5.24 TRIAZOLE FUNGICIDE METABOLITES

TOXICOLOGY

1,2,4-Triazole, triazole alanine, triazole acetic acid, triazole pyruvic acid and triazole lactic acid are the common metabolites derived from triazole-containing fungicides that act by inhibiting sterol synthesis. The levels of triazole pyruvic acid and triazole lactic acid found in metabolism studies are low, and no toxicological data on these compounds were available, therefore, they were not considered by the present Meeting. 1,2,4-Triazole, triazole alanine and triazole acetic acid are the commonly used names for IUPAC nomenclatures 1*H*-1,2,4-triazole (CAS No. 288-88-01), 1,2,4-triazolyl-3-alanine (CAS No. 10109-05-4), and 1*H*-1,2,4-triazol-l-ylacetic acid (CAS No. 28711-29-7),respectively. These three metabolites commonly occur as plant or soil metabolites and are collectively known as the "triazole derivative metabolites". Triazole alanine and triazole acetic acid residues are primarily associated with plant commodities, while 1,2,4-triazole is mainly associated with animal commodities, lesser amounts of this compound being found in plant commodities. 1,2,4-Triazole is found in studies of the metabolism of triazole fungicides in rats, where it may constitute approximately 1% to 65% of the dose, depending on the parent compound administered.

Triazole alanine was first evaluated by the JMPR in 1989. The Meeting concluded from the available data at that time that residues of triazole alanine arising from the use of triazole fungicides do not present a toxicological hazard. The Meeting has not previously evaluated 1,2,4-triazole and triazole acetic acid. These compounds were reviewed by the present Meeting at the request of CCPR and following recommendations made by the JMPR in 2007 (general consideration 2.3). A group of manufacturers of these pesticides have formed a taskforce known as the "Triazole Derivative Metabolite Group" (TDMG) and made a joint submission of toxicological data to the JMPR. All pivotal studies with triazole alanine and triazole acetic acid were certified as complying with GLP, unless otherwise stated in the toxicological monograph.

The toxicological database for 1,2,4-triazole was sufficient for the evaluation of this compound, while the toxicological databases for triazole alanine and triazole acetic acid were more limited. The Meeting concluded that adequate studies were available to establish an ADI for 1,2,4-triazole and a group ADI for triazole alanine and triazole acetic acid. This decision was based on the following considerations:

— The chemical structures of triazole alanine and triazole acetic acid are closely related and the two substances have similar physicochemical characteristics.

— Both triazole alanine and triazole acetic acid have the 1,2,4-triazole active (protonated) nitrogen bonded to carbon, which significantly reduces the toxicity of triazole alanine and triazole acetic acid.

— The available toxicological data suggest that triazole alanine and triazole acetic acid are less toxic than 1,2,4-triazole.

— Triazole alanine and triazole acetic acid have similar toxicokinetic profiles in that they are rapidly eliminated, primarily in the urine and mostly as the parent compound.

The Meeting recommended that the ADI and ARfD values established for these triazole metabolites may be used in risk assessment on a case-by-case basis, depending on the residue and toxicity profile of the parent compound. The Meeting also noted that these values may also be useful in a combined risk assessment, depending on the exposure situation, including whether exposure to these metabolites comes from more than one source of the parent conazoles.

1,2,4-TRIAZOLE

Biochemical aspects

In rats treated orally, radiolabelled 1,2,4-triazole was rapidly and completely absorbed and excreted mostly unchanged and mainly in the urine (80–94%) in first 24 h, irrespective of dose or route of administration. Approximately 0.1% of the administered dose was recovered within 30 h in expired air after oral and intravenous administration. Approximately 3 to 5% of the administered dose was recovered in faeces in 48 h. Approximately 2% of the administered dose was recovered in the gastrointestinal tract at 48 h. In bile-duct-fistulated rats, approximately 12% of the dose was recovered in the bile at 24 h after intravenous or in traduodenal application.

