This is a provisional English translation of an excerpt from the original full report.

Risk Assessment Report

Sulfonamide antimicrobial

(Antimicrobial-resistant bacteria)

Food Safety Commission of Japan (FSCJ)
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1. Background and history

In 2003, the Ministry of Agriculture, Forestry and Fisheries (MAFF) has requested FSCJ an assessment of sulfonamide synthetic antibacterial agents, including sulfaquinoxaline (designated as a feed additive) and sulfonamide synthetic antibacterial (an active ingredient of veterinary medicinal products). The use of sulfonamide synthetic antibacterial in livestock animals has a potential to develop selection of antimicrobial-resistant bacteria. FSCJ identified some hazards associated with the selection in accordance with the Assessment Guideline for the Effect of Food on Human Health Regarding Antimicrobial-Resistant Bacteria Selected by Antimicrobial Use in Food Animals[1].

Sulfonamide is used as a compounding agent (herein after referred to as ST mixture) such as trimethoprim-sulfamethoxazole combination and sulfamonomethoxine-ormetoprim combination, as it has been known that synergistic antimicrobial effect is obtained when sulfonamide is simultaneously administered with an antifolic such as trimethoprim or ormetoprim. Since resistance ratio trends or importance as human medicine are different between a single sulfonamide synthetic antibacterial and a ST mixture, FSCJ conducted an assessment of ST mixture apart from the assessment of a single sulfonamide synthetic antibacterial in this assessment.
FSCJ describes hereinafter the summary of the risk assessment of single sulfonamide synthetic antibacterial agents and ST mixture. The details of the assessment of single sulfonamide antimicrobials and ST mixture are described in Part 1 and Part 2 respectively.

2. Summary: A single sulfonamide synthetic antibacterial

FSCJ identified some hazards associated with the possible selection of antimicrobial-resistant bacteria developed by the use of a single sulfonamide synthetic antibacterial in livestock (cattle, horses, pigs and chicken) as a feed additive and as a veterinary medicinal product, in accordance with the Assessment Guideline for the Effect of Food on Human Health Regarding Antimicrobial-Resistant Bacteria Selected by Antimicrobial Use in Food Animals[2].
A single agent of sulfonamide antimicrobial has been used at livestock site, and was approved as a veterinary

[1] Food Safety Commission of Japan, September 30, 2004
[2] Food Safety Commission of Japan, September 30, 2004

medicinal product in 1960, designated as a feed additive in 1976. Although a single agent of sulfonamide antimicrobial has been recommended as a human medicine, any infectious disease which transmitted to human through livestock products has not been identified.
Selection of resistance to a single sulfonamide antimicrobial agent has been identified in E. coli, salmonella and campylobacter derived from domestic livestock animals, and these resistant bacteria may have potential to transmit to humans through food consumption. However, effective agents of other type against these infectious disease are sufficiently available so that a single sulfonamide antimicrobial agent has not been recommended.

The result of hazard identification indicates that the use of a single sulfonamide synthetic antibacterial in livestock animals could cause the selection of resistant bacteria. However, the resistant bacteria would not pose human health hazards via food consumption, because a single sulfonamide synthetic antibacterial is not recommended for use in human medicines, and effective alternative antimicrobial of other type are sufficiently available. Thus, FSCJ concludes that the risk to human health via food consumption arisen from the antimicrobial-resistant bacteria selected through the use of a single sulfonamide synthetic antibacterial in livestock animals is negligible.
FSCJ considers that the MAFF, a risk management organization, should continue to collect further information.

3. Summary: ST mixture of sulfonamide with trimethoprim or ormetoprim

FSCJ identified some hazards associated with the possible selection of antimicrobial-resistant bacteria developed by the use of ST mixture in livestock (cattle, horses, pigs and chicken) as a veterinary medicinal product.
Staphylococci and E. coli are bacteria which may spread through livestock products, and against which ST mixture is chosen for clinical treatment of human cases of infection. Therefore, FSCJ identified staphylococci and E. coli which acquired antimicrobial resistance as a result of the use of ST mixture in livestock as the hazard to be assessed.
FSCJ conducted the release assessment, the exposure assessment and the consequence assessment, and estimated the risk resulting from the use of ST mixture in livestock. The release assessment determined that the use of ST mixture has a potential to develop any hazard if it is used in livestock. And the level of risk from *staphylococci* and *E. coli* infection was considered to be moderate. The exposure assessment determined the potential where humans are exposed to the hazard through livestock products and its degree, by estimating how much the hazard is increased or reduced through possible pathway whereby humans are exposed to the hazard, and how foods are contaminated with the hazard. As the result, FSCJ considered the level of risk to be low. In the consequence assessment, the potential where therapeutic effect in human medicine is decreased or lost and its degree were evaluated. FSCJ concluded that the level of risk is low considering the therapeutic importance of ST mixture used in human medicine and the severity of infectious disease caused by the hazard.

After a comprehensive evaluation of risks to human health based on the results of these assessments (release assessment, exposure assessment, and consequence assessment), FSCJ concluded that the level of risk from each

hazard was low, although the following possibilities cannot be neglected: 1) selection of hazards such as *staphylococci* and *E. coli* as a result of the use of the assessed ST mixture in livestock as a veterinary medicinal product ; 2) loss or reduction of the efficacy of antimicrobial treatment of human diseases as a result of human exposure to the hazards through consumption of livestock products derived from cattle, pigs and chicken. The risk for the hazard was, however, judged to be low as a result of the overall estimation of the risk.

FSCJ considers that the MAFF, a risk management organization, should continue to collect further information.