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

Risk Assessment Report

Dazomet, Metam and Methyl isothiocyanate

(Pesticides)

Food Safety Commission of Japan (FSCJ)
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OVERALL ASSESSMENT

Dazomet and metam are dithiocarbamate nematicides, fungicides, insecticides and herbicides. Both compounds are known to exert their pesticidal effects as methyl isothiocyanate (MITC), their common metabolite.

The toxicity of these three compounds was evaluated independently, since the risk of these three compounds cannot be evaluated together as one compound. Therefore, FSCJ conducted a risk assessment on each of the compounds independently first, then conducted an overall assessment taking into account the fact that dazomet and metam are easily metabolized into MITC in an aqueous condition and thus most of them are present as MITC in plants.

The individual assessments of dazomet, metam as metam ammonium, metam sodium and metam potassium, and MITC are reported in the abstract-1, abstract-2 and abstract-3, respectively. Risk assessment report on MITC was referred in the risk assessment of dazomet and metam, because MITC is a metabolite of dazomet and metam.

(1) Abstarct-1. Assessment of dazomet

FSCJ conducted a risk assessment of dazomet (CAS No. 533-74-4), a dithiocarbamate nematicide, fungicide, insecticide and herbicide, based on summary reports submitted by the applicant and other materials including documents from the Joint FAO/WHO Meeting on Pesticide Residues (JMPR), and the governments of Australia and EU.

The data used in the assessment include fate in animals (rats), fate in plants (tomato and radish), residues in crops, subacute toxicity (rats and dogs), subacute neurotoxicity (rats), chronic toxicity (rats and dogs), carcinogenicity (rats and mice), two-generation reproductive toxicity (rats), developmental toxicity (rats and rabbits) and genotoxicity.

Major adverse effects of dazomet observed are decreased body weight gain, effects on blood such as anemia, increased organ weights in the liver, and hemosiderosis in the spleen. Dazomet showed no neurotoxicity, carcinogenicity, reproductive toxicity and genotoxicity relevant to human health.

In the developmental studies in rabbits, increased post implantation loss and decreased number of viable fetuses were observed. No teratogenicity was observed in rats.

The lowest no-observed-adverse-effect level (NOAEL) obtained was 0.4 mg/kg body weight/day in a one-year chronic toxicity study in dogs. Applying a safety factor of 100 to the NOAEL, FSCJ specified the acceptable daily intake (ADI) of 0.004 mg/kg bw/day.
The lowest NOAEL for potential adverse effects of a single oral administration of dazomet was 2.8 mg/kg bw/day in a 90-day subacute toxicity study in dogs. Applying a safety factor of 100 to the NOAEL, FSCJ specified an acute reference dose (ARfD) of 0.028 mg/kg bw.

(2) Abstarct-2. Assessment of metam

1. Assessment of metam ammonium

FSCJ conducted a risk assessment of metam ammonium (CAS No. 39680-90-5), a dithiocarbamate soil fumigant, based on results from various studies.

The data used in the assessment include fate in animals (rats), fate in plants (cabbage and Japanese radish), residues in crops, subacute toxicity (rats and mice), chronic toxicity (dogs), combined chronic toxicity/carcinogenicity (rats and mice), two-generation reproductive toxicity (rats), developmental toxicity (rats and rabbits) and genotoxicity.

Major adverse effects of metam ammonium observed are decreased body weight gain, effects on the stomach such as forestomach hyperkeratosis and epithelial hyperplasia of the glandular stomach mucosa. Metam ammonium showed no carcinogenicity, teratogenicity and genotoxicity relevant to human health.

In a two-generation reproduction study of metam ammonium in rats, a decrease in viable fetuses and an increase in stillborns were observed.

The lowest NOAEL obtained was 0.5 mg/kg body weight/day in a one-year chronic toxicity study in dogs and a two-generation reproduction study in rats. Applying a safety factor of 100 to the NOAEL, FSCJ specified an ADI of 0.005 mg/kg bw/day.

The lowest NOAEL for potential adverse effects of a single oral administration of metam ammonium was 3 mg/kg bw/day in a one-year chronic toxicity study in dogs. Applying a safety factor of 100 to the NOAEL, FSCJ specified an ARfD of 0.03 mg/kg bw.

2. Assessment of metam sodium and metam potassium

FSCJ conducted a risk assessment of metam sodium (CAS No. 137-42-8) and metam potassium (CAS No. 137-41-7), dithiocarbamate soil fumigants, based on summary reports submitted by the applicant and documents from the governments of EU and Australia.

FSCJ specified the ADI for metam potassium on the basis of results from various studies on metam sodium, because toxicity of metam potassium is considered to be equivalent to that of metam sodium.