Toxicological data

1,2,4-Triazole is of moderate toxicity when administered orally. The LD_{50} in rats treated orally was 1648 mg/kg bw. The LD_{50} in rats treated dermally was 3129 mg/kg bw. 1,2,4-Triazole appears to be more toxic dermally in rabbits than in rats. The dermal LD_{50} in rabbits was > 200 and < 2000 mg/kg bw. It is slightly irritating to the skin and severely irritating to the eyes of rabbits. It is not a skin sensitizer as determined by Magnusson & Kligman (maximization) test in guinea-pigs. The following clinical signs were observed after oral dosing: sedation, breathing difficulties, reduction in general well-being, hunched posture (at higher doses). These signs appeared within 1 h of administration and were observed for a maximum of 13 days after administration. Similar clinical signs were observed in rats treated dermally.

In short-term studies in mice and rats, neurotoxicity was seen in number of studies. In a 28-day toxicity study in mice, the only treatment-related effects were slight testicular degeneration accompanied by apoptotic bodies at 2000 ppm, equal to 356 mg/kg bw per day (the LOAEL). No effects were observed in females at doses up to and including 2000 ppm, equal to 479 mg/kg bw per day. The NOAEL in mice was 500 ppm, equal to 90 mg/kg bw per day.

In a 90-day study of toxicity in mice, decreased body weights, tremors (observed from day 30), decreased body weight, and loss of cerebellar Purkinje cells were observed in males and females at 6000 ppm, equal to 988 mg/kg bw per day. At 6000 ppm (the highest dose), 9 out of 11 males showing tremors also had Purkinje cell loss, while in females at this highest dose one out of three mice with tremors had Purkinje cell loss. Decreased testicular weights and histopathological findings in testes similar to the 28-day study were observed in males at 3000 and 6000 ppm. The NOAEL was 1000 ppm, equal to 161 mg/kg bw per day, on the basis of tremors, decreased brain weights, decreased testicular weights and histopathological changes in the testes seen in males at the LOAEL of 3000 ppm, equal to 487 mg/kg bw per day.

In a 90-day dietary study of toxicity in rats, retarded body-weight development, transient effects on the central nervous system, lower erythrocyte parameters (microcytic hypochromic erythrocytes, in males only) and hepatocellular fat accumulation (males only) were observed at 2500 ppm, equivalent to 212.3 mg/kg bw per day. The NOAEL was 500 ppm, equivalent to 37.9 mg/kg bw per day. In a combined short-term study of toxicity and neurotoxicity in rats, FOB effects were observed at 3000 ppm and 1000/4000 (equal to 183 and 210 mg/kg per day, respectively) and with increased incidence and severity at week 8. Males were more severely affected than females. Other effects observed were ungroomed appearance, red nasal and lachrymal stain, yellow urine stain, muscle fasciculations, tremors, gait incoordination, decreased activity in the open field, decreased rearing, uncoordinated righting reflex and increased foot splay. A decrease in motor and locomotor activity was also observed in males at 3000 ppm during week 4 only. Decreases in absolute brain weights and degenerative lesions were seen in the cerebellum, the lumbar dorsal root ganglion and other peripheral nerves at 3000 ppm and at 1000/4000 ppm. The brain lesions were

limited to the anterior, dorsal cerebellum and were coded overall as an increased incidence of cellular degeneration and necrosis. Findings were characterized by extensive loss of Purkinje cells, variable white-matter degeneration and gliosis. Subtle atrophy of the molecular layer, primarily at the cerebellar surface, or loss of granule cells was occasionally present. The NOAEL was 500 ppm, equal to 33 mg/kg bw per day, on the basis of decreased body weight and body-weight gain, tremor and incoordination, decreased absolute brain weight, and increased incidence of neuropathology findings in the peripheral and central nervous system at the LOAEL of 3000 ppm, equal to 183 mg/kg bw per day.

