

# ***WORKING DOCUMENT***

## **FRAMEWORK ON RISK ASSESSMENT**

**WITH RESPECT TO**

**APPLICATIONS REFERRED BY THE NATIONAL REGISTRATION AUTHORITY**

**FOR AGRICULTURAL AND VETERINARY CHEMICALS**

**TO**

**NHMRC EXPERT ADVISORY GROUP ON ANTIMICROBIAL RESISTANCE**

INCLUDING

- I. DEFINITION OF TERMS USED IN EAGAR RISK ASSESSMENTS
- II. TEMPLATE FOR RISK ASSESSMENT TO BE USED BY EAGAR DURING THEIR ASSESSMENT.

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### **Definition of terms used in qualitative risk assessments performed by EAGAR, when providing advice to the National Registration Authority for Agricultural and Veterinary Chemicals.**

Points to note:

1. Refer to Part 10 Special Data Requirements (NRA Requirements Series for Veterinary Chemicals at <http://www.nra.gov.au/guidelines/vetguideline10.pdf>, for the data requirements relevant to these assessments, and further definitions of terms used.
2. Different hazards and exposures are numbered I and II as they define different but sequential hazards and exposures.
3. This document links the terms used in Part 10 Special Data Requirements and in the AS/NZ 4360:1999 and AS/NZS HB 203:2000.
  - a. 'Negligible', 'Low', 'Medium', 'High' are terms used in the NRA Part 10 Special Data Requirements.
  - b. 'Rare', 'Unlikely', 'Possible', 'Likely', 'Almost certain' are qualitative measures of likelihood used in AS/NZS 4360:1999 (Risk management) and AS/NZS HB 203:2000 (Environmental risk management).
  - c. 'Insignificant', 'Minor', 'Moderate', 'Major', 'Catastrophic' are qualitative measures of impact used in AS/NZS 4360:1999 (Risk management) and AS/NZS HB 203:2000 (Environmental risk management).
4. Where 'animal gastrointestinal flora' is mentioned, it is accepted that bacteria can be exposed to antibiotics and resistant bacteria can also develop at other sites eg. respiratory tract, skin. Such risks also need consideration in the risk assessments.
5. The phrase 'resistant bacteria (or their transferable genetic elements) of animal origin' or similar includes bacteria that have either been transferred from animals or that contain transferable genetic elements arising from bacteria of animal origin.

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<b>TERM</b>		<b>RATING of probability or impact</b>				
	Definition	Negligible	Low	Medium	High	Not assessable
<b>Hazard I</b>	The antibiotic used in accordance with proposed use pattern					
<b>Exposure I</b>	the amount and frequency of exposure of microorganisms within the animal gastrointestinal flora to an antibiotic Three issues: i) Antibiotic can come in contact with bacteria in the flora ii) Exposure of bacteria to the antibiotic can occur iii) Resistant bacteria or transferable genetic elements can be broadly spread within the flora	Probability of exposure is extremely low or negligible <b>(rare)</b>	Probability of exposure is low but clearly possible <b>(unlikely)</b>	Probability of exposure is likely <b>(possible or likely)</b>	Probability of exposure is very likely or certain <b>(almost certain)</b>	Probability cannot be assessed
<b>Hazard II</b>	Antibiotic resistant microorganisms or their resistance transferable genetic elements (that have the potential to transfer to humans) within an animal species arising from the use of an antibiotic in an animal species					
<b>Exposure II</b>	the amount and frequency of exposure of susceptible humans to antibiotic-resistant microorganisms (or their transferable genetic elements) from animal sources Three issues: i) Resistant bacteria (or transferable genetic elements) of animal origin can come in contact with susceptible humans ii) Exposure of susceptible humans to resistant bacteria (or their transferable genetic elements) of animal origin can	Probability of exposure is extremely low or negligible <b>(rare)</b>	Probability of exposure is low but clearly possible <b>(unlikely)</b>	Probability of exposure is likely <b>(possible or likely)</b>	Probability of exposure is very likely or certain <b>(almost certain)</b>	Probability cannot be assessed

