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FOOD AND AGRICULTURE ORGANIZATION OF THE UNITED NATIONS

WORLD HEALTH ORGANIZATION

JOINT OFFICE: Viale delle Terme di Caracalla 00153 ROME Tel: 39 06 57051 www.codexalimentarius.net Email: codex@fao.org Facsimile: 39 06 5705 4593

Agenda Item 4 **CX/AMR 08/2/4 Add.1**
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JOINT FAO/WHO FOOD STANDARDS PROGRAMME

***AD HOC* CODEX INTERGOVERNMENTAL TASK FORCE ON ANTIMICROBIAL RESISTANCE**

Second Session

Seoul, Republic of Korea, 20-24 October 2008

PROPOSED DRAFT RISK ASSESSMENT GUIDANCE REGARDING FOODBORNE ANTIMICROBIAL RESISTANT ORGANISMS (REPORT OF THE PHYSICAL WORKING GROUP) (NO1-2008)
(Comments at Step 3)

The following comments have been received from: Argentina, Australia, Brazil, Costa Rica, Iran, Kenya, Mexico, New Zealand, Norway, Republic of Korea, The United States of America, Consumers International, IDF, IFAH

ARGENTINA

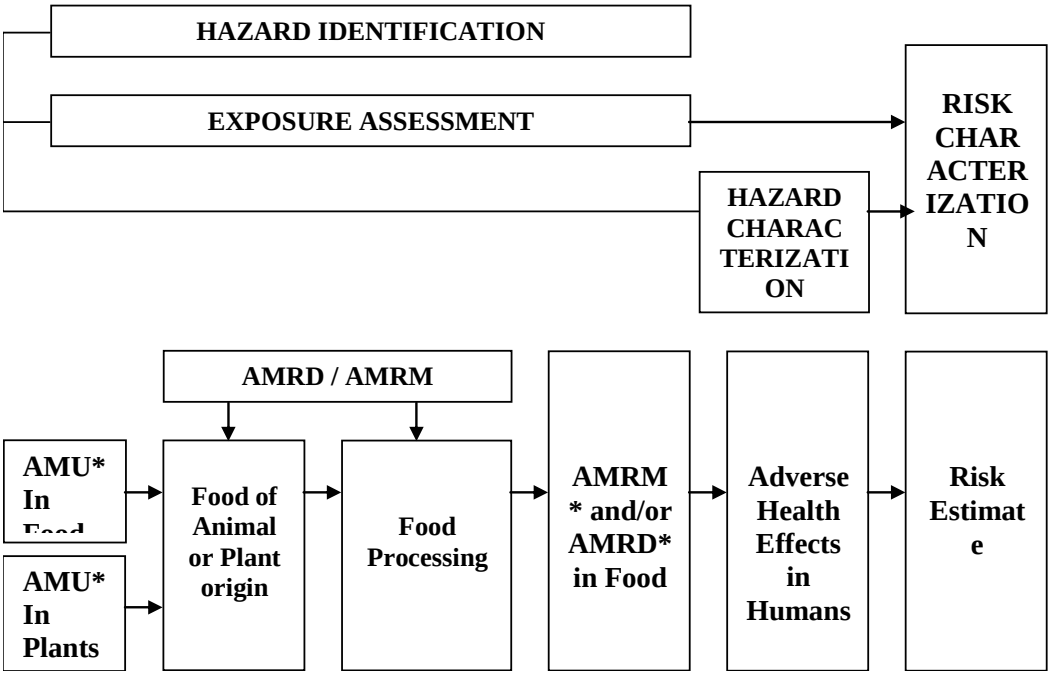
Argentina appreciates the opportunity to comment on this document.

General Comments;

In the Spanish version of the document, the word "should" is translated as "deberá", which we consider not to be very faithful. We therefore suggest that this word should be replaced with "debería".

Specific Comments;

As regards SECTION 2. SCOPE, Figure 1 should be changed to read as follows:



As regards **SECTION 3. DEFINITIONS** (p. 17), in the definition of **Cross resistance** the word "bacterium" should be replaced with "microorganism" for the sake of consistency in all the texts being developed.

In **SECTION 4. GENERAL PRINCIPLES** (p. 18), bullet point 3, the reference to "**unrelated** human infections" should be deleted as it would exceed the scope under the terms of reference of this Task Force.

In bullet point 4, the reference to the need to consider the dynamics of resistance within microbial populations in environment should be more circumscribed. Thus, the scope of this analysis should be more clearly defined. We suggest the deletion of the reference to the "**environment**".

In **SECTION 5.3 (p. 19), paragraph 17,** we believe that bullet point 3 should be deleted and the wording "**, which may include their interaction with the environment**" should be added in bullet point 5 at the end.

In **SECTION 6.2. EXPOSURE ASSESSMENT** (p. 20), paragraph 21 line 7, the original wording was "(microbial load)", which should be relocated as follows: "[…] may alter the level of resistant microorganisms (**microbial load**) or resistant determinants […]"

In paragraph 24, the *Recommended Code of Practice on Good Animal Feeding (CAC/RCP 5-2004)*, developed by the Ad Hoc Intergovernmental Task Force on Animal Feeding should be taken into consideration.

In the English version, on Table 1 (p. 20) "spaying" should be replaced with "spraying".

In **SECTION 6.4 RISK CHARACTERIZATION** (p. 24), paragraph 33, bullet point 1, the term "**sensitive sub-populations**" does not clearly reflect whether it refers to human populations with special vulnerability. Further clarification is requested.

In bullet point 7, we believe that giving the assessor "the degree of belief" regarding the validity of the assumptions that fill the critical data gaps gives rise to the possibility of make assertions that deviate from the basic principles established for risk analysis, particularly transparency in the analysis and decision making. We propose to delete the first question of the bullet point.

In **SECTION 10**, Appendices, Appendix 1, example 2, the term "rare" between brackets should be deleted.

PROPONED DRAFT RISK ASSESSMENT GUIDANCE REGARDING FOODBORNE ANTIMICROBIAL RESISTANT ORGANISMS.

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SECTION 1. INTRODUCTION

(This section may be revised with merged document – The AMR Risk Analysis Document)

1. Antimicrobial resistance (AMR) is a major global public health concern and a food safety issue. 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 an important vehicle for spread of resistant microorganisms from animals to humans.

2. 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 (AMRRA) 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.

3. 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.

4. 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 nonhuman 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). Risk analysis of AMR on animal feeds may also consider Codex Code of Practice on Good Animal Feeding (CAC/RCP 54-2004) as well as Animal Feed Impact on Food Safety (FAO/WHO, 2008a).

SECTION 2. SCOPE

5. The scope of this guidance document encompasses the overall risk to human health relating to antimicrobial resistant microorganisms and resistance determinants in food, food animals, food production/processing, and plants arising from the non-human use of antimicrobials.

6. 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 in food. A schematic presentation in Figure 1 shows the scope and relationship of the components of AMR-RA.

7. The extent of the farm-to-table pathway covered by the AMR-RA should fit its intended purpose. The scope of the risk assessment is determined by the risk managers in consultation with risk assessors. Considering the complexity of the AMR issue, specific issues raised or questions asked by risk managers should be as precise as possible (e.g. combinations of microorganism/antimicrobial class, particular use of antimicrobial, target species, specific geographical area etc.) for risk assessors to specifically address the risk issue.

8. Intended users of this document include the joint FAO/WHO meetings on microbiological risk assessment (JEMRA), the World Organisation for Animal Health (OIE), and national/regional food safety authorities 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. It can be adapted by member countries to conduct a pre- or post-market risk assessment of an antimicrobial intended for non-human use (either therapeutic or nontherapeutic)2, or to conduct an AMR-RA of food products (including imported food products).

[2] Consistent with Codex Code of Practice to Minimize and Contain Antimicrobial Resistance CAC/RCP 61-2005.

9. The risk assessment of AMR marker genes in recombinant-DNA plants3 or microorganisms4 or of certain food ingredients, which could potentially carry AMR genes such as probiotics5 and residue issues are outside the scope of this document.

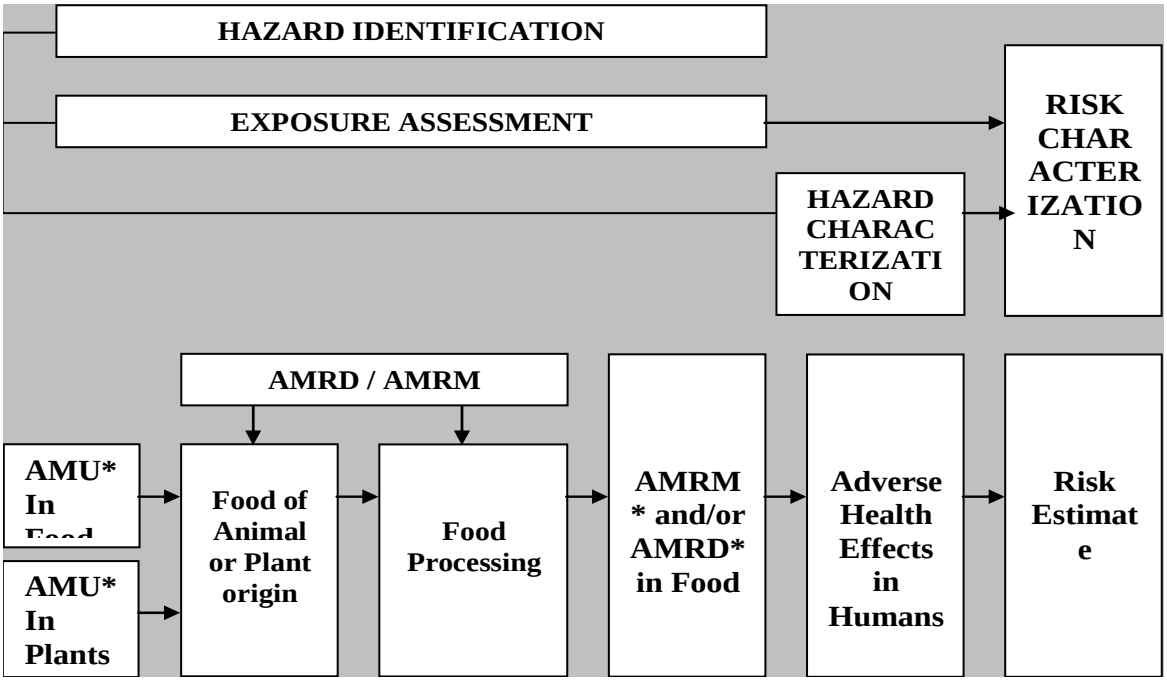

Figure 1. Schematic showing the scope and relationship of the components of AMR-RA

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

SECTION 3. DEFINITIONS

(This section may be finalized with merged AMR Risk Analysis Document)

10. 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) are applicable to this document. Some established Codex definitions are cited in *italics*. Definitions cited from existing FAO/OIE/WHO documents are referenced as appropriate.

Adverse Health Effect - An undesirable or unwanted outcome in humans. In this document, this refers to the human infections or their frequency caused by antimicrobial resistant microorganisms and resistance determinants in food or acquired from food of animal/plant origin as well as the increased frequency of infections and treatment failures, loss of treatment options and increased severity of infections manifested by prolonged duration of illness, increased frequency of bloodstream infections, increased hospitalization, and increased mortality (FAO/OIE/WHO, 2003).

Antimicrobials (Antimicrobial Agents) - Any substance of natural, semi-synthetic, or synthetic origin that at in vivo concentrations kills or inhibits the growth of micro-organisms by interacting with a specific target (FAO/OIE/WHO, 2008).

Antimicrobial class: Antimicrobial agents with related molecular structures, often with a similar mode of action because of interaction with a similar target and thus subject to similar mechanism of resistance. Variations in the properties of antimicrobials within a class often arise as a result of the presence of different molecular substitutions, which confer various intrinsic activities or various patterns of pharmacokinetic and pharmacodynamic properties.

[3] 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).

[4] 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).

[5] 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).

Antimicrobial Resistance - The ability of a microorganism to multiply or persist in the presence of increased level of an antimicrobial agent relative to the susceptible counterpart of the same species (FAO/OIE/WHO, 2008).

Commensal – Microorganisms participating in a symbiotic relationship in which one species derives some benefit while the other is unaffected.

Co-resistance: Various resistance mechanisms, each conferring resistance to an antimicrobial class, associated within the same bacterial host (FAO/OIE/WHO, 2008).

Cross-resistance: A single resistance mechanism in a ~~bacterium~~ **microorganism** conferring resistance at various levels to other members of the class or to different classes. The level of resistance depends on the intrinsic activity of the antimicrobial agent, in general the higher the activity, the lower the level of resistance. Cross-resistance implies crossselection for resistance (FAO/OIE/WHO, 2008).

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.*

Pathogen – A microorganism that causes illness or disease.

Pre-Harvest – The stage of food animal or plant production prior to the slaughtering or harvesting.

Post-Harvest – The stage of food animal or plant production following the slaughtering or harvesting, which often includes cooling, cleaning, sorting and packing.

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, thereby enabling horizontal transmission from resistant to susceptible strains.

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 theprobability 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

11. 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 or plants), 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/efficacy 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

12. 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.

13. 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. Similarly, input from stakeholders should be sought in identifying available data or information for AMR-RA. 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

14. The purpose of AMR-RA is to determine the human health risk associated with specific antimicrobial resistant microorganism(s) and/or specific resistance determinant(s) acquired from food and the impact of non-human antimicrobial use. It can also provide guidance to risk managers on appropriate risk management options.

5.2. QUALITATIVE AND QUANTITATIVE AMR-RA

15. 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

16. 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 gaps should be clearly presented using a weight of evidence approach (e.g., FAO/OIE/WHO, 2008; JETACAR, 1999).

Data and possible sources of information:

17. 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 taking into consideration epidemiologic and microbiological breakpoints.

• Epidemiological investigations of outbreaks and endemic cases associated with resistant microorganisms.

• Clinical studies including case reports on the relevant foodborne-related infectious disease prevalence, primary and secondary transmission, and antimicrobial therapy.

~~• Studies on interaction between microorganisms and their environment through the farm-to-table continuum.~~

• Non-human antimicrobial use data such as daily dosage, species-specific (including plants), route of administration, and duration.

