

**THIOPHANATE-METHYL (addendum)**

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**Explanation**

Thiophanate-methyl was evaluated toxicologically by the Joint Meeting in 1973, 1975, 1977, and 1995 (Annex 1, references 20, 24, 28, and 74). An ADI of 0–0.08 mg/kg bw was allocated in 1973, on the basis of a NOAEL of 8 mg/kg bw per day in a three-generation study of reproductive toxicity in rats and a safety factor of 100. This ADI was confirmed in 1975 and 1977. Additional data that became available were reviewed at the 1995 Joint Meeting within the CCPR periodic review programme, at which time an ADI of 0–0.02 mg/kg bw was established on the basis of a NOAEL of 2 mg/kg bw per day in a study of developmental toxicity in rabbits. New information on the metabolism of thiophanate-methyl and the results of a second study of developmental toxicity in rabbits have become available and were reviewed at the present Meeting.

**Evaluation for Acceptable Daily Intake****1. Biochemical aspects***(a) Absorption, distribution, and excretion*

The absorption, tissue distribution, and excretion in urine and faeces of [phenyl-<sup>14</sup>C]thiophanate-methyl (purity, 96%) was investigated in groups of five Fischer 344 rats of each sex after administration by gavage of a single dose of 14 or 170 mg/kg bw or doses of 14 mg/kg bw per day for 15 days. Thiophanate-methyl was rapidly absorbed from the gastrointestinal tract, reaching a maximum serum concentration by 4 h after administration. The extent of absorption may be dose-dependent, decreasing with increasing dose. The highest residual tissue levels were found in the liver, thyroid, and kidneys 96 h after dosing. Thiophanate-methyl was excreted rapidly, with > 90% elimination via the urine and faeces within 24 h of administration. At the low dose, the principal route of elimination was urinary, whereas at the high dose excretion was predominantly faecal. Repeated exposure to thiophanate-methyl also tended to shift excretion from the urinary to the faecal route (Tanoue, 1992 a,b).

*(b) Biotransformation*

There was no indication of potential bioaccumulation. The dose or duration of administration did not affect the metabolites identified in the urine. The major urinary metabolite was 5-(2-methoxycarbonylamino) benzimidazolyl sulfate (21–42%); 5-hydroxy-1*H*-benzimidazol-2-yl

carbamate and 4-hydroxythiophanate-methyl each represented approximately 2% of the radiolabel. The major faecal metabolites were 4-hydroxythiophanate-methyl (6–10%) and 5-hydroxy-1*H*-benzimidazol-2-yl carbamate (~2–5%). Unchanged thiophanate-methyl accounted for approximately 20–24% of the administered radiolabel after repeated low doses and 50% after the high dose. Carbendazim was a minor metabolite (2–3%) in rats. In plants, unchanged thiophanate-methyl and carbendazim accounted for approximately 65 and 30% of the residue, respectively, 7–14 days after application. A new metabolic pathway for thiophanate-methyl in rats has been proposed and is presented in Figure 1 (Tanoue, 1992a,b).

