), should be given due consideration. In this respect, antimicrobials considered critically important in human medicine would need more comprehensive assessment, given that human health consequences are likely to be more severe if the microorganisms are resistant to those antimicrobials. However, the probability of the adverse health effects occurring needs to be factored into the overall hazard characterization.

The major factors that can have an impact on the hazard characterization are included in Table 4.

Table 4. Points for Consideration in the Hazard Characterization

Element	Description or scope of data
Resistant microorganisms and resistance determinants	<ul style="list-style-type: none">• Resistance genotype and phenotype• Transferability (mobile elements) and persistence• Pathogenicity, virulence and their linkage to resistance• Food matrix related factors that can influence the survival capacity of the microorganisms while passing through the gastro-intestinal tract.
Antimicrobial	<ul style="list-style-type: none">• Pharmacodynamics/pharmacokinetics• Use data and pattern and selection pressure• Importance in human medicine (EAGAR, 2006; Health Canada, 2006; FAO/OIE/WHO, 2008; FDA, 2003)
Adverse health effect	<ul style="list-style-type: none">• Nature of the infection/illness• Host factors and susceptible population• Diagnostic aspects• Treatment with antimicrobial therapy and hospitalization• Severity of adverse health effects• Epidemiological pattern (outbreak or endemic)• Persistence of hazards in humans
Dose-response	<ul style="list-style-type: none">• Mathematical relationship between the exposed dose and probability of human illness
Possible output	<ul style="list-style-type: none">• Illness and additional consequences attributed to the hazards (severity of the adverse health effect)

6.4. RISK CHARACTERIZATION

The risk characterization step of AMR-RA integrates the information from the preceding components of the risk assessment and synthesizes overall conclusions about risk that is complete, informative and useful for risk managers. In addition to the risk estimate, risk characterization should clearly highlight both the confidence and the uncertainty associated with the risk assessment. Additional outputs of risk characterization, which would have been defined in the purpose of AMR-RA, may include evaluation of risk management options within the context of the risk assessment (FAO/WHO, 2006b).

The adverse human health effects of concern in AMR-RA encompass the severity and likelihood of the human infections associated with the resistant microorganisms. The risk estimate may be expressed by multiple risk measures, for example in terms of individual risk, population risk, important subgroups; per meal risk or annual risk based on consumption. Health effects may be translated into burden of disease measurements such as disability adjusted life years (DALYs). The selection of the final risk measures must generally have been defined within the purpose of AMR-RA in order to determine the appropriate exposure assessment and hazard characterization outputs for risk characterization.

The risk characterization considers the key findings from the hazard identification, exposure assessment and hazard characterization to estimate the risk. Other elements to consider, depending upon the purpose of the risk assessment and the detail necessary to adequately characterize the risk, are:

- Sensitive sub-populations and whether the potential risks/exposures/health impacts were adequately characterized?
- What were the key scientific assumptions used (stated in clear language and understandable by non-mathematicians)? How do these assumptions impact on the assessment's validity?
- An explicit description of the variability and uncertainty. The degree of confidence in the final estimation of risk will depend on the variability, uncertainty, and assumptions identified in all previous steps (FAO/WHO, 1999). Risk assessors must ensure that risk managers understand the impacts of these aspects on the risk characterization.
- Sensitivity and uncertainty analysis (Table 5). Quantitative uncertainty analysis is preferred; however it may be arrived at subjectively. In the context of quality assurance, uncertainty analysis is a useful tool for characterizing the precision of model predictions. In combination with sensitivity analysis, uncertainty analysis also can be used to evaluate the importance of model input uncertainties in terms of their relative contributions to uncertainty in the model outputs.
- Strengths and weaknesses/limitations of the risk assessment – what parts are more or less robust. Particularly for a complex issue such as the risk posed by antimicrobial resistant microorganisms, discussion of the robustness of data used, i.e., weight of evidence, will enhance the credibility of the assessment.
- What is the degree of belief the assessor has in that estimates or assumptions (expert opinion) adequately filled critical data gaps? What alternatives were considered, i.e., to what extent are there plausible alternatives, or other opinions? Does the AMR-RA adequately address the questions formulated at the outset of the work? What confidence do the assessors have about whether the conclusions can be relied upon for making decisions?
- Key conclusions as well as important data gaps and research needs.

The major factors to be considered in the risk characterization are presented in Table 5 (OIE, 2007).

