5.24 PENCONAZOLE (182)

TOXICOLOGY

Penconazole is the ISO-approved common name for 1-(2,4-dichloro-β-propylphenethyl)-1*H*-1,2,4-triazole (IUPAC), which has the CAS number 66246-88-6. Penconazole is a systemic triazole fungicide with preventive and curative properties for the control of powdery mildew. It stops the development of fungi by interfering with the biosynthesis of sterols in cell membranes and is used on grapes, pome and stone fruit, cucurbits and strawberries.

Penconazole was previously evaluated for toxicology by JMPR in 1992, when the Meeting established an ADI of 0–0.03 mg/kg bw on the basis of a NOAEL of 3 mg/kg bw per day in a 1-year study in dogs.

In 2008, a group of manufacturers of triazole fungicides formed a task force known as the "Triazole Derivative Metabolite Group" and made a joint submission of toxicological data on the common metabolites 1,2,4-triazole, triazole acetic acid and triazole alinine to JMPR. Triazole alanine and triazole acetic acid residues are primarily associated with plant commodities, whereas 1,2,4-triazole is mainly associated with animal commodities, lesser amounts of this compound being found in plant commodities.

In 2008, the Meeting established an ADI of 0–0.2 mg/kg bw for 1,2,4-triazole, based on a NOAEL of 16 mg/kg bw per day in a two-generation reproductive toxicity study in rats. The Meeting established an ARfD of 0.3 mg/kg bw for 1,2,4-triazole, based on a NOAEL of 30 mg/kg bw per day in a developmental toxicity study in rabbits.

In 2008, the Meeting established a group ADI of 0–1.0 mg/kg bw for triazole alanine and triazole acetic acid (alone or in combination), based on a NOAEL of 100 mg/kg bw per day in a developmental toxicity study in rats on triazole alanine. The 2008 Meeting concluded that it was unnecessary to establish an ARfD for triazole alanine and triazole acetic acid.

Penconazole was re-evaluated by the present Meeting as part of the periodic review programme of CCPR. Both the new data and previously submitted studies with penconazole were considered by the present Meeting. New data on the common rat and plant metabolites 1,2,4-triazole, triazole acetic acid and triazole alanine were considered by the present Meeting to evaluate whether a revision of the ADIs or ARfDs for these compounds was necessary.

All critical studies contained statements of compliance with GLP. The Meeting considered that the database was adequate for the risk assessment.

Biochemical aspects

Absorption was rapid and extensive following the administration of a single oral dose (0.5 or 25 mg/kg bw) of [^{14}C]penconazole to rats. At 50 mg/kg bw, maximum blood concentrations were reached in 4 hours in males and 6 hours in females. At this dose, peak tissue concentrations, observed at about 6 and 4 hours after dosing in males and females, respectively, were generally higher in males; the half-life of elimination was also longer in males than in females. Highest tissue concentrations of radioactivity were found in penis (probably related to contamination with urinary radioactivity), liver, lungs and kidneys. A sex difference was apparent in excretion profiles, with females excreting 73–85% of a 0.5 or 25 mg/kg bw dose of penconazole in urine and 14–32% in faeces over a 6-day period, whereas males excreted 62% of the same dose levels in urine and 37–39% in faeces over the same period. Excretion was more rapid in females, irrespective of dose level or position of radiolabel. Biliary elimination was greater in males than in females (55% and 40% of the administered dose, respectively). Less than 5% of the dose was excreted in faeces in bile duct–cannulated rats, indicating enterohepatic circulation of biliary metabolites. The excretion profiles in males and females were not affected by dose or predosing the rats with unlabelled penconazole for 14 or 90 days.

Primary metabolic reactions involved in the biotransformation of penconazole included cleavage of the triazole ring (estimated 15% of the dose), oxidation of the ω-position of the alkane chain to form the respective carboxylic acid (30% of the dose), oxidation of the 3- or 4-position of the

alkane chain to form monohydroxy and dihydroxy derivatives (2.5% of the dose) and oxidation of the triazole ring in the 3- or 5-position (0.7% of the dose). Cleavage of the penconazole molecule to free triazole was more extensive in males than in females. Secondary metabolic reactions include α-oxidation of the carboxylic acids to form α-hydroxy carboxylic acids (4.4% of the dose), decarboxylation following oxidation to α-ketocarboxylic derivative (9% of the dose), oxidation of the 3,4-dihydroxy derivatives to produce the corresponding 3- or 4-keto derivatives (0.5% of the dose) and conjugation of all alkanol derivatives with glucuronic acid (2.5% of the dose). A small amount of parent penconazole was identified in faeces and was considered to represent unabsorbed dose.

