

5.36 THIOPHANATE-METHYL (077)

TOXICOLOGY

Thiophanate-methyl is the International Organization for Standardization (ISO)–approved common name for dimethyl 4,4'-(*o*-phenylene)bis(3-thioallophanate) (International Union of Pure and Applied Chemistry [IUPAC]), which has the Chemical Abstracts Service (CAS) number 23564-05-8. Thiophanate-methyl is a systemically active benzimidazole fungicide that inhibits the synthesis of β -tubulin. Thiophanate-methyl was previously evaluated by the Joint Meeting on Pesticide Residues (JMPR) in 1973, 1975, 1977, 1995, 1998 and 2006. In 1998, an acceptable daily intake (ADI) of 0–0.08 mg/kg body weight (bw) was established based on the no-observed-adverse-effect level (NOAEL) of 8 mg/kg bw per day in a three-generation study of reproductive toxicity in rats and in a 1-year study in dogs (both of these studies have been evaluated at earlier meetings) and a safety factor of 100. In 2006, the Meeting concluded that it was not necessary to establish an acute reference dose (ARfD) for thiophanate-methyl.

Thiophanate-methyl was re-evaluated by the present Meeting as part of the periodic review programme of the Codex Committee on Pesticide Residues (CCPR). Both new toxicity studies with thiophanate-methyl and previously submitted studies were considered by the present Meeting. No toxicological data were submitted on carbendazim.

All critical studies contained statements of compliance with good laboratory practice (GLP) and were conducted in accordance with the relevant Organisation for Economic Co-operation and Development (OECD) test guidelines or similar guidelines of the European Union or United States Environmental Protection Agency, unless otherwise indicated.

Biochemical aspects

Thiophanate-methyl is rapidly and almost completely absorbed (88–89%) after oral administration of a dose of 14 mg/kg bw. Thiophanate-methyl is rapidly excreted (approximately 47% in urine and approximately 40% in bile) within 48 hours of administration. Plasma half-lives were 1.6–2.8 hours after a dose of 13 mg/kg bw and 2.4–7.8 hours after a dose of 140–170 mg/kg bw. Absorption and excretion patterns were similar in male and female rats. There is no potential for accumulation. Thiophanate-methyl is widely distributed, with highest levels in liver and thyroid. The major urinary metabolite was 5-hydroxycarbendazim sulfate (5-OH-MBC-S). Minor metabolites were 5- and 4-hydroxythiophanate-methyl, each representing approximately 2% of the administered radiolabel. The major faecal metabolites were 4-hydroxythiophanate-methyl (6–10%), 5-OH-MBC-S (2–5%) and carbendazim (2–3%). Unchanged thiophanate-methyl accounted for approximately 20–24% and 50% of the administered radiolabel after repeated low and high doses, respectively.

Toxicological data

In rats, the oral median lethal dose (LD₅₀) was greater than 5000 mg/kg bw, the dermal LD₅₀ was greater than 2000 mg/kg bw and the inhalation median lethal concentration (LC₅₀) was 1.7–1.98 mg/L. Thiophanate-methyl was not irritating to the skin or the eyes of rabbits. Thiophanate-methyl was a skin sensitizer in a Magnusson and Kligman test in guinea-pigs, but not in a Buehler test.

In repeated-dose oral toxicity studies with thiophanate-methyl in mice, rats and dogs, the most sensitive organs were the liver and thyroid.

In a pre-guideline 6-month dietary toxicity study (with limited investigations) in mice administered dietary thiophanate-methyl concentrations of 0, 12.8, 64, 320, 1600 or 8000 parts per million (ppm; equal to 0, 2, 10, 50, 250 and 1240 mg/kg bw per day in males and 0, 2, 11, 52, 231 and 1630 mg/kg bw per day in females, respectively), the NOAEL was 1600 ppm (equal to 231 mg/kg bw per day) based on decreased body weight gain and haematological changes indicative of slight anaemia in males and females at 8000 ppm (equal to 1240 mg/kg bw per day).

In a 13-week dietary toxicity study in rats administered dietary thiophanate-methyl concentrations of 0, 200, 2200, 4200, 6200 or 8200 ppm (equal to 0, 13.9, 155, 293, 427 and 565 mg/kg bw per day for males and 0, 15.7, 173, 323, 479 and 647 mg/kg bw per day for females, respectively), the NOAEL was 200 ppm (equal to 13.9 mg/kg bw per day) based on haematological changes indicative of slight anaemia, increased thyroid and liver weights, follicular hyperplasia and hypertrophy of the thyroid and hepatocellular hypertrophy and increased lipofuscin pigment in both sexes and increased severity of glomerulonephrosis in males observed at 2200 ppm (equal to 155 mg/kg bw per day).

