codex alimentarius commission E

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**
June 2008

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

At Step 3

(prepared by the physical Working Group led by Canada)

Governments and international organizations in Observer status with the Codex Alimentarius Commission wishing to submit comments at Step 3 on the Proposed Draft Risk Assessment Guidance Regarding Foodborne Antimicrobial Resistant Organisms are invited to do so **no later than 1 September 2008** as follows: Secretariat, *Ad Hoc* Codex Intergovernmental Task Force on Antimicrobial Resistance, Food Microbiology Division, Korea Food and Drug Administration, Eunpyeonggu, Seoul, 122-704, Republic of Korea (Telefax: + 82-2-355-6036, E-mail: kwakhyos@kfda.go.kr ***preferably***), with a copy to the Secretary, Codex Alimentarius Commission, Joint FAO/WHO Food Standards Programme, Viale delle Terme di Caracalla, 00153 Rome, Italy (Telefax: +39 06 5705 4593; E-mail: Codex@fao.org - ***preferably***).

BACKGROUND

1. During its First Session (Seoul, Republic of Korea, from 23 to 26 October 2007), the Codex *Ad Hoc* Intergovernmental Task Force on Antimicrobial Resistance agreed to undertake new work on the development of Risk Assessment Guidance regarding foodborne antimicrobial resistant microorganisms, subject to the approval by the 31st Session of the Commission (July 2008).

2. It further agreed to establish a physical Working Group, under the leadership of Canada, open to all delegations and observers and working in English, French and Spanish, which would prepare a proposed draft guidance document for circulation at Step 3 and further consideration at Step 4 at the Second Session of the Task Force.

3. 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 (including aquaculture), and the transmission through food and feed, of antimicrobial resistant microorganisms and resistance determinants.[1]

PROCEEDING OF THE WORKING GROUP

4. Canada requested the comments on the elements and considerations to be included in the first draft guidance document (Nov 28, 2007-Jan 15, 2008). Written comments were received from the following: Australia, Germany, Hungary, Japan, the Netherlands, the United States of America, Consumers International (CI) and the International Federation for Animal Health (IFAH). With consideration of these comments, Canada prepared and distributed the first draft working document/specific questions for comments (Version February 29, 2008 in early March 2008).

5. The comments on the first draft were received from: Australia, European Commission, France, Thailand, the United Sates of America, the Animal Health Institute (AHI)/Canadian Animal Health Institute (CAHI), CI, the International Dairy Federation (IDF) and IFAH. Canada revised and distributed (in early May 2008) the second draft document (Version April 15, 2008 in English, French and Spanish) prior to the Working Group meeting.

6. The physical Working Group was held in Brussels on May 26, 2008 and was chaired by the delegation of Canada. It was attended by 68 delegates representing 19 member governments and 4 observer organizations. The list of participants is attached in Appendix I. The Working Group was mandated:

- To discuss the draft guidance document on antimicrobial resistance risk assessment (AMR-RA) that was originally drafted by Canada (Version April 15, 2008) and which was circulated for input from participating member countries and observers. To improve on the draft, for further discussions at the Second Session of the CTFAMR (Seoul, Korea, October 2008)

GENERAL COMMENTS ON THE DRAFT DOCUMENT

7. France suggested that a distinction should be made between risk assessment policy and risk assessment process and that this document should focus on risk assessment policy, as per the Codex mandate. France questioned if Codex should be developing a prescriptive document, which outlines how risk assessment should be done and suggested modifying the document to fit Codex needs and mandate. Canada clarified the necessity for having appropriate details in the draft guidance document, indicating that there is currently no specific guidance on how to conduct an AMR-RA. Furthermore, a general broad risk assessment policy document might not be as useful as providing more concrete guidance on addressing problems when conducting an AMR-RA. The Task Force in Seoul should decide whether this should be a more general document or be more prescriptive.

8. The Working Group suggested that the introduction of the document should be common to all three Working Group documents (Risk Assessment, Risk Profiling/Prioritization and Risk Management) and perhaps it would be a good idea to harmonize the three documents. Several delegations agreed to have a common introduction and that it was extremely important for the three documents to complement each other. It was suggested that the three documents eventually be merged into one document and should be read together as a risk analysis process for antimicrobial resistance (AMR). Suggestion was made to include an overall flowchart as part of the introduction in the merged document, similar in nature to the one included in the scope section of this AMR-RA document. Similarly, a request was made to ensure that the scope in all three documents is consistent regarding the use of antimicrobials in the plant sector as well as to have one common definition section in all three working documents. The Working Group also decided that documentation and risk communication should be harmonized within the three working groups. It was also decided that there should be one reference list at the end of the larger document. The Codex secretariat clarified that the references will not be part of final guidance and should be limited only to working documents.

[1] ALINORM 08/31/42 paras 32-35 and Appendix III

DETAILED DISCUSSION ON THE DRAFT DOCUMENT

9. Scope: On lines 121-126. France sought clarification on whether this document should state explicitly who the intended recipients of this guidance are. Canada indicated that based on the mandate given to the Working Group, the primary recipients would be WHO, JEMRA, FAO. However, industries and other organizations might have interest in using the guidance provided in this document. The Working Group agreed that the Codex secretariat should have the final say regarding the intended users, but that JEMRA and OIE should be clearly mentioned. It was agreed to modify lines 121-125 to indicate the users of this document and include that the document could be adapted for other purposes (imported food, human safety evaluation of drugs being used/to be used in food animals).

10. Scope: There was a question whether the original text of the document (lines 98-99) was intended to include issues of antimicrobial residues. Canada expressed that the intent was to convey a microbial food safety issue with reference to antimicrobial use in plants or animals, not necessarily human health implications of antimicrobials being in food at time of consumption. Members suggested rewording this section to convey more clearly that the main scope is food safety in the context of AMR and not of antimicrobial residues.

11. Scope: The United States commented that Codex is not a drug regulatory organization but rather a food safety organization and the document should emphasize food safety. Consensus was reached to change the first paragraph (lines 93-105) to more clearly emphasize that the focus of the document is to develop guidance for AMR-RA focusing on food and relevant food safety issues. The use of antimicrobials in farm (e.g., food-producing) animals and its implications in emergence and dissemination of resistant microorganisms and resistance determinants of human and public health concern should be included in the assessment.

12. Scope: suggestions were made to modify the flow chart in Figure 1 to include plants, to delete feed, and include water as a source of contamination.

