Antimicrobial-resistant Bacteria Arising from the Use of Colistin Sulfate in the Livestock (Antimicrobial-resistant Bacteria)

Summary

Food Safety Commission of Japan

The Food Safety Commission of Japan (FSCJ) conducted a risk assessment on antimicrobial-resistant bacteria arising from the use of colistin sulfate, which is used as a feed additive and veterinary medicinal products in the livestock. Both *Salmonella* and *E. coli* were considered as potential antimicrobial-resistant bacteria to be selected under the use of colistin sulfate in the livestock. As only limited reports were available on the colistin-resistance in *Salmonella*, FSCJ conducted a risk assessment focusing on *E. coli* as a hazard, on which the information was rather available. In the release assessment, the degree of possible selection of the hazard was evaluated as "Medium". Considering proper cooking of the livestock products, the degree of possible human exposure to the resistant bacteria via livestock products was evaluated as "Low". The degree of possible reduction or loss of clinical effectiveness was evaluated as "High" considering the current situation of colistin use in human medicine. From the above, the overall estimation of the risk was "Medium".

Conclusion in Brief

The Food Safety Commission of Japan (FSCJ) conducted a risk assessment on antimicrobial-resistant bacteria arising from the use of colistin sulfate, which is used as a feed additive and veterinary medicinal products in the livestock (cattle, swine and chickens,) according to the "Assessment Guideline for the Effect of Food on Human Health Regarding Antimicrobial-Resistant Bacteria Selected by Antimicrobial Use in Food Animals" (September 30, 2004) (**Fig.1**).

Hazard Identification

Colistin sulfate, a polypeptide antibiotic substance, has been used for the livestock in Japan since the 1950s. Colistin injection formula had been suspended in human clinical use due to the frequent adverse effects such as renal dysfunctions, as well as the development of substitute antibiotics.

In 2015, a colistin methanesulfonate formula for injections was re-approved owing to the situation where infections with multidrug-resistant gram-negative bacilli became clinical issues in recent years.

Two-component regulatory systems associated with chromosomal genes have been known as a mechanism of colistin-resistance in gram-negative bacteria. In 2015, *Escherichia coli* (*E. coli*) strains harboring a gene (*mcr-1*) associated with colistin resistance on plasmids were reported in China. The susceptibilities of *E. coli* and *Salmonella* strains against colistin in Japan remain high, being judged from the monitoring results of these bacteria sampled from the livestock between 2000 and 2015. Strains carrying the *mcr-1* gene were, however, found among the samples.

Both *Salmonella* and *E. coli* were considered as potential antimicrobial-resistant bacteria to be selected under the use of colistin sulfate in the livestock. These resistant bacteria
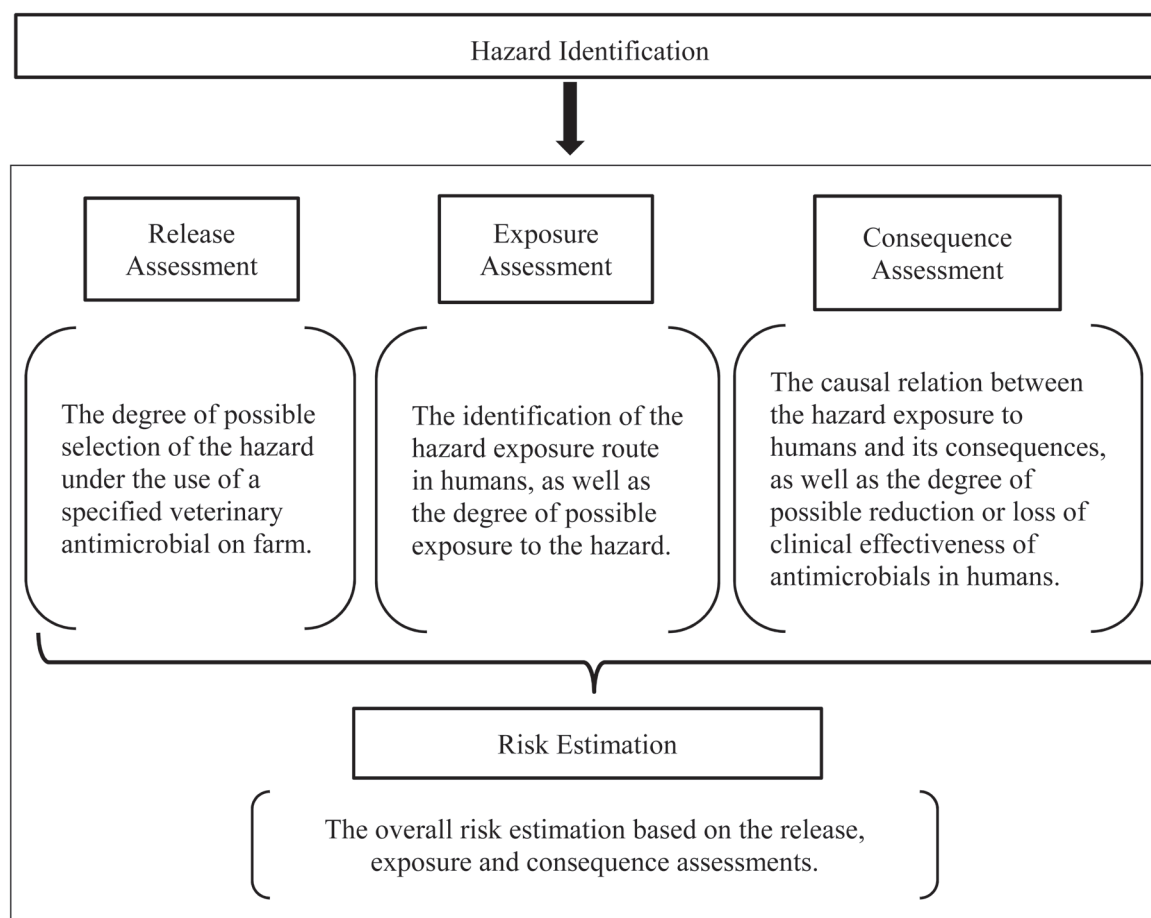
Fig. 1. Risk assessment procedure