Toxicological data

The acute toxicity of penconazole is low (rat: oral LD_{50} > 2000 mg/kg bw; dermal LD_{50} > 3000 mg/kg bw; inhalation LC_{50} > 4.0 mg/L). Penconazole was not irritating to the skin or the eyes of rabbits. Penconazole was not a skin sensitizer in a Magnusson and Kligman test in guinea-pigs.

In repeated-dose oral toxicity studies with penconazole in mice, rats and dogs, the main adverse effects were body weight changes and liver toxicity.

In a 90-day study in mice using dietary penconazole concentrations of 0, 10, 100, 300, 500, 1000 and 2400 ppm (equal to 0, 1.7, 17, 52, 85, 163 and 423 mg/kg bw per day for males and 0, 2.5, 24, 72, 116, 237 and 614 mg/kg bw per day for females, respectively), the NOAEL was 500 ppm (equal to 85 mg/kg bw per day), based on lower total protein and cholesterol levels and focal coagulative necrosis in the liver of both sexes at 1000 ppm (equal to 163 mg/kg bw per day).

In a second 90-day study in mice using dietary concentrations of 0, 100, 500, 1500, 3000 and 5000 ppm (equal to 0, 14, 69, 229, 437 and 837 mg/kg bw per day for males and 0, 18, 87, 274, 545 and 983 mg/kg bw per day for females, respectively), the NOAEL was 500 ppm (equal to 69 mg/kg bw per day), based on reductions in cholesterol levels in both sexes, a reduction in total protein and albumin levels in females and a reduction in body weight gain and increased nuclear pleomorphism in hepatocytes in males at 1500 ppm (equal to 229 mg/kg bw per day).

In a 28-day gavage study in rats using penconazole doses of 0, 100 and 500 mg/kg bw per day, a NOAEL could not be identified. The LOAEL was 100 mg/kg bw per day, based on changes in clinical chemistry and haematology parameters and minimal hypertrophy of the follicle epithelium of the thyroid.

In a 13-week study in rats using dietary penconazole concentrations of 0, 30, 300 and 3000 ppm (equal to 0, 2.0, 19 and 202 mg/kg bw per day for males and 0, 2.1, 21 and 209 mg/kg bw per day for females, respectively), the NOAEL was 300 ppm (equal to 19 mg/kg bw per day), based on reduced body weight gain and feed consumption in females and increased testes weight observed at 3000 ppm (equal to 202 mg/kg bw per day).

In a second 13-week dietary study in rats using penconazole concentrations of 0, 10, 30 and 100 ppm (equal to 0, 0.77, 2.1 and 7.1 mg/kg bw per day for males and 0, 0.78, 2.1 and 7.3 mg/kg bw per day for females, respectively), the NOAEL was 100 ppm (equal to 7.1 mg/kg bw per day), the highest dose tested.

In a third 13-week dietary study in rats using penconazole concentrations of 0, 10, 100, 300, 500, 100 and 2400 ppm (equal to 0, 0.81, 7.5, 23, 38, 72 and 179 mg/kg bw per day for males and 0, 0.96, 9.1, 28, 45, 86 and 209 mg/kg bw per day for females, respectively), the NOAEL was 300 ppm (equal to 23 mg/kg bw per day), based on an increased incidence of hepatocellular vacuolation and hypertrophy at 500 ppm (equal to 38 mg/kg bw per day).

In a 1-year study, dogs received a dietary penconazole concentration of 0, 100, 500 or 5000 ppm (equal to 0, 3.1, 16.9 and 133 mg/kg bw per day for males and 0, 3.3, 16.7 and 139 mg/kg bw per day for females, respectively). During week 20, the highest dose was reduced to 2500 ppm (equal to 86 mg/kg bw per day for males and 89 mg/kg bw per day for females, respectively), because of excessive reduction in feed consumption and body weight gain. The NOAEL was 100 ppm (equal to 3.1 mg/kg bw per day), based on reduced body weight gain, increased absolute and relative liver

weights and slight histopathological changes in the liver (hepatocyte necrosis associated with inflammatory cell infiltration) in males and females at 500 ppm (equal to 16.7 mg/kg bw per day).