13. Definitions: The Netherlands pointed out the need to add the indirect exposure under the definition of adverse health effects. Clarification was made that this pertains to ‘acquired from food’ which can be either direct or indirect

14. Definitions: Canada pointed out that the existing Codex definitions do not cover specifics to AMR. When using definitions from international organizations, we should not alter the definitions unless the task force decides otherwise. With regards to the definition of risk, it was decided to use the Codex definition. Thailand suggested that the Working Group could use a criterion to include/not include definitions and proposed that if a term is used several times, then it should be defined. Definitions should be practical and interpreted by global communities. The Netherlands observed that there is mention of “pathogens in humans” throughout the document. Normal intestinal flora can be pathogenic to people going to the hospitals. The question was asked whether we should include or exclude commensals when we use the word ‘pathogen’. Canada provided clarification that any organism that can cause illness or disease is a pathogen. The Netherlands suggested that this document should clearly define the term ‘pathogen’. It was requested to define commensal, pre-harvest/post-harvest, and to delete multiple drug resistance. The request for the new definitions was noted and tabled pending decisions by the task force regarding harmonization of definitions across the three working documents.

15. Definitions: There was a suggestion to modify the cross-resistance definition. The representative from the WHO was going to check with the experts present at the FAO/OIE/WHO 2007 Rome meeting and provide feedback with respect to this draft document.

16. General principles: Codex general principles for microbiological risk assessment (MRA) are applicable under this section. Canada asked the Working Group whether the document should include all key principles or just refer to these existing Codex documents. It was decided to refer to previous Codex documents on risk assessment.

17. General considerations-Purpose: Thailand suggested under section 5.1 that the purpose of an AMR-RA should be kept in line with the discussion on sources of data and evidence so that they flow in the same direction (i.e. uses of antimicrobials leads to resistance determinants). On line 282 it was suggested additional reference to the FAO/OIE/WHO 2008 document. The representative from the FAO requested Canada to ensure the list of data sources incorporates those considered on page 22 of the Joint FAO/WHO/OIE Expert Meeting on Critically Important Antimicrobials (2007 Rome meeting).

18. Hazard Identification: The Working Group discussed whether an antimicrobial should be considered as a hazard in the context of this document. It was agreed to delete footnote #7 since antimicrobials themselves are not hazards, in the sense that they might endanger human health, but rather that humans are exposed to a microorganism, which acquires resistance to antimicrobials.

19. Hazard Identification: Table 1 was deleted as the definitions of hazard and adverse health effect were already captured in the definition section. It was decided to reiterate the definition of hazard in the first paragraph of hazard identification.

20. Exposure Assessment: France suggested that lines 378-380 indicate that imported products should be assessed on more of a flexible basis, and less stringent than tests for locally produced products. Canada clarified that the intent of this statement regarding imported products was based on the fact that the exposure assessment will start at the point of when the food is imported (i.e. cannot go back to the farm source). Under this scenario, it would not likely be possible to do a full farm-to-fork exposure assessment, unlike the situation in domestic products. Australia commented that this is a practical aspect of what is available and hence would support the inclusion.

21. Exposure Assessment: The Working Group suggested revision of the title of Tables 2 and 3 to "Possible pre-harvest/post-harvest data requirements for exposure assessment". There were a few minor editorial changes to Tables 2 and 3.

22. Exposure Assessment: The representative from Consumers International suggested that Table 2 should include both how much is used and why an antimicrobial is used. It was stated by Canada that the issue of 'why' is not really relevant in the exposure assessment part of the risk assessment. However, it is pertinent in the risk management part of the process, particularly in balancing risks and benefits.

23. Exposure Assessment: The United States suggested clarifying that risk assessment needs to refer to the baseline resistance information that is a critical parameter for this exposure assessment. Since we can only consider resistance that emerges and disseminates and that is as a result of drug use, similar to the United States Food and Drug Administration Guideline 152, thus Table 2 was revised by adding text to capture this suggestion.

24. Hazard Characterization: The chair identified the issues under this section as:

- How to incorporate the recommendation from the Joint FAO/WHO/OIE Expert Meeting report (Rome 2007 meeting) in this document with respect to critically important antimicrobials.
- The need to account for cumulative effects of resistance.
- How risk assessment of resistant organisms could benefit from risk assessment of susceptible organisms.

25. Hazard characterization: France was concerned that Figure 2 did not accurately describe the OIE consequence assessment, in particular the three horizontal arrows on the right and the box at the bottom of the column. Canada explained that the figure reflects the process that was followed to incorporate JEMRA and OIE guidelines and how WHO/FAO defines consequence assessment. It was then adjusted to meet the needs of AMR-RA. Current JEMRA guidelines are not sufficient for AMR issues. Overall the objective of Figure 2 and text from lines 400-409 is essentially to demonstrate how the features of JEMRA and OIE were melded together to gain guidelines appropriate to AMR-RA for Codex. Also, the OIE guidance includes things that are already captured by the JEMRA approach. Only the bullets that are unique features for OIE consequence assessment to achieve the objectives of the AMR-RA for Codex have been included, and hence the difference. A suggestion was made to take out JEMRA and OIE references at the bottom of the figure. Canada agreed to take another look at the OIE consequence assessment list to make sure there was not anything missing from the list in Figure 2.

26. Hazard Characterization: minor changes were made to the text in Exposure Assessment arrows of Figure 2. It was also suggested that the title of Table 4 be changed to match the others in the exposure assessment section.

27. Risk Characterization: The Netherlands was concerned that the first bullet point under risk characterization covers the adverse effects caused by susceptible versus resistant organisms. For example, whether an MRSA (methicillin-resistant *Staphylococcus aureus*) causes more adverse health effects than an MSSA (methicillin-susceptible *Staphylococcus aureus*). Both are invasive, but are there more adverse health effects. This should be part of risk characterization point. Canada clarified that the possibility of additional severity of a resistant infection is captured. In Figure 2, traditional MRA stops at illness from resistant pathogens (illness from pathogens in MRA). However, AMR-RA is everything after that. Illness from resistant pathogens, plus all the additional impacts. The outcome of hazard context is built into the risk characterization. Canada agreed to include this concept in the risk characterization step in addition to what is already captured in the hazard characterization step: i.e., how much more impact is there because of resistant bacteria (e.g., *Campylobacter*).