1,2,4-Triazole gave negative results in a battery of assays for genotoxicity, including the Ames test in vitro, an assay for forward mutation, and a test for chromosomal aberration.

The Meeting concluded that 1,2,4-triazole is unlikely to be genotoxic.

No studies of carcinogenicity were submitted. However, the Meeting considered that 1,2,4-triazole is unlikely to be carcinogenic at anticipated levels of exposure since it does not bioaccumulate in the body, it is non-mutagenic, and because of the absence of pre-neoplastic changes with 1,2,4-triazole at high doses.

In a two-generation study of reproductive toxicity in rats, decreased body weights were observed in F_1 males at 250 ppm, equal to 16 mg/kg bw per day, the lowest dose tested. These changes in body weight were minor and were seen only in males and in only one generation and were not seen in short-term studies in rats given at doses. At 3000 ppm, parental animals (F_0) had statistically significantly reduced terminal body weights, and decreased absolute brain weights associated with mild to moderate degeneration/necrosis in the cerebellum. No F_1 offspring at the highest dose survived the lactation period. No offspring toxicity was observed at doses up to 500 ppm, equal to 30.9 mg/kg bw per day. The NOAEL for reproductive toxicity with 1,2,4-triazole was 250 ppm, equal to 16 mg/kg bw per day, on the basis of an increase in abnormal sperm in F_0 and F_1 males seen at the LOAEL of 500 ppm.

In two studies of developmental toxicity in rats, there was maternal toxicity (retarded weight gain) at 100 mg/kg bw per day or higher, developmental toxicity (decreased body weights, lower fetal and placental weights, and a higher incidence of minor skeletal deviations) at 100 mg/kg bw per day or higher, and an increased incidence of malformations (hydronephrosis, cleft palate, long-bone dysplasia, diaphragmatic hernia) at 200 mg/kg bw per day. The NOAEL for maternal toxicity and for developmental toxicity in rats was 30 mg/kg bw per day. In a study in rabbits, however, lower body-weight gain and clinical signs of systemic toxicity such as excess salivation, hyperpnoea and ptosis were evident at 45 mg/kg bw per day. Five out of 25 dams at this dose were sacrificed in a moribund condition. Developmental effects included lower body weights of fetuses at 45 mg/kg bw per day, and there were a few alterations in the urogenital system, which occurred in several fetuses. The NOAEL for maternal toxicity and for developmental toxicity was 30 mg/kg bw per day in rabbits.

The Meeting concluded that 1,2,4-triazole is teratogenic in rats and rabbits at maternally toxic doses.

No study of acute neurotoxicity was submitted. Clinical signs of neurotoxicity were observed in studies of acute toxicity in which very high doses were given dermally or orally. Neurotoxic effects observed in a short-term study of combined toxicity/neurotoxicity are described above.

The Meeting concluded that 1,2,4-triazole is neurotoxic.

The Meeting concluded that the existing database on 1,2,4-triazole was adequate to characterize the potential hazards to fetuses, infants and children.

Toxicological evaluation

The Meeting established an ADI of 0–0.2 mg/kg bw based on a NOAEL of 250 ppm, equal to 16 mg/kg per day, on the basis of testicular effects (sperm abnormalities, sperm counts) seen at

500 ppm, equal to 30.9 mg/kg bw per day, and using a safety factor of 100. At 250 ppm, reduced body weights and body-weight gains were observed in F_1 males; however, the Meeting noted that the reductions in body weight observed at 250 ppm were marginal (< 6%) and were seen only in one sex and in only one generation and were not seen in short-term studies with similar doses. The Meeting therefore concluded that it was not necessary to use an additional safety factor. This ADI is protective for neurotoxic effects seen at 3000 ppm, 183 mg/kg bw per day, in a short-term study of toxicity/neurotoxicity in rats in which the NOAEL was 500 ppm, equal to 33 mg/kg bw per day. The Meeting considered that it was not necessary to add an additional safety factor to allow for the lack of studies of carcinogenicity because 1,2,4-triazole is unlikely to be carcinogenic at anticipated levels of exposure since it does not bioaccumulate in the body, it is non-mutagenic, and because of the absence of pre-neoplastic changes at high doses.