Table 5. Points for Consideration in the Risk Characterization

Element	Description or scope of data
Factors in risk estimation	<ul style="list-style-type: none">• Number of people falling ill and the proportion of that number with resistant strains of microorganisms• Increased severity or duration of infectious disease• Number of person-days of illness per year• Deaths (total per year; probability per year or lifetime for a random member of the population or a member of a specific more exposed or more vulnerable subgroup)• Importance of pathology caused by the target microorganisms.• Absence of alternate antimicrobial therapy• Incidence of resistance observed in humans• Consequences to allow weighted summation of (e.g. illness and hospitalization) or some arbitrary scale of impact to allow weighted summation of different risk impacts
Sensitivity analysis	<ul style="list-style-type: none">• Effect of changes in model input values and assumption on model output• Robustness of model results (output)
Uncertainty and variability analysis	<ul style="list-style-type: none">• Range and likelihood of model predictions• Characterize the precision of model prediction• Relative contributions of uncertainties in model input to uncertainty in the model output

6.5. DOCUMENTATION

The AMR-RA should be fully documented to be consistent with the established principles in Codex CAC/GL-62 document (FAO/WHO, 2007).

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SECTION 8. APPENDICES

Appendix 1. Qualitative Ranking of the Outputs of AMR-RA

In risk assessment, it is important to provide an appropriate ranking of outputs from the key steps of the process. In a quantitative risk assessment, various outputs will be expressed numerically. The following examples are included to rank qualitatively the outputs from the Exposure Assessment, Hazard Characterization, and Risk Characterization steps.

1. Ranking the Exposure Assessment Output

The ranking of “**Negligible, Low, Medium, High, and Not Assessable**” may be used for qualitative determination of the probability of human exposure to a given resistant microorganism in a given food or feed commodity, animal species or plants. The different ranking is defined below:

- **Negligible (Rare):** The probability of exposure to susceptible people is extremely low.
- **Low (Unlikely):** The probability of exposure to susceptible people is low but possible.
- **Medium (Likely/Probable):** The probability of exposure to susceptible people is likely.
- **High (Almost Certain):** The probability of exposure to susceptible people is certain or very high.
- **Not assessable:** The probability of exposure to susceptible people cannot be assessed.

2. Ranking the Hazard Characterization Output

The AMR-related adverse human health effects (i.e., risk endpoints) may be ranked qualitatively as below (modified after National Cancer Institute, 2006. Common terminology criteria for adverse events v3.0. <http://ctep.cancer.gov/forms/ctcae3.pdf>). It is considered that adverse health effects associated with the microorganisms that are resistant to critically important antimicrobials in human medicine (FAO/WHO/OIE, 2008. http://www.fao.org/ag/agn/agns/files/Prepub_Report_CIA.pdf) will likely have a more severe consequence than those with microorganisms resistant to antimicrobials of other categories.

- **Negligible:** No adverse human health consequences or within normal limits.
- **Mild:** Symptoms are minimally bothersome and no therapy is necessary.
- **Moderate:** Symptoms are more pronounced, or of a more systemic nature than mild symptoms but not life threatening. Some form of treatment is usually indicated.
- **Severe:** Symptoms are potentially life threatening and require systematic

treatment and/or hospitalization. Increase severity may occur due to the AMR.

- **Fatal:** Directly or indirectly contributes to the death of the subject. Treatment failure is likely expected due to the AMR.

3. Ranking the Risk Characterization Output

In a qualitative risk assessment, the risk estimate may be integrated into the qualitative (descriptive) considerations of “**Negligible, Low, Medium, High, and Very High**” from the outputs of the Exposure Assessment and Hazard Characterization steps. An example of integration is presented in Table 6.

Table 6. Integration of the Outputs of Hazard Characterization and Exposure Assessment into the Qualitative Risk Estimation

Exposure Assessment -Probability of Exposure	Hazard Characterization -Severity of Adverse Health Effect	Qualitative Risk Estimation
Negligible	Negligible	Negligible
Low (Unlikely)	Negligible	Negligible
Medium (Possible)	Negligible	Low
High (Almost Certain)	Negligible	Low
Negligible	Low (Mild)	Low
Low (Unlikely)	Low (Mild)	Low
Medium (Possible)	Low (Mild)	Medium
High (Almost Certain)	Low (Mild)	Medium
Negligible	Medium (Moderate)	Low
Low (Unlikely)	Medium (Moderate)	Low
Medium (Possible)	Medium (Moderate)	High/Medium
High (Almost Certain)	Medium (Moderate)	High
Negligible	High (Severe)	Low
Low (Unlikely)	High (Severe)	Medium
Medium (Possible)	High (Severe)	High
High (Almost Certain)	High (Severe)	Very High
Negligible	Very High (Fatal)	Medium/Low
Low (Unlikely)	Very High (Fatal)	High
Medium (Possible)	Very High (Fatal))	Very High
High (Almost Certain)	Very High (Fatal)	Very High