• Investigations of the characteristics of resistant microorganisms and resistance determinants (in-vitro and in-vivo studies), **which may include their interaction with the environment.**

• Research on properties of antimicrobials including their resistance selection (in-vitro and in-vivo) potential and transfer of genetic elements and the dissemination of resistant bacteria in the environment.

• Field animal trials addressing the linkage of antimicrobial usage and resistance.

• Information on the link between resistance, virulence, and/or fitness of the bacterium

• Application of available pharmacokinetic/pharmacodynamic data in the development of drug use that may vary on a regional level

SECTION 6. PROCESS OF AMR-RA

18. 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[6] (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

19. The process of hazard identification recognizes that the hazards, resistant pathogenic and commensal microorganisms and/or resistance determinants of food, animal feed, and/or of animal/plant origin, have the potential to cause an adverse human health effect. The resistance determinants from resistant microorganisms (e.g., commensals) can disseminate both vertically and horizontally. Intra- or inter-species transfer occurs for mobile resistance determinants from both pathogenic and commensal microorganisms. In this document, hazard includes antimicrobial resistant microorganisms (pathogenic and commensal) and their resistance determinants (derived from food, animal feed, animals, and plants). The conditions under which the hazard produces adverse health effects include scenarios through which humans could become exposed to a pathogen which contains the resistance determinant. The scope of hazard identification (e.g., combinations of microorganisms/antimicrobial class, particular use of antimicrobial, target species, specific geographical area etc.) is guided by the question posed by risk managers for a specific AMR-RA.

20. 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.

6.2. EXPOSURE ASSESSMENT

21. The exposure assessment will address all the modular pathways as a consequence of non-human uses of antimicrobials resulting in 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 **(microbial load)** 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.

22. 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 1 and 2, 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, 2006a and 2008b; FAO/OIE/WHO, 2008; FDA, 2003; JETACAR, 1999; and OIE, 2003).

23. An AMR-RA addressing 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 to the extent possible the factors that increase their prevalence in food.

24. When the hazard of interest is the resistance determinant including those in commensal microorganisms, then exposure assessment should consider whether they can be transferred to human pathogens that subsequently become resistant. 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, AMR-RA may need to consider these factors.

The *Recommended Code of Practice on Good Animal Feeding (CAC/RCP 5-2004)* should be taken into consideration.

[6] 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 (FAO/WHO, 2008b), and risk characterization (in press).

Table 1. Possible pre-harvest data requirements for exposure assessment - Element Description or scope of data

	• Dosing regimen and duration of use • Number of administrations/administration periods in the defined time period • Cumulative effects of use of other antimicrobials in the defined time period
Target animal or crop and microbial factors affecting resistance development and spread	• Seasonal changes in microorganism prevalence • Rate of resistance development in commensal and zoonotic microorganisms in targets after administration of an antimicrobial agent • Resistance mechanisms, location of resistance determinants, occurrence and rate of transfer of resistance between microorganisms • Cross-resistance and/or co-selection for resistance to other antimicrobials (phenotypic or genotypic description) • Prevalence of commensals and zoonotic microorganisms in targets and proportion resistant to the antimicrobial (and minimal inhibitory concentration levels) • Primary and secondary transmission among targets • Animal management factors affecting immunity
Other possible sources of resistant microorganisms for the target	• Prevalence of other targets carrying microorganisms of interest; fraction that are resistant to antimicrobial agent in question • Prevalence of animal feed contaminated with resistant microorganisms • Prevalence of resistant microorganisms in soil or water, animal and human waste products
Possible outcome	Estimate or probability of the prevalence of the target animal or crop carrying resistant commensal and/or resistant zoonotic microorganisms presented for food harvest that is attributable to the use of the antimicrobial, and the level of contamination

Element	**Description or scope of data**
Selection pressure	Extent of antimicrobial agent use or proposed use • Number of animal, crop or target farms exposed to the antimicrobial agent in the defined time period • Geographical distribution of use and/or farms
	Intensity of non-human use of antimicrobials • How much is used per target (as quantitative as possible) in the defined time period • Methods and routes of administration of the antimicrobial agent (individual/mass medication/for plants-is that spaying?)

Table 2. Possible post-harvest data requirements for exposure assessment - Element Description or scope of data

Table 2. Possible post-harvest data requirements for exposure assessment

Element	Description or scope of data
Initial level of contamination of the food product	Prevalence and quantity of commensals and zoonotic microorganisms present in/on the target at slaughter or time of crop harvest and proportion resistant to the antimicrobial agent
Food production factors	Factors affecting the frequency and level of microorganism contamination: 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 behaviours	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 outcome	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

25. 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 when humans are exposed to resistant pathogens including increased frequency and severity of illness (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).

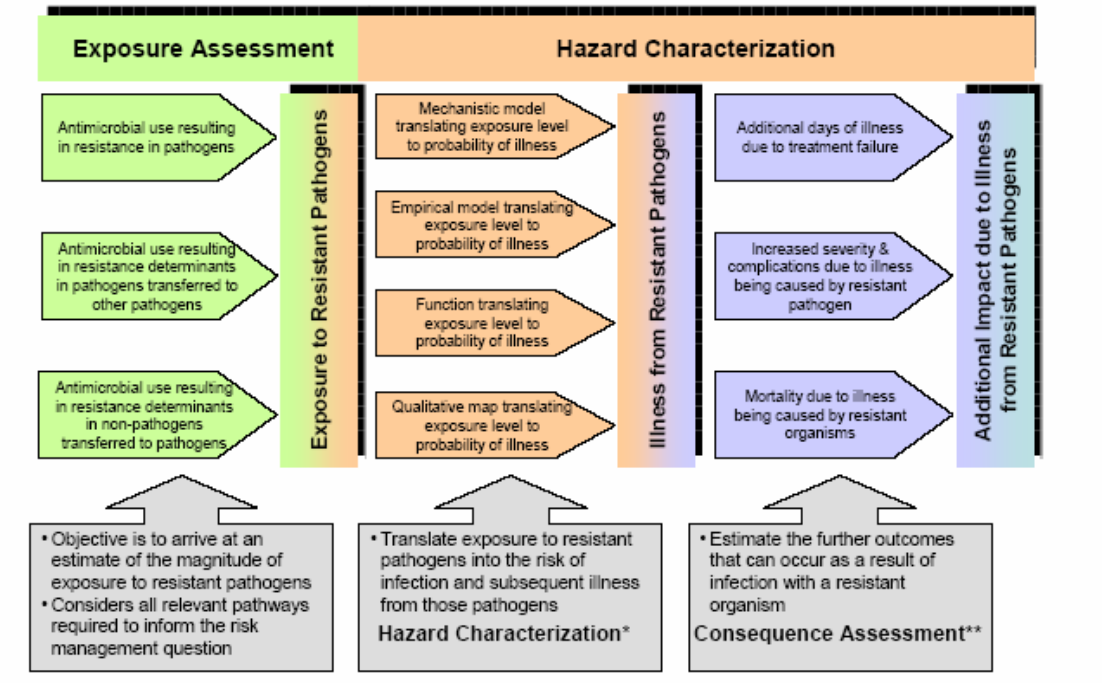

Figure 2. Scheme for the consolidated Hazard Characterization in AMR-RA
(*: concept adapted from the JEMRA [FAO/WHO, 2003a and 2006a]; **: concept adapted from the World Organisation for Animal Health [OIE, 2007])

26. 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.

27. In the situation where the resistant microorganisms are assessed and they do not exhibit increased virulence 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 including the increased frequency of infections. 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.

28. 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.

29. The major factors that can have an impact on the hazard characterization are included in Table 3.

Table 3. Possible data requirements for hazard characterization

Element Description or scope of data

Element	Description or scope of data
Resistant microorganisms and resistance determinants	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 agent	Pharmacodynamics/pharmacokinetics
	Importance in human medicine (FAO/OIE/WHO, 2008)
	Alternatives available in case of resistance, and potential impact of switching to alternative antimicrobial agent
Adverse health effect characteristics	Nature of the infection/illness
	Host factors and susceptible population
	Diagnostic aspects
	Treatment with antimicrobial agent and hospitalization
	Severity of adverse health effects
	Epidemiological pattern (outbreak or endemic)
	Persistence of hazards in humans
Dose-response	Mathematical relationship between the exposed dose of resistant pathogens or determinants and probability of human illness
Possible outcome	Probability of illness and additional consequences attributed to the resistance (severity of the adverse health effect)

6.4. RISK CHARACTERIZATION

30. 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. The purpose of risk characterization is to answer the original questions posed by risk managers and to put into context the findings from the risk assessment process including uncertainties and other findings that could have an impact on the risk management decision. As a result, the form that the risk characterization takes, and the outputs it produces will

vary from assessment to assessment as a function of the risk management request. This section provides guidance on the types of outcomes that may be informative in the risk characterization, but specific outputs such as if the risk outcome is to be measured using number of additional cases or other public health measures like disability adjusted life years (DALY's), will need to be established at the onset of the assessment process in conjunction with risk managers.

31. Additional outcomes of risk characterization, which would have been defined in the purpose of AMR-RA, may include scientific evaluation of risk management options within the context of the risk assessment (FAO/WHO, 2006b).

32. 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 DALYs. The selection of the final risk measures must generally have been defined within the purpose of AMR-RA, during the commissioning of the AMR-RA, in order to determine the appropriate exposure assessment and hazard characterization outcomes for risk characterization.

33. 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 nonmathematicians)? 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 4). 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.

• Existing microbial risk assessments

• 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.

34. The potential points for consideration in the risk characterization are presented in Table 4 (OIE, 2007).

Table 4. Potential Points for Consideration in the Risk Characterization

Element	Description or scope of data
Factors in risk estimation	Number of people falling ill and the proportion of that number with resistant strains of microorganisms
	Increased severity or duration of infectious disease due to resistance
	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 alternative antimicrobial agent
	Incidence of resistance
	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
Scientific evaluation of risk management options	Comparison of public health burden before and after interventions
Sensitivity analysis	Effect of changes in model input values and assumption on model output
	Robustness of model results (output)
Uncertainty and variability analysis	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

SECTION 7. DOCUMENTATION

(This section may be moved, potentially expanded, and included in the integrated AMR Risk Analysis Document)

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

SECTION 8. RISK COMMUNICATION

(This section may be moved, potentially expanded and included in the integrated AMR Risk Analysis Document**)**

36. Throughout the process of AMR-RA, there should be an effective communication between risk assessors and risk managers. Similarly, effective communication should be maintained between risk assessors and affected and interested stakeholders for gathering relevant input and to maintain the transparency of the AMR-RA process. The outcome of risk assessment, and management interventions where appropriate, should be communicated to all stakeholders and the general public in a timely fashion.

SECTION 9. REFERENCES

(This section may be harmonized with reference section for overall AMR Risk Analysis Document**)**

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SECTION 10. APPENDICES

Appendix 1. Outputs of Qualitative AMR-RA

A qualitative risk assessment is often preferred due to its potential lower data demands.

The level of scrutiny, review and standards of logic and reasoning to which a qualitative approach should be held are, however, no less than those that a quantitative approach is subjected to.

The following examples illustrate potential approaches that can be used to conduct a qualitative risk assessment; however this should not be viewed as a recommended or accepted default approach for adoption. The thought process and discussions that surround the development of categories for the exposure or the hazard characterization (e.g. “rare”, “high” etc) as well as how these categories translate into the ultimate risk outcome are a key part of the decision making and risk management process. The essential parts of developing a qualitative risk assessment could be grouped into three basic tasks:

• The development of qualitative statements or scores to describe the exposure assessment (e.g. “high”, “medium” etc), with careful consideration given to the implications and interpretation of these categorizations;

• The categorization of hazard characterization into qualitative statements or scores, with similar considerations as the exposure assessment into interpretation and implications;

• The process through which the different exposure and hazard characterization categories or scores are combined and integrated into overall risk levels (e.g. what does a “low” in exposure and a “high” in hazard characterization translate to, and is it different than a “medium” in both.

There are currently no pre-defined hazard characterization or exposure assessment categories that can be used, and different categories may be more suitable for certain situations. The approach used to integrate the exposure assessment and hazard characterization can also vary.

Example 1

Illustrative Exposure Assessment Scoring

Typically, in a qualitative risk assessment, the probability of the population being exposed to the hazard is translated into a series of qualitative statements. The qualitative risk assessment requires expert opinions, or other formalized,

transparent and documented process to take the existing evidence and convert it into a measure of the probability of exposure. To illustrate, the probability has been converted into the following categories and scores:

• **Negligible (0):** Virtually no probability that exposure to the hazard can occur (<1e-6)

• **Moderate (1):** Some probability for exposure to occur (1e-6 to 1e-4)

• **High (2):** Significant probability for exposure to occur (>1e-4)

The assignment of both a statement reflecting the exposure probability as well as a corresponding score is done in this example to facilitate the process through which the exposure and hazard characterization will subsequently be combined. The description of the categorical statements includes an assessment providing greater detail as to the interpretation behind each of the categories.

Illustrative Hazard Characterization Scoring

The hazard characterization translates the outcomes of this step into qualitative statements that reflect the implications of exposure to a hazard. While the exposure assessment qualitatively captures the probability of being exposed, the hazard characterization qualitatively estimates the implications of being exposed. In microbiological risk assessment, the focus of the hazard characterization step is to translate the probability of exposure to the probability of illness; however in AMR risk assessments, the focus is likely to be the implications of exposure to resistant organisms that are over and above those of being exposed to susceptible organisms. To illustrate, the following categories are proposed:

• **Negligible (0):** Probability of illness upon exposure is the same as for susceptible organisms and the outcomes as a result of illness is not different

• **Mild (1):** Probability of illness upon exposure is the same as for susceptible organisms, but the outcomes following illness are more serious requiring hospitalization

• **Moderate (2):** Probability of illness upon exposure is higher and outcomes following illness are more serious requiring hospitalization

• **Severe (3):** Probability of illness is higher and outcomes following illness are very serious requiring hospitalization as well as the potential for treatment failures requiring lengthy hospitalization

Illustrative Risk Characterization Output

Ultimately, the exposure assessment and hazard characterization need to be integrated in the risk characterization in order to estimate the risk. By assigning each of the qualitative categories (e.g. “high”, “medium” etc.) with a numerical score (e.g. 0, 1, 2, etc.), the results can be produced in a transparent way by simply multiplying the scores. The resulting risk characterization score can then be translated into meaningful qualitative risk categories. In this example, the products of the exposure assessment and hazard characterization are assigned the following categories:

• No Additional Risk: Value of 0

• Some Additional Risk: Value between 1 and 2

• High Additional Risk: Value between 3 and 4

• Very High Additional Risk: Value between 5 and 6

The results could also be presented graphically as shown below, providing a clear picture of how outcomes are judged to be “very high additional risk” or “no additional risk” for example.

