FOOD SAFETY

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Malathion

Executive Summary

Food Safety Commission of Japan

The Food Safety Commission of Japan (FSCJ) conducted a risk assessment of malathion (CAS No. 121–75-5), an organophosphorus pesticide, based on summary reports made by applicants and documents from JMPR, the governments of the US, EU and others. A major adverse effect of malathion observed is inhibition of ChE activity in the brain and red blood cells. None of the reproductive toxicity, teratogenicity, developmental neurotoxicity or genotoxicity relevant to human health was observed. No carcinogenicity was observed in rats. In an 18-month carcinogenicity study in mice, an increased incidence of hepatocellular adenomas was observed. However, a genotoxic mechanism was not likely to be involved in the tumor development, therefore it is reasonable to establish a threshold in the assessment. FSCJ specified the acceptable daily intake (ADI) for malathion at 0.29 mg/kg bw/day, applying a safety factor of 100 to the no-observed-adverse-effect level (NOAEL) of 29 mg/kg bw/day obtained in the two-year chronic toxicity study and two-year combined chronic toxicity/carcinogenicity study in rats. Since the lowest NOAEL after a single oral dose was 15 mg/kg bw observed in the randomized double-blind study in humans, FSCJ specified the acute reference dose (ARfD) of 1.5 mg/kg bw applying a safety factor of 10 (1 for a clinical single oral dosing study in humans and 10 for individual difference) to the NOAEL.

Conclusion in Brief

The Food Safety Commission of Japan (FSCJ) conducted a risk assessment of malathion (CAS No. 121–75-5), an organophosphorus pesticide, based on summary reports made by applicants and documents from JMPR, the governments of the US, EU and others.

The data used in the assessment include fate in animals (rats, mice, goats, and chickens), fate in plants (paddy rice, lettuce and others), residues in crops, subacute toxicity (rats and dogs), subacute neurotoxicity (rats), chronic toxicity (rats and dogs), combined chronic toxicity/carcinogenicity (rats), carcinogenicity (mice), two-generation reproductive toxicity (rats), three-generation reproductive toxicity (rats), developmental toxicity (rats and rabbits), developmental neurotoxicity (rats), and genotoxicity.

A major adverse effect of malathion observed is inhibition of ChE activity in the brain and red blood cells. None of the reproductive toxicity, teratogenicity, developmental neurotoxicity or genotoxicity relevant to human health was observed. No carcinogenicity was observed in rats. In an 18-month carcinogenicity study in mice, an increased incidence of hepatocellular adenomas was observed. However, a genotoxic mechanism was not likely to be involved in the tumor development, therefore it is reasonable to establish a threshold in the assessment.

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Based on the results from various studies, FSCJ specified malathion (parent compound only) as the residue definition for this dietary risk assessment in agricultural products and livestock products. FSCJ specified the acceptable daily intake (ADI) for malathion at 0.29 mg/kg bw/day, applying a safety factor of 100 to the no-observed-adverse-effect level (NOAEL) of 29 mg/kg bw/day obtained in the two-year chronic toxicity study and two-year combined chronic toxicity/carcinogenicity study in rats.

Since the lowest NOAEL after a single oral dose was 15 mg/kg bw observed in the randomized double-blind study in humans, FSCJ specified the acute reference dose (ARfD) of 1.5 mg/kg bw applying a safety factor of 10 (1 for a clinical single oral dosing study in humans and 10 for individual difference) to the NOAEL.

Risk Assessment

FSCJ conducted a risk assessment of malathion (CAS No. 121–75-5), an organophosphorus pesticide, based on summary reports made by applicants and documents from JMPR, the governments of the US, EU and others.

On the fate in animals using ^{14}C-malathion (10 mg/kg bw) in rats, T_{max} was one hour after the administration. Biphasic disappearance was observed where $T_{1/2}$ of α-phase and of β-phase were 18.5 min and 7.16 hours, respectively. Within 24 hours after administration, 83.4–93.0% of the total administered radioactivity (TAR) was excreted in urine, 5.51–8.54% of TAR in feces and 2.77–5.08% of TAR in expiration. Malathion was thus predominantly excreted in urine, suggesting the high oral bioavailability (approximately 90% of TAR). The highest tissue level of ^{14}C-malathion was found in the adrenal gland at 24 hours after the administration. The main metabolite found in urine was metabolite-B (malaoxon), followed by metabolite-C (α-malathion monocarboxylic acid)/-D (β-malathion monocarboxylic acid) and -E (malathion dicarboxylic acid). The excretion of unchanged malathion was minimal (0.01% of TAR in urine). Approximately 50% of TAR was excreted in urine within 48 hours after the intraperitoneal administration of ^{32}P-malathion. The main metabolite of ^{32}P-malathion administered intraperitoneally was metabolite-E, followed by metabolite-D, -F (desmethyl malathion), -R (dimethyl phosphorodithioate), -S (dimethyl phosphorothioate) and -U (dimethyl hydrogenphosphate).

Mice excreted 59.5% of TAR in urine at 60 min after the oral administration of ^{14}C-malathion (1 mg/kg bw). The bioavailability of more than 88.8% was indicated from the total radioactivity of urinary excretion, expiration and tissue residues. The main metabolite after the intraperitoneal administration of ^{32}P-malathion in mice was metabolite-D, followed by metabolite-R, -T (dimethyl hydrogenphosphorothioate) and -U.