28. Risk Characterization: The chair requested the United States delegation to clarify their written comments on how risk assessment of susceptible organisms can benefit the AMR-RA process. Their comments indicated that for certain cases of bug-drug-commodity combinations, there may already be a MRA conducted. Resistant bacteria may represent a similar risk as susceptible ones, plus the added effect of the resistance. Canada added a bullet under risk characterization to include information from existing MRA.

29. Risk Characterization - the chair outlined the issues that were highlighted under this section:

- Is the output of Risk Characterization appropriate for risk managers?
- How to integrate outputs of Hazard Characterization and Exposure Assessment to derive the risk estimate.

30. The decision matrix on how to integrate the section may reside with risk managers and hence was suggested to pass these issues/bullets to the Risk Management Working Group. The chair pointed out that these are issues that have been raised by the comments sent via e-mail, hence it would be good to achieve consensus.

31. Risk Characterization: Canada identified some of the outcome measures relevant for Risk Characterization in the text, including burden of disease measurements such as disability adjusted life years (DALYs). Canada asked the group whether this level of detail is necessary. These should be ideally inputs from the risk managers. It is important within the guidance for AMR-RA that all the various outcomes that might be candidates for Risk Characterization are listed in this section. The risk managers may state what risk outcomes they are interested in, but in the guidance document there should be a broader description of outcomes and context around this.

32. Risk Characterization: It was decided that while the risk managers should be in discussion with the risk assessors defining the outcomes that they want, it is valuable in this document to spell out the options. Section 6.4 and the table regarding evaluation of risk management options was revised based on items discussed. Around line 497, the first paragraph was revised on the purpose of Risk Characterization to capture the uses of Risk Characterization for risk managers, add another bullet on page 16 for the usefulness of MRA, and on page 17 line 510, change sentence to reflect title of Table 5. Bullet #7 in Table 5 was changed by deleting “observed in humans”.

33. References: The chair mentioned that FAO has shared the pre-publication guidelines on Exposure Assessment by the JEMRA with Canada. This reference will be included and Canada will take these guidelines into account when drafting the next version.

34. Appendices. The chair identified the issues of length, outline and usefulness of the appendices and solicited input from the Working Group.

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.

36. Appendices: It was suggested to include clear text on differences between Appendices 1 and 2. Canada clarified that Appendix 2 was not just for quantitative RA, but was a layout of what data/sections that would be needed in a typical risk assessment.

37. Appendices: The delegation of the European Community (EC) questioned the terminology such as 'negligible' and suggested the use of the word 'rare' instead. Denmark suggested discussing these comments regarding the word 'negligible'. Does 'negligible' imply that you do not need to look at it further? Is the word 'rare' better? If exposure is high but adverse health effect is zero, result is zero. Need to use another word?

38. Appendices: Philippines mentioned in relation to question of use of integration of outputs of exposure assessment and hazard characterization mentioned that Table 6 is an example of qualitative risk estimation.

39. Appendices: The United States mentioned that the two appendices cover the key areas mandated by this task force. In general the two appendices are what is being practiced in the United States and compatible with the general approach. Whether a multidrug resistant or single drug resistant organism involving critically important antimicrobial(s), but the pathogen(s) may present more (or added) challenges for treatment (different from virulence). No suggestions for changing wording at this time. The critically important antimicrobials are important for priority setting but can be used in AMR-RA when we have a multidrug resistance issues. This should be discussed more detail as it is a critical issue.

40. Appendices: The delegation of the EC mentioned that they are happy to keep the appendices. In Appendix 1, the EC proposed to delete Table 6 rather than change it. This will be difficult to agree on what is low/medium etc. The outcome of 'low' will be difficult to agree on. In real life that this table will be used, but this seems not practical as it does not add too much to the document.

41. Appendices: The chair asked the floor whether they agreed to delete Table 6. Brazil mentioned that they see 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 here. Table 6 has merit as an example, though it is not mandatory. Brazil mentioned that the Table 6 provides the picture of activity of risk assessment in a satisfactory way. Thailand supported the view point of Brazil. Thailand mentioned that we have to have an innovative approach in order to progress further. The document should make a strong attempt to advance qualitative assessment. Consider ranges from negligible to fatal. The title of Table 6 may have to be adjusted to make it consequential exposure-hazard. We should mention that action has been made to set an example.

42. Appendices: Canada clarified that they were uncomfortable with the concept of putting something in this document construed to be a well thought out sequence of events. Table 6 implies that if you have 1, 2, and 3 this leads to another output. The beginning paragraph could easily be forgotten over time. There has not been enough time spent on how to do a qualitative risk assessment. The FAO and JEMRA have been working with this for 6 years. There is no agreement on qualitative risk assessment. Will this appendix take on a life of its own? Given the duration of the task force, is it long enough to develop this as relatively crude guidance? Canadian recommendation would be that a simplified version of qualitative risk assessment is provided and recommendations given that the FAO and WHO/JEMRA spends time on developing good qualitative risk assessment. At this Working Group level we are not in the position to do this justice. The Netherlands agreed with concerns raised by Canada. The way it is written now is an oversimplified way of doing things, and will take on a life of its own. The Netherlands was in favor of describing it in a simplified way, even if this table is described as an example it will be used and would not address the complexity of the issue.

43. Appendices: The representative from the FAO informed the members that after 5 years of discussion, the JEMRA guidelines on Risk Characterization will be available later this year. This is a general review on what the experts think on this matter. Denmark supported Canada in that we need to do something and that we have not the time to develop this thoroughly. It was suggested to give a few examples, i.e. negligible combined with negligible and what happens. Then delete the rest of the table. We will have a hard time on agreeing on all of the points of the table. The chair summarized the decision - to modify the Appendix 1 to include some of the examples of how to combine the information at a qualitative level and build this into the text.

44. Appendices: Brazil commented that some delegations have expressed their agreement to leave the table 'as is', while others have suggested the need for further discussion. The text we are producing will be submitted for further consideration of the task force. Keep both and leave it for the task force to decide. Canada clarified that the compromise is reasonable, we have the appendix and give an example and add text to illustrate other examples on how to do a qualitative ranking to reinforce that there is not only one way, but there are several ways. We have to make a conscious decision on how to put these steps together. Remove thinking that the way in this appendix is the only way to go, when in reality there are several approaches. Netherlands supported the Canadian suggestion and was seconded by the United States.

45. Appendices: The chair asked the floor if there were any issues with Appendix 2 which is just a snapshot of what is required. It was suggested to revise the title to bring clarity.