		Exposure Assessment		
		Negligible	Moderate	High
Hazard Characterization	Negligible	0	0	0
	Mild	0	1	2
	Moderate	0	2	4
	Severe	0	3	6

LEGEND	
	No Additional Risk
	Some Additional Risk
	High Additional Risk
	Very High Additional Risk

Example 2

Illustrative Exposure Assessment Scoring

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.

Illustrative Hazard Characterization Scoring

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/ctcaev3.pdf). In this example, 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.

Illustrative Risk Characterization Scoring

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 5.

Table 5. 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 for an AMR-RA

This appendix lists the suggested elements to include in an AMR-RA and the level of details of the data may vary caseto- case.

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. Intrinsic and acquired resistance in pathogenic and commensal microorganisms

2.2.6. Mechanism of resistance and their prevalence among human and non-human microflora

2.2.7. Importance of antimicrobials in human medicine

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. Commensals (species/strain) that likely acquire resistance determinants in non-human hosts and transmit them to human pathogens

2.3.3. Potential routes of transmission

2.3.4. Mechanisms of antimicrobial resistance

2.3.5. Association of resistance with virulence and pathogenicity

2.3.6. Location of resistance determinants and their frequency of transfer to related and unrelated microorganism species

2.3.7. Co- and cross-resistance and/or multiple resistance, and importance of other antimicrobials whose efficacy is likely to be compromised

2.4. Relationship of presence of antimicrobial resistant microorganisms or determinants in/on food and potential adverse human health impacts

2.4.1. Clinical studies

2.4.2. Epidemiological studies and surveillance

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. Resistance transferability

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 by resistant microorganisms

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

AUSTRALIA

Australia is pleased to provide the attached comments in response to Agenda Item 4: Proposed Draft Risk Assessment Guidance Regarding Foodborne Antimicrobial Resistant Organisms at Step 3 (CX/AMR 08/2/4).

General comments;

Australia commends the Working Group led by the Canadian Codex delegation for developing the draft Risk Assessment Guidance Regarding Foodborne Antimicrobial Resistant Organisms. Australia considers that the draft document presents a comprehensive overview and guidance on the assessment of risks from the exposure to AMR organisms or AMR determinants via food. It is consistent with Codex guidelines on microbiological risk assessment.

As noted in the draft document, it would be beneficial to consolidate the INTRODUCTION section into a single AMR Risk Analysis Document. As it stands, there are a number of inconsistencies in the description of the intent and scope of the document, for example:

Paragraph 2. "….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."

Paragraph 4. "…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 nonhuman use of antimicrobial agents."

Paragraph 5. "….risk to human health relating to antimicrobial resistant microorganisms and resistance determinants in food, food animals, food production/processing, and plants arising from the non-human use of antimicrobials."

Australia considers that the words provided in paragraph 14 are much more succinct i.e. to determine the human health risk associated with specific antimicrobial resistant microorganism(s) and/or specific resistance determinant(s) acquired from food and the impact of non-human antimicrobial use. Further details on the commodities, parts of the supply chain, usages etc. that need to be considered can then be elaborated on in the body of the document.

The inclusion of examples in Appendix 1 on qualitative methods for assessing risks from AMR organisms is supported, however, it is important that they are consistent with the JEMRA Risk Characterization guidelines (soon to be published). Further consideration of the qualitative descriptors for severity is recommended.

Page	Section/Paragraph	Comments	Suggestion
5	DETAILED DISCUSSION ON THE DRAFT DOCUMENT 35. Appendices: In general, there was support for the inclusion of two appendices. Canada clarified that it should be made explicit and clear that Appendix 1 is simply an illustration on how a qualitative ranking might be done. The concern is that this could be construed as a template on to how to do a qualitative risk assessment. It is difficult to define terms such as negligible because they are value- laden judgments as to what is low, medium, etc. This is not what should be done necessarily without a lot of thought. It is recommended that at the beginning of the appendix a paragraph be added to make a strong case that it is an illustration.	The importance of "value- laden judgments" needs full emphasis and is currently not well captured in the appendix on qualitative AMR-RA	
15	SECTION 2. SCOPE 6. 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 likelihood, magnitude and severity of the adverse effects of that exposure in food. A schematic presentation in Figure 1 shows the scope and relationship of the components of AMR-RA.	Risk assessment has a strong focus on probability or likelihood of occurrence of an adverse event.	
16	Figure 1. Schematic showing the scope and relationship of the components of AMR-RA	It would be useful to include in the text a statement that the arrows connecting each of the lower boxes can represent a multitude of steps, each a potential intervention or critical control point.	
16	SECTION 3. DEFINITIONS	Agree, better to incorporate into single AMR Risk Analysis Document. Will also need to be consistent with previous Codex definitions.	

17	Commensal – Microorganisms participating in a symbiotic relationship in which one species derives some benefit while the other is unaffected.	This definition of commensal does not generally reflect what is understood by the term. Propose that a new definition be considered, for example, the definitions by the Alliance for the Prudent Use of Antibiotics (APUA) available at: http://www.tufts.edu/med/apua/Miscellaneous/Glossary.html Commensal Usually refers to a microorganism that lives in close contact with a host organism (human, animal or plant) without causing disease in the host. Commensal organisms can be beneficial to the host. Some microorganisms can be a commensal for one host species but cause disease in a different species.	
17	Hazard Characterization - The qualitative and/or quantitative evaluation of the nature of the adverse health effects associated with the hazard, including attendant uncertainties.	Just as included in the definition of "risk characterisation" it is important to explicitly identify and describe limitations and uncertainties.	
17	Post-Harvest – The stage of food animal or plant production following the slaughtering or harvesting, which often includes cooling, cleaning, sorting and packing, transport and storage.	Although transport and storage may be implicit in the original definition, these aspects of the post-harvest period can be critical periods for risk management.	
18	SECTION 5.1 PURPOSE 14. The purpose of AMR-RA is to determine the human health risk associated with specific antimicrobial resistant microorganism(s) and/or specific resistance determinant(s) acquired from food and the impact of non-human antimicrobial use.	This is a much more succinct description of the focus of AMR-RA.	Suggest using throughout the document (see "general comments").
18	SECTION 5.2 QUALITATIVE AND QUANTITATIVE AMR-RA 15. 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 carefully and with full appreciation of the strengths and limitations of either approach. 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.	The statement "quantitative data should be used to the greatest extent possible" is strongly supported.	

19	SECTION 5.3 SOURCES OF DATA OR EVIDENCE Data and possible sources of information: 17. 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 taking into consideration epidemiologic and microbiological breakpoints. Information on factors reducing or impeding the dissemination and transfer of resistance determinants.	Information on barriers to the transfer of resistance determinants could also be added to the list of considerations.	
20	SECTION 6.2 EXPOSURE ASSESSMENT 21. The exposure assessment will address all the modular pathways as a consequence of non-human uses of antimicrobials resulting in the emergence and dissemination of resistant microorganisms and resistance determinants to humans via the food chain.	It is not clear what is meant or implied by the description "modular pathways".	
20	23. An AMR-RA addressing 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 to the extent possible the factors that increase and decrease their prevalence in food.	The direction of factors included in assessment of risk can either add to or subtract from the final estimate.	
23	SECTION 6.3 HAZARD CHARACTERIZATION 26. First sentence "The hazard characterizaion step translates exposure levels to risk levels…"	The translation of exposure levels to <u>risk</u> levels is the function of risk characterization.	The output from the hazard characterization, including the dose-response relationship where available, assists in translating levels of exposure to a likelihood of an adverse outcome. Paramount to this is that….
23	Table 3. Possible data requirements for hazard characterization Pharmacodynamics/pharmacokinetics	It is not obvious how pharmacodynamics/pharmacokinetics information will contribute to and be incorporated into hazard characterisation. Selection of and referral to an appropriate reference source would be very helpful.	
23	Table 3. Possible data requirements for hazard characterization	As with Table 4, explicit identification of uncertainty and variability would be an important consideration.	
24	SECTION 6.4	These dot points are not necessarily specific to AMR-RA and will most	Suggest incorporating the

	RISK CHARACTERIZATION 33. Dot points	likely be covered in the JEMRA Risk Characterization Guidelines. There is also a degree of overlap with information provided in Table 4.	information from dot points into Table 4.
27	SECTION 10 APPENDICES Appendix 1 Outputs of Qualitative AMR-RA First sentence "A qualitative risk assessment is often preferred due to its potential lower data demands."	The introductory paragraph of this appendix on qualitative AMR-RA does not reflect the limitations and cautions inherent in such an approach. As one example, there is no caution about or against the use of "value- laden judgments", as first highlighted by Canada on page 5. A qualitative risk assessment may be undertaken for a number of reasons, including the quantity and quality of available data (i.e. insufficient to undertake a quantitative assessment) needs of the risk managers resources expertise etc.	Although quantitative risk assessments are encouraged, qualitative assessments are often preferred due to their potential lower data demands.
27	Example 1. Illustrative Exposure Assessment Scoring • Negligible (0): Virtually no probability that exposure to the hazard can occur (<1e-6) • Moderate (1): Some probability for exposure to occur (1e-6 to 1e-4) • High (2): Significant probability for exposure to occur (>1e-4)	It is unclear what the exponential terms in brackets represent. They are clearly derived from a quantitative RA and it is not obvious how they relate to qualitative descriptions. The inclusion of quantitative terms could be interpreted as endowing the qualitative AMR-RA with a degree of quantitation that it does not have.	
31	Appendix 2. Outline of Information for an AMR-RA 2. Hazard Identification "2.2.7 Importance of antimicrobials in human medicine"	May need to consider individual or multiple antimicrobials.	2.2.7 Importance of antimicrobial(s) in human medicine
31	3. Exposure Assessment "3.1.3. Pharmacodynamics and pharmacokinetics of antimicrobial"	Exposure assessment information "3.1.3. Pharmacodynamics and pharmacokinetics of antimicrobial" may more properly belong as part of Hazard Characterisation.	
32	3.3.1. Primary or secondary transmission of resistance determinants/resistant microorganisms among animals, food, feed, environment and humans	There is no definition or description of "Primary or secondary transmission".	
33	4. Hazard Characterization "4.4 Dose-response relationship: Mathematical…"	There could be other endpoints measured in dose-response model e.g. illness, infection, death etc.	4.4 Dose-response relationship: Mathematical relationship between the exposed dose and probability of adverse outcome (e.g. infection, illness, treatment failure)

BRAZIL

General comments:

1. Brazil supports the suggestion made by the Woorking Group regardind the unification of the three documents.

2. Brazil believes that the antimicrobial use in agriculture should be more emphasized in the document CX/AMR 08/02/06 jun.08. So, we consider that it may be necessary to ask to IPCC for some advice.

Specific Comments:

1. AGENDA ITEM 4 - CX/AMR 08/2/4 - PROPOSED DRAFT RISK ASSESSMENT GUIDANCE REGARDING FOODBORNE ANTIMICROBIAL RESISTANT ORGANISMS - AT STEP 3 (REPORT OF THE PHYSICAL WORKING GROUP)

PARAGRAF 17

Eigth bullet point (page 19):

Brazil would like to have some clarification about the meaning of the expression “fitness of the bacterium”.

Ninth bullet point

Brazil would like to suggest the deletion of the expression “development of” and “on a regional level”.

Application of available pharmacokinetic/pharmacodynamic data in the ~~development of~~ drug use that may vary ~~on a regional level.~~

Justification: The expression “development of the drug use” may be misunderstood and the use may vary on a country level, regional level, etc. Brazil understands that the register of one antimicrobial drug is always based on available pharmacokinetic/pharmacodynamic data of its efficacy, safety and recommended dose to animal specimen, that provide the indications of responsible drug use.

APPENDICES

Brazil sees Appendix 1 as an important part of this document, though it was recognized that it does not have a binding nature. It provides good guidance to the work that the task force is trying to produce. Tables have merit as an example, though it is not mandatory and provides the picture of activity of risk assessment in a satisfactory way.

COSTA RICA

Costa Rica is grateful for the opportunity to express its comments on this proposed draft:

This very technical and scientific proposed draft covers a component of the risk assessment part of risk analysis: antimicrobial resistance of organisms. Costa Rica is generally in agreement and wishes to thank Canada, the coordinating country, for kindly leading this working group.

1. In Appendix 1. Outputs of Qualitative AMR-RA: We consider that the term “negligible” should be used, as this is more common in our terminology than the proposed word “rare”, which does not clearly define what is referred to in this context.

2. We agree with the scope, as this encompasses the risk that antimicrobial resistant microorganisms present to human health and considers, with transparent and science-based criteria, the determinants of resistance in food animals and plants.

3. In paragraph 7, we agree with the complexity of the AMR issue from farm-to-table, considering the different parameters and scenarios. However, we would like the “management of animal and plant production” to be included in risk assessment for antimicrobial resistance.

4. Figure 1, page 4, presents a logical and practical flowchart for assessment from farm-to-table. However, we consider that water should be included in the flow. The link between “AMU in Food Animals” and “AMU in Plants” should also be included.

5. In paragraph 11, General Principles, we agree that the approach of risk assessment for antimicrobial resistance should be consistent with the Working Principles for Risk Analysis for Food Safety for Application by Governments. Under the farm-to-table approach, principal factors, including therapeutic and non-therapeutic uses, should consider key medicines used in the treatment of diseases and existing protocols in hospitals and health centres.

6. In Appendix 1, Illustrative Exposure Assessment Scoring, delete the word in brackets “rare” and leave only the word “negligible”.

7. Costa Rica agrees with Appendix 2 - Outline of Information for a Risk Assessment of Antimicrobial Resistance, and considers that information from a survey by the OIE and FAO could be included.

