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

Risk Assessment Report

Cartap, Thiocyclam, Bensultap

(Pesticides)

Food Safety Commission of Japan (FSCJ)
June 2019

Comparing evaluation of Cartap hydrochloride, thiocyclam hydrogenoxalate and bensultap

Cartap hydrochloride, thiocyclam hydrogenoxalate and bensultap are reported to be metabolized/degradated commonly via nereistoxin, a major chemical used as an insecticide. Studies on toxicity and others of these three compounds are conducted separately, and FSCJ couldnot conduct a group assessment targetting these three compounds as a unit of group. Therefore, FSCJ evaluated each compound separately as the first step. FSCJ then considered it appropriate to conduct a group assessment of these three compounds, because of their common profile of metoblism through nereistoxin in animals and plants, and because of common major metabolite(s) among them. Data on toxicological profiles of nereistoxin described in the reports of thiocyclam hydrogenoxalate and bensultap were reffered in this group assessment.

The evaluation for establishing individual and group ADIs and/or ARfDs

Cartap hydrochloride, thiocyclam hydrogenoxalate and bensultap were metabolized/degradated commonly via nereistoxin, a major chemical used as an insecticide. These three compounds showed common major adverse effects such as suppressed body weight and tremor and convulsion in the toxicity study of each compounds, which suggested that their adverse effects on animals were attributable to the common metabolite.

According to tierring step of evaluation, FSCJ first specified ADI and ARfD for each compound based on the results of toxicity studies of each compound, and progressed to the next step for specification of a group ADI and group ARfD for three compounds.

FSCJ noted some toxicity data inadequate due to no accordance with current test-guidelines partly on such as administration period in the devevolmental toxicity study of cartap hydrochloride, and dose setting in the combined chronic toxicity/carcinogenicity study and three-generation reproduction study of thiocyclam hydrogenoxalate. However, FSCJ considered it possible to assess the adverse effects on reproductionay, teratogenicity and carcinogenicity of three compounds based on the following points. First, no effects on reproductivity, teratogenicity and genotoxicity relevant to human health were observed for all the three compounds including bensultap. Second, cartap hydrochloride had no carcinogenicity. While an incidence of testicular interstitial cell tumors was increased by a treatment with bensultap in male rats, a genotoxic mechanism was unlikely involved in tumor induction and thus it was considered possible to determine the threshold.

The lowest value of NOAELs of cartap hydrochloride was 3.0 mg/kg bw/day obtained in two-year chronic toxicity study in monkeys. The lowest value of NOAELs of thiocyclam hydrogenoxalate was

2.11 mg/kg bw/day (2.13 mg/kg bw/day as converted to the value of cartap hydrochloride[1]) obtained in two-year chronic toxicity study in dogs. The lowest value of NOAELs of bensultap was 2.52 mg/kg bw/day (1.60 mg/kg bw/day as converted the value of cartap hydrochloride[2]). As the lowest value of these three NOAELs converted for cartap hydrochloride was 1.60 mg/kg bw/day for bensultap, FSCJ specified the group ADI of cartap hydrochloride, thiocyclam hydrogenoxalate and bensultap to be 0.016 mg/kg bw/day applying the safety factor of 100 to the NOAEL.
The lowest NOAEL for adverse effects of a single oral administration of cartap hydrochloride was 10 mg/kg bw/day obtained in acute neurotoxicity study in rats and in general pharmacology data in mice. The lowest NOAEL for adverse effects of a single oral administration of thiocyclam hydrogenoxalate was 10 mg/kg bw/day (10.1 mg/kg bw/day as converted the value of cartap hydrochloride) obtained in developmental toxicity study in rabbits. The lowest NOAEL for potential adverse effects of a single oral administration of bensultap was 30 mg/kg bw/day (19.0 mg/kg bw/day as converted the value of cartap hydrochloride) obtained in general pharmacology data of mice. As the lowest value of these three NOAELs converted for cartap hydrochloride was 10 mg/kg bw/day for cartap hydrochloride and thiocyclam hydrogenoxalate, FSCJ specified the group ARfD of cartap hydrochloride, thiocyclam hydrogenoxalate and bensultap to be 0.1 mg/kg bw/day applying the safety factor of 100 to the NOAEL.

On the basis of overall consideration of relevant substance for the residue definition for dietary risk assessment identified for each product, the relevant substances for the residue definition for dietary risk assessment in the agricultural products were cartap hydrochloride, cartap, thiocyclam hydrogenoxalate, thiocyclam, bensultap, and metabolite A (including nereistoxin), and metabolites that are composed to A by hydrolysis/oxidization under alkaline condition)

<Group ADI and Group ARfD of cartap hydrochloride, thiocyclam hydrogenoxalate and bensultap>

ADI	0.016 mg/kg bw/day
The critical study for setting ADI	Two-generaion reproductivity study (bensultap)
Species	Rats
Term	Two generations
Route of administration	Dietary administration
NOAEL	1.60 mg/kg bw/day (converted to that of cartap hydrochloride)
Safety Factor	100

ARfD	0.1 mg/kg bw
The 1st critical study for setting ARfD	Acute neurotoxicity study (cartap hydrochloride)
Species	Rats
Term	Single
Route of administration	Gavage administration
NOAEL	10 mg/kg bw (converted to that of cartap hydrochloride)

[1] NOAEL of thiocyclam hydrogenoxalate was converted to that of cartap hydrochloride using the conversion factor of 1.01.
[2] NOAEL of bensultap was converted to that of cartap hydrochloride using the conversion factor of 0.634.

The 2nd critical study for setting ARfD	General pharmacology data (cartap hydrochloride)
Species	Mice
Term	Single
Route of administration	Gavage administration
NOAEL	10 mg/kg bw (converted to that of cartap hydrochloride)

The 3rd critical study for setting ARfD	Developmental toxicity study (thiocyclam hydrogenoxalate)
Species	Rabbits
Term	From gestation day 6 to 18
Route of administration	Gavage administration
NOAEL	10.1 mg/kg bw (converted to that of cartap hydrochloride)
Safety Factor	100

The exposure levels shall be confirmed based on this assessment when the provisional standards will be reviewed.

<References>

1. Summary reports submitted by applicants Thiocyclam (pesticides) (Revised on 3 March 2017): Nippon Kayaku Co., Ltd.
2. Summary reports submitted by applicants Bensultap (pesticides) (Revised on 1 March 2017): Sumitomo Kagaku Co., Ltd.