## 2. Toxicological studies

### (a) Developmental toxicity

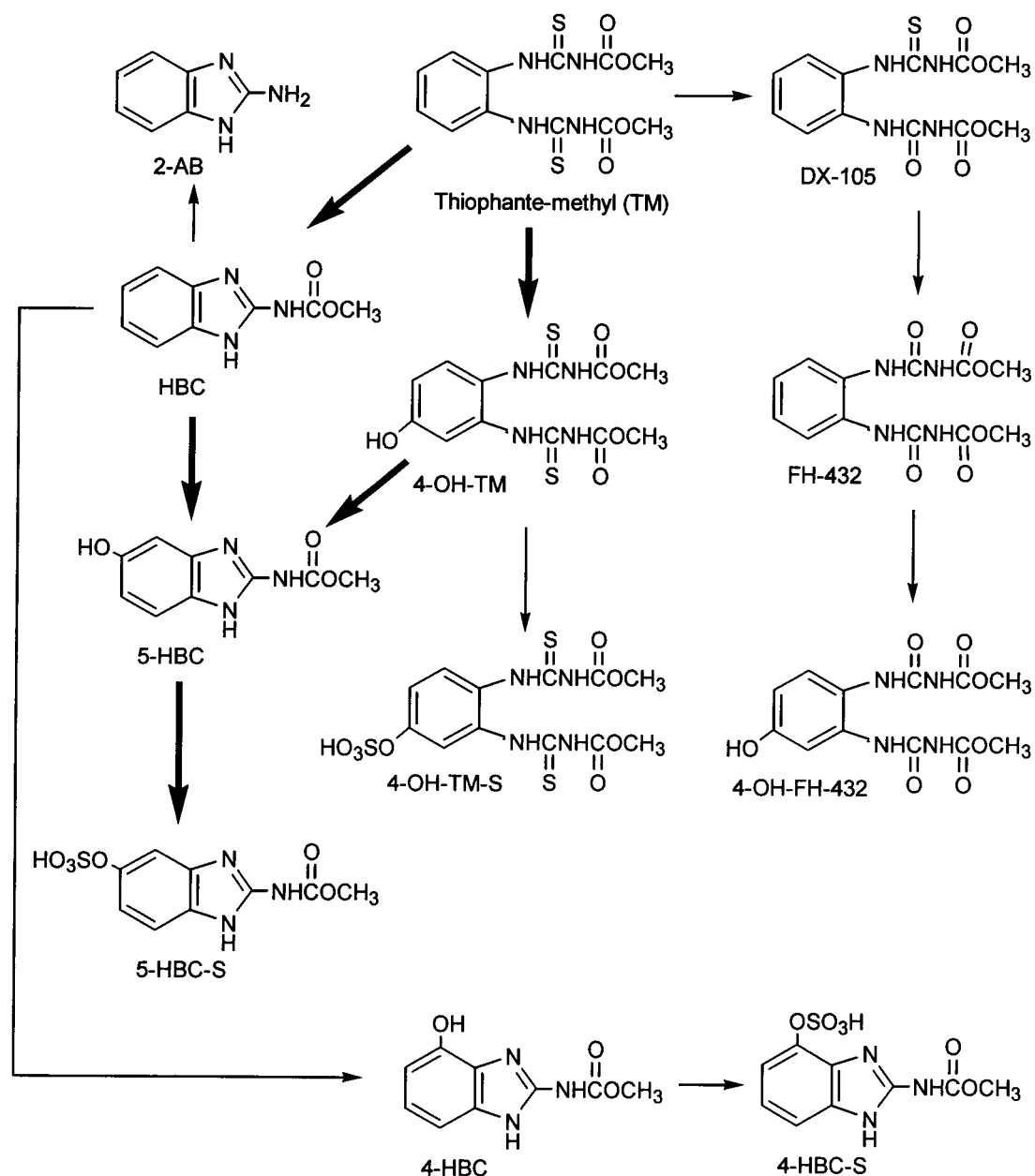
#### *Rabbits*

Groups of 15 female New Zealand white rabbits received thiophanate-methyl (purity, 96.2%) at a dose of 0, 2, 6, or 20 mg/kg bw per day by gavage on days 6–19 of gestation. The concentrations of thiophanate-methyl were found to be acceptable in samples of test solutions taken during the first and last weeks of treatment. The animals were killed on day 29 of gestation. No treatment-related maternal deaths or clinical effects and no subsequent effects were seen. Dose-related losses in maternal body weight were observed mainly at the beginning of treatment (days 6–8 of gestation) with 6 mg/kg bw per day and during days 6–14 of gestation at 20 mg/kg bw per day. The food consumption of animals treated with 20 mg/kg bw per day was less than that of the control group from the start of treatment, and large reductions seen during days 6–12 of gestation were generally associated with subsequent abortion or sacrifice *in extremis*. Water consumption was unaffected. One of 12 animals treated with 2 mg/kg bw per day, one of 14 animals treated with 6 mg/kg bw per day, and two of 13 animals in the control group aborted. One control animal and one animal treated with 20 mg/kg bw per day had only one implantation, which was resorbed early. No treatment-related trends were observed in resorptions, preimplantation losses, or fetal or placental weights. The numbers of viable young were slightly decreased in animals treated with 20 mg/kg bw per day, due to abortions and total litter losses.