IRAN

The Iranian committee for Antimicrobial Resistance has reviewed the drafts and consensus has been made on the following comments:

General comments;

1. Antimicrobial resistance is not just a national problem and all of countries and national authorities should work together to solve the problem. An international agreement on antimicrobial usage that enforces the parties to work together and take their decisions and measures mutually under the agreement is a powerful tool. As a future plan, the Task Force may organize for preparing such a protocol in the international and regional levels.

2. Risk communication is one of the important steps in risk analysis. A data bank or a clearing house working under protocol or Task Force can facilitate the exchange of scientific, technical and legal information on antimicrobials and resistant microorganisms as well as the decisions and measures taken on risk assessments and risk managements. Such a bank serves as a means through which required information (including the national strategic plans for antimicrobial usage) is made available for the purpose of risk assessment and profiling process. If any database for antimicrobials exists, it can be improved and adopted for risk profiling and assessment as well.

3. Risk assessment and further actions for risk management on antimicrobial resistance are complex cases that need skilled and trained personnel. International or regional workshops or capacity building programs by FAO/WHO could help the countries which are less skilled in this field to implement legal actions. It is strongly recommended the Task Force coordinate for strengthening of human resources and institutional capacities for appropriate actions in developing countries (e.g. developing the strategic plans, tracing antimicrobials in food by standard test methods and assessing risks of antimicrobials and resistant microorganisms in food).

4. It is recommended that the titles as well as the method of numbering and bulleting in the three documents to be harmonized.

5. Since in many cases the term of “pathogen” does not cover the meaning of the text, it is suggested “Foodborne pathogens” to be substituted by “Foodborne microorganisms”.

6. “Foodborne” is a more familiar term rather than “acquired from food” which contains all of microorganisms transmitted via food and has been used commonly in food microbiology texts.

7. “Organisms”, “bacteria”, or any other term that means microorganism, should be replaced with “microorganisms”, in order to make harmonization in the whole of the texts.

Specific Comments;

- Title:

1- “Antimicrobial resistant **microorganisms**” is read “Antimicrobial resistant **organisms**”, although in many cases organism is used as microorganism, due to harmonization in codex documents, it is preferred to mention “**Antimicrobial resistant microorganisms**” in the title.

Page 15:

- Scope:

1- It is questioned that “**Food and Food Animals**” in the scope encompasses all foods (such as honey), so it is suggested to modify the scope in order to make it more comprehensive.

2- It is to be questioned if **animal feed** is an important vehicle for resistant microorganisms for human health or not. It has been frequently considered in different parts of the document as a source of AMR (such as Page 19- Data and possible sources of information) while it has not been mentioned in the scope!

Page 17:

- Definitions:

1. It is suggested that “**Resistant microorganisms**” should also be defined in addition to “**Resistance Determinant**”.

2. Different forms of lettering of “**Microorganism**” should be same in the whole document, it is written as “micro-organism” in the definition of **Antimicrobial agents**, which would be better to change to “**Microorganism**”.

Pages 20 & 21:

- Exposure assessment:

It is suggested that some descriptions should be added to the content of table. The proposed comments are **in BOLD.**

Table 1: Possible pre-harvest data requirements

Element	Description or scope of data
Selection pressure	Extent of antimicrobial agent use or proposed use - Number of animal, crop or target farms exposed to the antimicrobial agent in the defined time period - Geographical distribution of use and/or farms - **possibility of extra-label use of antimicrobial agent**
	Intensity of non-human use of antimicrobials - How much is used per target (as quantitative as possible) in the defined time period - Methods and routes of administration of the antimicrobial agent (individual/mass medication/for plants-is that spaying?) - Dosing regimen and duration of use - **Withdrawal time/period (e.g. between administration and milking or slaughtering)** - Number of administrations/administration periods in the defined time period - Cumulative effects of use of other antimicrobials in the defined time period

Table 2. Possible post-harvest data requirements for exposure assessment

Element	Description or scope of data
Initial level of contamination of the food product	Prevalence and quantity of commensals and zoonotic microorganisms present in/on the target at slaughter or time of crop harvest and proportion resistant to the antimicrobial agent
Food production factors	Factors affecting the frequency and level of microorganism contamination: - Sanitation and process controls **such as GMP and HACCP** - Methods of processing **Production/processing** - Points for cross-contamination - Packaging - **Probable use of additives and preservatives (due to their activities or impacts on growth or numbers of microorganisms** - **Starter cultures (type and number of microorganisms) used as ingredients** - Distribution, and storage - Regional or seasonal differences in quantity and quality of food products produced
Consumer behaviours	- **Storage and cooking and handling (appropriate application according to the intended use)** - Cross-contamination - Role of food handler as a source of contamination - Human-to-human transmission of the microorganisms (**including sanitation behavior**) - Overall per capita consumption - Patterns of consumption and socio-economic, cultural, ethnic and regional differences

KENYA

Kenya would like to thank the working Group lead by Canada for developing rational, science-based guidance, taking full account of the prior work on risk assessment principles and standards of Codex and other relevant international organizations, such as FAO, WHO and OIE, as well as of national/regional authorities during the first session.

Kenya would like to submit its comments as follows

SECTION 2. SCOPE

5. The scope of this guidance document encompasses the overall risk to human health relating to antimicrobial resistant microorganisms and their resistance determinants in food, food animals, food production/processing, and plants arising from the non-human use of antimicrobials.

Comment

Kenya propose the a above mentioned scope to read as follow,

The scope of this guidance document encompasses the overall risk to human health relating to antimicrobial resistant microorganisms and their resistance determinants in food microoganisms, food animals, food production/processing, and plants arising from the non-human use of antimicrobials.

This is because the resistance determinants are in the micro organisms as stated under the definition of Antimicrobial Resistance which states that it is the ability of a microorganism to multiply or persist in the presence of increased level of an antimicrobial agent relative to the susceptible counterpart of the same species

7 .The extent of the farm-to-table pathway covered by the AMR-RA should fit its intended purpose. The scope of the risk assessment is determined by the risk managers in consultation with risk assessors. Considering the complexity of the AMR issue, specific issues raised or questions asked by risk managers should be as precise as possible (e.g. combinations of microorganism/antimicrobial class, particular use of antimicrobial, target species, specific geographical area etc.) for risk assessors to specifically address the risk issue.

Comment

We propose that this paragraph7 mentioned above should be moved to the introduction part since it is a clarification of the scope of this standard.

9. The risk assessment of AMR marker genes in recombinant-DNA plants[3] or microorganisms[4] or of certain food ingredients, which could potentially carry AMR genes such as probiotics[5] and residue issues are outside the scope of this document.

Comment

We propose that the word "Food of" to be deleted in the second row in the Box of "Food of Animal or plant Origin" so it reads "Animal or Plant origin". However we have no problem with the rest of the schematic.

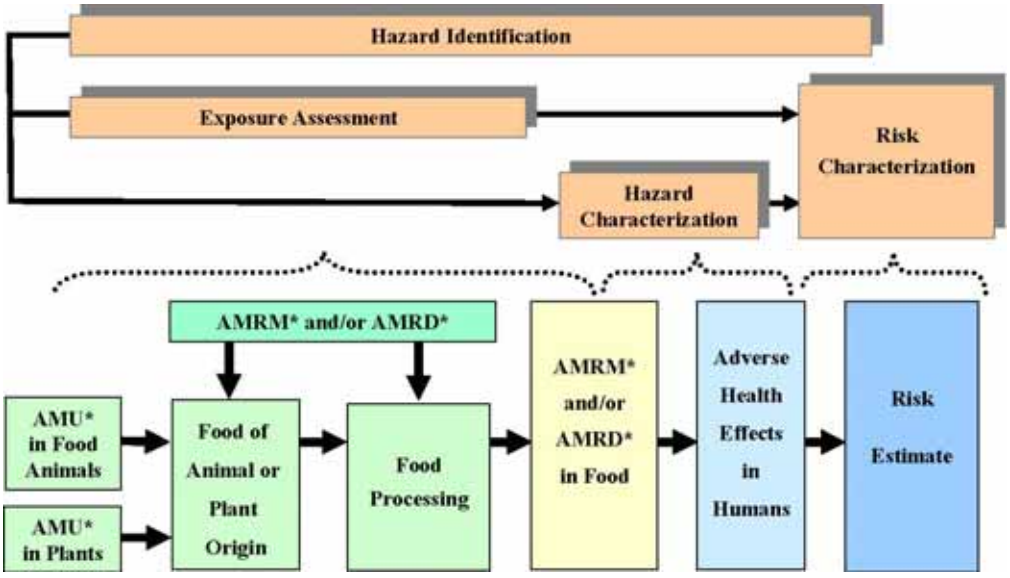

Figure 1. Schematic showing the scope and relationship of the components of AMR-RA

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

6.3. HAZARD CHARACTERIZATION

Kenya concurs with the AMR risk assessments, the focus is likely to be the implications of exposure to resistant organisms that are over and above those of being exposed to susceptible organisms and also accept the proposed categories mentioned below in figure 2 with the addition of "Fatal" illustration.

- **Negligible (0)**: Probability of illness upon exposure is the same as for susceptible organisms and the outcomes as a result of illness is not different
- **Mild (1)**: Probability of illness upon exposure is the same as for susceptible organisms, but the outcomes following illness are more serious requiring hospitalization
- **Moderate (2)**: Probability of illness upon exposure is higher and outcomes following illness are more serious requiring hospitalization
- **Severe (3)**: Probability of illness is higher and outcomes following illness are very serious requiring hospitalization as well as the potential for treatment failures requiring lengthy hospitalization
- **Fatal**: Directly or indirectly contributes to the death of the subject. Treatment failure is likely expected due to the AMR.

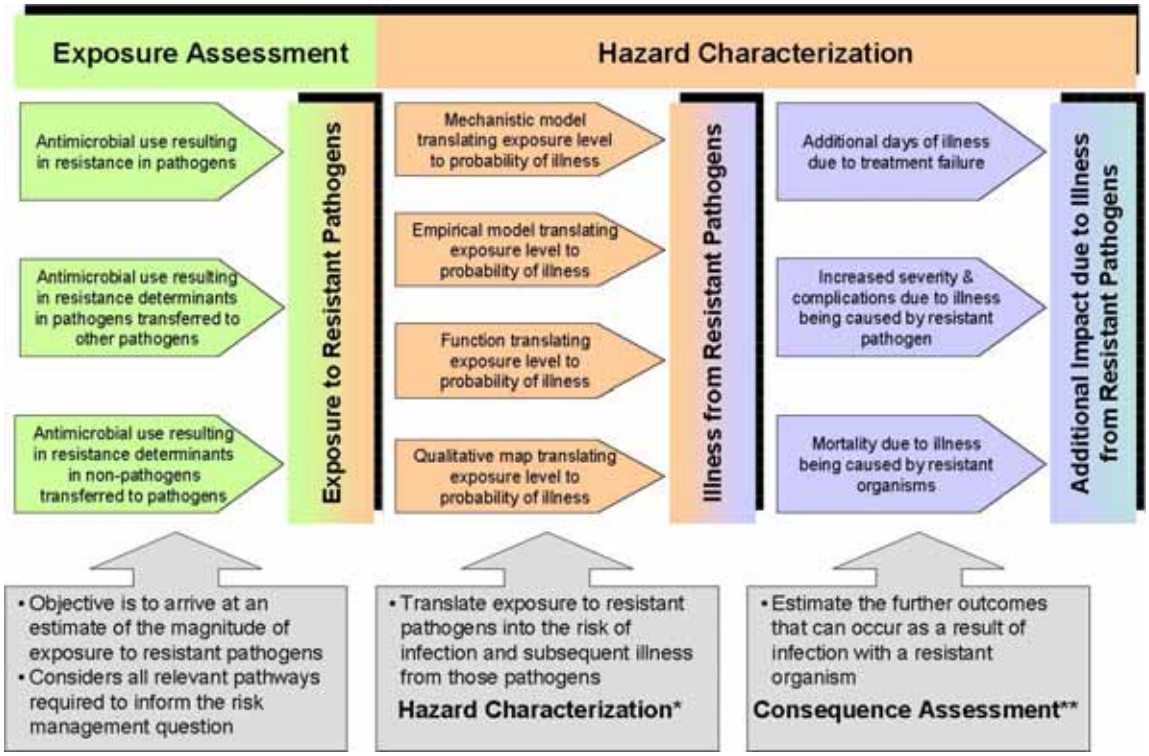

Figure 2. Scheme for the consolidated Hazard Characterization in AMR-RA

(*: concept adapted from the JEMRA [FAO/WHO, 2003a and 2006a]; **: concept adapted from the World Organisation for Animal Health [OIE, 2007])

MEXICO

Mexico welcomes the opportunity to comment on documents CX/AMR 08/2/4, CX/AMR 08/2/5 and CX/AMR 08/2/6.

CX/AMR 08/2/4 Proposed Draft Risk Assessment Guidance Regarding Foodborne Antimicrobial Resistant Organisms.

Mexico congratulates the Working Group on the clear structure and layout of the document.

Mexico suggests that antimicrobials be included in the definition of "cross-resistance" to better convey the idea, so that the text reads: Cross-resistance: A single resistance mechanism in a bacterium conferring resistance at various levels to other members of the **antimicrobial** class or to different classes of **antimicrobials..."**

Mexico suggests including a definition of Probiotics for greater clarity, given that the term is used, so the text reads: "Probiotics: live microorganisms which when administered in adequate amounts confer a health benefit on the host."

In paragraph 17, bullet 5, we suggest clearly stating the importance of conducting studies on microorganism resistance in an external environment (litter, water, faeces, channel).

Paragraph 19 includes commensals as an example, but this term excludes mutualists, so we suggest replacing the term "commensals" with "normal microbiota", and harmonizing this term in the documents CX/AMR 08/2/4, CX/AMR 08/2/5 and CX/AMR 08/2/6.

Paragraph 19 only considers pathogens. As the document considers microorganisms in general without distinguishing between those that are pathogenic and those that are not, we suggest replacing the term "pathogens" with "microorganisms" and harmonizing this term in the documents CX/AMR 08/2/4, CX/AMR 08/2/5 and CX/AMR 08/2/6.

In Table 3, we suggest including in the description of the first element "Intrinsic resistance to non-specific defence mechanisms of the host", as this is a resistance mechanism that has not been included and, because once inside the host, this factor needs to be known as it is part of the characteristic of microorganism resistance.

NEW ZEALAND

New Zealand is pleased to offer the following comments in response to the above:

Congratulations to Canada and the physical Woking Group on producing an excellent proposed draft.