In a pre-guideline 6-month dietary toxicity study (with limited investigations) in rats administered dietary thiophanate-methyl concentrations of 0, 12.8, 64, 320, 1600 and 8000 ppm (equal to 0, 1, 4, 20, 95 and 500 mg/kg bw per day in males and 0, 1, 5, 22, 110 and 660 mg/kg bw per day in females, respectively), the NOAEL was 1600 ppm (equal to 95 mg/kg bw per day) based on decreased body weight gain, haematological changes indicative of slight anaemia, decreased glucose levels and increased cholesterol levels, increased thyroid weights and histological changes in the thyroid in males and females at 8000 ppm (equal to 500 mg/kg bw per day).

In a 3-month toxicity study in dogs, administering thiophanate-methyl by gelatin capsule at doses of 0, 50, 200 and 800/400 mg/kg bw per day, the lowest-observed-adverse-effect level (LOAEL) was 50 mg/kg bw per day based on the hypertrophy of the follicular epithelial cells of the thyroid at this dose level.

In a 1-year toxicity study in dogs administered thiophanate-methyl by gelatin capsule at doses of 0, 8, 40 or 200 mg/kg bw per day, the NOAEL was 8 mg/kg bw per day based on effects on thyroid weight in both sexes and minimal to moderate hypertrophy of the follicular epithelium of the thyroid gland of females observed at 40 mg/kg bw per day.

In a pre-guideline 2-year toxicity study (with limited investigations) in dogs administered thiophanate-methyl by gelatin capsule at doses of 0, 2, 10, 50 or 250 mg/kg bw per day, the NOAEL was 10 mg/kg bw per day based on effects on thyroid weight and histopathology of the thyroid in both sexes at 50 mg/kg bw per day.

The overall NOAEL for the studies in dogs was 10 mg/kg bw per day, and the overall LOAEL was 40 mg/kg bw per day.

In a pre-guideline 2-year dietary carcinogenicity study (with limited investigations) in mice administered dietary thiophanate-methyl concentrations of 0, 10, 40, 160 and 640 ppm (equal to 0, 1.2, 4.4, 20 and 82 mg/kg bw per day for males and 0, 1.3, 5.0, 19 and 82 mg/kg bw per day for females, respectively), the NOAEL was 160 ppm (equal to 20 mg/kg bw per day) based on reduced body weight gain and histopathological changes in testes of males at 640 ppm (equal to 82 mg/kg bw per day).

In an 18-month dietary carcinogenicity study in mice administered dietary thiophanate-methyl concentrations of 0, 150, 640, 3000 or 7000 ppm (equal to 0, 24, 99, 468 and 1079 mg/kg bw per day for males and 0, 29, 123, 558 and 1329 mg/kg bw per day for females, respectively), the NOAEL was 150 ppm (equal to 29 mg/kg bw per day) based on the hepatocellular centrilobular hypertrophy at 9 months and hepatocellular adenomas in females observed at 640 ppm (equal to 123 mg/kg bw per day).

In a 2-year combined chronic toxicity/carcinogenicity study in rats administered dietary thiophanate-methyl concentrations of 0, 75, 200, 1200 or 6000 ppm (equal to 0, 3.3, 8.8, 54 and 281 mg/kg bw per day for males and 0, 3.8, 10.2, 64 and 335 mg/kg bw per day for females, respectively), the NOAEL was 200 ppm (equal to 8.8 mg/kg bw per day) based on reduced body weight gain in both sexes; increased total cholesterol and total protein in both sexes; decreased albumin/globulin ratio in both sexes at 12 and/or 18 months; decreased levels of chloride and potassium; decreased thyroxine (T₄) and triiodothyronine (T₃) and increased thyroid-stimulating hormone (TSH) in males at 24 months; increased urinary protein and granular kidneys in males; follicular cell hyperplasia and hypertrophy in the thyroid in both sexes at 12 and 24 months; a possible increase in the incidence of thyroid follicular cell adenoma in males; centrilobular hepatocellular

hypertrophy and occurrence of lipofuscin pigment in both sexes at 12 and 24 months; lipidosis of the adrenal cortex in females at 12 months; and increased severity of nephropathy in both sexes at 24 months observed at 1200 ppm (equal to 54 mg/kg bw per day). In males, the incidence of thyroid follicular cell adenoma was increased at 1200 ppm and above, but reached statistical significance only at 6000 ppm.