46. The chair thanked the working group members for their excellent participation and constructive comments.

RECOMMENDATIONS TO THE 2nd SESSION OF THE TASK FORCE

47. The revised document (included in Appendix II) should be distributed to the Codex members and observers for consideration at the Second Session of the Task Force and be advanced through the step procedure of Codex.

48. It was recognized that a functional separation between risk assessment and risk management may not be feasible or practical. Hence this working group recommends the three working group documents could be most usefully read by intended audiences as one integrated guidance document. With this approach, certain sections such as introduction, definitions, documentation, and risk analysis general principles could be harmonized resulting in a more consistent and understandable guidance document. Furthermore, this approach would allow the inclusion of an overall flow chart that would guide the reader through the range of activities discussed in the three separate but overlapping working group documents. Finally, the integrated document would include a harmonized section on risk communication, which is critical to all activities addressed by the guidance.

Appendix I

LIST OF PARTICIPANTS
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AUSTRALIA - AUSTRALIE

Dr Angelo VALOIS
Manager, Technical and International Policy
Australian Government Department of Agriculture, Fisheries and Forestry,
GPO Box 858, Canberra ACT 2601
Australia
Tel: +61 2 6272 5566
Fax: +61 2 6272 5697
E-mail: angelo.valois@daff.gov.au

BRAZIL - BRÉSIL - BRASIL

Dr Clea CAMARGO
Coordinator, ABIQUIf AH
Av. Morumbi, 8264
Sao Paulo 04703-002
Brazil
Tel: +55 11 2144 6849
Fax: +55 11 2144 6198
E-mail: camargo_clea@lilly.com

Mrs Daniela GOMES
Government Employee-Expert on Regulation
Brazilian Health Surveillance Agency
Sepn 511 – Bloco A – Edificio Bittar II – Asa Norte
Brasilia 70750-641
Brazil
Tel: +55 61 3448 6281
Fax: +55 61 3448 6274
Email: daniela.gomes@anvisa.gov.br

Dr João PALERMO-NETO
Full Professor of Pharmacology and Toxicology
Ministry of Agriculture, Livestock
Av. Prof. Dr. Orlando Marques de Paiva, 87
CEP: 05508-200 Sao Paulo, Sao Paulo
Brazil
Tel: +55 11 3901 7957
Fax: +55 11 3901 7829
E-mail: jpalermo@usp.br

Mr Adauto RODRIGUES
Federal Inspection Officer
Ministry of Agriculture, Livestock
Esplanada dos Ministerios
Anexo do Ministerio da Agricultura
Bloco D 4 Andar - Sala 439-A
Brazil
Tel: +55 61 3218 2458
Fax: +55 61 3218 2727
E-mail: adauto.rodrigues@agricultura.gov.br

Mrs Ligia SCHREINER
Government Employee-Expert on Regulation
Brazilian Health Surveillance Agency
Sepn 511 – Bloco A – Edificio Bittar II – Asa Norte
Brasilia 70750-641
Brazil
Tel: +55 61 3448 6290
Fax: +55 61 3448 6274
Email: ligia.schreiner@anvisa.gov.br

Mrs Fabiana XAVIER
Federal Inspection Officer
Ministry of Agriculture, Livestock
Esplanada dos Ministerios|
Anexo do Ministerio da Agricultura
Bloco D 4 Andar - Sala 448-A
Brazil
Tel: +55 61 3218 2469
Fax: +55 61 3218 2874
E-mail: fabiana.xavier@agriculturea.gov.br

CANADA- CANADÁ

Dr Lateef ADEWOYE
Team Leader
Veterinary Drugs Directorate
Health Products and Food Branch
Health Canada
11 Holland Avenue, Suite 14
Ottawa, Ontario K1A 0K9
Canada
Tel: +1 613 941 9237
Fax: +1 613 957 3861
E-mail: lateef_adewoye@hc-sc.gc.ca

Dr Carolee CARSON
Veterinary Epidemiologist/Risk Assessor
Laboratory for Foodborne Zoonoses
Public Health Agency of Canada
160 Research Lane, Suite 103
Guelph, Ontario N1G 5B2
Canada
Tel: +1 519 826 2346
Fax: +1 519 826 2255
E-mail: carolee_carson@phac-aspc.gc.ca

Dr Aamir FAZIL
Risk Assessment Specialist
Laboratory for Foodborne Zoonoses
Public Health Agency of Canada
160 Research Lane, Suite 206
Guelph, Ontario N1G 5B2
Canada
Tel: +1 519 826 2370
Fax: +1 519 826 2367
E-mail: aamir_fazil@phac-aspc.gc.ca

Dr Rebecca IRWIN
Director
Laboratory for Foodborne Zoonoses
Public Health Agency of Canada
160 Research Lane, Suite 103
Guelph, Ontario N1G 5B2
Canada
Tel: +1 519 826 2183
Fax: +1 519 826 2255
E-mail: rebecca_irwin@phac-aspc.gc.ca

Dr Xian-Zhi LI
A/Team Leader
Veterinary Drugs Directorate
Health Products and Food Branch
Health Canada
11 Holland Avenue, Suite 14
Ottawa, Ontario K1A 0K9
Canada
Tel: +1 613 941 8736
Fax: +1 613 957 3861
E-mail: xianzhi_li@hc-sc.gc.ca

Dr Manisha MEHROTRA
Director, Human Safety Division
Veterinary Drugs Directorate
Health Products and Food Branch
Health Canada
11 Holland Avenue, Suite 14
Ottawa, Ontario K1A 0K9
Canada
Tel: +1 613 941 8775
Fax: +1 613 957 3861
E-mail: manisha_mehrotra@hc-sc.gc.ca

CZECH REPUBLIC – RÉPUBLIQUE TCHÈQUE – REPÚBLICA CHECA

Mrs Pavla NOVOTNA
DVM
Institute for State Control of Veterinary Biologicals and Medicaments
Hudcova 56a, Brno 62100
The Czech Republic
Tel: +420 541518269
Fax: +420 541212607
E-mail: novotna@uskvbl.cz

DENMARK- DANEMARK - DINAMARCA

Dr Frank M. AARESTRUP
Professor, National Food Institute, Technical University of Denmark
Bülowsvej 27, 1790 Copenhagen V
Denmark
Tel: +45 7234 6000
Fax: +45 7234 6001
E-mail: faa@food.dtu.dk