New Zealand has withheld some of our comments until the meeting of Task Force. This is because we support the working recommendation of one integrated guidance document. This approach will probably resolve some issues we have identified so we will reserve our comments until the Task Force's response to the recommendation.

Specific comments;

Care is needed to ensure that there is consistency in terminology e.g. paragraphs 2, 5 and 14. In paragraph 17 the heading appears incorrect. This seems to be a listing of sources rather than of data requirements. It is assumed that a bullet has been omitted before "Monitoring …". It would be preferable if the ordering has some logic to it (unless we are not recognising it) e.g. organism – human. Also that it was in accord with Appendix 2. In paragraph 25 there is a consistency issue with 'non-pathogen' and 'commensal'.

In Appendix 1 New Zealand supports the use of examples, especially demonstrating alternative approaches. While it is stated in paragraph 3 of the introduction prior to Example 1 that these are potential approaches and not recommendations, New Zealand recommends that further thought is given to strengthening both wording and presentation. We consider the message is unfortunately lost to some extent with the amount of detail that follows and, in our view there is an appreciable risk of these examples thus being misconstrued or even misused.

Appendix 2 should be re-examined by the drafters to ensure consistency in elements covered and wording between it and in the same topics in the main body of the text.

NORWAY

Norway takes the opportunity to thank the representatives from Canada, USA and Denmark/France (EC) for successful development of the draft guidance documents.

1. Terms and definition

In the title, objectives and terms of reference (TOR) for the TFAMR, the terms antimicrobial resistance, microorganisms and antimicrobials are applied. Furthermore, in CX/AMR 08/2/4 (Agenda Item 4), page 17, the following definition of antimicrobials (antimicrobial agents) is applied: Any substance of natural, semi-synthetic, or synthetic origin that at in vivo concentrations kills or inhibits the growth of microorganism by interacting with a specific target.

The term microorganisms includes bacteria, virus and fungi and the expression antimicrobial agents (consequently) includes antibacterial, antiviral and antifungal drugs. In modern text books in pharmacology the term antibacterial drugs is applied for natural, semi-synthetic and synthetic medicinal substances that kills or inhibits the growth of bacteria (see e.g. Rang and Dale's Pharmacology, 6th edition, 2007, Elsevier Limited). Unless antimicrobial agents in general are to be included in the TFAMR, the term antibacterial drugs should be applied throughout the document. However, when such substances are used for plant protection or as growth promoter, the term antibacterial agents have to be applied because such use is not included in the common definition of drugs. It should be noted that the expression antibacterial drug is applied by e.g. U.S. Food and Drug Administration and the European Medicine Evaluation Agency (EMEA). Furthermore, in the proposed draft guidance documents CX/AMR 08/2/4, CX/AMR 08/2/5 and CX/AMR 08/2/6 the term antimicrobial, leaving agent, is often applied. As antimicrobial (or antibacterial) is not a noun, but an adjective, the wording should be antibacterial drugs and antibacterial agents, respectively.

E.g. CX/AMR 08/2/4 includes a list of definitions. Norway is in favour of only including in this list terms/words that are defined differently in the literature, as those who are performing risk assessment or risk profiling in the field of antibacterial drug resistance should be expected to be familiar with terms such as cross-resistance and co-resistance.

2. Proposed draft guidance document on risk assessment (CX/AMR 08/2/4)

The four elements to be included in AMR-RA are clearly defined in Appendix 2 to the proposed draft guidance document on risk assessment (RA) (CX/AMR 08/2/4) and are the elements usually applied for risk assessment. The human health hazards are, as defined in TOR, the antibacterial resistance and resistance determinants in food, not the antibacterial drugs causing the hazard. Therefore, description of selection pressure as part of exposure assessment in e.g. Table 1, description of the antibacterial drugs as part of the hazard characterization in e.g. Table 3 and point 2.2 and 4.2 (Appendix 2) do not fit in. As the objective of the TFAMR is also to "develop appropriate risk management advice based on that assessment to reduce the risk", analysis of usage data etc of antibacterial drugs (agents for plants) is vital. Unless such an analysis is completed through a risk profiling prior to the risk assessment, such an analysis should be included in the RA but in a separate point.

REPUBLIC OF KOREA

First, Republic of Korea would like to sincerely thank to the diligent and enthusiastic chairs of three TFAMR physical working groups for the successful development of the draft guidance documents. Republic of Korea supports the current draft guidance in principle and suggests a few comments.

Section 3. Definition

When describing the dose-response, the additional possible adverse health effects in addition to human illness from exposure to antimicrobial resistant microorganisms or resistant determinants should be carefully taken into account. For the clarification of effects to human health by exposure to antimicrobial resistant microorganisms, we suggest to add the definition of Dose-Response on antimicrobial resistant microorganisms in Section 3. Definition as follows;

Dose-Response: Mathematical relationship between the exposed dose of resistant pathogens or determinants and probability of human illness and adverse health effects.

6.2 Exposure assessment

Food is an important vehicle for spread of resistant microorganisms from animals to humans. Risk assessment is an essential tool in assessing the overall risk to human health from food-borne antimicrobial resistant microorganisms.

The contamination level of antimicrobial resistant pathogens from the foods in the market should be monitored, because people get illness from the foods. So, the data of contamination level related to antimicrobial resistant microorganisms in retail foods as well as to food production level is also necessary for the post-harvest exposure assessment. It is suggested that Table 2 is modified as follows;

Table. 2 The requirement for Exposure Assessment post-harvest data

Elements	Description or scope of data
Initial level of contamination of the food product	• Antimicrobial resistance rate of microorganisms present in/on the target at slaughter or time of crop harvest. • **Antimicrobial resistance rate of microorganisms present in the retail food**
Food production factors	Factors affecting the frequency and level of microorganism contamination: o Sanitation and process controls; o Methods of processing; o Points for cross-contamination; o Packaging; o Distribution, and storage. o Regional or seasonal differences in quantity of food products produced
Consumer behaviors	o Storage and cooking o Cross-contamination o Role of food handler as a source of contamination o Human-to-human transmission of the microorganisms

	o Overall per capita consumption o 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

UNITED STATES OF AMERICA

The United States of America is pleased to offer the following comments in response to the Proposed Draft Risk Assessment Guidance Regarding Food-borne Antimicrobial Resistance Organisms (CX/AMR 08/2/4).

The U.S. delegation would like to express its appreciation to the Canadian delegation for the excellent leadership at the Brussels meeting and for the well-documented meeting report as well as the revised risk assessment (RA) guidance document. Our comments below are for consideration by all Codex delegations in preparation of discussion on the risk assessment guidance at the second session of the TFAMR in October.

General comments;

1. With respect to the inter-relationship of the three WGs draft guidance, we would like to emphasize that:

- The harmonized document will need to integrate Risk Assessment (or RA) as a component within the early risk management activities, as outlined in the Risk Profiling and prioritization document. Also, harmonization of the endpoints contained in the Risk Management and Risk Profiling documents will need to be aligned. Finally, the definition section within the RA document will need to be moved to a new section where all terms in the guidance will be placed. Similarly, the Principles, Introduction and other sections will need to be adjusted.

- Risk Assessment is commissioned, as per the sequence of activities outlined in the Risk Profiling/Prioritization guidance, so that Risk Assessors and Risk Managers consider the scope of the RA, determine which risk management Options are available and how to best implement the RA to obtain the most meaningful outcomes to guide the selection of those options.

- The commissioning of the Risk Assessment requires risk managers to interact with risk assessors to ensure the appropriate dialog among themselves; this is a key element of Risk Communication

2. Scope

It should be well discussed among delegates to understand that the mandate of Codex is food safety and consumer protection and fair trade practices. Thus, the focus is about food and its safety, which should be consistent with the scope for TFAMR RA (as well as the other accompanying guidance documents of the task force). If no AMR microorganisms are on a food commodity, then there would be no reason to conduct RA or RM steps to be taken. This statement does not preclude the necessity of having a baseline of information for antimicrobial susceptible food-borne microorganisms that is necessary for comparisons further on in the RA process.

Section 2 Scope, paragraph 8 - It is stated "Intended users of this document include the joint FAO/WHO meetings on microbiological risk assessment (JEMRA), the World Organisation for Animal Health (OIE), and national/regional food safety authorities 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." It is not clear why OIE is included in risk assessment guidance. OIE was not listed in the ALINORM 08/31/42 Appendix III, where the intended use was originally defined. The original language is as below:

"1. Purpose and scope of the proposed work

The purpose of the proposed work is to develop rational, science-based guidance, taking full account of the prior work on risk assessment principles and standards of Codex and other relevant international organizations, such as FAO, WHO and OIE, as well as of national/regional authorities. The intent of this guidance is to support JEMRA and/or national/regional authorities in assessing the potential overall risk to human health associated with the presence in food and feed (including aquaculture), and the transmission through food and feed, of antimicrobial resistant microorganisms and resistance determinants."

The CAC/RCP 38-1993, CAC/RCP 61-2005, and the OIE Terrestrial Code 3.9.4 may serve as templates for Regulatory Authorities to use to evaluate new animal antimicrobial product candidates with respect to antimicrobial resistance concerns. The inter-relationship of these guidance documents may need to be clarified, so that the purpose and scope of the currently proposed TFAMR work are clear to member states.

3. Co- and cross-resistance

Under the “exposure assessment”, what role and to what extent co-resistance and/or cross-resistance should be played in the causal relation pathway? The draft guidance is not clear enough on these factors.

The risk profile will aid in the determination of which antimicrobial agents might be prioritized for RA with regard to cross-resistance. The risk assessors and risk managers will need to consider this aspect in the conduct of the RA. Similarly, as for co-resistance, some determination of its potential role in maintaining and extending multiple-drug resistant strains will need to be considered. The presence of a multidrug resistant microorganism may take many different routes of evaluation, depending on the bacterial species, the antimicrobials involved, etc.

Specific comments;

1. Section 4 General Principles

The General Principles section will need to be harmonized with the Principles in the other two draft documents in order to make certain the following questions are covered.

What is the purpose of Risk Assessment? Is it a function of risk assessors to guide the evaluation and selection of Risk Management Options? Should risk assessors "address the risk question" (page 18, line 10) and determine a risk estimate. In addition, whether the “purpose of risk assessment” is to guide risk management? Whether it also assesses risk associated with the presence of resistant microorganism/resistance determinant in food as well as help selection of risk management options?

2. Definitions

The section should be moved to a single glossary as part of the harmonized document.

The meaning of “in or on food or acquired from food of …” in the definition of “adverse health effect” may be too broad and needs to be further discussed. If possible, it should be consistent in using an existing Codex definition with respect to the scope and purpose of this task force.

Some definitions such as Pathogen, Commensal, Pre-harvest, Post-harvest, Resistance determinant, etc., require further discussion.

3. “Pathogen” versus “commensals”, and “resistant microorganism vs resistance determinant”

Clearly, these terms will have different impacts on hazard identification. In general, a commensal microorganism is not necessarily a frank pathogen nor may it exhibit more pathogenic properties when it acquires a resistance phenotype, while a resistant food-borne pathogen would remain as a capable food-borne pathogen. A food-borne pathogen may cause food-borne illness while a commensal generally does not in an otherwise healthy individual with a similar dose-response exposure relationship setting. Thus, it is suggested that the document provide some guidance on how to apply the difference in the risk assessment.

Another potential role of commensals is not in causing illness, but in carrying a resistance determinant that is passed to a pathogen, while both are in a same host. Resistance determinant or determinants may reside in the same or different microorganism (pathogen or commensal).

If the hazard is so broad that it may include resistant pathogens, commensal microorganisms, resistance determinants (single drug or multiple drug resistance genes), and different drug:microorganisms or drug:resistance-determinant combination entities, the guidance on RA may need to separate these hazards with respect to their respective impact in adverse health effects. This needs to be captured for producing better transparency and science-based guidance.

4. Exposure assessment

As discussed at the Brussels WG physical meeting, it should be noted that, without proper assessment, quantity of antibiotics used does not equate to misuse, partially due to lack of proper data base to trace accurate drug use for the purpose of monitoring resistance. This may present a challenge for providing guidance on what and which drug usage data base to use in the RA. We support that “why” antibiotics are used (i.e., therapeutic, disease control and prevention, and growth promotion/feed efficiency) is important in balancing risks and benefits. In addition, with respect to exposure assessment, we should mainly consider resistance that emerges and disseminates as a result of drug use.

5. Hazard characterization

The discussion of RA of susceptible organisms is important and well illustrated under paragraph 27. One may not know how much more impact there is of a resistant organism with respect to illness development unless you look at the susceptible organism too. The listed issues may impact not only on RA but also other aspects of the risk analysis, thus it warrants further discussion.

However, it needs to be kept in mind that currently Codex only has microbiological risk assessment (without considering resistance) for food-borne pathogens in some food commodities. Thus, it will be a challenge if one needs to compare resistant and non-resistant microorganisms where there is no exhibition of increased virulence, such as in the commensal microorganisms in a non-food-borne bacterial disease.

6. Risk characterization

We were encouraged by the increasing clarity that is developing about AMR-RA; the risk here is the additional harm resulting from resistance. Although not necessarily always true for every case, another way to look at is the preventable fraction or "reversibility": how much of the harm would go away if the antimicrobial and its effects were removed from the system. This would allow an opportunity to seriously consider priority in the selection of measurements that may guide realistic output for risk management options, which is the primary purpose of the RA. The endpoints needed to reach the decision-making step as to the choice of risk management options needs to be communicated by the Risk Assessors and Risk Managers.

7. Consequences

There are at least two ways that a resistant microorganism can be a hazard; if they make more people ill (increased infectivity) or if they make people sick longer or more severely (increased pathogenicity). Also, other endpoints may be contained in the currently defined "adverse health effect", given it covers a broad range. Thus we need to be clear with respect to which consequence we are measuring in a specific risk assessment to commission.

As mentioned above, clarification regarding resistant microorganisms (frank food-borne pathogens and commensals), and resistance determinants (to various antimicrobial drugs, such as critically important, highly important, etc.) would be helpful. Is there any difference in adverse health impact among these drug:microorganism or drug:gene combinations? If yes, what guidance may be provided to differentiate their impact in the RA?