A mechanistic study showed that thiophanate-methyl induced cytochromes CYP450 (not further specified) and CYPb5 and UDP-glucuronosyltransferase (UGT), an enzyme that plays an important role in the clearance of T₄ in the liver. Thiophanate-methyl also inhibited porcine thyroid microsomal peroxidase, an enzyme involved in thyroid hormone synthesis. T₄ supplementation counteracted the hypertrophy of the thyroid and the TSH response, indicating that thiophanate-methyl caused the hypertrophy by negative feedback mechanism. The mechanistic study demonstrates that the thyroid effects resulting from thiophanate-methyl are likely to be the result of a reduction in thyroid hormones. In another study, thiophanate-methyl induced increases in CYP3A and CYP2B1 in the liver of rats.

The Meeting concluded that thiophanate-methyl is carcinogenic in mice and rats. The Meeting considered the different modes of action that might underlie the observed tumour induction. The effects on the thyroid, including the induction of thyroid follicular cell adenoma may be secondary effects resulting from liver enzyme induction that enhances thyroid hormone excretion and leads to perturbations in systemic thyroid hormone levels (i.e. decreased thyroid T₄ and T₃ hormone values and, as a consequence, an increase in TSH concentration). The continuous stimulation of the thyroid gland by TSH is known to result in follicular cell hypertrophy/hyperplasia and, depending on dose and time, in follicular cell adenomas/adenocarcinomas. Rats are particularly sensitive to decreases in T₄ and T₃ levels resulting from liver enzyme induction; these reductions eventually lead to thyroid tumour formation. This is a well-established adverse outcome pathway without relevance for humans. The thiophanate-methyl-induced increase in hepatocellular adenomas may be a consequence of activation of nuclear receptors involved in the induction of the cytochrome P450 drug metabolizing system. Another possible mode of action for the carcinogenic effect may be the interference of the thiophanate-methyl metabolite carbendazim with mitotic spindle proteins leading to aneuploidy (see below).

Thiophanate-methyl was tested in an adequate range of *in vitro* and *in vivo* assays for genotoxicity. Thiophanate-methyl does not cause gene mutations or structural chromosomal aberrations; however, it causes changes in chromosome number (aneuploidy) both *in vitro* and *in vivo*. Induction of micronucleus formation in mice was seen after single doses (500 mg/kg bw and above), but the response was weak (about six times lower) when compared with that for the metabolite of thiophanate-methyl, carbendazim.

Carbendazim causes changes in chromosome number (aneuploidy) both *in vitro* and *in vivo* (in somatic cells and germ cells) as a result of its interference with mitotic spindle proteins. The mechanism by which aneuploidy is induced by carbendazim is well understood and consists of inhibition of the polymerization of tubulin, the protein that is essential for the segregation of the chromosomes during cell division. The nature of the mechanism is thus consistent with the identification of a threshold dose below which no toxicological effect would occur. Like thiophanate-methyl, carbendazim does not cause gene mutations or structural chromosomal aberrations.

The Meeting concluded that the genotoxic effect of thiophanate-methyl is a threshold phenomenon and is likely related to the production of carbendazim.

The Meeting concluded that thiophanate-methyl is unlikely to pose a carcinogenic risk to humans at dietary doses.

In a two-generation dietary reproductive toxicity study in rats administered thiophanate-methyl at dietary doses of 0, 200, 630 or 2000 ppm (equal to pre-mating doses of 0, 14.6, 46.0 and 147.1 mg/kg bw per day in males and 16.8, 52.2 and 164.3 mg/kg bw per day in females, respectively), the NOAEL for parental toxicity was 200 ppm (equal to 14.6 mg/kg bw per day) based on thyroid hyperplasia in males and increased TSH levels in females at 630 ppm (equal to 46 mg/kg

bw per day). The NOAEL for offspring toxicity was 200 ppm (equal to 16.8 mg/kg bw per day) based on decreased body weights (in F_{2b}) during lactation at 630 ppm (equal to 52.2 mg/kg bw per day). The NOAEL for reproductive toxicity was 2000 ppm (equal to 147 mg/kg bw per day), the highest dose tested.