Gross examination of the fetuses showed an apparent treatment-related trend in skeletal abnormalities of the ribs, vertebrae, and pelvis in animals treated with 6 or 20 mg/kg bw per day, that was generally close to, or slightly greater than, the upper limit of values for historical controls. The treatment-related effects included increased incidences of 13 pairs of ribs, incomplete or asymmetric ossification of costal elements of the sacral vertebrae, 27 presacral vertebrae, and asymmetric pelvises associated with various sacral vertebrae. At 20 mg/kg bw per day, the incidence of one or more ribs thickened at the costal cartilage was significantly increased. The NOAEL for both maternal and developmental toxicity was 2 mg/kg bw per day on the basis of a decrease in maternal growth rate and increased incidences of skeletal abnormalities at higher doses (Tesh et al., 1986, Annex 1, reference 76).

The data on fetuses from the above study were reanalysed by Christian (1997), who noted that the slight decrease in viable young and the skeletal abnormalities were probably associated with poor maternal health, technical problems, and the relatively few animals available for evaluation. Although the increased incidences of supernumerary ribs were identified by the study author as an effect at doses of 6 and 20 mg/bw per day, reanalysis of the data showed that these incidences were within the expected normal range and were not statistically significant. All other variations in skeletal ossification identified in the study also occurred at incidences that were not statistically significant, indicating that they were unrelated to treatment. The NOAEL for maternal toxicity was 6 mg/kg bw per day, and the NOAEL for developmental toxicity was 20 mg/kg bw per day. Owing to the deficiencies in the study of Tesh et al. (1986), the Committee considered that it should be reclassified as a range-finding study.

**Figure 1. Proposed metabolic pathway for thiophanate-methyl in rats**



TM (common name), thiophanate methyl; 4-OH-TM, 4-hydroxythiophanate-methyl; 4-OH-TM-S, 3,4-bis-(*N'*-methoxycarbonylthioureido)phenyl sulfate; HBC (common name), carbendazim; 5-HBC, 5-hydroxy-1*H*-benzimidazol-2-yl carbamate; 5-HBC-S, 5-(2-methoxycarbonylamino)benzimidazolyl sulfate; 4-HBC, 4-hydroxy-1*H*-benzimidazol-2-yl carbamate; 4-HBC-S, 4-(2-methoxycarbonylamino)benzimidazolyl sulfate; 2-AB, 2-aminobenzimidazole; DX-105, methyl *N*-[2-(*N'*-methoxycarbonylthioureido)phenylamino] carbamate; FH-432, dimethyl-4,4'-*ortho*-phenylenebisallophanate; 4-OH-FH-432, 4-hydroxy-dimethyl-4,4'-*ortho*-phenylenebisallophanate; 4-OH-FH-432-S, 3,4-bis(*N'*-methoxycarbonylureido)phenyl sulfate