Dr Yvonne AGERSØ
Senior Scientist
National Food Institute, Technical University of Denmark
Bulowsvej 27, 1790 Copenhagen V
Denmark
Tel: +45 7234 6000
Fax: +45 7234 6001
E-mail: ya@food.dtu.dk

Dr Justin C. AJUFO
Veterinary Officer
Danish Veterinary and Food Administration
Moerkhoej Bygade 19, DK-2860 Soeborg
Denmark
Tel: +45 3395 6000
Fax: +45 3395 6001
E-mail: jca@fvst.dk

ESTONIA - ESTONIE

Mrs Ingrid VESMES
Head of the Food Hygiene Bureau
Ministry of Agriculture
LAI STR 39/41, Tallinn 15056
Estonia
Tel: +372 625 6272
Fax: +372 625 6272
E-mail: ingrid.vesmes@agri.ee

EUROPEAN COMMUNITY (MEMBER ORGANIZATION) – COMMUNAUTÉ EUROPÉENNE (ORGANISATION MEMBRE) – COMUNIDAD EUROPEA (ORGANIZACIÓN MIEMBRO)

Dr Marta HUGAS
Head of Unit Biological Hazards
European Food Safety Authority (EFSA)
Largo N. Pali 5/A
I-43100 Parma
Italy
Tel: +39 052103611
Fax: +39 052103600
E-mail: marta.hugas@efsa.europa.eu

Mrs Bernadette KLINK-KHACHAN
Coordinator, European Commission
Health and Consumer Protection Directorate-General
Rue Froissart 101 - 1049 Brussels
Belgium
Tel: +32 2 295 7908
Fax: +32 2 299 8566
E-mail: bernadette.klink-khachan@ec.europa.eu

Dr Ernesto LIEBANA
Senior Scientific Officer
European Food Safety Authority (EFSA)
Largo N. Palli 5/A
I-43100 Parma
Italy
Tel: +39 0521 036854
Fax: +39 0521 036854
Email: ernesto.liebana@efsa.europa.eu

Ms Marta SOBIERAJ
Administrator, European Commission
DG Health and Consumer Protection
Rue Froissart 101 - 1049 Brussels
Belgium
Tel: +32 2 292 1432
Fax: +32 2 299 8566
E-mail: marta.sobieraj@ec.europa.eu

Mr Kari TOLLIKKO
Principal Administrator
General Secretariat of the Council of the European Union (EU)
Rue de la Loi 175
BE-1048 Brussels
Belgium
Tel: +32 2 281 7841
Fax: +32 2 281 6198
Email: kari.tollikko@consilium.euopa.eu

Dr Karolina TORNEKE
Associate Professor
CVMP

Lakemedelsverket P.O. Box 26, SE-75103
Uppsala
Sweden
Tel: + 46 18174904
Fax: +46 18548566
Email: karolina.torneke@mpa.se

Dr Jordi TORREN
Scientific Secretary
Veterinary Medicines and Inspections European Medicine Agency (EMEA)
7, Westferry Circus, Canary Wharf
London, E14 4HB
United Kingdom

Tel: +44 2074188400
Fax: +44 2074188447
Email: jordi.torren@emea.europa.eu

Dr Eva ZAMORA ESCRIBANO
Administrator, European Comisión
Health and Consumer Protection Directorate-General
Rue Froissart 101 - 1049 Brussels
Belgium
Tel: +32 2 299 8682
Fax: +32 2 299 8566
E-mail: eva-maria.zamora-escribano@ec.europa.eu

FRANCE - FRANCIA

Mr Pascal AUDEBERT
Point de contact du Codex Alimentarius en France
Premier Ministre – Secrétariat général des Affaires européennes
2, boulevard Diderot, 75572 Paris Cedex 12
France
Tel: +33 1 44 87 16 03
Fax: +33 1 44 87 16 04
E-mail: sgae-codex-fr@sgae.gouv.fr;
pascal.audebert@sgae.gouv.fr

Dr Vincent JECHOUX
Administrator DVN
251 Rue de Vaugirard
75732 Paris Cedex 15
France
Tel: +33 1 49 55 51 39
Fax: +33 1 49 55 43 98
E-mail: vincent.jechoux@agriculture.gouv.fr

Mrs Catherine LAMBERT
International Affairs
AFSSA-ANMV
La Haute Marche, Javené
35302 Fougeres
France
Tel: +33 2 99 94 78 87
Fax: +33 2 99 94 78 99
E-mail: c.lambert@anmv.afssa.fr

Dr Françoise LEBLANC
SIMV Antibiotic Group
Vetoquinol
50, rue de Paradis
75010 Paris
France
Tel: +33 3 84 62 59 14
Fax: +33 3 84 62 55 16
E-mail: francoise.leblanc@vetoquinol.com

GERMANY- ALLEMAGNE – ALEMANIA

Dr Annemarie KAESBOHRER
Head of Unit, Epidemiology and Zoonoses
Federal Institute for Risk Assessment (BFR)
National Reference Laboratory for Antimicrobial Resistance
Diedersdorfer weg 1, 12277 Berlin
Germany
Tel: +49 30 8412 2202
Fax: +49 30 8412 2952
E-mail: annemarie.kaesbohrer@bfr.bund.de

IRELAND- IRLANDE - IRLANDA

Dr John EGAN
Senior Superintending Research Officer
Department of Agriculture, Fisheries and Food
Central Veterinary Research Laboratory, Backweston Campus,
Young's Cross, Celbridge, Co. Kildare
Ireland
Tel: +353 1 6157138
Fax: +353 1 6157116
Email:john.egan@agriculture.gov.ie

ITALY- ITALIE - ITALIA

Mr Ciro IMPAGNAIELLO
Ministero delle Plitiche Agricole,
Alimentari e Forestali
Via XX Settembre, 20
00187 Rome
Italy
Tel: +39 6 46656046
Fax: +39 6 4880273
E-mail: c.impagnatiello@politicheagricole.it

JAPAN- JAPON - JAPÓN

Ms Keiko AKIMOTO
Officer, Animal Products Safety Division,
Food Safety and Consumer Affairs Bureau
Ministry of Agriculture, Forestry and Fisheries
1-2-1 Kasumigaseki, Chiyoda-ku,
Tokyo 100-8950
Japan
Tel: +81 3 3502-8702
Fax: +81 3 3502-8275
Email: keiko_akimoto@nm.maff.go.jp