In a 2-year carcinogenicity study in mice using dietary concentrations of 0, 5, 75, 150 and 300 ppm (equal to 0, 0.75, 9.8, 19 and 41 mg/kg bw per day for males and 0, 0.67, 8.8, 17 and 36 mg/kg bw per day for females, respectively), the NOAEL was 300 ppm (equal to 36 mg/kg bw per day), the highest dose tested. No treatment-related tumours were observed in mice in this study.

In an 80-week carcinogenicity study in mice using dietary concentrations of 0, 25, 200 and 1500 ppm (equal to 0, 2.7, 22 and 178 mg/kg bw per day for males and 0, 3.5, 28 and 222 mg/kg bw per day for females, respectively), the NOAEL was 200 ppm (equal to 22 mg/kg bw per day), based on decreased body weight gain and absolute and relative spleen weights and increased incidence and severity of hepatocellular vacuolation in both sexes and increased absolute and relative liver weights in males at 1500 ppm (equal to 178 mg/kg bw per day). No treatment-related tumours were observed in mice in this study.

The overall NOAEL for the long-term toxicity studies in mice was 300 ppm (equal to 36 mg/kg bw per day), and the overall LOAEL was 1500 ppm (equal to 178 mg/kg bw per day).

In a 27-month toxicity and carcinogenicity study in rats using dietary concentrations of 0, 5, 75, 150 and 300 ppm (equal to 0, 0.30, 3.8, 7.3 and 15 mg/kg bw per day for males and 0, 0.31, 4.0, 8.1 and 17 mg/kg bw per day for females, respectively), the NOAEL was 150 ppm (equal to 8.1 mg/kg bw per day), based on increased absolute and relative liver weights and an increase in gamma-glutamyltransferase levels at 1 year in females at 300 ppm (equal to 17 mg/kg bw per day). No treatment-related tumours were observed in rats in this study.

The Meeting concluded that penconazole is not carcinogenic in mice or rats.

Penconazole was tested for genotoxicity in an adequate range of assays, both in vitro and in vivo. There was no evidence of genotoxicity.

The Meeting concluded that penconazole is unlikely to be genotoxic.

In view of the lack of genotoxicity and the absence of carcinogenicity in mice and rats, the Meeting concluded that penconazole is unlikely to pose a carcinogenic risk to humans.

In a two-generation reproductive toxicity study in rats using penconazole at dietary concentrations of 0, 80, 400 and 2000 ppm (equal to 0, 5.5, 29 and 146 mg/kg bw per day for males and 0, 7.5, 40 and 202 mg/kg bw per day for females of the F_0 generation and 0, 6.5, 31 and 166 mg/kg bw per day for males and 0, 8.5, 43 and 227 mg/kg bw per day for females of the F_1 generation, respectively), the NOAEL for parental toxicity was 400 ppm (equal to 43 mg/kg bw per day), based on increased relative liver weights and the observation of hepatocellular necrosis in F_1 parental females at 2000 ppm (equal to 227 mg/kg bw per day). The NOAEL for offspring toxicity was 2000 ppm (equal to 146 mg/kg bw per day), the highest dose tested. The NOAEL for reproductive toxicity was 400 ppm (equal to 40 mg/kg bw per day), based on a lower gestation index and a longer gestation duration in F_0 and F_1 females at 2000 ppm (equal to 202 mg/kg bw per day).

In a second two-generation reproductive toxicity study in rats using dietary penconazole concentrations of 0, 25, 250 and 2500 ppm, premating dietary intakes were equal to 0, 2.0, 20 and 191 mg/kg bw per day for males and 0, 2.4, 24 and 238 mg/kg bw per day for females of the F_0 generation and 0, 2.2, 22 and 219 mg/kg bw per day for males and 0, 2.5, 25 and 246 mg/kg bw per day for females of the F_1 generation, respectively. The NOAEL for parental toxicity was 250 ppm (equal to 24 mg/kg bw per day), based on reduced body weight gain and feed consumption during the premating period in F_0 and F_1 females at 2500 ppm (equal to 238 mg/kg bw per day). The NOAEL for offspring toxicity was 250 ppm (equal to 20 mg/kg bw per day), based on an increased number of pups that were born dead or died during PNDs 0–4 and a decreased body weight gain of pups during lactation at 2500 ppm (equal to 191 mg/kg bw per day). The NOAEL for reproductive toxicity was 250 ppm (equal to 20 mg/kg bw per day), based on a decreased mating index at 2500 ppm (equal to 191 mg/kg bw per day).