Groups of 20 naturally bred New Zealand white rabbits [Hra:(NZW)SPF] were given technical-grade thiophanate-methyl (purity, 97.28%) in 1% methylcellulose by gavage at doses of 0, 5, 10, 20, or 40 mg/kg bw per day on days 6–28 of gestation, the day of mating being considered day 0. The rabbits were sacrificed on day 29 of gestation. The does were observed for viability, clinical signs, body weight, food consumption, and the number of corpora lutea, and the thoracic, abdominal, and pelvic viscera were examined. Their uteri were excised and examined for the number and distribution of implantation sites, live and dead fetuses, and early and late resorptions. The fetuses were observed for sex, body weight, and gross external, visceral, brain, and skeletal alterations. At a dose of 20 mg/kg bw per day, there was a transient but significant reduction in maternal body-weight gain and statistically significant reduced absolute and relative feed consumption. At a dose of 40 mg/kg bw per day, faecal output was reduced, in conjunction with significantly reduced maternal body-weight gain and absolute and relative feed consumption; however, body-weight gain and food consumption recovered after the initial week of dosing. It is likely that the observed reduction in feed consumption during this period contributed to the observed decreases in body weight, body-weight gain, and faecal output. In the fetuses, the dose of 40 mg/kg bw per day was associated with supernumerary thoracic ribs only at the two higher of maternally toxic doses. In addition, there appeared to be an increased incidence of resorptions in rabbits treated with 40 mg/kg bw per day, the numbers of litters with  $\geq 20\%$  resorptions per litter being 2/20 in controls, 2/17 at 5 mg/kg bw per day, 2/18 at 10 mg/kg bw per day, 0/17 at 20 mg/kg bw per day, and 5/20 at 40 mg/kg bw per day. The historical control range for dead or resorbed conceptuses per litter was 0–18.3%. Thiophanate-methyl was not selectively toxic to embryo or fetal viability, growth, or morphology and was not teratogenic. The NOAEL for maternal toxicity was 10 mg/kg bw per day and that for developmental effects was 20 mg/kg bw per day (York, 1997a,b).

Comparison of the studies of Tesh et al. (1986) and York (1997b) revealed a consistent profile of maternal toxicity, comprising a dose-related, statistically significant, transient reduction in food consumption and body weight and/or body-weight gain, accompanied by reduced faecal output during the two-week period after the beginning of treatment. The transient, significant loss in maternal body-weight at 20 mg/kg bw per day in the first study was not seen at the same dose in the second study, although a transient reduction in body-weight gain in conjunction with reduced food consumption was noted. In the second study, a dose of 40 mg/kg bw per day was required to produce a significant loss in maternal body weight, which was transient, and subsequently a significant reduction in maternal body-weight gain. In both studies, food consumption, maternal body-weight gain, and faecal output steadily recovered towards the end of the study, even though the dosing period was longer in the second study. Neither study provided maternal body weights corrected for gravid uterine weight. The maternal effects described above occurred at lower doses in the first study (Tesh et al., 1986), probably because of compromised maternal health. Treatment with doses up to 20 mg/kg bw per day (Tesh et al., 1986) or 40 mg/kg bw per day (York, 1997b) did not significantly affect fetal body weights or litter size. Neither study showed treatment-related malformations.

The study of Tesh et al. (1986) showed increased incidences of resorptions or abortions at 20 mg/kg bw per day that were associated with poor maternal health, which was not treatment-related, or were within the historical control ranges. All does killed *in extremis* (two, one, one, and one at 0, 2, 6, and 20 mg/kg bw per day, respectively) had severe infections in their lungs and/or abdominal cavities. Of the six abortions (0/1, 1/1, 1/1, and 2/3 at 0, 2, 6, and 20 mg/kg bw per day, respectively) that occurred in surviving does, four were in does that had clear signs of infection. Nine out of 60 does either died or aborted due to severe infections in this study. In addition, a common finding at necropsy was the presence of precipitates or milkiness in the amniotic fluid of does that delivered, an indication of uterine infection. Owing to the high incidence of maternal disease in this study, the health status of the does that delivered litters was questionable, and the increased incidence of resorptions or abortions is unlikely to be treatment-related. As a result of the high incidence of deaths and abortions in the first study, only 12, 10, 12, and 9 litters were available for analysis at doses of 0, 2, 6, and 20 mg/kg bw per day, respectively. Removal of does with litters containing only 1 or 2 implants to reduce bias in any statistical analysis resulted in only

11, 9, 10, and 7 litters available for analysis at doses of 0, 2, 6, and 20 mg/kg bw per day, respectively. Even without the exclusion of does with small litters, the number of litters available for analysis was not sufficient for evaluation under current standards.