In a developmental toxicity study in rats administered gavage doses of thiophanate-methyl of 0, 100, 300 or 1000 mg/kg bw per day, the NOAEL for maternal toxicity was 300 mg/kg bw per day based on a reduced body weight gain at 1000 mg/kg bw per day. The NOAEL for embryo/fetal toxicity was 1000 mg/kg bw per day, the highest dose tested.

In a developmental toxicity study in rabbits administered gavage doses of thiophanate-methyl of 0, 5, 10, 20 and 40 mg/kg bw per day, the NOAEL for maternal toxicity was 10 mg/kg bw per day based on a reduced body weight gain at 20 mg/kg bw per day. The NOAEL for embryo/fetal toxicity was 20 mg/kg bw per day based on supernumerary thoracic ribs at 40 mg/kg bw per day. This effect was considered unlikely to be an effect of a single dose.

The Meeting concluded that thiophanate-methyl is not teratogenic.

In a study of acute neurotoxicity in rats administered gavage doses of thiophanate-methyl of 0, 50, 125, 500, 1000 or 2000 mg/kg bw, the NOAEL for general toxicity was 125 mg/kg bw based on transient reductions in body weight gains (including body weight losses) and feed consumption at 500 mg/kg bw. The NOAEL for neurotoxicity was 2000 mg/kg bw, the highest dose tested.

In a 13-week study of neurotoxicity in rats administered thiophanate-methyl at dietary doses of 0, 100, 500 or 2500 ppm (equal to 0, 6.2, 30 and 150 mg/kg bw per day for males and 0, 6.8, 35 and 166 mg/kg bw per day for females, respectively), the NOAEL for general toxicity was 500 ppm (equal to 30 mg/kg bw per day) based on decreased body weights and feed consumption in females and increased liver and thyroid weights in both sexes at 2500 ppm (equal to 150 mg/kg bw per day). The NOAEL for neurotoxicity was 2500 ppm (equal to 150 mg/kg bw per day), the highest dose tested.

The Meeting concluded that thiophanate-methyl is not neurotoxic.

No immunotoxicity tests with thiophanate-methyl were available. However, the data from the available toxicity studies did not indicate an immunotoxic potential of thiophanate-methyl.

The Meeting concluded that thiophanate-methyl is unlikely to be immunotoxic.

Toxicological data on metabolites and/or degradates

Studies of acute oral toxicity and genotoxicity were performed with metabolites and impurities of thiophanate-methyl. For DX-105, a photodegradation product and a metabolite also found in mice and rats, the acute oral toxicity LD₅₀ was greater than 5000 mg/kg bw; for the impurities of technical thiophanate-methyl DX-189 and FH-613 the acute oral toxicity LD₅₀ was 5000 and 1776 mg/kg bw, respectively; and for CM-0237, a major plant metabolite, the acute oral toxicity LD₅₀ was greater than 2000 mg/kg bw. In addition, a very concise report was available that indicated that the animal metabolites FH624, CF-44 and FH-622, the plant and animal metabolites FH-432 and FH-278, and the impurities TFY-61, FH-46, AV-1951 and FH-73 have low acute toxicity in mouse and/or rat. Negative results in an in vitro bacterial gene mutation test were obtained for CM-0237 and for FH-37, a plant metabolite of thiophanate-methyl.

The major residues in crops and livestock were thiophanate-methyl, carbendazim, 5-OH-MBC and 5-OH-MBC-S.

Carbendazim itself is used as a pesticide, and JMPR established an ADI in 1995 and an ARfD in 2005. No specific toxicity studies on the metabolites 5-OH-MBC and 5-OH-MBC-S of thiophanate-methyl, which are also metabolites of carbendazim, were available. However, 5-OH-MBC-S was found in rats at more than 40% of the absorbed dose in a toxicokinetic study with thiophanate-methyl and at 21–43% of the absorbed dose in a toxicokinetic study with carbendazim. 5-OH-MBC is an intermediate in the metabolic pathway leading to the formation of 5-OH-MBC-S. The

toxicity of the rat metabolites 5-OH-MBC and 5-OH-MBC-S is therefore considered to be covered by that of thiophanate-methyl and carbendazim.

Human data

Thiophanate-methyl has been commercially produced since 1969. No health effects related to thiophanate-methyl have been reported in manufacturing plant personnel or from agricultural use.