may reduce or lose the effectiveness of clinical antibiotic treatment, in cases of occurrences of human infectious diseases due to the bacteria via livestock products, which are originated from cattle, swine and chickens. As only limited reports were available on the colistin-resistance in *Salmonella*, it was decided that the information on *Salmonella* was not enough to conduct a risk assessment at this point. FSCJ thus conducted a risk assessment focusing on *E. coli* as a hazard, on which the information was rather available.

Release Assessment

The release assessment discussed the degree of possible selection of the hazard, antimicrobial-resistant *E. coli*, arising from the use of colistin sulfate in the livestock. Japan first reported the detection of a *mcr-1* positive *E. coli* isolate, which was sampled from diseased swine in 2007. Two percent of *E. coli* isolates from healthy livestock in 2015 carried the *mcr-1* gene. Although the gene has been shown to be transferred among *E. coli* and other *Enterobacteriaceae*, many issues, such as fitness costs associated with its carriage, remain to be elucidated. Thus close attention needs to be paid to the trends of the amount of colistin use and

genes associated with colistin resistance through continuous collection of relevant information. Considering the above, the degree of possible selection of the hazard was evaluated as "Medium" (**Table 1**).

Exposure Assessment

E. coli survives occasionally in meat, and thus human exposure to antimicrobial-resistant *E. coli* is possible via the livestock products. Colistin-resistant strains were, however, scarcely isolated from these products. Considering proper cooking of the livestock products, the degree of possible human exposure to the resistant bacteria via livestock products was evaluated as "Low" (**Table 2**).

Consequence Assessment

The degree of possible reduction or loss of clinical effectiveness was evaluated as "High" considering the current situation of colistin use in human medicine (**Table 3**).

Risk Estimation

The following possibilities were considered: 1) selection of the hazard arising from the use of colistin in the livestock as

Table 1. Release assessment of the hazard (*E. coli*)

Assessment Outcome: "Medium"		
	Relevant parameter	Concern
	1) Emergence	"Moderate"
	2) Susceptibility	"Moderate"
	3) Other concerns	"Moderate"

See reference.

Table 2. Exposure assessment of the hazard (*E. coli*)

Assessment Outcome: "Low"		
	Relevant parameter	Concern
	1) Biological properties	"Moderate"
	2) Food contaminations	"Little"
	3) Other concerns	"Little"

See reference

Table 3. Consequence assessment of the hazard (*E. coli*)

Assessment Outcome: "High"		
	Relevant parameter	Concern
	1) Importance in clinical use	"Great"
	2) Severity of infectious diseases	"Moderate"
	3) Other concerns	"Great"

See reference

Table 4. Outcome of overall risk estimation of the hazard (*E. coli*)

Outcome of overall risk estimation: "Medium"		
		Outcome of concern	Score
	Release assessment	"Medium"	2
	Exposure assessment	"Low"	1
	Consequence assessment	"High"	3
			Total 6

See reference

feed additive and veterinary medicinal products; 2) human exposure to the hazard via livestock products; 3) reduction or loss of clinical effectiveness of antimicrobials in humans. The overall estimation of the risk was "Medium" (**Table 4**).