The only treatment-related fetal effect identified by York (1997b) was an increase in the incidence of supernumerary ribs, only at maternally toxic doses. This variation was also noted at 80 mg/kg bw per day, but not at 40 mg/kg bw per day, in the dose range-finding study of York (1997a); both doses were maternally toxic. In the study of Tesh et al. (1986), extra ribs occurred in 44/88, 48/78, 68/95, and 36/51 fetuses from 10/12, 10/10, 11/12, and 8/9 litters at 0, 2, 6, and 20 mg/kg bw per day, respectively, with incidences of 12/13 and 13/13 rib pairs combined. Although the incidence was significantly increased at 6 and 20 mg/kg bw per day, it was not significant on a litter basis and was within the historical control range. When calculated as the mean number of rib pairs per fetus per litter, as was done in the study of York (1997b), the means were 12.58, 12.58, 12.64, and 12.63 at 0, 2, 6, and 20 mg/kg bw per day, respectively. In the study of York (1997b), extra ribs occurred in 85/168, 76/141, 87/164, 78/115, and 142/160 fetuses from 17/19, 16/17, 18/18, 16/16, and 19/19 litters at 0, 5, 10, 20, and 40 mg/kg bw per day, respectively, with incidences of 12/13 and 13/13 rib pairs combined. Expressed as the mean number of rib pair per fetus per litter, 12.45, 12.44, 12.45, 12.58, and 12.85 mean rib pairs occurred at doses of 0, 5, 10, 20, and 40 mg/kg bw per day, respectively, which was significant at 40 mg/kg bw per day. The historical control values for rib pairs were: litter range, 12.34–12.67; fetal mean, 12.47. The incidence of extra ribs was considered to be treatment-related at 40 mg/kg bw per day. The two studies are consistent for this effect.

The two studies could not be compared directly with respect to the increased numbers of presacral vertebrae, asymmetrical pelvises, and incomplete or asymmetric ossification of the costal elements of the sacral vertebrae, because of differences in the methods of examination and tabulation and in terminology. However, an increased incidence of 27 presacral vertebrae, asymmetrical pelvises, and incomplete or asymmetric ossification of the costal elements of the sacral vertebrae, which were believed to be interrelated findings, was noted in the study of Tesh et al., (1986) but not in the study of York (1997b). These findings probably represent either delays or variability in the ossification of the ilia, the relative position of the iliac crest, and the degree of ossification of the sacral vertebrae or processing artefacts such as the degree of staining and/or realignment of the pelvis. The degree of ossification may have been reduced by poor maternal health in the first study. No difference in the degree of ossification at the sites evaluated was noted by York.

### Comments

Thiophanate-methyl was rapidly absorbed in rats after oral administration. The extent of absorption may be dose-dependent, decreasing with increasing dose; a study of biliary excretion would be useful to confirm this hypothesis. The highest residual levels occurred in the liver, thyroid, and kidneys. The elimination of thiophanate-methyl was rapid, with more than 90% in the urine and faeces within 24 h of administration. There was a shift towards faecal elimination between the low and high doses and after repeated doses. There was no indication of potential bioaccumulation. The major urinary metabolite was 5-hydroxycarbendazim sulfate (21–42%); 5-hydroxycarbendazim and 4-hydroxythiophanate-methyl each represented approximately 2% of the radiolabel. The major faecal metabolites were 4-hydroxythiophanate-methyl (6–10%) and 5-hydroxycarbendazim (2–5%); carbendazim (2–3%) was also found. Unchanged thiophanate-methyl accounted for approximately 20–24% and 50% of the administered radiolabel after repeated low and high doses, respectively. In plants, unchanged thiophanate-methyl and carbendazim accounted for approximately 60 and 30% of the residue respectively, 7–14 days after treatment.

