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

Risk Assessment Report

Bismuth Subnitrate, Heavy

(Exempted Substances [1])

Food Safety Commission of Japan (FSCJ)
March 2023

ABSTRACT

The FSCJ conducted a risk assessment of heavy bismuth subnitrate (BSN: CAS No. 1304-85-4) to apply to a designated exempted substance defined by the Minister of Health, Labour and Welfare (MHLW). The exempted substance does not have adverse effects on human health in accordance with the provision of Article 13 paragraph (3) of the Food Sanitation Act (Act No. 233 of 1947).

The results of a pharmacokinetics study suggested that BSN bioavailability in humans and animals is very low. The reason is that bismuth administered orally to animals is excreted in urine and feces containing bile, even if absorbed, and would not accumulate *in vivo*.

In a pharmacokinetics study, a single dose of mammary infusion of BSN as an active substance was administered to dry cows. Bismuth concentration in the blood of the cows before and after administration was below the LOD (Limit of Detection) at all measurement time points.

In a residue test, a single dose of a mammary infusion was administered to dry cows. Bismuth concentration level in milk increased by administration of the formulation while it tended to decline in line with milking frequency and fell further by filtering or centrifuging. For centrifuged samples, no significant difference was observed between the formulation-administered and non-administered groups.

In a genotoxicity study, both the *in vitro* gene mutation test and the chromosomal aberration test for BSN indicated negative. The reverse mutation test using bismuth subsalicylate (BSS) was negative, and BSN is presumed to be also negative in that test. Consequently, the FSCJ assumed that BSN is not genotoxic because the bioavailability absorption level of bismuth salts containing BSN is extremely low and its necessity is not significant despite the unavailability of *in vivo* test results.

In a subacute toxicity study, no toxicity finding attributed to administration was observed, and the FSCJ determined the NOAEL of 1,000 mg/kg bw per day, the maximum dose.

In a developmental toxicity study, no toxicity finding attributed to administration was observed, either. The FSCJ identified the NOAEL of 1,000 mg/kg bw per day, the maximum dose for dams and fetuses, and determined that there was no teratogenicity.

For the intake of BSN in Japan, the estimated intake of bismuth from milk and dairy produced by cows administered by mammary infusion was the maximum 17.0 µg/person per day for those aged 7 to 14 years. BSN is used as a human drug mainly for diarrhea via an oral dose of 2g per day. In Europe, it is reported that the human intake of bismuth from food is 5-20 µg/person per day and most of them is directly excreted in the feces without being absorbed.

Therefore, the FSCJ determined that the bismuth concentration level in milk and dairy from cows is not an amount that affects human health.

Given the above, the FSCJ concluded with a reasonable certainty that no adverse effects would occur in human health from dietary exposure to the residues of BSN as long as the substance is normally used as a veterinary medical product.

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[1] On May 29, 2006 the Ministry of Health, Labour and Welfare (MHLW) introduced the positive list system for agricultural chemicals remaining in foods- the system to prohibit the distribution of foods that contain agricultural chemicals above a certain level if maximum residue limits (MRLs) have not been established. Exempted Substances are defined by the MHLW as substances having no potential to cause damage to human health, based on the provision of Article 13, paragraph (3) of the Food Sanitation Act. These substances are not subject to the positive list system.