Dr Yuuko ENDOH
Chief, General Medicament Section, Assay Division II
National Veterinary Assay Laboratory
Ministry of Agriculture, Forestry and Fisheries
1-15-1 Tokura, Kokubunji
Tokyo 185-8511
Japan
Tel: +81 42 321 1849
Fax: +81 42 321 1769
Email: endoyuk@nval.go.jp

Mr Yoshiyuki INAMORI
Section Chief, Assessment Division
Food Safety Commission Secretariat, Cabinet Office
2-13-10 Prudential Tower 6th Floor, Nagata-cho,
Chiyoda-ku Tokyo 100-8989
Japan
Tel: +81 3 5251 9218
Fax: +81 3 3591 2237
Email: yoshiyuki.inamori@cao.go.jp

Dr Hideaki KARAKI
Professor/Special Adviser
Food Safety Commission, Cabinet Office
2-13-10 Prudential Tower 6th Floor, Nagata-cho
Chiyoda-ku Tokyo 100-8989
Japan
Tel: +81 3 5251 9218
Fax: +81 3 3591-2237
Email: karaki@gakushikai.jp

NETHERLANDS - PAYS-BAS – PAÍSES BAJOS

Dr Dik MEVIUS
Professor, Central Veterinary Institute Department KAZ
PO Box 2004, 8203 AA Lelystad
The Netherlands
Tel: +31 320238413
Fax: +31 320238153
E-mail: dik.mevius@wur.nl

NEW ZEALAND - NOUVELLE-ZÉLANDE - NUEVA ZELANDIA

Dr Donald CAMPBELL
Principal Advisor (Public Health)
New Zealand Food Safety Agency
PO Box 2835, Wellington
New Zealand
Tel: +64 4 894 2649
Fax: +64 4 894 2530
E-mail: donald.campbell@nzfsa.govt.nz

NORWAY - NORVÈGE - NORUEGA

Prof Kari GRAVE
Professor, National Veterinary Institute
Department of Health Surveillance and
Norwegian Scientific Committee for Food Safety
PO Box 8156, Dep, N–0033 Oslo
Norway
Tel: +47 95 81 54 48
Fax: +47 22 96 47 52
E-mail: kari.grave@vetinst.no

PHILIPPINES - FILIPINAS

Ms Karen Kristine ROSCOM
Chief Science Research Specialist
Department of Agriculture
Bureau of Agriculture & Fisheries Standards
Bureau of Plant Industry Compound
Visayas Avenue
Quezon City – 1101
Tel: +632 920 6131
Fax: +632 455 2858
E-mail: bafps@yahoo.com

REPUBLIC OF KOREA – RÉPUBLIQUE DE CORÉE – REPÚBLICA DE COREA

Dr Hyo-Sun KWAK
Deputy Director, Korea Food and Drug Administration
#194, Tongil-ro, Eunpyung-gu, Seoul, 122-744
Republic of Korea
Tel: +82 2 380 1682
Fax: +82 2 355 6036
E-mail: kwakhyos@kfda.go.kr

Dr Kwang-Jick LEE
Senior Scientific Officer
Toxicopharmacologist of Veterinary Drug & Biologicals Division
Korea National Veterinary Research & Quarantine Service
480, Anyang 6-dong, Manan-gu
Anyang- City, Gyeonggi-do
Republic of Korea
Tel: +82 31 467 1726
Fax: +82 31 467 1795
E-mail: leekwj@nvrqs.go.kr

Mr Sang-Hyeon YOON
Scientific Officer, Korea Food and Drug Administration
#194, Tongil-ro, Eunpyung-gu, Seoul, 122-744, Korea
Tel: +82 2 380 1682
Fax: 82 2 355 6036
E-mail: xanga@kfda.go.kr

SPAIN - ESPAGNE - ESPAÑA

Maria Gema CORTES RUIZ
Senior Asesor
Agencia Espanola de Medicamentos y Productos Sanitarios
Ministerio de Sanidad y Consume
C/Campezo 1, ED. 8
ES-28022-Madrid
Spain
Tel: +34 91 822 54 31
Fax: +34 91 822 54 43
E-mail: gcortes@agemed.es

THAILAND - THAÏLANDE - TAILANDIA

Dr Sasi JAROENPOJ
Senior Veterinarian, Department of Livestock Development
Phayathai Road, Rachtaevee
Bangkok 10240
Thailand
Tel: +662 6534444 ext. 3142
Fax: +662 6534917
E-mail: sasijaroenpoj@yahoo.com

Ms Yupa LAOJINDAPUN
Standards Officer, National Bureau of Agricultural Commodity and Food Standards
3 Raidamnem Nok Ave
Bangkok 10200
Thailand
Tel: +662 2831693
Fax: +612 2803899
E-mail: yupa@acfs.go.th

Dr Kraisid TONTOSIRIN
Advisor, Institute of Nutrition, Mahidol University
Salaya, Nakorn Pathom
73170 Thailand
Tel: +662 4419740
Fax: +662 9383604
E-mail: raktt@mahidol.ac.th; kraisid.tontisirin@gmail.com

UNITED STATES OF AMERICA – ÉTATS-UNIS D'AMÉRIQUE – ESTADOS UNIDOS DE AMÉRICA

Dr Neena ANANDARAMAN
Veterinary Epidemiologist
Office of Public Health Sciences
USDA Food Safety and Inspection Services
1400 Independence Ave, SW
343 Aerospace Center
Washington, DC 20250-3700
USA
Tel: +1 202 690 6429
Fax: +1 202 720 8213
E-mail: neena.anandaraman@fsis.usda.gov

Dr Barry HOOBERMAN
Risk Analyst, US FDA Centre for Veterinary Medicine
7519 Standish Place, HFV-150
Rockville, MD 20855
USA
Tel: +1 240 453 6835
Fax: +1 240 453 6880
E-mail: barry.hooberman@fda.hhs.gov

Dr Scott HURD
Deputy Undersecretary for Food Safety
U.S. Department of Agriculture
1400 Independence Ave, SW Rm 227-E
Washingnton, DC 20250-0121
USA
Tel: +1 202 720 0351
Fax: +1 202 690 0802
E-mail: scott.hurd@usda.gov

Ms Edith KENNARD
Staff Officer, US Codex Office
FSES/US Department of Agriculture
1400 Independence Ave, SW, Room 4861 South Bldg
Washington, DC 20250
USA
Tel: +1 202 720 5261
Fax: +1 202 720 3157
E-mail: edith.kennard@fsis.usda.gov