WHO has classified thiophanate-methyl as unlikely to present an acute hazard in normal use (WHO, 1996).

In a study of developmental toxicity in rabbits, thiophanate-methyl was administered by gavage at 0, 5, 10, 20, or 40 mg/kg bw per day. The NOAEL for maternal toxicity was 10 mg/kg bw per day, as doses at and above 20 mg/kg bw per day caused transient but significant reductions in

maternal body-weight gain and feed consumption. Additionally, faecal output was reduced at 40 mg/kg bw per day. The NOAEL for developmental toxicity was 20 mg/kg bw per day, as the incidence of supernumerary thoracic ribs was increased at 40 mg/kg bw per day, a variation that occurred only at the higher of two maternally toxic doses. Thiophanate-methyl did not affect embryonic or fetal viability, growth, or morphology and was not teratogenic.

In the study of developmental toxicity in rabbits reviewed by the 1995 Joint Meeting, the NOAEL for maternal and developmental toxicity was 2 mg/kg bw per day, on the basis of reduced maternal body-weight gain and treatment-related increased incidences of supernumerary ribs, ribs thickened at the costal cartilage, incomplete or asymmetric ossification of costal elements of sacral vertebrae, 27 presacral vertebrae, and asymmetric pelvises at 6 and 20 mg/kg bw per day. Because of reporting deficiencies, compromised maternal health, and an unacceptably small number of litters available for analysis, the present Meeting concluded that the status of this study should be reduced to that of a range-finding study. The new study submitted to the present Meeting was considered to be more appropriate for the identification of the NOAEL for developmental toxicity in rabbits, as modern methods were used, the reporting was adequate, and the population of rabbits was larger and healthier.

A two-generation study of reproductive toxicity in rats was evaluated by the 1995 Joint Meeting, which considered 10 mg/kg bw per day to be the LOAEL for parental toxicity; however, after re-examining this study, the present Meeting concluded that 10 mg/kg bw per day should be considered the NOAEL. The effects in the liver observed in all treated groups were considered to be non-adverse at this dose, and the slight changes in the thyroid occurred in the absence of a measurable effect on thyroid hormones.

An ADI of 0–0.08 mg/kg bw per day was established on the basis of the NOAEL of 8 mg/kg bw per day in a three-generation study of reproductive toxicity in rats and in a one-year study in dogs, both of which were evaluated at earlier meetings, and a safety factor of 100.

The Meeting concluded that an acute RfD was not required because thiophanate-methyl is of low acute toxicity when administered orally or dermally and is only slightly toxic when administered by inhalation. The Meeting concluded that the acute intake of residues is unlikely to present a risk to consumers.

Although the toxicities of thiophanate-methyl and carbendazim are qualitatively different, carbendazim is an important metabolite in plants but a minor metabolite in animals. The risk assessment for residues in plants and plant products should therefore include consideration of both thiophanate-methyl and carbendazim. The ADI for the latter, established by the 1995 JMPR, is 0–0.03 mg/kg bw.

## Toxicological evaluation

### *Levels that cause no toxic effect*

Mouse:	150 ppm, equal to 29 mg/kg bw per day (18-month study of toxicity and carcinogenicity) 1000 mg/kg bw per day (maternal toxicity and teratogenicity in study of reproductive toxicity) 500 mg/kg bw per day (study of developmental toxicity)
Rat:	200 ppm, equal to 9 mg/kg bw per day (two-year study of toxicity and carcinogenicity) 160 ppm, equivalent to 8 mg/kg bw per day (study of reproductive toxicity) 1000 mg/kg bw per day (study of developmental toxicity) 300 mg/kg bw per day (maternal toxicity in a study of developmental toxicity)
Rabbit:	10 mg/kg bw per day (maternal toxicity in a study of developmental toxicity) 20 mg/kg bw per day (teratogenicity and fetotoxicity in a study of developmental toxicity)
Dog:	10 mg/kg bw per day (studies of toxicity of up to two years)