Appendix 2. Outline of Information Required for Conducting an AMR-RA

1. Purpose and Scope

2. Hazard Identification

- 2.1. Identification of hazard of concern: antimicrobial resistant microorganisms and resistance determinants in food and animal feed (and non-human antimicrobial use)
- 2.2. The antimicrobial and its properties
 - 2.2.1. Description of the antimicrobial – name, formulation, etc.
 - 2.2.2. Class of antimicrobial
 - 2.2.3. Mode of action and spectrum of activity
 - 2.2.4. Existing or potential non-human uses of the antimicrobial and related agents
 - 2.2.5. Related agents used in human medicine and their importance
 - 2.2.6. Intrinsic and acquired resistance in pathogenic and commensal microorganisms
 - 2.2.7. Mechanism of resistance and their prevalence among human and non-human microflora
- 2.3. Microorganisms and resistance related information
 - 2.3.1. Potential human pathogens (species/strain) that likely acquire resistance in non-human hosts
 - 2.3.2. Potential human health impacts from resistant infections
 - 2.3.3. Commensals (species/strain) that likely acquire resistance determinants in non-human hosts and transmit them to human pathogens
 - 2.3.4. Potential routes of transmission
 - 2.3.5. Mechanisms of antimicrobial resistance
 - 2.3.6. Association of resistance with virulence and pathogenicity
 - 2.3.7. Location of resistance determinants and their frequency of transfer to related and unrelated microorganism species
 - 2.3.8. Co- and cross-resistance and/or multiple resistance, and importance of other antimicrobials whose efficacy is likely to be compromised
 - 2.3.9. Ability of resistant microorganisms to survive in the food chain including during processing, storage and handling of foods
 - 2.3.10. Interaction of the resistant microorganisms with the environment and further growth and contamination of food and water
- 2.4. Relationship of presence of antimicrobial resistant microorganisms or determinants in/on food and potential adverse human health impacts

3. Exposure Assessment

- 3.1. Factors affecting prevalence of hazard on-farm (pre-harvest)
 - 3.1.1. Resistance selection pressure: frequency, quantity and duration of non-human use of antimicrobials
 - 3.1.2. Methods and routes of antimicrobial administration
 - 3.1.3. Pharmacodynamics and pharmacokinetics of antimicrobial
 - 3.1.4. Microorganisms/resistance determinants of concern
 - 3.1.5. Resistance mechanism and transferability
 - 3.1.6. Co- and cross-resistance and multiple antimicrobial resistance other potential sources of resistance selection
- 3.2. Factors affecting prevalence of hazard in food (post-harvest)
 - 3.2.1. Frequency and level of resistant organism/resistance determinants in food
 - 3.2.2. Microbial ecology in food: survival capacity and redistribution of microorganism in the food chain
 - 3.2.3. Occurrence and probability of resistance gene transfer from resistant microorganisms to human commensals/pathogens
 - 3.2.4. The level of sanitation and process control in food processing, and likely environmental contamination
- 3.3. Transfer of hazard
 - 3.3.1. Primary or secondary transmission of resistance determinants/resistant microorganisms among animals, food, feed, environment and humans
 - 3.3.2. Resistance gene transferability
 - 3.3.3. Potential human exposure from direct contact to primary production environments
 - 3.3.4. Potential human to human transmission of resistant organism
- 3.4. Exposure to hazard
 - 3.4.1. Quantity of various food commodities consumed
 - 3.4.2. Point of food consumption (home or commercial establishment)
 - 3.4.3. Human demographics, socio-cultural etiquettes in relation to food consumption and susceptibility
 - 3.4.4. Food handlers as a source of contamination
 - 3.4.5. Factors favouring resistance enrichment (e.g., use of antimicrobial for unrelated purpose)
 - 3.4.6. Consumption of a particular food commodity could be qualitatively classified as low, medium or high

4. Hazard Characterization

- 4.1. Resistant microorganisms and resistance determinants
 - 4.1.1. Description of microorganism including pathogenicity
 - 4.1.2. Resistance occurrence
 - 4.1.3. Epidemiological patterns

4.2. Antimicrobial

- 4.2.1. Pharmacodynamics/pharmacokinetics
- 4.2.2. Use data and pattern, and selective pressure
- 4.2.3. Importance in human medicine

4.3. Human host and adverse health effects

- 4.3.1. Host factors and susceptible population
- 4.3.2. Nature of the infection, illness or disease
- 4.3.3. Persistence of hazard in humans
- 4.3.4. Diagnostic aspects
- 4.3.5. Epidemiological pattern (outbreak or endemic)
- 4.3.6. Treatment with antimicrobial therapy and hospitalization
- 4.3.7. Drug selection for infections
- 4.3.8. The overall antimicrobial drug importance ranking

4.4. Dose-Response relationship: Mathematical relationship between the exposed dose and probability of human illness

5. Risk Characterization

5.1. Risk estimate

- 5.1.1. Integrates the outcome of hazard identification, hazard characterization and exposure assessment to determine the probability and severity of adverse human health impacts
- 5.1.2. Probability and severity should be calculated for each endpoint defined, and for general population as well as specific (e.g., susceptible) sub-populations

5.2. Uncertainty and variability analyses

5.3. Sensitivity analysis