The Meeting established an ARfD of 0.3 mg/kg bw based on a NOAEL of 30 mg/kg bw per day, identified on the basis of alterations of the urogenital system that occurred in several fetuses at the LOAEL of 45 mg/kg bw per day and clinical signs of neurotoxicity in the dams in a study of developmental toxicity in rabbits, and using a safety factor of 100.

A toxicological monograph was prepared.

Levels relevant to risk assessment

Species	Study	Effect	NOAEL	LOAEL
Mouse	90-day study of toxicity[a]	Toxicity	1000 ppm, equal to 161 mg/kg bw per day	3000 ppm, equal to 487 mg/kg bw per day
Rat	90-day study of toxicity[a]	Toxicity	500 ppm, equal to 33 mg/kg bw per day	3000 ppm, equal to 183 mg/kg bw per day
	Multigeneration study of reproductive toxicity[a]	Parental toxicity	250 ppm, equal to 16.0 mg/kg bw per day[d]	500 ppm, equal to 31 mg/kg bw per day[c]
		Offspring toxicity	500 ppm, equal to 31 mg/kg bw per day[c]	—
	Developmental toxicity[b]	Maternal toxicity	30 mg/kg bw per day	100 mg/kg bw per day
		Embryo and fetal toxicity	30 mg/kg bw per day	100 mg/kg bw per day
Rabbit	Developmental toxicity[b]	Maternal toxicity	30 mg/kg bw per day	45 mg/kg bw per day[c]
		Embryo and fetal toxicity	30 mg/kg bw per day	45 mg/kg bw per day[c]

[a] Dietary administration.

[b] Gavage administration.

[c] Highest dose tested.

[d] Marginal effects on body weight, only seen in F_1 males.

Estimate of acceptable daily intake for humans

0–0.2 mg/kg bw per day

Estimate of acute reference dose

0.3 mg/kg bw

Information that would be useful for continued evaluation of the compound

Results from epidemiological and other such observational studies of human exposures

Critical end-points for setting guidance values for exposure to 1,2,4-triazole

Absorption, distribution, excretion, and metabolism in mammals	
Rate and extent of oral absorption	Rapid and nearly complete absorption
Distribution	Widely distributed in tissues
Potential for accumulation	Low, no evidence of significant accumulation
Rate and extent of excretion	Approximately 80–94% of the administered dose excreted in urine in first 24 h
Metabolism in animals	No significant metabolism
Toxicologically significant compounds (animals, plants and environment)	1,2,4-triazole
Acute toxicity	
Rat, LD_{50}, oral	1650 mg/kg bw
Rat, LD_{50}, dermal	3129 mg/kg bw
Rat, LC_{50}, inhalation	No adequate data
Rabbit, dermal irritation	Slight irritation
Rabbit, ocular irritation	Severe irritation
Guinea-pig, dermal sensitization	Not a sensitizer (Magnusson & Kligman test)
Short-term studies of toxicity	
Target/critical effect	Nervous system, brain
Lowest relevant oral NOAEL	500 ppm, equal to 33 mg/kg bw per day (90-day study in rats)
Lowest relevant dermal NOAEL	No data
Lowest relevant inhalation NOAEL	No data
Genotoxicity	
	Unlikely to be genotoxic
Long-term studies of toxicity and carcinogenicity	
Target/critical effect	No data
Lowest relevant NOAEL	No data