In a developmental toxicity study in rats using gavage penconazole doses of 0, 30, 100 and 300 mg/kg bw per day, the NOAEL for maternal toxicity was 100 mg/kg bw per day, based on mortality and reduced body weight gain observed at the end of gestation at 300 mg/kg bw per day. The NOAEL for embryo and fetal toxicity was 100 mg/kg bw per day, based on delayed ossification observed at 300 mg/kg bw per day.

In a second developmental toxicity study in rats using gavage penconazole doses of 0, 5, 100 and 500 mg/kg bw per day, the NOAEL for maternal toxicity was 100 mg/kg bw per day, based on mortality observed after 5 and 6 days of treatment, clinical signs observed early during treatment, a reduction in net body weight gain and feed consumption on GD 6, stomach lesions and an increased incidence of late resorptions at 500 mg/kg bw per day. The NOAEL for embryo and fetal toxicity was 100 mg/kg bw per day, based on a slight increase in the occurrence of cervical ribs and an increase in the total number of fetuses/litters with abnormal findings at 500 mg/kg bw per day.

The overall NOAEL for maternal and embryo and fetal toxicity in the two developmental toxicity studies in rats was 100 mg/kg bw per day, and the overall LOAEL was 300 mg/kg bw per day.

In a developmental toxicity study in Chinchilla-type rabbits administered penconazole doses of 0, 25, 75 and 150 mg/kg bw per day by gavage (vehicle was 0.5% aqueous sodium carboxymethyl cellulose), the NOAEL for maternal toxicity was 75 mg/kg bw per day, based on reduction of body weight gain and feed consumption during treatment at 150 mg/kg bw per day. The NOAEL for embryo and fetal toxicity was 75 mg/kg bw per day, based on the increased incidences of microphthalmia and hydroencephalus at 150 mg/kg bw per day.

In a second developmental toxicity study in New Zealand White rabbits administered penconazole doses of 0, 10, 50 and 200 mg/kg bw per day by gavage (vehicle was 3% aqueous corn starch), the NOAEL for maternal toxicity was 200 mg/kg bw per day, the highest dose tested. The NOAEL for embryo and fetal toxicity was 50 mg/kg bw per day, based on the reduced number of live fetuses at 200 mg/kg bw per day.

The Meeting concluded that penconazole is teratogenic in rabbits, but not in rats.

No neurotoxicity studies with penconazole were provided. In view of the absence of evidence of neurotoxicity in other acute and repeated-dose toxicity studies, the Meeting concluded that penconazole is unlikely to be neurotoxic.

A special study in rats and mice indicates that penconazole at gavage doses of 10, 80, 160 and 320 mg/kg bw per day for 14 days induces liver enzyme induction, liver enlargement and proliferation of smooth endoplasmic reticulum and shares some characteristics with a phenobarbital class of monooxygenase inducers.

Toxicological data on metabolites and/or degradates

1,2,4-Triazole

In a 12-month toxicity study in rats using dietary 1,2,4-triazole concentrations of 0, 125, 375, 1000 and 2000 ppm (equal to 0, 6.9, 21, 58 and 113 mg/kg bw per day for males and 0, 8.3, 26, 71 and 136 mg/kg bw per day for females, respectively), the NOAEL was 375 ppm (equal to 21 mg/kg bw per day), based on a reduction in body weight gain at 1000 ppm (equal to 58 mg/kg bw per day).

Triazole acetic acid

In a 28-day toxicity study in mice using dietary triazole acetic acid concentrations of 0, 1000, 3000 and 7000 ppm (equal to 0, 159, 483 and 1067 mg/kg bw per day for males and 0, 183, 542 and 1357 mg/kg bw per day for females, respectively), the NOAEL was 7000 ppm (equal to 1067 mg/kg bw per day), the highest dose tested.

In a 29-day toxicity study in rats using triazole acetic acid at dietary concentrations of 0, 3250, 6500 and 13 000 ppm (equal to 0, 243, 483 and 993 mg/kg bw per day for males and 0, 260,

519 and 940 mg/kg bw per day for females, respectively), the NOAEL was 13 000 ppm (equal to 940 mg/kg bw per day), the highest dose tested.

In a 13-week combined toxicity and neurotoxicity study in rats, dietary triazole acetic acid concentrations were adjusted weekly based on body weight and feed consumption in order to obtain target test substance intakes of 0, 100, 500 and 1000 mg/kg bw per day. Actual mean intakes were 0, 94, 495 and 1002 mg/kg bw per day for males and 0, 119, 627 and 1181 mg/kg bw per day for females, respectively. The NOAEL was 1002 mg/kg bw per day, the highest dose tested.