8. Section 6.3 – Hazard Characterization, paragraph 28

The sentence in paragraph 28 (page 23, lines 20-22)

" 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."

This statement may require further clarity. Should a risk assessment be conducted before a risk management decision is made with respect to all critically important antimicrobial drugs? It would also be helpful to clarify whether the resistant bacteria cause more challenges in treatment than the susceptible strains within a specified adverse health consequence, and not just focus on whether or not they are resistant to drugs on the CIA list. Each category of critically important drugs may have different role played in systemic therapy in the treatment of infections caused by resistant food-borne pathogens and commensal microorganisms.

9. Figures

Figure 1 would be easier to understand if it clearly indicates the relationship of the tan boxes to the green and blue boxes. The dashed brackets may be little confusing with regard to where the information is to be used. It is suggested that an existing Codex RA template might be used and modified to include the blue and green boxes.

When Figure 1 is compared to Figure 2, it becomes confusing as to what pathway is to be followed. How do the two figures inter-relate?

10. Tables

Section 10, Appendix 1. The example of RA given here should serve as guidance to select risk management options. The caution statement in the first sentence in the first paragraph is moved to the Top and bolded to clearly note that this is an example and not a pathway to be followed "as is".

CONSUMERS INTERNATIONAL

General comments;

CI would like to thank Canadian delegation for the excellent work done so far in leading the Risk Assessment Working Group. CI supports the current draft and has a few recommendations on ways that it could be strengthened.

CI in comments on earlier drafts has recommended that excess infections be included in the potential adverse health impacts of antimicrobial resistance. CI believes that the current draft does a better job at addressing this issue, but we feel that the risk assessment guidance could be further clarified in several places to make sure that this aspect of antimicrobial resistance risk is not lost.

The presence of resistance can lead to increased frequency of infection in at least two ways. First, if resistance is linked to increased virulence then there can be a direct impact on number of infections. In addition to increased virulence, antimicrobial resistance can lead to additional infections in persons taking antibiotics for reasons other than the resistant pathogen. In this case, a resistant pathogen will be more likely to compete in the human body and therefore cause illness when an antimicrobial to which it is resistant is taken for an unrelated cause. This selective effect was described by Barza and Travers (2002) with additional infections that occur due to the presence of resistant pathogens described as

the “attributable fraction”. CI recommends that the guidance document specifically mention both these ways (increased virulence and selective effect) by which resistance can lead to increased infections.

CI also recommends that the draft better address the potential negative impacts that could occur when the presence of resistance acquired from food leads to the switching from one antibiotic to another. CI understands that the drafters have attempted to capture potential cumulative effects of resistance, but feel that this has still not been adequately covered. Unless a risk assessment accounts for the negative effects that likely will occur when antimicrobial choice is limited by resistance, the risk will almost certainly be underestimated leading to inadequate risk management.

Finally, CI recommends that the draft clarify that this is an assessment of the risk of antimicrobial resistance not of resistant infections per se. The presence of resistance makes pathogens more risky and also creates risk in organisms that normally are not considered as hazards because of the ability to transference resistance determinants. These additional risks are the scope of this task force and should be the focus of the risk assessment.

CI will provide specific suggestions on ways to address these three major concerns along with other recommendations below.

Specific recommendations;

Document Title. CI recommends that the document title be modified to be consistent with the emphasis in the document on both resistant organisms and resistance determinants acquired from food. We recommend that the new title be “Risk Assessment Guidance on Resistant Organisms and Resistance Determinants Acquired from Food.”

Paragraph 6. For greater clarity, CI recommends that the first sentence in paragraph 6 be modified by moving “in food" to read. “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 in food and to describe the magnitude and severity of the adverse effects of that exposure.”

Section 3. Definitions. CI recommends that the definition of “extended co-resistance” from FAO/WHO/OIE 2008 be included. This would address the concern raised under paragraph 15 in the Detailed Discussion on the Draft Document.

‘Extended co-resistance’: A single mechanism conferring resistance to various antimicrobial classes. An example would be overexpression of an efflux pump with a broad substrate range.

Under the definition for “Adverse Health Effect”, CI recommends that the definition be clarified to limit it to impacts of resistance, so that infection by a resistant microorganism itself is not an adverse health impact of resistance unless the infection would not have occurred without the resistance. It would then read “An undesirable or unwanted outcome in humans. In this document, this refers to outcomes related to the presence of resistant organisms or resistant determinants in food or acquired from food, including increased frequency of infection and treatment failures, loss of treatment options and increased severity of infections manifested by prolonged duration of illness, increased frequency of bloodstream infections, increased hospitalisation, and increased mortality.”

Paragraph 11. For clarity, CI recommends dropping “approach” from the first bullet, so that it would read “AMR-RA should address the risk question taking into account the whole farm-to-table continuum, where appropriate, encompassing the food pathway of production, processing, storage, distribution and consumption.”

Paragraph 17. Bullet point 3 should be expanded to include information on the impact of resistance on the frequency of infection. It would then read “Clinical studies including case reports on the relevant foodborne-related infectious disease prevalence, primary and secondary transmission, antimicrobial therapy, and impacts of resistance on disease frequency and severity.”

Another bullet point should mention regional treatment recommendations for pathogens under consideration and the medical importance and potential impacts of resistance developing to alternative treatments. This should help with better defining cumulative effects of resistance. CI recommends the following bullet point.

- Regional treatment guidelines for zoonotic pathogens including information on the medical importance of and potential impacts of increased resistance in target or other bacteria to alternative treatments.

Paragraph 19. CI recommends removing the “(e.g., commensals)” from the second sentence as dissemination is not limited to commensal bacteria.

Page 20. Table 1. Under “Selection pressure – Extent of antimicrobial agent use or proposed use” add a bullet point describing factors that influence extent of use including information on trends in antimicrobial use. One of the criticisms of current AR risk assessments in FAO/OIE/WHO 2003 is that there is too much focus on what has happened not on what is likely to happen (pg. 20). CI recommends adding the following bullet point.

- Data on trends in antimicrobial use and information on emerging diseases, changes in farm management, or other changes in production that are likely to impact antimicrobial use.

Paragraph 27. CI does not understand the meaning of the first sentence of this paragraph. One interpretation is that increased virulence is the only way in which resistance impacts number of infection, so that when there is no increased virulence then the number of infections is the same as for susceptible infection. This ignores the impact of the selective effect or attributable fraction. We recommend changing the first sentence to read. "Determining the number of infections is similar to non-AMR microbiological risk assessment except that potential increased virulence of resistant microorganisms and selection effects in patients treated with the antibiotics of concern must be incorporated into the assessment." The rest of the paragraph could be clarified to make clear that this assessment focuses on the impacts of resistance. CI recommends the paragraph be changed to read as follows:

Determining the number of infections based on exposure is similar to non-AMR microbiological risk assessment except that potential increased virulence of resistant microorganisms and selection effects in patients treated with the antibiotics of concern must be incorporated into the assessment. The risk outcome in AMR-RA, like microbiological risk assessments, will focus on illness, except in this case the focus is on additional adverse health effects attributed to resistance in pathogens. It 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.

Paragraph 28. CI recommends that this paragraph include a sentence about the potential negative effects that occur when antimicrobial resistance acquired from food leads to switching from one antibiotic to another of higher medical importance. CI recommends adding the following statement. "In addition, the assessment should consider the potential adverse human health effects that occur when the presence of resistance leads to an increased use of antimicrobials of higher medical importance."

Paragraph 29. Table 3. The first item under "Resistant microorganisms and resistance determinants" should refer to cross/co-resistance. "Resistance genotype and phenotype including cross-resistance, co-resistance, and extended co-resistance."

Paragraph 33. Given the complexity of antimicrobial resistance risk assessment, it is likely that any AR risk assessment will focus on a limited number of bacterial species. Because of this, a certain part of the risk of the antimicrobial use under consideration will not be included in the assessment. The risk characterisation should make clear the limitations of the questions asked by risk managers. CI recommends that the following be added to bullet point 6 of paragraph 33. "Weaknesses linked to the limited number of bacterial species considered or for which resistance data is available should be made clear."

Paragraph 34. Table 4. The "Factors in risk estimation" should include increased numbers of infections due to resistance."

IDF

General comments;

IDF would like to congratulate to Chairs of the three TFAMR physical Working Groups for the excellent work done as is reflected in the resulting Codex documents CX/AMR 08/2/4, CX/AMR 08/2/5 and CX/AMR 08/2/06.

IDF supports the proposal to merge the 3 documents into one with the objective of providing coherent and harmonized Codex guidance on the risk analysis process with regard to foodborne antimicrobial resistant microorganisms. IDF would like to propose using the wording that can be found in CX/AMR 08/2/4, para. 3 (section "Background") as a common introduction to explain the purpose and scope of the document.

Specific comments;

Page 18, SECTION 4.GENERAL PRINCIPLES

IDF would like to propose the insertion of an additional bullet point (before the last bullet point) to address animal health:

AMR-RA should consider the impact of AMR on the effectiveness/efficacy of the available antimicrobial agents in veterinary medicine in view of ensuring the appropriate medical treatment of animals.

Page 18, SECTION 5.1. PURPOSE (para 14)

The wording should be harmonized with the text of the introduction that can be found in CX/AMR 08/2/4, para. 3 (section "Background").

Page 20, Table 1, 4th bullet point

The exposure assessment should make a distinction between local treatments (wounds, mastitis) versus general administration of antimicrobial agents to animals. IDF proposes to amend the last bullet point to read:

- Methods and routes of administration of the antimicrobial agent (individual/mass medication, local/general application / for plants ….

Page 21, Table 1, section "Target animal or crop …" In order to be consistent with the scope of the document an extra bullet point referring to plant management should be added. IDF proposes insertion of:

- Plant management

IFAH

IFAH is pleased to provide the following suggestions for revision and comments on specific sections as requested by the Working Group on Risk Assessment. IFAH has used brackets [ ] to indicate a bullet point or section which has been edited or commented upon, and providing some rationale for the action.

GENERAL COMMENTS;

- Risk Assessment is done primarily to guide Risk Management Option selection
- Risk Assessment follows Risk Profiling/Risk Prioritization
- The commissioning of the Risk Assessment requires Risk Managers to interact with Risk Assessors to ensure the appropriate scope of the Risk Assessment

SPECIFIC COMMENTS;

SECTION 1. INTRODUCTION

(This section may be revised with merged document – The AMR Risk Analysis Document)

Antimicrobial resistance (AMR) is a major global public health concern and a food safety issue. 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 an 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). Risk analysis of AMR on animal feeds may also consider Codex Code of Practice on Good Animal Feeding (CAC/RCP 54-2004) as well as Animal Feed Impact on Food Safety (FAO/WHO, 2008a).

SECTION 2. SCOPE

[IFAH comment: The mandate of Codex is food safety. Only food contaminated with AMR bacteria are within the scope. If no AMR are on food, then there can be no RA or RM taken.]The scope of this guidance document encompasses the overall risk to human health relating to antimicrobial resistant microorganisms and resistance determinants in food, food animals, food production/processing, and plants arising from the non-human use of antimicrobials.

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 in food. A schematic presentation in Figure 1 shows the scope and relationship of the components of AMR-RA.

IFAH comments that Figure 1 extends beyond the table and into human disease and adverse treatment events, yet this sentence ends at the table] The extent of the farm-to-table pathway covered by the AMR-RA should fit its intended purpose. The scope of the risk assessment is determined by the risk managers in consultation with risk assessors. Considering the complexity of the AMR issue, specific issues raised or questions asked by risk managers should be as precise as possible (e.g. combinations of microorganism/antimicrobial class, particular use of antimicrobial, target species, specific geographical area etc.) for risk assessors to specifically address the risk issue. [IFAH comments that Risk managers need to use Risk Assessment to guide the selection of RM options. It may be of low value to address academic questions or risk issues to derive a general risk estimate. That is not what Codex RA is intended to do.]

[IFAH comments that OIE is not an intended user per the TFAMR discussions]Intended users of this document include the joint FAO/WHO meetings on microbiological risk assessment (JEMRA)~~, the World Organisation for Animal Health (OIE),~~ and national/regional food safety authorities 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. It can be adapted by member countries to conduct a pre- or post-market risk assessment of an antimicrobial intended for non-human use (either therapeutic or non-therapeutic)[1], or to conduct an AMR-RA of food products (including imported food products). [IFAH comments that Codex is not a regulatory authority and so this RA cannot be used for drug approval purposes. Currently, the OIE Terrestrial Code Risk Assessment document is the template for Regulatory Authorities to use to evaluate new animal antimicrobial product candidates. <u>It should be noted that this Risk Assessment cannot be applied by national regulatory authorities for the purpose of antimicrobial product registration or reviews. The OIE Terrestrial Code may be a more appropriate document to use as a template for that particular purpose.]</u>

The risk assessment of AMR marker genes in recombinant-DNA plants[2] or microorganisms[3] or of certain food ingredients, which could potentially carry AMR genes such as probiotics[4] and residue issues are outside the scope of this document.

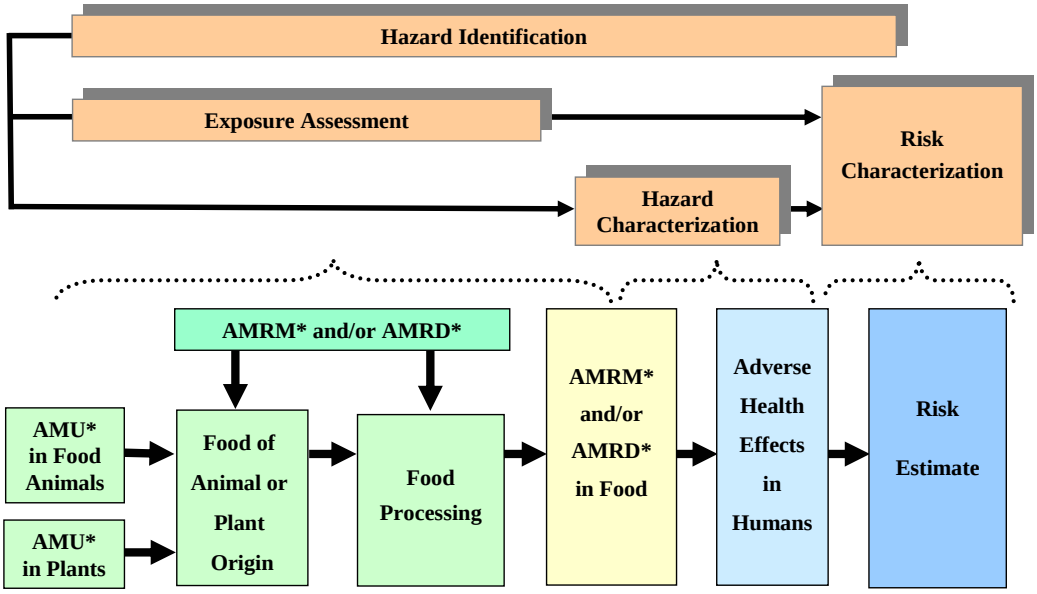

Figure 1. Schematic showing the scope and relationship of the components of AMR-RA

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

[1] Consistent with Codex Code of Practice to Minimize and Contain Antimicrobial Resistance CAC/RCP 61-2005.
[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).