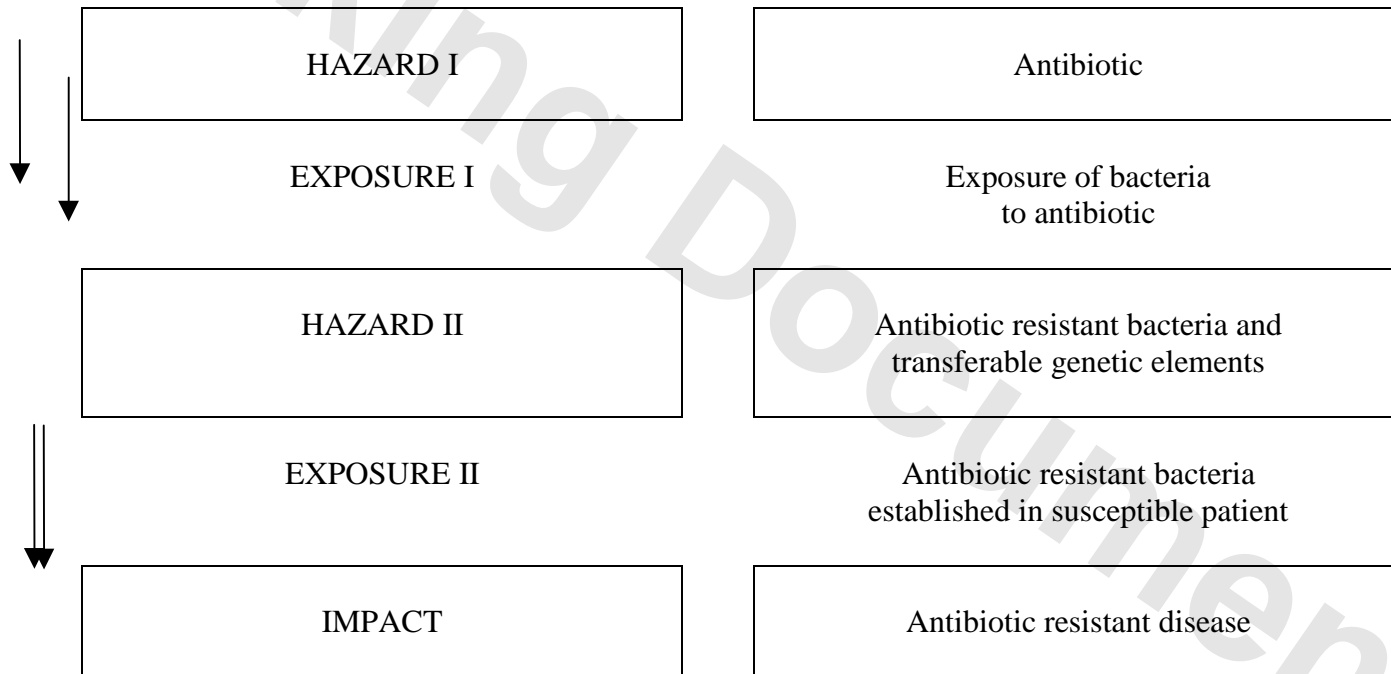
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	occur iii) Resistant bacteria or transferable genetic elements of animal origin can be broadly spread within the human population					
<b>Impact</b>	the disease/s (caused by infections by antibiotic-resistant pathogens of animal origin) in susceptible humans					
<b>Risk probability</b>	Probability of disease due to infection in susceptible humans after exposure to antibiotic-resistant microorganisms (and transferable genetic elements) of animal origin	There is little probability of disease	There is some probability of disease	There is a moderate possibility of disease	There is a high possibility of disease	Risk probability cannot be assessed
<b>Severity of impact</b>	the severity of the impact of exposure on susceptible humans.	Disease occurs in a limited group and/or has negligible impact on health and quality of life; There is little impact if susceptible humans are exposed to antibiotic-resistant bacteria ( <b>insignificant</b> )	There is a limited range of people who suffer disease with minor impact on health ; There are some consequences if susceptible humans are exposed to antibiotic-resistant bacteria ( <b>minor</b> )	There is a moderately broad range of people who suffer disease and/or moderate impact on health ; There are moderate consequences if susceptible humans are exposed to antibiotic-resistant bacteria ( <b>moderate to major</b> )	Disease occurs in a broad range of people and/or with severe impact on health and quality of life; There are serious consequences if susceptible humans are exposed to antibiotic-resistant bacteria ( <b>catastrophic</b> )	Impact cannot be assessed or the consequences cannot be assessed

\* **Probability:** the likelihood or chance that an effect will follow, when an event occurs (an example of an event occurring is exposure to a hazard)

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Diagrammatic representation of hazard, exposure and impact for risk analysis related to veterinary antimicrobials and potential transfer of antibiotic resistance to human pathogens.



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In the descriptions above there are terms highlighted in **bold**. These are qualitative, descriptive terms used in AS/NZS 4360:1999 (Risk Management) and AS/NZS HB 203:2000 (Environmental risk management) - further explanations are provided below:

**Qualitative measures of likelihood** (AS/NZS 4360:1999 (Risk Management) and AS/NZS HB 203:2000 (Environmental risk management))

<b>Level</b>	<b>Descriptor</b>	<b>Description</b>
A	Almost certain	Is expected to occur in most circumstances
B	Likely	Will probably occur in most circumstances
C	Possible	Could occur
D	Unlikely	Could occur but not expected
E	Rare	Occurs only in exceptional circumstances

**Qualitative measures of impact** (AS/NZS 4360:1999 (Risk Management) and AS/NZS HB 203:2000 (Environmental risk management))

<b>Level</b>	<b>Descriptor</b>	<b>Example of description</b>
1	Catastrophic	Death
2	Major	Extensive loss
3	Moderate	Medical treatment required
4	Minor	First aid treatment required
5	Insignificant	No injuries