In a one-generation reproductive toxicity study in rats, dietary triazole acetic acid concentrations were adjusted weekly based on body weight and feed consumption in order to obtain target test substance intakes of 0, 100, 300 and 1000 mg/kg bw per day. Actual premating test substance intakes were 0, 96, 287 and 959 mg/kg bw per day for males and 0, 98, 293 and 976 mg/kg bw per day for females of the F_0 generation and 0, 93, 280 and 926 mg/kg bw per day for males and 0, 78, 246 and 770 for females of the F_1 generation, respectively. The NOAEL for parental toxicity was 287 mg/kg bw per day, based on reduced body weight gain and feed consumption in males at 959 mg/kg bw per day. The NOAEL for offspring toxicity was 770 mg/kg bw per day, the highest dose tested. The NOAEL for reproductive toxicity was 959 mg/kg bw per day, the highest dose tested.

In a developmental toxicity study in rats administered triazole acetic acid at a dose of 0, 100, 300 or 1000 mg/kg bw per day by gavage (vehicle was 0.5% carboxymethyl cellulose), the NOAEL for maternal toxicity was 300 mg/kg bw per day, based on mortality, clinical signs, and reduced body weight gain and feed consumption observed early during treatment at 1000 mg/kg bw per day. Although there are indications that the findings may be due to a local effect on the gastrointestinal tract, no signs of local irritation of the stomach or gut were reported. Therefore, the Meeting could not discount the possibility that the findings were due to a systemic effect of the compound. The NOAEL for embryo and fetal toxicity was 300 mg/kg bw per day. As severe clinical signs in the dams at 1000 mg/kg bw per day necessitated early termination, the effect of triazole acetic acid on fetal development could not be assessed at this dose.

In a developmental toxicity study in rabbits using gavage triazole acetic acid doses of 0, 100, 750 and 1000 mg/kg bw per day, the NOAEL for maternal toxicity was 100 mg/kg bw per day, based on mortality (first observed on day 4 of treatment), clinical signs, and reduced body weight gain and feed consumption (first observed at/after 1 day of treatment) at 750 mg/kg bw per day. As most of these animals had stomach lesions, generally described as numerous discoloured (black) erosions/ulcerations (pinpoint to 1.0 cm in diameter) on the mucosal surface, these effects are probably caused by a local effect on the gastrointestinal tract. The NOAEL for embryo and fetal toxicity was 100 mg/kg bw per day, based on decreased fetal weights at 750 mg/kg bw per day.

Triazole alanine

In a 12-month toxicity study in rats using dietary triazole alanine concentrations of 0, 600, 2000, 6000 and 20 000 ppm (equal to 0, 28, 93, 278 and 916 mg/kg bw per day for males and 0, 36, 120, 375 and 1273 mg/kg bw per day for females, respectively), the NOAEL was 20 000 ppm (equal to 916 mg/kg bw per day), the highest dose tested.

In a developmental toxicity study in rabbits using gavage triazole alanine doses of 0, 30, 100 and 250 mg/kg bw per day, the NOAEL for maternal toxicity was 100 mg/kg bw per day, based on increased incidences of soft or liquid faeces (first observed after 5 days of treatment) and decreased body weight gain and feed consumption observed at 250 mg/kg bw per day. The NOAEL for embryo and fetal toxicity was 100 mg/kg bw per day, based on decreased fetal weight and increased incidences of hyoid, angulated ala and thickened ribs observed at 250 mg/kg bw per day.

Human data

No adverse health effects in plant personnel during the manufacture or formulation of penconazole-containing products over a 20-year period were reported. In incidents related to intentional misuse, occupational and accidental exposure, generally no or only minor symptoms were reported.

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

Toxicological evaluation

Penconazole

The Meeting reaffirmed the ADI of 0–0.03 mg/kg bw for penconazole on the basis of a NOAEL of 3.1 mg/kg bw per day for reduced body weight gain, increased absolute and relative liver weights and slight histopathological changes in the liver (hepatocyte necrosis associated with inflammatory cell infiltration) in a 1-year study in dogs, using a safety factor of 100.