[IFAH comments that it would be easier to understand this if it were in a top-down linear format and clearly indicated the relationship of the tan boxes to the green and blue boxes. The dashed brackets are confusing with regard to where the information is to be used. It is suggested that an existing Codex RA template might be used and modified to include the blue and green boxes.]

SECTION 3. DEFINITIONS

(To be finalized with merged AMR Risk Analysis Document)

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) are applicable to this document. Some established Codex definitions are cited in italics. Definitions cited from existing FAO/OIE/WHO documents are referenced as appropriate.

Adverse Health Effect - An undesirable or unwanted outcome in humans. In this document, this refers to the human infections or their frequency caused by antimicrobial resistant microorganisms and resistance determinants in food or acquired from food of animal/plant origin as well as the increased frequency of infections and treatment failures, loss of treatment options and increased severity of infections manifested by prolonged duration of illness, increased frequency of bloodstream infections, increased hospitalization, and increased mortality (FAO/OIE/WHO, 2003).

Antimicrobials (Antimicrobial Agents) - Any substance of natural, semi-synthetic, or synthetic origin that at in vivo concentrations kills or inhibits the growth of micro-organisms by interacting with a specific target (FAO/OIE/WHO, 2008).

Antimicrobial class: Antimicrobial agents with related molecular structures, often with a similar mode of action because of interaction with a similar target and thus subject to similar mechanism of resistance. Variations in the properties of antimicrobials within a class often arise as a result of the presence of different molecular substitutions, which confer various intrinsic activities or various patterns of pharmacokinetic and pharmacodynamic properties.

Antimicrobial Resistance - The ability of a microorganism to multiply or persist in the presence of increased level of an antimicrobial agent relative to the susceptible counterpart of the same species (FAO/OIE/WHO, 2008).

Commensal – Microorganisms participating in a symbiotic relationship in which one species derives some benefit while the other is unaffected.

Co-resistance: Various resistance mechanisms, each conferring resistance to an antimicrobial class, associated within the same bacterial host (FAO/OIE/WHO, 2008).

Cross-resistance: A single resistance mechanism in a bacterium conferring resistance at various levels to other members of the class or to different classes. The level of resistance depends on the intrinsic activity of the antimicrobial agent, in general the higher the activity, the lower the level of resistance. Cross-resistance implies cross-selection for resistance (FAO/OIE/WHO, 2008).

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.

Pathogen – A microorganism that causes illness or disease.

Pre-Harvest – The stage of food animal or plant production prior to the slaughtering or harvesting.

Post-Harvest – The stage of food animal or plant production following the slaughtering or harvesting, which often includes cooling, cleaning, sorting and packing.

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, thereby enabling horizontal transmission from resistant to susceptible strains.

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. [IFAH notes that additional definitions from other sections will be assembled into a harmonized document glossary. For the present, IFAH provides the following suggestions for definitions pertinent to this RA guidance:

CODEX-SOURCE ADDITIONS:

From CAC/GL21 "Principles for the Establishment & Microbiological Criteria for Foods" Section 5, in particular see 5.1.3 and 5.1.4. "Mere finding, with a presence/absence... test does not necessarily indicate a threat to public health"; and also 5.1.4 gives a preference for testing pathogens over indicator microbes, or if indicator microorganisms are used, a clear statement about how they relate to unhygienic practice or a health hazard. Consider similar phrasing for AMR bacteria

5. MICROBIOLOGICAL ASPECTS OF CRITERIA

5.1 Microorganisms, parasites and their toxins/metabolites of importance in a particular food

5.1.1 For the purpose of this document these include:

- bacteria, viruses, yeasts, moulds, and algae;
- parasitic protozoa and helminths;
- their toxins/metabolites.

5.1.2 The microorganisms included in a criterion should be widely accepted as relevant - as pathogens, as indicator organisms or as spoilage organisms - to the particular food and technology. Organisms whose significance in the specified food is doubtful should not be included in a criterion.

5.1.3 The mere finding, with a presence-absence test, of certain organisms known to cause foodborne illness (e.g. Clostridium perfringens, Staphylococcus aureus and Vibrio parahaemolyticus) does not necessarily indicate a threat to public health.

5.1.4 Where pathogens can be detected directly and reliably, consideration should be given to testing for them in preference to testing for indicator organisms. If a test for an indicator organism is applied, there should be a clear statement whether the test is used to indicate unsatisfactory hygienic practices or a health hazard.

From CAC/GL1 "General Guidelines on Claims" Under Section 3 (Prohibited Claims)

3.5 "Claims which could give rise to doubt about the safety of similar food or which could arouse or exploit fear in a consumer". So claims about fears about AMR resistant bacteria because of given animal feeding regimens, would be prohibited if it's just arousing or exploiting fear rather than offering claims based on scientific proof of a significant hazard.

CODEX DEFINITIONS

The following terms were included in End Note 1 for CAC/RCP 61-2005 (A. Franklin, et al. 2001 Rev. sci tech. Off. int. Epiz. 20(3):859-870) referring to monitoring and surveillance programs. They could be considered for inclusion in the TFAMR Definitions. The term "Commensal/Indicator Bacteria" might be useful as it was used in CAC/GL21 (described above) to distinguish it and actually gives them a lower priority vs. true foodborne pathogens.

-Animal Bacterial Pathogen: Referring to bacteria which cause diseases in animals and are of primary concern to veterinary medicine.

-Zoonotic Bacteria: Referring to Salmonella, Campylobacter, and Enterohaemorrhagic Escherichia coli. Essentially synonymous with "Foodborne pathogens", using "zoonotic" implies that a foodborne pathogen is proven to be coming from the animal to the food, whereas "foodborne" alone leaves the question open.

-Commensal/indicator bacteria. Escherichia coli and enterococci are commensal bacteria common to all animals. These bacteria are considered to constitute a reservoir of resistance genes, which may be transferred to pathogenic bacteria causing disease in animals or humans. They also may have non-transferable, intrinsic resistance to a given drug.

Draft RA document definitions needing revision:

-Antimicrobial Resistance. Although The Draft RA document references FAO/OIE/WHO, 2008 as the source, this definition is not microbiologically accurate: it includes the term "The ability of a microorganism to multiply or persist

in the presence of increased level...", by this definition, bacteria are always resistant to bacteriostatic drugs (e.g. penicillins, chloramphenicol) since they prevent multiplication but do not directly kill the microorganism (the microorganism thus "persists"). See below for a suggested alternative definition.

-Cross Resistance- The given definition is very wordy. Suggest a simpler "A single resistance mechanism that confers resistance to other antimicrobials of the same or related class".

-Resistance Determinant- The last sentence is excessively long and is not a comprehensive example, recommend deleting it and just using the first sentence.

ALTERNATIVE/ADDITIONAL DEFINITIONS:

Here are some suggested definitions that would be simpler and more scientifically accurate than those provided in the draft. Since terms need to be understood by all disciplines involved (i.e. food scientists, veterinarians, microbial ecologists, risk assessors, medical laboratorians, etc.), it is important to use succinct and scientifically accurate definitions. To that goal, here are a set of suggested terms for consideration:

Source: Brock, Biology of Microorganisms, 11th edition. Madigan, M.T. & Martinko, J.M. Pearson Prentice Hall, 2006. pp G1-G15 (glossary).

"Antimicrobial Drug Resistance: The acquired ability of a microorganism to grow in the presence of an antimicrobial drug to which the microorganism is usually susceptible"

"Opportunistic infection: An infection usually observed only in an individual with a dysfunctional immune system."

"Opportunistic pathogen: An organism that causes disease in the absence of normal host resistance."

"Pathogen: An organism, usually a microorganism, that causes disease."

"Conjugation: Transfer of genes from one prokaryotic cell to another by a mechanism involving cell-to-cell contact."

"Transduction: Transfer of host genes from one cell to another by a virus."

"Transformation: Transfer of genetic information via free DNA."]

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. [IFAH comments that this is not the mandated purpose or application of RA in Codex. The purpose of RA is guide the selection of RM options and not simply to address the risk question.]

- AMR-RA should essentially consider the principal contributing factors, such as non-human antimicrobial use (including both therapeutic and non-therapeutic uses in animals or plants), to the emergence and dissemination of AMR among pathogenic and commensal microorganisms that have food reservoirs.[IFAH comments that food is dynamic in that it is eaten or disposed of quickly so how can it be a reservoir?]

- AMR-RA should consider the impact of AMR on the effectiveness/efficacy of the available antimicrobial agents in human medicine which are needed to treat related and unrelated human infections. [IFAH asks how does this determine which RM options to implement?]

- 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. [IFAH comments that environmental considerations are outside of the Codex mandate and scope so this should be deleted.]

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. Similarly, input from stakeholders should be sought in identifying available data or information for AMR-RA. 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 microorganism(s) and/or specific resistance determinant(s) acquired from food and the impact of non-human antimicrobial use. It can also provide guidance to risk managers on appropriate risk management options. [IFAH comments that the purpose of RA is to guide the selection of RM options. The last sentence needs to be the sole purpose of the AMR-RA]

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 gaps should be clearly presented using a weight of evidence approach (e.g., FAO/OIE/WHO, 2008; JETACAR, 1999).

Data and possible sources of information:

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 taking into consideration epidemiologic and microbiological breakpoints. [IFAH proposes that references be provided to the monitoring and surveillance information on plants and animal feeds.]

- Epidemiological investigations of outbreaks and endemic cases associated with resistant microorganisms.
- Clinical studies including case reports on the relevant foodborne-related infectious disease prevalence, primary and secondary transmission, and antimicrobial therapy.
- Studies on interaction between microorganisms and their environment through the farm-to-table continuum.
- Non-human antimicrobial use data such as daily dosage, species-specific (including plants), route of administration, and duration.
- Investigations of the characteristics of resistant microorganisms and resistance determinants (in-vitro and in-vivo studies).
- Research on properties of antimicrobials including their resistance selection (in-vitro and in-vivo) potential and transfer of genetic elements and the dissemination of resistant bacteria in the environment.
- Field animal trials addressing the linkage of antimicrobial usage and resistance.
- Information on the link between resistance, virulence, and/or fitness of the bacterium
- Application of available pharmacokinetic/pharmacodynamic data in the development of drug use that may vary on a regional level

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, resistant pathogenic and commensal microorganisms and/or resistance determinants of food, animal feed, and/or of animal/plant origin, have the potential to cause an adverse human health effect. The resistance determinants from resistant microorganisms (e.g., commensals) can disseminate both vertically and horizontally. Intra- or inter-species transfer occurs for mobile resistance determinants from both pathogenic and commensal microorganisms. In this document, hazard includes antimicrobial resistant microorganisms (pathogenic and commensal) and their resistance determinants (derived from food, animal feed, animals, and plants). The conditions under which the hazard produces adverse health effects include scenarios through which humans could become exposed to a pathogen which contains the resistance determinant. The scope of hazard identification (e.g., combinations of microorganisms/antimicrobial class, particular use of antimicrobial, target species, specific geographical area etc.) is guided by the question posed by risk managers for a specific AMR-RA. [IFAH comments that the Risk Managers need to ask which risk management options will be the most effective in minimizing and containing AMR from a particular use in a particular food animal species and/or food products from that species.]

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.

6.2. EXPOSURE ASSESSMENT

The exposure assessment will address all the modular pathways as a consequence of non-human uses of antimicrobials resulting in 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 1 and 2, 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, 2006a and 2008b; FAO/OIE/WHO, 2008; FDA, 2003; JETACAR, 1999; and OIE, 2003).

An AMR-RA addressing 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 to the extent possible the factors that increase their prevalence in food. [IFAH comments that unless the overall risk is needed by Risk Managers to select from among several RM options, the overall risk seems to be an academic exercise and not within the scope of Codex.]

[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 (FAO/WHO, 2008b), and risk characterization (in press).

When the hazard of interest is the resistance determinant including those in commensal microorganisms, then exposure assessment should consider whether they can be transferred to human pathogens that subsequently become resistant. 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, AMR-RA may need to consider these factors. [IFAH comments that since this is not a food contamination issue at this point, it is outside the scope of Codex TFAMR. This concept should be terminated because it is too far removed from food.]

Table 1. Possible pre-harvest data requirements for exposure assessment

Element	Description or scope of data
Selection pressure	Extent of antimicrobial agent use or proposed use - Number of animal, crop or target farms exposed to the antimicrobial agent in the defined time period - Geographical distribution of use and/or farms
	Intensity of non-human use of antimicrobials - How much is used per target (as quantitative as possible) in the defined time period - Methods and routes of administration of the antimicrobial agent (individual/mass medication/for plants-is that spaying?) - Dosing regimen and duration of use - Number of administrations/administration periods in the defined time period - Cumulative effects of use of other antimicrobials in the defined time period
Target animal or crop and microbial factors affecting resistance development and spread	- Seasonal changes in microorganism prevalence - Rate of resistance development in commensal and zoonotic microorganisms in targets after administration of an antimicrobial agent - Resistance mechanisms, location of resistance determinants, occurrence and rate of transfer of resistance between microorganisms - Cross-resistance and/or co-selection for resistance to other antimicrobials (phenotypic or genotypic description) - Prevalence of commensals and zoonotic microorganisms in targets and proportion resistant to the antimicrobial (and minimal inhibitory concentration levels) - Primary and secondary transmission among targets - Animal management factors affecting immunity
Other possible sources of resistant microorganisms for the target	- Prevalence of other targets carrying microorganisms of interest; fraction that are resistant to antimicrobial agent in question - Prevalence of animal feed contaminated with resistant microorganisms - Prevalence of resistant microorganisms in soil or water, animal and human waste products
Possible outcome	Estimate or probability of the prevalence of the target animal or crop carrying resistant commensal and/or resistant zoonotic microorganisms presented for food harvest that is attributable to the use of the antimicrobial, and the level of contamination

Table 2. Possible post-harvest data requirements for exposure assessment

Element	Description or scope of data
Initial level of contamination of the food product	Prevalence and quantity of commensals and zoonotic microorganisms present in/on the target at slaughter or time of crop harvest and proportion resistant to the antimicrobial agent
Food production factors	Factors affecting the frequency and level of microorganism contamination:

	- 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 behaviours	- 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 outcome	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 when humans are exposed to resistant pathogens including increased frequency and severity of illness (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).