Dr Donald PRATER
Leader, Aquaculture Drugs Team
US FDA Centre for Veterinary Medicine
7500 Standish Place
Rockville, MD 20855
USA
Tel: +1 240 276 8343
Fax: +1 240 276 8350
E-mail: donald.prater@fda.hhs.gov

Dr Thomas SHRYOCK
Senior Research Advisor, Elanco Animal Health
2001 W. Main Street, GL21,
Greenfield, IN 46140
USA
Tel: +1 317 277 5087
Fax: +1 317 651 6075
E-mail: thomas.r.shryock73@lilly.com

Dr Rondall SINGER
Associate Professor of Epidemiology
Department of Veterinary and Biomedical Science
University of Minnesota
1971 Commonwealth Ave
St. Paul, MN 55108
USA
Tel: +1 612 625 6271
Fax: +1 612 625 5203
E-mail: singe024@umn.edu

Dr Merton SMITH
Special Assistant for International Activities
U.S. FDA Centre for Veterinary Medicine
7519 Standish Place
Rockville, MD 20855
USA
Tel: +1 240 276 9025
Fax: +1 240 276 9001
E-mail: merton.smith@fda.hhs.gov

Dr Mary E. TORRENCE
National Program Leader, Food Safety
U.S. Department of Agriculture, ARS
5601 Sunnyside Ave Room 4-2194
GWCC-BLTSVL
Beltsville, MD 20705
USA
Tel: +1 301 504 4616
Fax: +1 301 504 5467
E-mail: mary.torrence@ars.usda.gov

Dr Jean WHICHARD
Acting Leader, National Antimicrobial Resistance Surveillance Team
National Center for Zoonotic, Vectorborne, and Enteric Diseases
Center for Disease Control and Prevention
1600 Clifton Road
Atlanta, GA 30333
USA
Tel: +1 404 639 2000
Fax: +1 404 639 4290
E-mail: zyr3@cdc.gov

Dr David WHITE
Director, National Antimicrobial Resistance Monitoring System
Director, Division of Animal and Food Microbiology
U.S. FDA Centre for Veterinary Medicine
Office of Research 8401 Muirkirk Rd Laurel, MD 20708, USA
Tel: +1 301 210-4187
Fax: +1 301 210 4298
E-mail: david.white@fda.gov

Dr Ching Ching WU
Professor of Veterinary Microbiology/Infection Disease
Purdue University
406 S University Street
West Lafayette, IN 47907-2065, USA
Tel: +1 765 494 7459
Fax: +1 765 494 9181
E-mail: wuc@purdue.edu

Dr Steve YAN
Microbiologist
U.S. FDA Centre for Veterinary Medicine
7500 Standish Place, HFV-150
Rockville, MD 20855, USA
Tel: +1 240 276 8202
Fax: +1 240 276 8118
E-mail: steve.yan@fda.hhs.gov

INTERNATIONAL NON-GOVERNMENTAL ORGANIZATIONS- ORGANISATIONS NON-GOUVERNMENTALES INTERNATIONLS - ORGANIZATIONS INTERNACIONALES NO GUBERNAMENTALES

CONSUMERS INTERNATIONAL

Mr Steven ROACH
Director, Public Health Program, Food Animal Concerns Trust
1127 N. 2nd Street
Ames, IA 50010
USA
Tel: +1 515 232 2278
Fax: +815 301 1889
E-mail: sroach@foodanimalconcerns.org

INTERNATIONAL FEDERATION OF ANIMAL HEALTH - FÉDÉRATION INTERNATIONALE POUR LA SANTÉ ANIMALE (IFAH)

Dr Richard CARNEVALE
Vice-President, Regulatory, Scientific, and International Affairs
Animal Health Institute
1325 G Street NW, Suite 700
Washington, DC 20005, USA
Tel: +1 202 637 2440
Fax: +1 203 393 1667
E-mail: rcarnevale@ahi.org

Dr Olivier ESPEISSE
Manager, European Corporate Affairs
International Federation of Animal Health
52 Stoofstraat B 1000 Brussels
Belgium
Tel: +32 2 548 86 06
Fax: +32 2 512 51 50
E-mail: espeisse_olivier@lilly.com

Ms Sondra FLICK
Director, Government & Industry Affairs
Alpharma Inc.
440 Route 22 East Bridgewater, NJ 08807, USA
Tel: +1 908 566 3860
Fax: +1 908 566 4129
E-mail: sandy.flick@alpharma.com

INTERNATIONAL GOVERNMENTAL ORGANIZATIONS - ORGANISATIONS GOUVERNEMENTALES INTERNATIONALES - ORGANIZACIONES GUBERNAMENTALES INTERNACIONALES

CODEX SECRETARIAT - SECRETARIAT DU CODEX – SECRETARIA DEL CODEX

Mr Ym-Shik LEE
Food Standards Officer
Joint FAO/WHO Food Standards Program
C-204, FAO
Viale delle Terme di Caracalla
00153 Rome, Italy
Tel: +39 06570 55854
Fax: +39 06 570 54593
E-mail: ymshik.lee@fao.org

FOOD AND AGRICULTURE ORGANIZATION OF THE UNITED NATIONS - ORGANISATION DES NATIONS UNIES POUR L'ALIMENTATION E L'AGRICULTURE - ORGANIZACION DE LAS NACIONES UNIDAS PARA LA AGRICULTURA Y LA ALIMENTACION (FAO)

Dr Maria de Lourdes COSTARRICA GONZALEZ
Senior Officer
Nutrition and Consumer Protection Division
Food and Agriculture Organization of the United Nations
Viale delle Terme di Caracalla
00153 Rome, Italy
Tel: +39 06 57056060
Fax: +39 06 57054593
E-mail: lourdes.costarrica@fao.org

WORLD HEALTH ORGANIZATION (WHO) – ORGANISATION MONDIALE DE LA SANTÉ (OMS) /ORGANIZACIÓN MONDIAL DE LA SALUD (OMS)

Dr Awa AIDARA-KANE
Scientist
World Health Organization
Avenue Appia, 20
Ch 1211 Geneva 27
Switzerland
Tel: +41 22 791 24 03
Fax: +41 22 791 48 93
E-mail: aidarakanea@who.int

Appendix II

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

(At step 3 of the elaboration procedure)

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 (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.

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 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

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 non-therapeutic)[2], or to conduct an AMR-RA of food products (including imported food products).

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.

