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

# Risk Assessment Report

# Hypobromous Acid Water

(Food Additives)

Food Safety Commission of Japan (FSCJ)

October 2018

## ABSTRACT

FSCJ conducted a risk assessment of hypobromous Acid Water (CAS No. 13517-11-8, as hypobromous acid (HOBr)), an additive used as fungicide, based on results from various studies.

The data used in the assessment include genotoxicity, repeated dose toxicity, carcinogenicity and reproductive developmental toxicity of 5,5-dimethylhydantoin (DMH) and its bromides. DMH is a degraded-product of 1,3-dibromo-5,5-dimethylhydantoin (DBDMH) which is the raw material of the additive "Hypobromous Acid Water".

This additive, "Hypobromous Acid Water", is available as "hypobromous acid water -1" and "hypobromous acid water-2", but either is a solution composed of hypobromous acid as the major ingredient. The major ingredient of the former is HOBr obtained by dissolving DBDMH in water, and that of the later is HOBr produced by reaction of hydrogen bromide with a chloride donor such as sodium hypochlorite, potassium hypochlorite or calcium hypochlorite. The additive, "Hypobromous Acid Water" includes not only HOBr as the main ingredient but also DMH in "hypobromous acid water -1" or sodium chloride, potassium chloride or calcium chloride in "hypobromous acid water-2".

When meat is treated with additive "Hypobromous Acid Water", HOBr is rapidly changed to its bromides by organic substances present on the meat surface. Consequently, the residues such as bromides and DMH, or bromides and sodium chloride, potassium chloride or calcium chloride may be found on the meat surface. In addition, trihalomethanes (chloroform, BDCM, DBCM, bromoform) and bromic acid have been considered as such residues by FAO/WHO (2008).

Among these, sodium chloride, potassium chloride and calcium chloride are ingredients contained in ordinal foods. Intakes of sodium, potassium and calcium from use of the additive "Hypobromous Acid Water" were 0.01%, 0.02% and 0.05% of the dietary intake, respectively. Considering the above, FSCJ decided to assess the safety of the additive "Hypobromous Acid Water, comprehensively, by evaluating the results of toxicity studies on DMH and its bromides.

In addition, FSCJ have already conducted the risk assessment of trihalomethanes (chloroform, BDCM, DBCM, bromoform) in 2009 and that of bromic acid in 2008, and after the assessments new findings relevant to safety concern of trihalomethanes were not observed according to the designation requesters and the amendment requesters of the specification and standards.

1. DMH

Data on pharmacokinetics of DMH suggested that DMH is rapidly absorbed, hardly metabolized, and excreted unchanged mainly in the urine.

FSCJ judged that DMH has no genotoxicity relevant to human health.

FSCJ determined the NOAEL of DMH as 100 mg/kg bw/day which was obtained in developmental toxicity study in rabbits based on the acute toxicity study, repeated dose toxicity study and reproductive developmental toxicity study of DMH. In addition, carcinogenicity was not observed.

FSCJ concluded that an ADI for DMH needs to be specified considering the estimated daily intake (EDI) of DMH in Japan (0.015 mg/kg bw/day). Accordingly, FSCJ specified the ADI for DMH as 1 mg/kg bw/day applying a safety factor of 100 to the NOAEL of 100 mg/kg bw/day obtained in a developmental toxicity study in rabbits.

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| ADI | 1 mg/kg bw/day |
| The critical study for setting ADI | Developmental toxicity study in rabbits |
| Animal species | Rabbits |
| Dosing method | Oral administration |
| Findings used as a basis for establishing NOAEL | Increased incidence of anterior sacral vertebra number 27 (skeletal variations) |
| NOAEL | 100 mg/kg bw/ day |
| Safety factor | 100 |

2. Bromides

Data on pharmacokinetics of bromides indicated that bromides remained in blood for a long, partially transferred to the central nervous system and thyroid, but the tissue concentration was lower than the blood concentration. Bromides crossed the placenta from mother to fetus. The plasma concentration of bromides was higher as the intake of chlorides was lower, suggesting that chlorides affect excretion of bromides.

FSCJ judged that bromides have no genotoxicity relevant to human health.

FSCJ determined the NOAEL of bromides as 9 mg/kg bw/day (as bromide ions) which was obtained in human intervention study based on the acute toxicity study, repeated dose toxicity study, reproductive developmental toxicity study and human study of bromides. As for carcinogenicity, FSCJ concluded that carcinogenicity of bromides can be hardly judged since the results of carcinogenicity study were unclear and the relevant study was with only one dose.

FSCJ concluded that an ADI for bromides needs to be specified considering the estimated daily intake (EDI) of bromides in Japan (0.019 mg/kg bw/day (as bromide ions)). Accordingly, FSCJ specified the ADI for DMH as 0.9 mg/kg bw/day (as bromide ions) applying a safety factor of 10 to the NOAEL of 9 mg/kg bw/day (as bromide ions) obtained in a human intervention study.

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| ADI | 0.9 mg/kg bw/day (as bromide ions) |
| The critical study for setting ADI | Human intervention study |
| Animal species | Humans |
| Dosing method | Oral administration |
| Findings used as a basis for establishing NOAEL | The maximum dose |
| NOAEL | 9 mg/kg bw/ day (as bromide ions) |
| Safety factor | 10 |

3. Trihalomethanes and bromic acid

FSCJ determined the EDI (Estimated Daily Intake) of chloroform, BDCM, DBCM, and bromoform derived from use of the additive “Hypobromous Acid Water” as 0.008 μg/person/day (0.00015 μg/kg bw/day), 0.022 μg/person/day (0.00040 μg/kg bw/day), 0.025 μg /person/day (0.00045 μg/kg bw/day), and 0.253 μg/person/day (0.0046 μg/kg bw/day) respectively. FSCJ thus confirmed that these EDIs were all below the respective TDIs that have been specified by FSCJ in 2009 as 12.9 μg/kg bw/day, 6.1 μg/kg bw/day, 21.4 μg/kg bw/day and 17.9 μg/kg bw/day.

FSCJ determined the EDI of bromic acid derived from use of the additive “Hypobromous Acid Water” as 0.039 μg/person/day (0.00071 μg/kg bw/day). In the evaluation of bromic acid by FSCJ in 2008, the intake that corresponds to carcinogenic risk levels $10^{-4}$, $10^{-5}$, and $10^{-6}$ were estimated to be 3.57, 0.357, and 0.0357 μg/kg bw/day, respectively. FSCJ confirmed that the EDI of bromic acid derived from use of the additive “Hypobromous Acid Water” was below the intake corresponding to carcinogenic risk level $10^{-6}$.

4. Additive “Hypobromous Acid Water”

On the basis of the above, FSCJ considered that the additive “Hypobromous Acid Water” is of no concern for food safety as long as used appropriately as a food additive.