[IFAH suggests that the Task Force indicates how the adverse outcome information, within the Consequence component of the RA, will be used by Risk Managers to guide the selection of risk management options at the level of animal feed, crop production, animal production or food processing.]

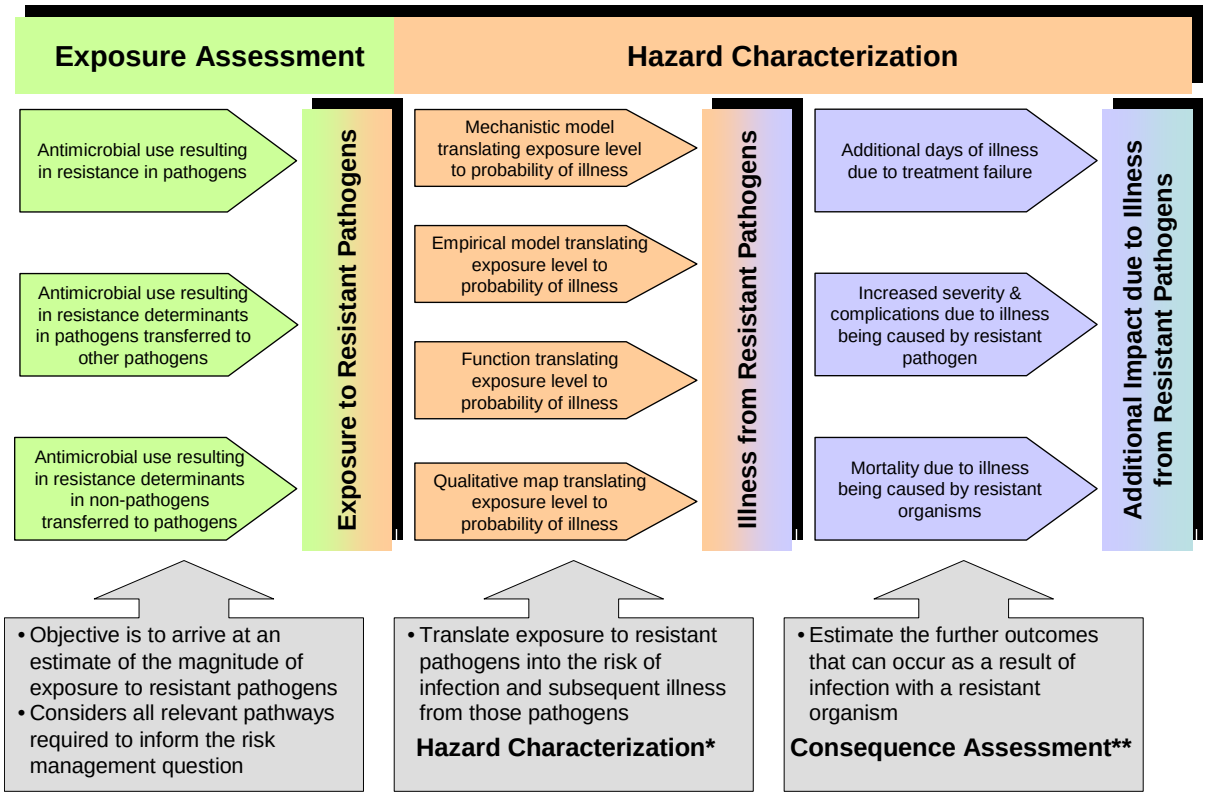

Figure 2. Scheme for the consolidated Hazard Characterization in AMR-RA

(*: concept adapted from the JEMRA [FAO/WHO, 2003a and 2006a]; **: concept adapted from the 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 virulence 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 including the increased frequency of infections. 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. [IFAH proposes that the Task Force indicates how the risk managers will use this part of the RA to determine which RM options to select and implement at the level of animal feed, crop production, animal production or food processing. IFAH suggests also that the Task Force indicates what the monitoring tools for assessing effectiveness may be.]

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. [IFAH comments that the statement regarding critically important antimicrobials biases the risk assessor to expect that resistant bacteria will always result in more severe consequences.]

The major factors that can have an impact on the hazard characterization are included in Table 3.

Table 3. Possible data requirements for hazard characterization

Element	Description or scope of data
Resistant microorganisms and resistance determinants	- 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 agent	- Pharmacodynamics/pharmacokinetics - Importance in human medicine (FAO/OIE/WHO, 2008) - Alternatives available in case of resistance, and potential impact of switching to alternative antimicrobial agent
Adverse health effect characteristics [IFAH suggests that the task force indicates how the risk manager will use this part of the RA to determine which RM options to select and implement. IFAH suggest also to indicate what the monitoring tools for assessing effectiveness may be.]	- Nature of the infection/illness - Host factors and susceptible population - Diagnostic aspects - Treatment with antimicrobial agent and hospitalization - Severity of adverse health effects - Epidemiological pattern (outbreak or endemic) - Persistence of hazards in humans
Dose-response	- Mathematical relationship between the exposed dose of resistant pathogens or determinants and probability of human illness
Possible outcome	- Probability of illness and additional consequences attributed to the resistance (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. The purpose of risk characterization is to answer the original questions posed by risk managers and to put into context the findings from the risk assessment process including uncertainties and other findings that could have an impact on the risk management decision. As a result, the form that the risk characterization takes, and the outputs it produces will vary from assessment to assessment as a function of the risk management request. This section provides guidance on the types of outcomes that may be informative in the risk characterization, but specific outputs such as if the risk outcome is to be measured using number of additional cases or other public health measures like disability adjusted life years (DALY's), will need to be established at the onset of the assessment process in conjunction with risk managers. [IFAH comments that the risk managers need to ask the question as to which risk management options may be most effective. The output may not be at the level of human adverse events.]

Additional outcomes of risk characterization, which would have been defined in the purpose of AMR-RA, may include scientific evaluation of risk management options within the context of the risk assessment (FAO/WHO, 2006b). [IFAH comments that this is the main purpose of RA and has already been noted previously]

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 DALYs. The selection of the final risk measures must generally have been defined within the purpose of AMR-RA, during the commissioning of the AMR-RA, in order to determine the appropriate exposure assessment and hazard characterization outcomes for risk characterization. [IFAH comments that the risk managers need to ask the question as to which risk management options may be most effective. The output may not be at the level of human adverse events.]

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 4). 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.

- Existing microbial risk assessments

- 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 potential points for consideration in the risk characterization are presented in Table 4 (OIE, 2007).

Table 4. Potential Points for Consideration in the Risk Characterization

Element	Description or scope of data
Factors in risk estimation	- Number of people falling ill and the proportion of that number with resistant strains of microorganisms - Increased severity or duration of infectious disease due to resistance - 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 alternative antimicrobial agent - Incidence of resistance - 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
Scientific evaluation of risk management options	- Comparison of public health burden before and after interventions
Sensitivity analysis	- Effect of changes in model input values and assumption on model output - Robustness of model results (output)
Uncertainty and variability analysis	- 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

SECTION 7. DOCUMENTATION

(This section will be moved, potentially expanded, and included in the integrated AMR Risk Analysis Document)

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

SECTION 8. RISK COMMUNICATION

(This section will be moved, potentially expanded and included in the integrated AMR Risk Analysis Document)

Throughout the process of AMR-RA, there should be an effective communication between risk assessors and risk managers. Similarly, effective communication should be maintained between risk assessors and affected and interested stakeholders for gathering relevant input and to maintain the transparency of the AMR-RA process. The outcome of risk assessment, and management interventions where appropriate, should be communicated to all stakeholders and the general public in a timely fashion.

SECTION 9. REFERENCES

(To be harmonized with reference section for overall AMR Risk Analysis Document)

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SECTION 10. APPENDICES

[IFAH comments that the example of RA given here does not reflect the purpose within the TF mandate, which is to guide risk management option selection. The Appendix needs to be modified or deleted.]

Appendix 1. Outputs of Qualitative AMR-RA

A qualitative risk assessment is often preferred due to its potential lower data demands.

The level of scrutiny, review and standards of logic and reasoning to which a qualitative approach should be held are, however, no less than those that a quantitative approach is subjected to.

[IFAH proposes that the first the first sentence in this paragraph be moved to the Top and bolded, if this section is to be retained] The following examples illustrate potential approaches that can be used to conduct a qualitative risk assessment; however this should not be viewed as a recommended or accepted default approach for adoption. The thought process and discussions that surround the development of categories for the exposure or the hazard characterization (e.g. “rare”, “high” etc) as well as how these categories translate into the ultimate risk outcome are a key part of the decision making and risk management process. The essential parts of developing a qualitative risk assessment could be grouped into three basic tasks:

- The development of qualitative statements or scores to describe the exposure assessment (e.g. “high”, “medium” etc), with careful consideration given to the implications and interpretation of these categorizations;
- The categorization of hazard characterization into qualitative statements or scores, with similar considerations as the exposure assessment into interpretation and implications;
- The process through which the different exposure and hazard characterization categories or scores are combined and integrated into overall risk levels (e.g. what does a “low” in exposure and a “high” in hazard characterization translate to, and is it different than a “medium” in both.

There are currently no pre-defined hazard characterization or exposure assessment categories that can be used, and different categories may be more suitable for certain situations. The approach used to integrate the exposure assessment and hazard characterization can also vary.

Example 1

Illustrative Exposure Assessment Scoring

Typically, in a qualitative risk assessment, the probability of the population being exposed to the hazard is translated into a series of qualitative statements. The qualitative risk assessment requires expert opinions, or other formalized, transparent and documented process to take the existing evidence and convert it into a measure of the probability of exposure. To illustrate, the probability has been converted into the following categories and scores:

- Negligible (0): Virtually no probability that exposure to the hazard can occur (<1e-6)
- Moderate (1): Some probability for exposure to occur (1e-6 to 1e-4)
- High (2): Significant probability for exposure to occur (>1e-4)

The assignment of both a statement reflecting the exposure probability as well as a corresponding score is done in this example to facilitate the process through which the exposure and hazard characterization will subsequently be combined. The description of the categorical statements includes an assessment providing greater detail as to the interpretation behind each of the categories.

Illustrative Hazard Characterization Scoring

The hazard characterization translates the outcomes of this step into qualitative statements that reflect the implications of exposure to a hazard. While the exposure assessment qualitatively captures the probability of being exposed, the hazard characterization qualitatively estimates the implications of being exposed. In microbiological risk assessment, the focus of the hazard characterization step is to translate the probability of exposure to the probability of illness; however in AMR risk assessments, the focus is likely to be the implications of exposure to resistant organisms that are over and above those of being exposed to susceptible organisms. To illustrate, the following categories are proposed:

- Negligible (0): Probability of illness upon exposure is the same as for susceptible organisms and the outcomes as a result of illness is not different
- Mild (1): Probability of illness upon exposure is the same as for susceptible organisms, but the outcomes following illness are more serious requiring hospitalization
- Moderate (2): Probability of illness upon exposure is higher and outcomes following illness are more serious requiring hospitalization
- Severe (3): Probability of illness is higher and outcomes following illness are very serious requiring hospitalization as well as the potential for treatment failures requiring lengthy hospitalization

Illustrative Risk Characterization Output

Ultimately, the exposure assessment and hazard characterization need to be integrated in the risk characterization in order to estimate the risk. By assigning each of the qualitative categories (e.g. “high”, “medium” etc.) with a numerical score (e.g. 0, 1, 2, etc.), the results can be produced in a transparent way by simply multiplying the scores. The resulting risk characterization score can then be translated into meaningful qualitative risk categories. In this example, the products of the exposure assessment and hazard characterization are assigned the following categories:

- No Additional Risk: Value of 0
- Some Additional Risk: Value between 1 and 2
- High Additional Risk: Value between 3 and 4
- Very High Additional Risk: Value between 5 and 6

The results could also be presented graphically as shown below, providing a clear picture of how outcomes are judged to be “very high additional risk” or “no additional risk” for example.

		Exposure Assessment		
		Negligible	Moderate	High
Hazard Characterization	Negligible	0	0	0
	Mild	0	1	2
	Moderate	0	2	4
	Severe	0	3	6

LEGEND	
	No Additional Risk
	Some Additional Risk
	High Additional Risk
	Very High Additional Risk

Example 2

Illustrative Exposure Assessment Scoring

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.

Illustrative Hazard Characterization Scoring

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/ctcaev3.pdf). In this example, 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.

Illustrative Risk Characterization Scoring

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 5.

Table 5. 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 for an AMR-RA

This appendix lists the suggested elements to include in an AMR-RA and the level of details of the data may vary case-to-case.

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. Intrinsic and acquired resistance in pathogenic and commensal microorganisms

2.2.6. Mechanism of resistance and their prevalence among human and non-human microflora

2.2.7. Importance of antimicrobials in human medicine

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. Commensals (species/strain) that likely acquire resistance determinants in non-human hosts and transmit them to human pathogens

2.3.3. Potential routes of transmission

2.3.4. Mechanisms of antimicrobial resistance

2.3.5. Association of resistance with virulence and pathogenicity

2.3.6. Location of resistance determinants and their frequency of transfer to related and unrelated microorganism species

2.3.7. Co- and cross-resistance and/or multiple resistance, and importance of other antimicrobials whose efficacy is likely to be compromised

2.4. Relationship of presence of antimicrobial resistant microorganisms or determinants in/on food and potential adverse human health impacts

2.4.1. Clinical studies

2.4.2. Epidemiological studies and surveillance

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. Resistance transferability

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 by resistant microorganisms

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