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

Risk Assessment Report

An injection for veterinary use in piglets, containing gleptoferron and toltrazuril as an active substance: Baycox Iron

(Veterinary Medicinal Products)

Food Safety Commission of Japan (FSCJ)
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ABSTRACT

FSCJ conducted a risk assessment of baycox iron based on data in the written application for the approval of manufacture and sales of new veterinary medicinal products.

Baycox Iron is a combination injection for veterinary use in piglets, containing gleptoferron (an iron containing compound) and toltrazuril as active substances.

Both gleptoferron solution and toltrazuril, main substances of this product, are used as a veterinary medicinal product in Japan and other countries.

FSCJ considered it appropriate to assess gleptoferron as iron since it is a polymer complex of β-iron oxyhydroxides and dextran glucoheptonic acid which absorbs and releases iron *in vivo*. Iron is an essential trace element *in vivo* and is an Exempted Substance[1]. In EU, it is not required to set the residue standards in foods. JECFA has specified a PMTDI of 0.8 mg/kg bw/day for iron, and FSCJ has specified the upper limit of intakes of 0.66 mg/kg bw/day for adult (2017).
FSCJ set an ADI of 0.01 mg/kg bw/day for baycox iron in 2008.

FSCJ concluded that the risk to human health from the intake of these substances in this product is negligible, considering the usage, existing toxicity data, and the dosage.

A toxicokinetics study in piglets with a single intramuscular injection of this product showed a slow absorption of toltrazuril, and a long-term retention in plasma of toltrazuril and its metabolites, namely toltrazuril sulfoxide (T sulfoxide) and toltrazuril sulfone (T sulfone). In residue analysis with a single intramuscular injection of this product into piglets, concentrations of toltrazuril and T sulfoxide were

[1] On May 29, 2006, the Ministry of Health, Labour and Welfare (MHLW) introduced the positive list system for agricultural chemicals remaining in foods to prohibit the distribution of foods that contain agricultural chemicals above a certain level if maximum residue limits (MRLs) were unestablished. Exempted Substances are designated as substances with no potential to cause damage to human health by the Minister of Health, Labour and Welfare, based on the provision of Paragraph 3, Article 11 of the Food Sanitation Act, and these substances are not subjected to the positive list system.

below detection limit or below quantification limit in every tissue, on and after 42 days of administration and 28 days after administration (after 42 days in the case of the liver and the kidney) respectively. Whilst T sulfone showed rather high residue level in all tissues, but it was below quantification limit except in the liver and the kidney after 56 days of administration, and the concentration became bellow detection limit in every tissue after 75 days of administration.

In the safety study of this product in piglets, tolerance was observed in a single intramuscular injection of a dose five-fold higher than the recommended dose. Thus, safety of this product at dosage and administration (a single administration only once in life) was shown. In the clinical studies of this product in piglets, adverse effects due to the administration of this product were not observed.
Hence, FSCJ concluded that risk to human health from the assessed item through food is negligible as long as it is appropriately used.

Table 1. *Levels relevant to toxicological evaluation of toltrazuril*

Species	Study	Dose (mg/kg bw/day)	NOAEL (mg/kg bw/day)[1)]
Mouse	24-month combined chronic toxicity/carcinogenicity study	0, 20, 80, 180 ppm (Feeding)	M: 9.9 F: 11.9
Rat	3-month subacute toxicity study	M: 0, 1.1, 4.2, 16.6 F: 0, 1.2, 4.7, 17.4 (Feeding)	M: 1.1 F: 1.2
	30-month combined chronic toxicity/carcinogenicity study	0, 20, 60, 180 ppm (Feeding)	M: 1.0 F: 1.3
	Two-generation reproductive toxicity study	0, 4, 15, 60 ppm (Feeding)	1.25
	Teratogenicity study (the 1st study)	0, 3, 10, 30 and 0, 1	Dams: 1 Fetuses: 10
	Teratogenicity study (the 2nd study)	0, 1, 3, 10, 30	Dams: 3 Fetuses: 10
	Teratogenicity study (the 3rd study)	0, 10, 30, 90 and 0, 300 (T sulfone)	Dams: 90 Fetuses: 90
Dog	13-week subacute toxicity study	0, 1.5, 4.5, 13.5	1.5
	13-week subacute toxicity study	0, 200, 1 000, 5 000 ppm (Feeding with T sulfone)	M: 8.3 F: 8.6
Rabbit	Teratogenicity study	0, 0.5, 0.75, 1, 2	Dams: 90 Fetuses: 90
Toxicological ADI		NOAEL: 1.0 SF: 100 ADI: 0.01	
The critical study for setting toxicological ADI		30-month combined chronic toxicity/carcinogenicity study and Teratogenicity study in rats	
ADI		ADI: 0.01	

ADI: Acceptable daily Intake, NOAEL: No-observed-adverse-effect level, SF: Safety factor
[1)] The adverse effect observed at LOAEL.