Carcinogenicity	Unlikely to be carcinogenic
Reproductive toxicity	
Reproduction target/critical effect	Sperm abnormalities, decreases in body weights
Lowest relevant reproductive NOAEL	250 ppm, equal to 16 mg/kg bw per day
Developmental target/critical effect	Urogenital alterations in rabbits
Lowest relevant developmental NOAEL	30 mg/kg bw per day (rats and rabbits)
Neurotoxicity/delayed neurotoxicity	
Neurotoxicity	Evidence of clinical signs of neurotoxicity and cerebellum lesions
Mechanistic data	
	No studies were submitted
Medical data	
	No data

Summary

	Value	*Study*	*Safety factor*
ADI	0–0.2 mg/kg bw per day	Rat, two-generation studies of reproductive toxicity	100
ARfD	0.3 mg/kg bw	Rabbit, study of developmental toxicity	100

TRIAZOLE ALANINE AND TRIAZOLE ACETIC ACID

Biochemical aspects

In rats given a single dose of radiolabelled triazole alanine (up to 994 mg/kg bw) by gavage, almost all the administered dose was absorbed on the basis of urinary excretion (69–98%). Approximately, 3–18% of the administered dose was recovered in the faeces after 7 days. Less than 0.5% of the administered dose was recovered in the expired air. No significant bioaccumulation of triazole alanine was observed. Approximately 8–30% of the excreted dose in the urine and < 1% of the dose in faeces was identified as *N*-acetyl-D,L-triazole alanine, the remainder was parent compound.

In rats given a single dose of radiolabelled triazole acetic acid by gavage, almost all the administered dose (96–112%) was absorbed on the basis of urinary excretion. Triazole acetic acid was rapidly absorbed and excreted mainly via the urine (87–104% after 7 days). Approximately 1.2–7.4% of the administered dose was recovered in the faeces after 7 days. Total radioactivity in tissues after 7 days ranged from 0.8% to 3.1% of the administered dose. Only the parent compound was found in the urine.

Toxicological data

Triazole alanine is of low acute toxicity when administered orally. The oral LD_{50} in mice and rats was > 5000 mg/kg bw. No treatment-related clinical signs or mortalities were observed in these studies.

Triazole acetic acid is of low acute toxicity when administered orally. The oral LD_{50} in rats was > 5000 mg/kg bw. A slight to moderate increase in the incidence of dyspnoea, exophthalmos, ruffled fur, and hunched posture were observed after dosing and subsided within 10 days.

For triazole alanine, no target organ or any treatment-related toxicity was observed in short-term studies in rats and dogs, except for reduced body-weight gains observed in 90-day studies of toxicity in rats and dogs (females only). No long-term studies were submitted.

For triazole acetic acid, no target organ or any treatment-related toxicity was observed in a short-term study in rats. No long-term studies were submitted.

No treatment-related toxicity was observed in a 14-day study in rats given drinking-water containing triazole alanine at concentrations up to 10 000 ppm, equal to 1491 mg/kg bw per day. Haematological and clinical chemistry parameters were not measured in this study. No treatment-related effects were seen in the 28-day study of oral toxicity in which rats were given triazole alanine at doses of up to 400 mg/kg bw per day by oral gavage. In this study, haematological, clinical chemistry and histopathological analyses were incomplete.

In a 90-day dietary study of toxicity in rats fed triazole alanine, decreased body weight gains was observed at the highest dose of 20 000 ppm, equal to 1510 mg/kg bw per day. Small decreases in concentrations of leukocytes, triglycerides and bilirubin were observed, but were considered to be of no toxicological significance since the changes were small and may have been secondary to the decreased body weights. The NOAEL was 5000 ppm, equal to 370 mg/kg bw per day.

In a 90-day dietary study of toxicity in dogs fed triazole alanine, decreased body-weight gain and food consumption was observed in females at the highest dose of 20 000 ppm, equal to 902 mg/kg bw per day. The NOAEL was 8000 ppm, equal to 322 mg/kg bw per day.

No treatment-related toxicity was observed in a 14-day study in rats given diets containing triazole acetic acid at doses of up to 8000 ppm, equal to 703.5 mg/kg bw per day.