**Qualitative risk analysis matrix: level of risk** (AS/NZS 4360:1999 (Risk Management) and AS/NZS HB 203:2000 (Environmental risk management))

<b>Likelihood</b>	<b>Consequence</b>				
	<b>Catastrophic</b>	<b>Major</b>	<b>Moderate</b>	<b>Minor</b>	<b>Insignificant</b>
Almost certain	E	E	E	H	H
Likely	E	E	H	H	M
Possible	E	E	H	M	L
Unlikely	E	H	M	L	L
Rare	H	H	M	L	L

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**Assessment of risk and risk mitigation strategy required** (AS/NZS 4360:1999 (Risk Management) and AS/NZS HB 203:2000 (Environmental risk management))

E: extreme risk, immediate action required

H: high risk; senior management attention required

M: moderate risk; management responsibility must be specified

L: low risk; manage by routine procedures.

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## **II. Template for risk assessment**

### **EXPERT ADVISORY GROUP ON ANTIMICROBIAL RESISTANCE**

#### **Antimicrobial Resistance Transfer Risk Assessment**

**- for the National Registration Authority for Agricultural and Veterinary Chemicals**

**- Proposed or Varied Registration of a Veterinary Chemical Product**

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#### **BACKGROUND DATA**

**Product**

**Sponsor**

**Active Ingredient**

**Class**

**Mode of Action**

**Mechanism of Resistance**

**Status of Class in Humans**

**Status of Class in Animals in Australia**

**Related Human Agents**

**Related Animal Agents In Australia**

**JETACAR Human Importance Rating**

**JETACAR Animal Importance Rating**

**New Agent or Extended Indication/Species?**

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## **Proposed Usage Pattern**

### **For Use in Food-Producing Animals?**

### **Proposed Indications and Species**

### **Potential Cross-Resistance to Animal Agents**

### **Potential Cross-Resistance to Human Agents**

### **Potential Co-selection for Unrelated Resistance in Animal Bacteria**

## **RISK ASSESSMENT**

### **1. Hazard Characterisation**

HAZARD = (antibiotic proposed for use in a veterinary chemical product)

HAZARD = (antibiotic-resistant bacteria, or their transferable genetic elements, of concern to human health)

#### **1.1 Bacterial resistance**

##### **1.1.1 Bacterial species likely to be affected**

##### **1.1.2 Resistance data in targeted animal bacterial species**

##### **1.1.3 Resistance data on animal strains of indicator organisms of relevance to humans**

##### **1.1.4 Resistance data on human strains of indicator organisms**

##### **1.1.5 Cross-resistance data in animal isolates (target and indicator organisms)**

##### **1.1.6 Cross-resistance data in human isolates (indicator organisms)**

##### **1.1.7 Data on co-selection of resistance (by unrelated antibiotics)**

#### **1.2 Genetics of resistance**

##### **1.2.1 Resistance genes**

##### **1.2.2 Location of resistance genes (chromosome, transferable elements)**

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## **1.2.3 Data on transfer of resistance genes from animal to animal isolates**

## **1.2.4 Data on transfer of resistance genes from animal to human isolates**

## **2. Exposure**

### **2.1 Exposure of animal bacteria to the antibiotic**

#### **2.1.1 Projected amount of usage**

#### **2.1.2. Projected extent of usage**

#### **2.1.3 Projected pattern of usage**

#### **2.1.4 Are doses, dosing schedule and drug distribution adequate to minimise selection for resistance?**

### **2.2 Exposure of humans to resistant animal bacteria or antibiotic itself**

#### **2.2.1 Likely routes of bacterial transmission to humans**

#### **2.2.2 Mitigation procedures likely to reduce bacterial transmission to humans**

#### **2.2.3 Proposed Maximum Residue Limits (MRLs) and Acceptable Daily Intakes (ADIs)**

## **3. Impact**

DISEASES (CAUSED BY ANTIBIOTIC-RESISTANT PATHOGENS) IN SUSCEPTIBLE HUMANS =

### **3.1 Importance of class of antibiotic in human medicine**

### **3.2 Importance of disease if transmitted from animals**

### **3.3 Impact of failure of antibiotic treatment in humans**

### **3.4 Benefits of antibiotic in animal health**

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## 4. Risk characterisation

PROBABILITY AND SEVERITY OF DISEASE/S DUE TO INFECTION IN SUSCEPTIBLE HUMANS AFTER EXPOSURE TO ANTIBIOTIC-RESISTANT MICROORGANISMS (AND/OR TRANSFERABLE GENETIC ELEMENTS) OF ANIMAL ORIGIN

	Negligible	Low	Medium	High	Not assessable
Exposure I (animal gut Bacteria to antibiotic)					
Exposure II (humans to Bacteria or genetic material)					
Overall risk probability					
Severity of impact					
Level of risk					

## RECOMMENDATION

The following should be considered in the Recommendations section.

1. Compliance with JETACAR, as appropriate
2. Consideration of MRLs
3. Advice on appropriate label restraints
4. Advice on scheduling