*Estimate of acceptable daily intake for humans*

0–0.08 mg/kg bw

*Estimate of acute reference dose*

Not allocated (unnecessary)

*Studies that would provide information useful for continued evaluation of the compound*

1. Study of excretion in the bile
2. Further observations on humans

**List of relevant end-points for setting guidance values for dietary and non-dietary exposure***Absorption, distribution, excretion and metabolism in mammals*

Rate and extent of absorption	Rapid (~70% by urinary excretion, 96 h)
Dermal absorption	No data
Distribution	Thyroid, liver, kidney
Potential for accumulation	No indication of bioaccumulation
Rate and extent of excretion	Rapid/complete, > 90% within 24 h
Metabolism in animals	Predominantly metabolized (71–88%)
Toxicologically significant compounds (animals, plants and environment)	Urine (rats): 5-hydroxy-carbendazim sulfate, 5-hydroxy-carbendazim and 4-hydroxy-thiophanate-methyl Faeces (rats): 4-hydroxy-thiophanate-methyl and 5-hydroxy-carbendazim Plants: unchanged thiophanate-methyl and carbendazim

*Acute toxicity*

Rat: LD <sub>50</sub> oral	7000 mg/kg bw
Rabbit: LD <sub>50</sub> dermal	> 10 000 mg/kg bw
Rat: LC <sub>50</sub> inhalation	1.8 mg/L air
Skin irritation	Not irritating
Eye irritation	Mildly irritating
Skin sensitization	Sensitizing (maximization test) Not sensitizing (Buehler test)

*Short-term toxicity*

Target/critical effect	Thyroid, liver: hypertrophy of thyroid epithelium, increased thyroid and liver weights (rats, dogs); increased liver weight (mice)
Lowest relevant oral NOAEL/NOEL	Dog: 10 mg/kg bw per day (capsule, overall NOAEL)
Lowest relevant dermal NOAEL/NOEL	No data
Lowest relevant inhalation NOAEL/NOEL	No data

*Genotoxicity*

Not mutagenic, weak aneugenic potential

*Long-term toxicity and carcinogenicity*

Target/critical effect	Thyroid hyperplasia, increased thyroid-stimulating hormone, decreased thyroxine (rats, dogs); thyroid adenoma (rats); hepatocellular adenoma (mice)
Lowest relevant NOAEL/NOEL	Dog: 8 mg/kg bw per day (1 year)
Carcinogenicity	Hepatocellular adenoma (mice); thyroid adenoma (rats) at high doses

*Reproductive toxicity*

Reproduction target/critical effect	Increased ovary/testis weights (no histological findings)
Lowest relevant reproductive NOAEL/NOEL	Rat: 8 mg/kg bw per day (decreased litter size, reduced pup body-weight gain in F <sub>1</sub> , F <sub>2</sub> , F <sub>3</sub> )

Developmental target/critical effect	Supernumerary ribs (rabbit); not teratogenic in rat or rabbit
Lowest relevant developmental NOAEL/NOEL	Rabbit: 20 mg/kg bw per day
<i>Neurotoxicity/Delayed neurotoxicity</i>	No data. No indication of neurotoxic potential in other studies
<i>Other toxicological studies</i>	
Mechanistic studies	Inhibition of thyroid microsomal peroxidase involved in thyroid hormone synthesis
<i>Medical data</i>	No adverse effects on health of personnel involved in manufacturing process

<i>Summary</i>	<i>Value</i>	<i>Study</i>	<i>Safety factor</i>
ADI	0–0.08 mg/kg bw	3-generation, rat; 1 year, dog	100
Acute reference dose	Not allocated (unnecessary)		

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