Triazole alanine gave negative results in a adequate battery of tests for genotoxicity in vivo and in vitro.

Triazole acetic acid gave negative results in an Ames test in vitro, and in assays for mutation or cytogenotoxicity in mammalian cells.

The Meeting concluded that triazole alanine and triazole acetic acid are unlikely to be genotoxic.

No studies of carcinogenicity were available; however, triazole alanine and triazole acetic acid are unlikely to be carcinogenic at anticipated levels of exposure since they do not bioaccumulate in the body, are non-mutagenic, are not chemically reactive, and no specific target-organ toxicity was identified in the available toxicological studies with doses of up to 1510 mg/kg bw per day.

In a non-guideline, one-generation study of reproductive toxicity in rats given triazole alanine, no systemic toxicity was seen in parental animals at doses of up to 10 000 ppm, equivalent to 1000 mg/kg bw per day. In this study, a statistically significantly increase in pre-coital interval and slight reductions in neonatal weights of males and females were observed at 10 000 ppm. The NOAEL for reproductive and developmental toxicity was 2500 ppm, equal to 250 mg/kg bw per day. In a two-generation study of reproductive toxicity in rats, no systemic toxicity was observed in the parental animals at doses of up to and including 10 000 ppm. No reproductive toxicity was observed at doses of up to and including 10 000 ppm, equal to 929 mg/kg bw per day), the highest dose tested. The NOAEL for offspring toxicity was 2000 ppm, equal to 192 mg/kg bw per day, on the basis of reduced mean litter weights seen at the LOAEL of 10 000 ppm, equal to 929 mg/kg bw per day. In a study of developmental toxicity in rats given triazole alanine, no systemic toxicity was observed with triazole alanine at doses of up to and including 1000 mg/kg bw per day given by oral gavage. Increased incidences of skeletal findings were seen in the offspring at the intermediate and highest doses. These skeletal findings included unossified odontoid processes at 300 and 1000 mg/kg bw per

day, with partially ossified transverse processes of the seventh cervical vertebra (bilateral), unossified fifth sternebra, and partially ossified thirteenth thoracic centrum observed only at 1000 mg/kg bw per day. The NOAEL for developmental toxicity was 100 mg/kg bw per day.

The Meeting concluded that triazole alanine was not teratogenic. Triazole acetic is unlikely to be teratogenic on the basis of its structural and toxicological similarity with triazole alanine.

No studies of neurotoxicity with triazole alanine were submitted. However, there was no evidence that exposure to triazole alanine results in neurotoxicity in the short-term studies in rats and dogs, the study of developmental toxicity in rats, or studies of reproductive toxicity in rats.

No studies of neurotoxicity with triazole acetic acid were submitted. In a study of acute lethality, a slight to moderate increase in the incidence of dyspnoea, exophthalmos, ruffled fur, and curved body position were observed after dosing, and subsided within 10 days. These clinical signs were considered to be non-specific and attributable to bolus dosing with a very high dose (5000 mg/kg bw) by gavage rather than specific neurotoxicity.

The Meeting concluded that triazole alanine and triazole acetic acid are unlikely to be neurotoxic on the basis of the available data.

The Meeting concluded that the existing database on triazole alanine was adequate to characterize the potential hazards to fetuses, infants and children. This conclusion was also applicable to triazole acetic acid for the reasons described above.

Toxicological evaluation

The Meeting established a group ADI for triazole alanine and triazole acetic acid (alone or in combination) of 0–1.0 mg/kg bw based on a NOAEL of 100 mg/kg bw per day for developmental toxicity in a study of developmental toxicity in rats given triazole alanine, on the basis of delayed ossification seen in rats at the LOAEL 300 mg/kg bw per day, and using a safety factor of 100. The Meeting concluded that it was not necessary to use an additional safety factor for the lack of studies of carcinogenicity because the compounds are unlikely to be carcinogenic at anticipated levels of exposure, do not bioaccumulate in the body, are non-mutagenic, are not chemically reactive, and no specific target-organ toxicity was identified in the available toxicological studies with doses of up to 1510 mg/kg bw per day.