Fate of ^{14}C-malathion in livestock was also studied. In goats, 45–70% of TAR was excreted in urine and feces (urine > feces) within 24 hours after the oral administration of 172 mg/head/day for five days. The maximal concentration (2.5 μg/g) of malathion in the milk was found during the five-day successive administrations at the same dose. The highest residual radioactivity was found in the liver at 24 hours after the final administration. Malathion was converted into endogenous substances including triglyceride and TCA cycle intermediates in the liver. Some metabolites including metabolite-C/-D and -E were detected in the kidney. Unchanged malathion was detected but was less than 0.05 μg/g in all the tissues examined. In chicken, approximately 26% of the TAR was excreted within 24 hours after the oral administration (3.8 mg/head/day for 4 days). Maximal levels of total malathion radioactivity (0.96 and 0.33 μg equiv./g) in the egg yolk and egg white were found after four-day administration, respectively. The highest residual radioactivity was detected in kidney (1.08 μg equiv./g) among organs and tissues. The unchanged malathion was detected but was less than 0.02 μg/g throughout the tissues examined.

The fate of ^{14}C-malathion in plants is as follows: The major constituents were the unchanged malathion, and its metabolite-D, -M (monoethyl fumarate) and -I (desmethyl malathion β-acid) in unpolished rice. None of them however exceeded 10% of the total radioactive residue (TRR). The unchanged malathion was the main constituent in wheat, lettuce, cotton and alfalfa. The metabolite-I (11.9% of TRR) and -C (12.8% of TRR) were also found in rice straw and in lettuce, respectively, as showing over 10% of TRR.

Residual unchanged malathion in various crops was also determined, and the maximum residual level (8.52 mg/kg) was found in mandarin orange peel.

In livestock feeding studies of lactating cows, unchanged malathion in the milk was below the detection limit at any sampling points during daily administration for 28 days. In livestock feeding studies of broilers, hen and pigs, malathion residues in edible tissues and eggs were below the detection limit.

A major adverse effect of malathion observed is inhibition of ChE activity in the brain and red blood cells after the oral administration. None of the reproductive toxicity, teratogenicity, developmental neurotoxicity or genotoxicity

relevant to human health was observed in studies of experimental animals. No carcinogenicity was observed in rats. In 18-month carcinogenicity study in mice, an increased incidence of hepatocellular adenomas was observed. Genotoxic mechanism was however unlikely to be involved in the tumor development. Therefore it is reasonable to establish a threshold in the assessment.

In plants, metabolite-C and -I were present as exceeded 10% of TRR. Metabolite-C and metabolite-F, which assumingly is a precursor of metabolite-I, are detectable in rats. FSCJ specified the residue definition for this dietary risk assessment in agricultural products and livestock products to be malathion (parent compound only).

Among NOAELs in all studies, the minimal value was 4 mg/kg bw/day obtained in the 13-week subacute neurotoxicity study of rats. The lowest-observed-adverse-effect level (LOAEL) in this study was 352 mg/kg bw/day. The NOAEL value of 29 mg/kg bw/day and the LOAEL of 50 mg/kg bw/day were obtained as an overall evaluation from the two-year chronic toxicity study and the two-year combined chronic toxicity/carcinogenicity study in rats. Considering that the discrepancy in these two values of NOAEL is attributable to the difference in the dose setting and also that the latter two tests are the tests for longer period than the period of 13-week subacute neurotoxicity test, FSCJ concluded that overall NOAEL in rats is 29 mg/kg bw/day. A NOAEL of 25 mg/kg bw/day, which is close to 29 mg/kg bw/day in rats, has been obtained based on the inhibition of weight gain of maternal parents in the developmental toxicity test in rabbits. The NOAEL (29 mg/kg bw/day) obtained in rats was from the study with inhibition of ChE activity, which is the most relevant end-point for exposure to malathion. Hence, it is appropriate to specify the ADI for malathion based on the NOAEL of 29 mg/kg bw/day obtained in rats. FSCJ specified an ADI for malathion at 0.29 mg/kg bw/day, applying a safety factor of 100 to the NOAEL of 29 mg/kg bw/day obtained in the two-year chronic toxicity study and two-year combined chronic toxicity/carcinogenicity study in rats.

Since the lowest NOAEL after a single oral dose was 15 mg/kg bw observed in the randomized double-blind study in humans, FSCJ specified the ARfD of 1.5 mg/kg bw applying a safety factor of 10 (1 for a clinical single oral dosing study in humans and 10 for individual difference) to the NOAEL.

ADI: 0.29 mg/kg bw/day
A basis for establishing ADI: Chronic toxicity study and combined chronic toxicity/carcinogenicity study
Animal species: Rats
Period: 2 years
Dosing method: Mixed in feed
NOAEL: 29 mg/kg bw/day
Safety factor: 100

ARfD: 1.5 mg/kg bw
A basis for establishing ARfD: A single oral dosing study
Animal species: Humans
Period: Single
Dosing method: Oral administration
NOAEL: 15 mg/kg bw
Safety factor: 10