The data used in the assessment include fate in animals (rats), fate in plants (Japanese radish and tomato), residues in crops, subacute toxicity (rats, mice and dogs), chronic toxicity (dogs), combined chronic toxicity/carcinogenicity (rats), carcinogenicity (mice), two-generation reproductive toxicity (rats), developmental toxicity (rats and rabbits) and genotoxicity.

Major adverse effects of metam sodium observed are decreased body weight gain, anemia, epithelial hyperplasia of the fore stomach mucosa and mucosal epithelial hyperplasia of the urinary bladder. Metam sodium showed no carcinogenicity, reproductive toxicity and genotoxicity relevant to human health. In the developmental toxicity study in rats and rabbits, meningocele was observed at the dose with maternal toxicity.

The lowest NOAEL obtained was 0.75 mg/kg bw/day in a one-year chronic toxicity study in dogs. Applying a safety factor of 100 to the NOAEL, FSCJ specified an ADI of 0.0075 mg/kg bw/day.

The lowest NOAEL for potential adverse effects of a single oral administration of metam sodium and of metam potassium was 2.16 mg/kg bw/day in developmental toxicity studies in rats and rabbits. Applying a safety factor of 100 to the NOAEL, FSCJ specified an ARfD of 0.021 mg/kg bw.

(3) Abstract-3. Assessment of methyl isothiocyanate

FSCJ conducted a risk assessment of methyl isothiocyanate, (MITC: CAS No. 556-61-6), a nematicide, fungicide, insecticide and herbicide, based on summary reports submitted by the applicant and documents from the governments of EU and Australia.

The data used in the assessment include fate in animals (rats and dogs), fate in plants (tomato and Japanese white radish), residues in crops, subacute toxicity (rats, mice and dogs), subacute neurotoxicity (rats), chronic toxicity (dogs), combined chronic toxicity/carcinogenicity (rats and mice), two-generation and three-generation reproductive toxicity (rats), developmental toxicity (rats and rabbits) and genotoxicity.

Major adverse effects of MITC observed are decreased body weight gain, increased organ weights in the liver, hepatocellular fatty degeneration and hypertrophy of the forestomach. MITC showed no neurotoxicity, carcinogenicity, reproductive toxicity and genotoxicity relevant to human health.

The lowest NOAEL obtained was 0.4 mg/kg bw/day in a 90-day subacute toxicity study and a one-year chronic toxicity study in dogs. Applying a safety factor of 100 to the NOAEL, FSCJ specified an ADI of 0.004 mg/kg bw/day.

The lowest NOAEL for potential adverse effects of a single oral administration of MITC was 10 mg/kg bw/day in general pharmacology studies in mice and rabbits. Applying a safety factor of 100 to the NOAEL, FSCJ specified an ARfD of 0.1 mg/kg bw.

4. Overall assessment

As for the overall assessment of dazomet, metam and MITC, FSCJ considered it appropriate to specify the ADI for all the compounds based on the assessment of MITC, considering that MITC is a common metabolite of both dazomet and metam in an aqueous condition and thus both compounds remain as MITC in plants after being sprayed. Accordingly, FSCJ identified MITC as the residue definition for dietary risk assessment in agricultural products. The lowest NOAEL obtained in all tests conducted for MITC was 0.4 mg/kg bw/day in a 90-day subacute toxicity study and a one-year chronic toxicity study in dogs. FSCJ specified a group ADI for all of dazomet, metam and MITC to be 0.004 mg/kg bw/day. The lowest NOAEL for potential adverse effects of a single oral administration of MITC was 10 mg/kg bw/day in general pharmacology studies in mice and rabbits. FSCJ specified a group ARfD of 0.1 mg/kg bw applying a safety factor of 100 to the NOAEL, for all of dazomet, metam and MITC.

＜Group ADI and Group ARfD for Dazomet, Metam and MITC＞

ADI	0.004 mg/kg bw/day
(A source data ① for specifying ADI)	Subchronic toxicity study
（Animal species tested）	Dogs
（Duration of exposure）	90 days
（Rout of administration）	Gavage administration
（NOAEL）	0.4 mg/kg bw/day
(A source data ② for specifying ADI)	Chronic toxicity study
（Animal species tested）	Dogs
（Duration of exposure）	One year
（Rout of administration）	Gavage administration
（NOAEL）	0.4 mg/kg bw/day
（Safety factor）	100
ARfD	0.1 mg/kg bw
(A source data for specifying ARfD)	General pharmacology study
（Animal species tested）	Mice and rabbits
（Duration of exposure）	Single dose
（Rout of administration）	Gavage administration
（NOAEL）	10 mg/kg bw
（Safety factor）	100