The Meeting concluded that the existing database on thiophanate-methyl was adequate to characterize the potential hazards to the general population, including fetuses, infants and children.

Toxicological evaluation

Thiophanate-methyl

The Meeting established an ADI of 0–0.09 mg/kg bw for thiophanate-methyl on the basis of a NOAEL of 8.8 mg/kg bw per day based on reduction in body weight gain and clinical chemistry, urine analysis and histopathological changes in the kidney, thyroid, liver and adrenals in a 2-year study in rats. This ADI is supported by the overall NOAEL of 10 mg/kg bw per day based on increased thyroid weight and histopathological changes in the thyroid observed in 3-month, 1-year and 2-year toxicity studies in dogs. A safety factor of 100 was used.

The upper bound of the ADI provides a margin of exposure of 600 relative to the LOAEL for thyroid follicular cell adenoma in male rats (54 mg/kg bw per day) and about 3100 relative to the LOAEL for hepatocellular adenomas in female mice (280 mg/kg bw per day).

The Meeting established an ARfD of 1 mg/kg bw for thiophanate-methyl on the basis of a NOAEL of 125 mg/kg bw for transient reductions in body weight gains (including body weight losses) and feed consumption in an acute neurotoxicity study in rats, using a safety factor of 100.

Carbendazim

Since plant and food residues are expressed as carbendazim, the ADI and ARfD established for that compound must be taken into consideration.

No toxicological studies on carbendazim were available for the present evaluation.

JMPR last evaluated carbendazim to establish an ADI in 1995. The Meeting established an ADI of 0–0.03 mg/kg bw based on a NOAEL of 2.5 mg/kg bw per day, on the basis of hepatotoxicity observed at 12.5 mg/kg bw per day in a 2-year study in dogs. A safety factor of 100 was applied.

The need for an ARfD for carbendazim was considered in 2005. At that time the Meeting established an ARfD of 0.1 mg/kg bw based on an overall NOAEL of 10 mg/kg bw per day for developmental toxicity from three studies in rats and one study in rabbits, and a safety factor of 100. The 2005 Meeting concluded that this ARfD applies only to women of childbearing age.

For the general population, including children, the Meeting established an ARfD of 0.5 mg/kg bw based on the NOAEL of 50 mg/kg bw in the study of toxicity to the male reproductive system in rats and supported by the studies on micronucleus or aneuploidy induction in vivo, using a safety factor of 100.

An additional safety factor for the severity of the effects was considered to be unnecessary, since the underlying mechanism is clearly understood and there is a clear threshold for these effects.

A toxicological monograph was prepared.

Levels relevant to risk assessment of thiophanate-methyl

Species	Study	Effect	NOAEL	LOAEL
Mouse	Eighteen-month study of toxicity and carcinogenicity ^a	Toxicity	150 ppm, equal to 29 mg/kg bw per day	640 ppm, equal to 123 mg/kg bw per day
		Carcinogenicity	150 ppm, equal to 29 mg/kg bw per day	640 ppm, equal to 123 mg/kg bw per day
Rat	Acute neurotoxicity study ^b	Toxicity	125 mg/kg bw	500 mg/kg bw
		Neurotoxicity	2 000 mg/kg bw ^{b,c}	–
	Thirteen-week neurotoxicity study ^a	Neurotoxicity	2 000 ppm, equal to 150 mg/kg bw per day ^{b,c}	–
	Two-year studies of toxicity and carcinogenicity ^a	Toxicity	200 ppm, equal to 8.8 mg/kg bw per day	1 200 ppm, equal to 54 mg/kg bw per day
		Carcinogenicity	200 ppm, equal to 8.8 mg/kg bw per day	1 200 ppm, equal to 54 mg/kg bw per day
	Two-generation study of reproductive toxicity ^a	Reproductive toxicity	2 000 ppm, equal to 147 mg/kg bw per day ^c	–
		Parental toxicity	200 ppm, equal to 14.6 mg/kg bw per day	630 ppm, equal to 46 mg/kg bw per day
		Offspring toxicity	200 ppm, equal to 16.8 mg/kg bw per day	630 ppm, equal to 52.2 mg/kg bw per day
	Developmental toxicity study ^b	Maternal toxicity	300 mg/kg bw per day	1 000 mg/kg bw per day
		Embryo/fetal toxicity	1 000 mg/kg bw per day ^c	–
Rabbit	Developmental toxicity study ^b	Maternal toxicity	10 mg/kg bw per day	20 mg/kg bw per day
		Embryo/fetal toxicity	20 mg/kg bw per day	40 mg/kg bw per day
Dog	Thirteen-week, 1-year and 2-year studies of toxicity ^{d,e}	Toxicity	10 mg/kg bw per day	40 mg/kg bw per day

^a Dietary administration.^b Gavage administration.^c Highest dose tested.^d Two or more studies combined.^e Capsule administration.