The Meeting established an ARfD of 0.8 mg/kg bw for penconazole, on the basis of a NOAEL of 75 mg/kg bw per day for increased incidences of microphthalmia and hydrocephalus in a developmental toxicity study in rabbits. The Meeting concluded that this ARfD applies to the general population on the basis of the NOAEL of 100 mg/kg bw per day for early clinical signs, reduced body weight gain and mortality, which might be due to systemic effects, observed in dams in a developmental toxicity study in rats. A safety factor of 100 was applied.

1,2,4-Triazole

The present Meeting reaffirmed the ADI of 0–0.2 mg/kg bw, established by JMPR in 2008, based on a NOAEL of 16 mg/kg bw per day for testicular effects (sperm abnormalities, sperm counts) observed at 30.9 mg/kg bw per day in a two-generation study of reproductive toxicity in rats, using a safety factor of 100. This ADI is supported by a new 12-month dietary toxicity study in rats with a NOAEL of 21 mg/kg bw per day, based on a reduction in body weight gain at 58 mg/kg bw per day.

The present Meeting reaffirmed the previously established ARfD of 0.3 mg/kg bw for 1,2,4-triazole, based on a NOAEL of 30 mg/kg bw per day for alterations of the urogenital system that occurred in several fetuses at 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.

Triazole alanine and triazole acetic acid

The present Meeting reaffirmed the group ADI for triazole alanine and triazole acetic acid (alone or in combination) of 0–1 mg/kg bw, established by JMPR in 2008, based on a NOAEL of 100 mg/kg bw per day for delayed ossification in a developmental toxicity study in rats given triazole alanine, a NOAEL of 100 mg/kg bw per day for increased incidences of soft or liquid faeces and decreased body weight gain and feed consumption in a new developmental toxicity study with triazole alanine in rabbits, a NOAEL of 100 mg/kg bw per day for decreased fetal weight and an increased in hyoid, angulated ala and thickened ribs in a new developmental toxicity study with triazole alanine in rabbits, a NOAEL of 100 mg/kg bw per day for mortality, clinical signs, reduced body weight gain and feed consumption in a new developmental toxicity study in rabbits with triazole acetic acid and a NOAEL of 100 mg/kg bw per day based on decreased fetal weights in a new developmental toxicity study in rabbits with triazole acetic acid. A safety factor of 100 was used. This group ADI is expressed as triazole alanine.

The present Meeting established an ARfD of 3 mg/kg bw for triazole alanine and triazole acetic acid, based on a NOAEL of 300 mg/kg bw per day on the basis of mortality, clinical signs, reduced body weight gain and feed consumption observed early during treatment at 1000 mg/kg bw per day in a new developmental toxicity study with triazole acetic acid in rats. A safety factor of 100 was used.

A toxicological monograph was prepared.

Levels relevant to risk assessment of penconazole

Species	Study	Effect	NOAEL	LOAEL
Mouse	Two-year and 80-week studies of toxicity and carcinogenicity[a,b]	Toxicity	300 ppm, equal to 36 mg/kg bw per day	1 500 ppm, equal to 178 mg/kg bw per day
		Carcinogenicity	1 500 ppm, equal to 178 mg/kg bw per day[c]	–
Rat	Twenty-seven-month study of toxicity and carcinogenicity[a]	Toxicity	150 ppm, equal to 8.1 mg/kg bw per day	300 ppm, equal to 17 mg/kg bw per day
		Carcinogenicity	300 ppm, equal to 15 mg/kg bw per day[c]	–
	Two-generation study of reproductive toxicity[a]	Reproductive toxicity	250 ppm, equal to 20 mg/kg bw per day	2 500 ppm, equal to 191 mg/kg bw per day
		Parental toxicity	250 ppm, equal to 24 mg/kg bw per day	2 500 ppm, equal to 238 mg/kg bw per day
		Offspring toxicity	250 ppm, equal to 20 mg/kg bw per day	2 500 ppm, equal to 191 mg/kg bw per day
	Developmental toxicity studies[b,d]	Maternal toxicity	100 mg/kg bw per day	300 mg/kg bw per day
		Embryo and fetal toxicity	100 mg/kg bw per day	300 mg/kg bw per day
Rabbit	Developmental toxicity study[d]	Maternal toxicity	75 mg/kg bw per day	150 mg/kg bw per day
		Embryo and fetal toxicity	75 mg/kg bw per day	150 mg/kg bw per day
	Developmental toxicity study[d]	Maternal toxicity	200 mg/kg bw per day[c]	–
		Embryo and fetal toxicity	50 mg/kg bw per day	200 mg/kg bw per day
Dog	One-year study of toxicity[a]	Toxicity	100 ppm, equal to 3.1 mg/kg bw per day	500 ppm, equal to 16.7 mg/kg bw per day

[a] Dietary administration.
[b] Two or more studies combined.
[c] Highest dose tested.
[d] Gavage administration.