Further information is necessary to understand the novel mechanisms of resistance conferred by the genes such as *mcr-1* and the significance, even in *E. coli*. Latest scientific findings and information are a key to future risk assessment.

Reference

1) Guidance for Release Assessment, Exposure Assessment and Consequence Assessment

Based on the guideline for risk assessment, qualitative risk assessment on identified hazard(s) shall be conducted using the latest information on the release assessment, exposure assessment and consequence assessment. Risk assessment shall be conducted by considering comprehensively the concern levels for three relevant parameters according to criteria shown in **Table 5**.

2) Guidance for Risk Estimation

Based on the guideline for risk assessment, the risk of the hazard shall be cumulatively estimated based on the results of "release assessment", "exposure assessment" and "consequence assessment". Accordingly, the risk shall be estimated according to the sum of scores from the risk assessment components as shown in **Table 6**.

In cases extremely severe human diseases are expected or if any other relevant reasons exist, the overall risk may be estimated by raising the weight of the consequence assessment.

Table 5. Criteria and outcomes of release assessment, exposure assessment and consequence assessment

Relevant parameters	Classification of concern	Outcome of Concern
Release Assessment 1) Are there any concerns about emergence of the hazard (eg, mechanisms of acquired resistance, genetic information)? 2) Are there any concerns about susceptibility distribution of bacteria including the hazard? 3) Are there any concerns about other factors (eg, pharmacokinetics, usage, amount applied)? Statements for the concern are classified as follows on each item 1)~3): The concern is "Great", "Moderate" or "Little".	Two or more items assessed as "Great".	"High": The hazard* is selected with high probability.
	Only one item assessed as "Great", or two or more items assessed as "Moderate".	"Medium": The hazard is selected with certain extents of probability.
	One item assessed as "Moderate" and no item assessed as "Great".	"Low": The hazard is selected with reduced extents of probability.
	Three items assessed as "Little".	"Negligible": The hazard is unlikely to be selected.
Exposure Assessment 1) Are there any concerns about biological properties of bacteria including the hazard (eg, survival, proliferation)? 2) Are there any concerns about food contaminations with bacteria including the hazard? 3) Are there any concerns about other factors (eg, meat processing process, marketing channels)? Statements for the concern are classified as follows on each item 1)~3): The concern is "Great", "Moderate" or "Little".	Two or more items assessed as "Great".	"High": Human exposure to the hazard is highly probable.
	Only one item assessed as "Great", or two or more items assessed as "Moderate".	"Medium": Human exposure to the hazard is of certain probability.
	One item assessed as "Moderate" and no item assessed as "Great".	"Low": Human exposure to the hazard is of reduced probability.
	Three items assessed as "Little".	"Negligible": Human exposure to the hazard is unlikely.
Consequence Assessment 1) (a) Is the antimicrobial ranked as "I: Critically important as human antimicrobials"? (b) Is the antimicrobial a primary one for the human infectious disease caused by bacteria including the hazard? For item 1), statement for the concern is classified as follows: The concern is "Great" if both (a) and (b) suffice, "Moderate" if either (a) or (b) suffices, or "Little" if neither (a) nor (b) suffices. 2) Are there any concerns about the severity and incidences of human diseases caused by the hazard? 3) Are there any concerns about other factors (eg, availability of alternative drugs, status of antimicrobial resistance in hospitals)? Statements for the concern are classified as follows on each item 1)~3): The concern is "Great", "Moderate" or "Little".	Two or more items assessed as "Great".	"High": Reduction or loss of clinical effectiveness to diseases caused by the hazard is highly probable.

*"Hazard" is antimicrobial-resistant bacteria arising from the use of antibiotic substances.

Table 6. Risk estimation

Outcome of the risk assessment components			Risk
Release assessment (Score) High (3) Medium (2) Low (1) Negligible (0)	*Exposure assessment* (Score) High (3) Medium (2) Low (1) Negligible (0)	*Consequence assessment* (Score) High (3) Medium (2) Low (1) Negligible (0)	
Sum of scores: 8–9			High
Sum of scores: 5–7			Medium
Sum of scores: 2–4			Low
Sum of scores: 0–1			Negligible