Estimate of acceptable daily intake (ADI)

0–0.09 mg/kg bw

Estimate of acute reference dose (ARfD)

1 mg/kg bw

Information that would be useful for the continued evaluation of the compound

Results from epidemiological, occupational health and other such observational studies of human exposure

Critical end-points for setting guidance values for exposure to thiophanate-methyl*Absorption, distribution, excretion and metabolism in mammals*

Rate and extent of oral absorption	Rapid and almost complete (rats)
Dermal absorption	≥ 53% at 0.3 mg/rat; ≥ 23% at 32 mg/rat
Distribution	Widespread distribution, highest concentrations found in liver and thyroid
Potential for accumulation	Low potential for accumulation
Rate and extent of excretion	Rapid; 87% in 48 h
Metabolism in animals	Extensively metabolized, major metabolite is 5-OH-MBC-S
Toxicologically significant compounds in animals and plants	Thiophanate-methyl, carbendazim

Acute toxicity

Rat, LD ₅₀ , oral	> 5 000 mg/kg bw
Rat, LD ₅₀ , dermal	> 2 000 mg/kg bw
Rat, LC ₅₀ , inhalation	> 1.7 mg/L
Rabbit, dermal irritation	Not irritating
Rabbit, ocular irritation	Not irritating
Guinea-pig, dermal sensitization	Sensitizing (maximization test)

Short-term studies of toxicity

Target/critical effect	Liver, thyroid, haematological effects
Lowest relevant oral NOAEL	10 mg/kg bw per day (dog)
Lowest relevant dermal NOAEL	No data
Lowest relevant inhalation NOAEC	No data

Long-term studies of toxicity and carcinogenicity

Target/critical effect	Body weight, clinical chemistry, urine analysis, histopathology of liver, thyroid, kidney, adrenal
Lowest relevant NOAEL	8.8 mg/kg bw per day (rat)
Carcinogenicity	Carcinogenic in mice and rats ^a

*Genotoxicity*Genotoxic, threshold phenomenon (aneuploidy)^a*Reproductive toxicity*

Target/critical effect	No reproductive effects
Lowest relevant parental NOAEL	14.6 mg/kg bw per day (rat)
Lowest relevant offspring NOAEL	16.8 mg/kg bw per day (rat)
Lowest relevant reproductive NOAEL	147 mg/kg bw per day, highest dose tested (rat)
<i>Developmental toxicity</i>	
Target/critical effect	Supernumerary ribs
Lowest relevant maternal NOAEL	10 mg/kg bw per day (rabbit)
Lowest relevant embryo/fetal NOAEL	20 mg/kg bw per day (rabbit)
<i>Neurotoxicity</i>	
Acute neurotoxicity NOAEL	2 000 mg/kg bw, highest dose tested (rat)
Subchronic neurotoxicity NOAEL	166 mg/kg bw per day, highest dose tested (rat)
Developmental neurotoxicity NOAEL	No data
<i>Studies on toxicologically relevant metabolites</i>	
Carbendazim	Major toxicologically relevant metabolite is carbendazim. Last evaluated by JMPR in 1995 (ADI: 0.03 mg/kg bw) with an addendum in 2005 (ARfD: 0.1 mg/kg bw).
Other metabolites	Low acute toxicity for DX-105, DX-189, FH-613 and CM-0237. Negative results in an in vitro gene mutation test for CM-0237 and FH-37
<i>Human data</i>	
No adverse effects reported	

^a Unlikely to pose a carcinogenic risk to humans via exposure from the diet.

Summary

	Value	Study	Safety factor
ADI	0–0.09 mg/kg bw	Two-year study (rats)	100
ARfD	1 mg/kg bw	Acute neurotoxicity study (rats)	100

RESIDUE AND ANALYTICAL ASPECTS

The meeting did not receive any information on the toxicology of carbendazim. The meeting was unable to complete its evaluation for residues.