Levels relevant to risk assessment of 1,2,4-triazole

Species	Study	Effect	NOAEL	LOAEL
Mouse	Ninety-day study of toxicity[a]	Toxicity	1 000 ppm, equal to 161 mg/kg bw per day	3 000 ppm, equal to 487 mg/kg bw per day
Rat	**One-year study of toxicity[a]**	**Toxicity**	**375 ppm, equal to 21 mg/kg bw per day**	**1 000 ppm, equal to 58 mg/kg bw per day**
	Multigeneration study of reproductive toxicity[a]	Parental toxicity	250 ppm, equal to 16 mg/kg bw per day	500 ppm, equal to 31 mg/kg bw per day
		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
		Embryo and fetal toxicity	30 mg/kg bw per day	45 mg/kg bw per day

Studies in bold are new studies. All other studies are derived from the 2008 JMPR evaluation.

[a] Dietary administration.
[b] Gavage administration.
[c] Highest dose tested.

Levels relevant to risk assessment of triazole acetic acid

Species	Study	Effect	NOAEL	LOAEL
Rat	**Thirteen-week study of toxicity and neurotoxicity[a]**	**Toxicity**	**1 002 mg/kg bw per day[b]**	–
		Neurotoxicity	**1 002 mg/kg bw per day[b]**	–
	One-generation study of reproductive toxicity[a]	Parental toxicity	287 mg/kg bw per day	959 mg/kg bw per day
		Offspring toxicity	770 mg/kg bw per day[b]	–
		Reproductive toxicity	959 mg/kg bw per day[b]	–
	Developmental toxicity study[c]	Maternal toxicity	300 mg/kg bw per day	1 000 mg/kg bw per day
		Embryo and fetal toxicity	300 mg/kg bw per day[b]	–
Rabbit	Developmental toxicity study[c]	Maternal toxicity	100 mg/kg bw per day	750 mg/kg bw per day
		Embryo and fetal toxicity	100 mg/kg bw per day	750 mg/kg bw per day

Studies in bold are new studies. All other studies are derived from the 2008 JMPR evaluation.

[a] Dietary administration.
[b] Highest dose tested.
[c] Gavage administration.

Levels relevant to risk assessment of triazole alanine

Species	Study	Effect	NOAEL	LOAEL
Rat	**Twelve-month study of toxicity[a]**	**Toxicity**	**916 mg/kg bw per day[c]**	–
	Multigeneration study of reproductive toxicity[a]	Parental toxicity	10 000 ppm, equal to 929 mg/kg bw per day[c]	–
		Offspring toxicity	2 000 ppm, equal to 192 mg/kg bw per day	10 000 ppm, equal to 929 mg/kg bw per day
	Developmental toxicity study[b]	Maternal toxicity	1 000 mg/kg bw per day[c]	–
		Embryo and	100 mg/kg bw per day	300 mg/kg bw per day

		fetal toxicity		
Rabbit	**Developmental toxicity study[b]**	**Maternal toxicity**	**100 mg/kg bw per day**	**250 mg/kg bw per day**
		Embryo and fetal toxicity	**100 mg/kg bw per day**	**250 mg/kg bw per day**
Dog	Ninety-day study of toxicity[b]	Toxicity	8 000 ppm, equal to 345 mg/kg bw per day	20 000 ppm, equal to 850 mg/kg bw per day

Studies in bold are new studies. All other studies are derived from the 2008 JMPR evaluation.

[a] Dietary administration.
[b] Gavage administration.
[c] Highest dose tested.