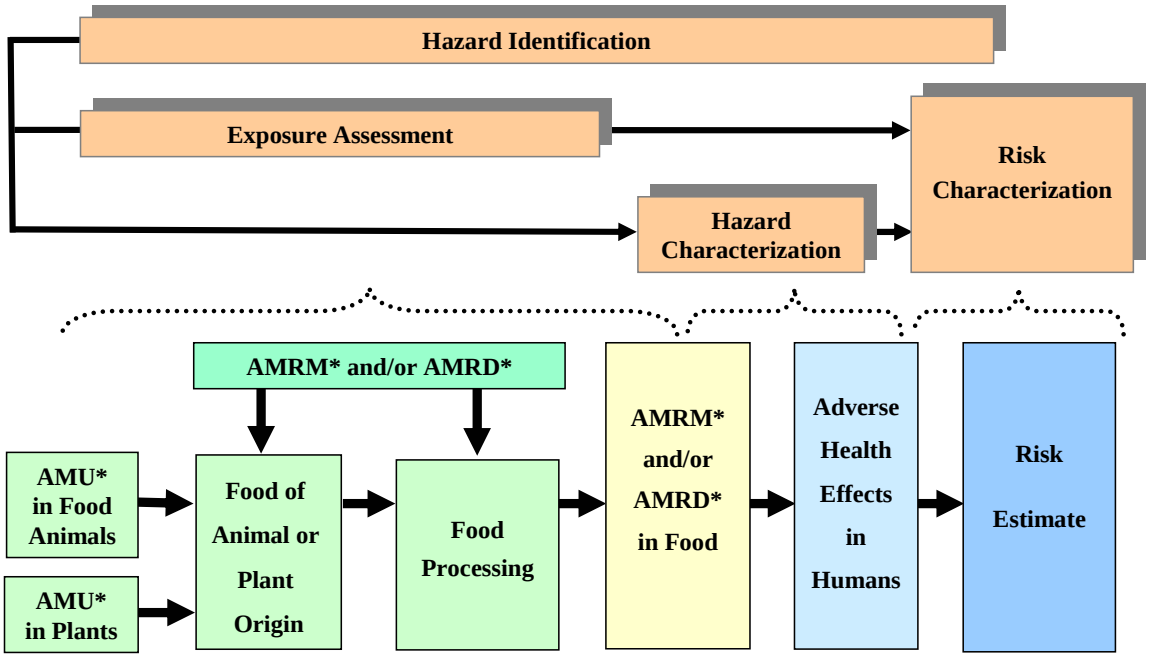

Figure 1. Schematic showing the scope and relationship of the components of AMR-RA

(*: 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.

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

[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).

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.

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).
- 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.

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[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).

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 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.

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

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).

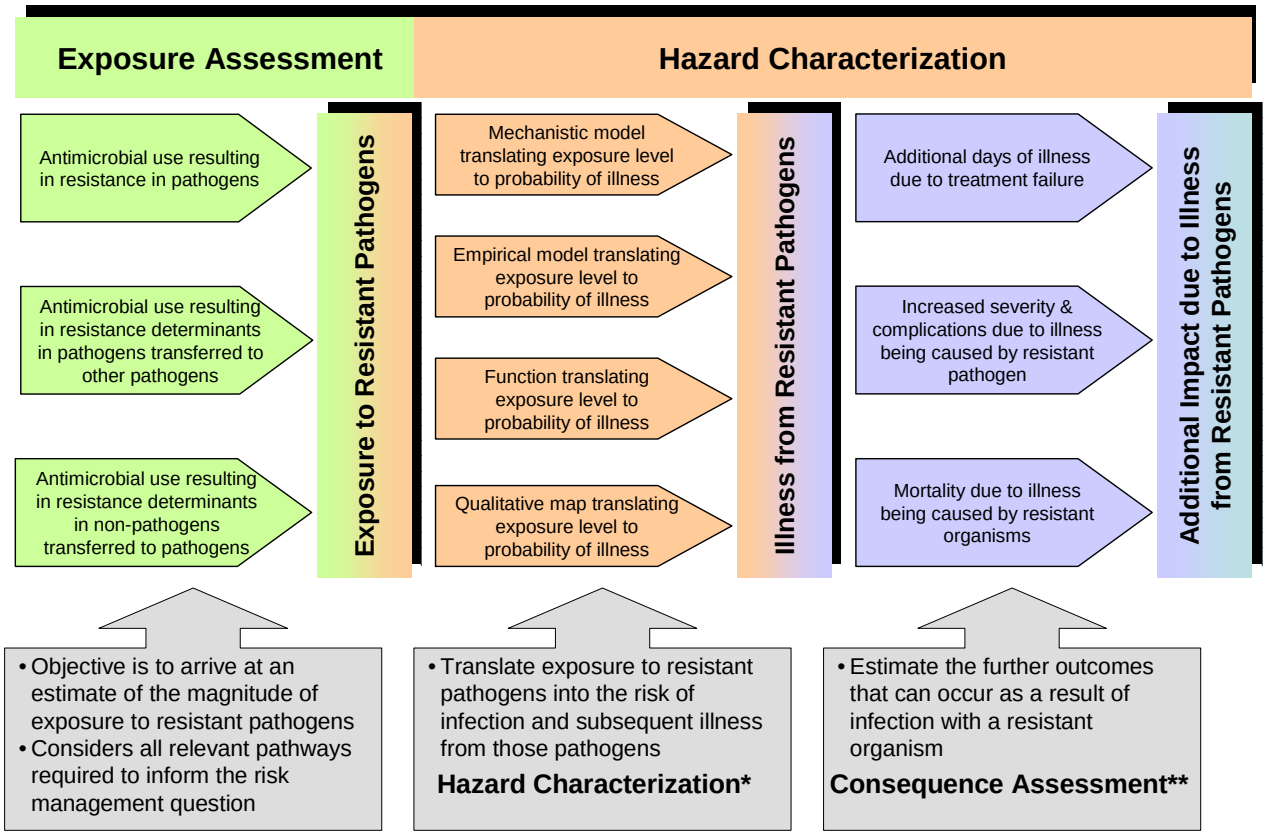

Figure 2. Scheme for the consolidated Hazard Characterization in AMR-RA
(*: concept adapted from the JEMRA [FAO/WHO, 2003a and 2006a];
**: concept adapted from the World Organisation for Animal Health [OIE, 2007])

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
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 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.

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

Exposure Assessment -**Probability of Exposure**	**Hazard Characterization** -**Severity of Adverse Health Effect**	**Qualitative Risk Estimation**
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