The Meeting concluded that it was unnecessary to establish an ARfD for triazole alanine and triazole acetic acid because no toxicity could be attributed to a single exposure in the available database, including a study of developmental toxicity in rats.

A toxicological monograph for triazole alanine and triazole acetic acid was prepared.

Levels relevant to risk assessment

Based on data for triazole alanine

Species	Study	Effect	NOAEL	LOAEL
Rat	Multigeneration study of reproductive toxicity[a]	Parental toxicity	10 000 ppm, equal to 929 mg/kg bw per day[c]	—
		Offspring toxicity	2000 ppm equal to 192 mg/kg bw per day	10 000 ppm, equal to 929 mg/kg bw per day[c]
	Developmental toxicity[b]	Maternal toxicity	1000 mg/kg bw per day[c]	—

		Embryo and fetal toxicity	100 mg/kg bw per day	300 mg/kg bw per day
Dog	90-day study of toxicity[b,]	Toxicity	8000 ppm, equal to 345 mg/kg bw per day	20 000 ppm, equal to 850 mg/kg bw per day[c]

[a] Dietary administration.

[b] Gavage administration.

[c] Highest dose tested.

Estimate of acceptable daily intake for humans

Group ADI for triazole alanine and triazole acetic acid: 0–1 mg/kg bw per day

Estimate of acute reference dose

Unnecessary

Information that would be useful for continued evaluation of the compound

Results from epidemiological and other such observational studies of human exposure.

Critical end-points for setting guidance values for exposure to triazole alanine

Absorption, distribution, excretion, and metabolism in mammals	
Rate and extent of oral absorption	Rapid and nearly complete absorption
Distribution	Widely distributed in tissues
Potential for accumulation	Low, no evidence of significant accumulation
Rate and extent of excretion	Approximately 96–99% of the administered dose excreted in urine in first 24 h
Metabolism in animals	Limited, about 8–19% excreted as *N*-acetyl triazole alanine in the urine. No metabolism of triazole acetic acid.
Toxicologically significant compounds (animals, plants and environment)	Triazole alanine; triazole acetic acid
Acute toxicity	
Rat, LD_{50}, oral	> 5000 mg/kg bw for triazole alanine and triazole acetic acid
Rat, LD_{50}, dermal	No data
Rat, LC_{50}, inhalation	No data
Rabbit, dermal irritation	No data
Rabbit, ocular irritation	No data
Dermal sensitization	No data

S*hort-term studies of toxicity*	
Target/critical effect	Decreased body-weight gain
Lowest relevant oral NOAEL	5000 ppm, equal to 370 mg/kg bw per day (90-day study in rats)
Lowest relevant dermal NOAEL	No data
Lowest relevant inhalation NOAEL	No data
Genotoxicity	
	Unlikely to be genotoxic (triazole alanine and triazole acetic acid)
Long-term studies of toxicity and carcinogenicity	
Target/critical effect	No data
Lowest relevant NOAEL	No data
Carcinogenicity	Unlikely to be carcinogenic (triazole alanine and triazole acetic acid)
Reproductive toxicity	
Reproduction target/critical effect	No toxicologically relevant effects
Lowest relevant reproductive NOAEL	10 000 ppm, equal to 929 mg/kg bw per day (rats; highest dose tested)
Developmental target/critical effect	Delayed ossifications
Lowest relevant developmental NOAEL	100 mg/kg bw per day (rats)
Neurotoxicity/delayed neurotoxicity	
Acute neurotoxicity	No indication of neurotoxicity from other studies
Mechanistic data	
	No data
Medical data	
	No data

Summary

	Value	*Study*	*Safety factor*
ADI	0–1 mg/kg bw per day	Rat, study of developmental toxicity (rats)	100
ARfD	Unnecessary	—	—