Penconazole

Estimate of acceptable daily intake (ADI)

0–0.03 mg/kg bw

Estimate of acute reference dose (ARfD)

0.8 mg/kg bw

1,2,4-Triazole

Estimate of acceptable daily intake (ADI)

0–0.2 mg/kg bw

Estimate of acute reference dose (ARfD)

0.3 mg/kg bw

Triazole alanine and triazole acetic acid

Estimate of acceptable daily intake (group ADI), expressed as triazole alanine

0–1 mg/kg bw

Estimate of acute reference dose (ARfD)

3 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 penconazole

Absorption, distribution, excretion and metabolism in mammals	
Rate and extent of oral absorption	Rats: Rapid; > 95% in both sexes at 0.5 mg/kg bw
Dermal absorption	No data
Distribution	Rats: Widespread distribution, highest concentrations found in liver and kidney

Potential for accumulation	Low potential for accumulation
Rate and extent of excretion	Rapid; 67% and 94% in male and female rats, respectively, in 24 h. Higher urinary excretion in females (73–85%) than in males (62%). Higher biliary excretion in males (55%) than in females (40%).
Metabolism in animals	Extensively metabolized (14 metabolites identified)
Toxicologically significant compounds in animals and plants	Penconazole, 1,2,4-triazole, triazole acetic acid, triazole alanine
Acute toxicity	
Rat, LD_{50}, oral	> 2 000 mg/kg bw
Rat, LD_{50}, dermal	> 3 000 mg/kg bw
Rat, LC_{50}, inhalation	> 4.0 mg/L
Rabbit, dermal irritation	Not irritating
Rabbit, ocular irritation	Not irritating
Guinea-pig, dermal sensitization	Not sensitizing (maximization test)
Short-term studies of toxicity	
Target/critical effect	Reduced body weight gain, liver
Lowest relevant oral NOAEL	3.1 mg/kg bw per day (dog)
Lowest relevant dermal NOAEL	2 000 mg/kg bw per day (rabbit)
Lowest relevant inhalation NOAEC	No data
Long-term studies of toxicity and carcinogenicity	
Target/critical effect	Liver
Lowest relevant NOAEL	8.1 mg/kg bw per day (rat)
Carcinogenicity	Not carcinogenic in mice or rats[a]
Genotoxicity	
	Unlikely to be genotoxic in vivo[a]
Reproductive toxicity	
Target/critical effect	Decreased mating index
Lowest relevant parental NOAEL	24 mg/kg bw per day (rat)
Lowest relevant offspring NOAEL	20 mg/kg bw per day (rat)
Lowest relevant reproductive NOAEL	20 mg/kg bw per day (rat)
Developmental toxicity	
Target/critical effect	Reduced number of live fetuses
Lowest relevant maternal NOAEL	75 mg/kg bw per day (rabbit)
Lowest relevant embryo/fetal NOAEL	50 mg/kg bw per day (rabbit)
Neurotoxicity	
Acute neurotoxicity NOAEL	No data
Subchronic neurotoxicity NOAEL	No data
Developmental neurotoxicity NOAEL	No data
Other toxicological studies	

Studies on toxicologically relevant metabolites	1,2,4-Triazole
	Reproductive toxicity: NOAEL 16 mg/kg bw per day (rat)
	One-year toxicity: NOAEL 21 mg/kg bw per day (rat)
	Triazole acetic acid
	No toxicity up to 1 002 mg/kg bw per day in a 13-week study of toxicity and neurotoxicity in rats
	Acute toxicity: NOAEL 300 mg/kg bw per day for mortality, clinical signs, reduced body weight gain and feed consumption observed early during treatment at 1 000 mg/kg bw per day in a developmental toxicity study in rats
	No evidence of reproductive or offspring toxicity in rats at highest doses tested (959 and 770 mg/kg bw per day, respectively)
	No evidence of developmental toxicity in rats at 300 mg/kg bw per day
	Triazole alanine
	No toxicity up to 916 mg/kg bw per day in a 12-month study of toxicity in rats
	Embryo and fetal toxicity: NOAEL 100 mg/kg bw per day (rat, rabbit)
Medical data	
	Generally no or only minor symptoms after intentional, accidental or occupational exposure incidents

[a] Unlikely to pose a carcinogenic risk to humans from the diet.

Summary

	Value	Study	Safety factor
Penconazole			
ADI	0–0.03 mg/kg bw	One-year study of toxicity (dog)	100
ARfD	0.8 mg/kg bw	Developmental toxicity study (rabbit)	100
1,2,4-Triazole			
ADI	0–0.2 mg/kg bw	Multigeneration reproduction toxicity study (rat), one-year study of toxicity (rat)	100
ARfD	0.3 mg/kg bw	Developmental toxicity study (rabbit)	100
Triazole alanine and triazole acetic acid			
Group ADI	0–1 mg/kg bw	Developmental toxicity studies (rat, rabbit)	100
ARfD	3 mg/kg bw	Developmental toxicity study (rat)	100