5.21 TEBUCONAZOLE (189)

TOXICOLOGY

Tebuconazole is the International Organization for Standardization (ISO)–approved name for (*RS*)-1-*p*-chlorophenyl-4,4-dimethyl-3-(1H-1,2,4-triazol-1-ylmethyl)pentan-3-ol (International Union of Pure and Applied Chemistry [IUPAC]), for which the Chemical Abstracts Service (CAS) No. is 107534-96-3. Tebuconazole is a triazole fungicide that acts by inhibiting sterol biosynthesis in fungi (demethylation inhibitor).

The toxicity of tebuconazole was first evaluated by the 1994 Joint FAO/WHO Meeting on Pesticide Residues (JMPR). That Meeting established an acceptable daily intake (ADI) of 0–0.03 mg/kg body weight (bw) on the basis of a no-observed-adverse-effect level (NOAEL) of 2.9 mg/kg bw per day for histopathological alterations in the adrenal glands seen at 4.4 mg/kg bw per day and above in two 52-week toxicity studies in dogs and using a safety factor of 100.

Tebuconazole was re-evaluated by the present Meeting at the request of the Codex Committee on Pesticide Residues (CCPR). Three new studies (acute neurotoxicity study, subacute neurotoxicity study and a developmental neurotoxicity study) since the last review by the JMPR were made available. All pivotal studies with tebuconazole were certified as complying with good laboratory practice (GLP) unless otherwise stated.

Biochemical aspects

In a toxicokinetic study, groups of male and female rats were given tebuconazole uniformly labelled with ^{14}C in either the phenyl ring or the 3,5-triazole ring as a single dose at 2 or 20 mg/kg bw or as 14 repeated doses of 2 mg/kg bw per day, followed by a single oral dose of radioactive tebuconazole at 2 mg/kg bw. Tebuconazole was rapidly absorbed from the gastrointestinal tract of rats and rapidly excreted from the body. Between 86% and 98% of the dose was excreted in the urine and faeces in 72 h; most excretion occurred in the first 48 h. Faecal excretion within 72 h after administration was about 80% of the applied dose in males and about 65% in females; urinary excretion amounted to about 16% of the applied dose in males and about 33% in females. No significant differences in the absorption, distribution and excretion occurred following administration of single oral low dose or high dose or repeated doses. Male rats with biliary fistulae excreted 90.7% of the dose with the bile, 7.4% in the urine and 1.5% in faeces within 48 h, suggesting complete absorption of tebuconazole in intact rats. Only 0.3% of the radioactivity was detected in exhaled air within 72 h following oral administration of tebuconazole. After 72 h, less than 1% of the administered dose could be detected in the organs, tissues and the remaining carcass, indicating no potential for bioaccumulation. Highest residues were found in the liver and kidney. Tebuconazole was rapidly distributed (within 1 h) in the body, as determined by whole-body radioautography. The peak concentration of radioactivity in plasma was found at 0.33–1.7 h. The terminal half-life of radiolabel was 32.0–52.5 h. Tebuconazole was extensively metabolized in the body following oral administration. Less than 0.7% of parent tebuconazole was detected in the excreta at 72 h after administration. The metabolic pathway in rats also demonstrated sex-related differences. The main metabolites of tebuconazole in male rats were the oxidation products of one of the methyl groups of the tertiary butyl moiety (i.e., the alcohol and the carboxylic acid). Metabolism in female animals resulted preferentially in simple oxidation products (e.g., hydroxy and carboxy metabolites) and then conjugation to the glucuronide and sulfate, with only minor cleavage of the triazole moiety. In male animals, the primary oxidation products were further oxidized to triol and keto acid derivatives; in addition, cleavage of the triazole ring occurred, as indicated in trials with triazole-labelled compound. The free triazole accounted for about 5% of the administered dose in the urine of the males and 1.5% in that of females.

Toxicological data

Tebuconazole has low to moderate acute toxicity in mice and rats via the oral route. The oral median lethal dose (LD_{50}) of tebuconazole was 1700 and 4000 mg/kg bw in fasted female and male rats, respectively. The oral LD_{50} of tebuconazole in mice was 3025 and 1615 mg/kg bw in fasted female and male mice, respectively. The LD_{50} in rats treated dermally was greater than 2000 mg/kg bw. The median lethal concentration (LC_{50}) in rats treated by inhalation (nose only) was greater than 0.82 mg/L. Tebuconazole was non-irritating to the eyes and skin of rabbits. Tebuconazole was not a skin sensitizer in guinea-pigs, as determined by the Magnusson and Kligman (maximization) test and the Buehler test.

In a non-GLP 28-day gavage study of toxicity in rats, decreases in haemoglobin concentration and haematocrit values were observed at 100 and 300 mg/kg bw per day. At 100 and 300 mg/kg bw per day, the weights of the liver and spleen were increased in both sexes, and the weight of the kidney was increased in females. A reduced iron content was observed in the spleen of females at 100 mg/kg bw per day. The NOAEL in the 28-day gavage study in rats was 30 mg/kg bw per day, on the basis of changes in haematological and clinical chemical parameters and organ weights at 100 mg/kg bw per day. In a 90-day dietary toxicity study in rats, reduced body weight gain was observed at 400 ppm in females during the first 6 weeks. Histopathological examination revealed an increased incidence of intraplasmatic vacuoles in the cells of the zona fasciculata of the adrenals (probably lipid accumulation) in some females at 400 ppm and in all females at 1600 ppm. The NOAEL was 100 ppm (equal to 10.8 mg/kg bw per day), based on a reduction in body weights in females at 400 ppm (equal to 46.5 mg/kg bw per day).

The NOAEL in a 90-day dietary study of toxicity in dogs was 200 ppm (equal to 8.5 mg/kg bw per day), based on decreased body weight gain and food consumption at 1000 ppm (equal to 41 mg/kg bw per day). Two 1-year dietary studies of toxicity were conducted in dogs with tebuconazole. The overall NOAEL was 100 ppm (equal to 2.9 mg/kg bw per day), based on intracytoplasmic vacuoles in cells of the zona fasciculata of the adrenals and slight hypertrophy accompanied by an increased incidence of large fatty vacuoles seen at 150 ppm (equal to 4.4 mg/kg bw per day) and above.

The carcinogenic potential of tebuconazole was studied in mice and rats. Two carcinogenicity studies were conducted in mice. In the first study, the NOAEL was 20 ppm (equal to 5.9 mg/kg bw per day), based on the increased incidence of centrilobular fine vacuolization in the liver of males at 60 ppm (equal to 18 mg/kg bw per day). There was no evidence of any carcinogenic potential, but the effects on the liver at the lowest-observed-adverse-effect level (LOAEL) and above were not very marked in intensity, posing a question as to whether a maximum tolerated dose (MTD) had been reached in this study. Therefore, a second carcinogenicity study was conducted at higher doses. In the second study, no NOAEL was identified. The LOAEL was 500 ppm (equal to 85 mg/kg bw per day), based on liver toxicity. The incidence of liver tumours in male and female mice was significantly elevated at 1500 ppm (equal to 279 mg/kg bw per day) and was markedly above the range of spontaneous incidences observed in this mouse strain.

In the carcinogenicity study in rats, the NOAEL was 300 ppm (equal to 15.9 mg/kg bw per day), based on body weight depression in both sexes and an increased incidence of pigment deposits in the Kupffer cells in the liver of females at 1000 ppm (equal to 55 mg/kg bw per day). No treatment-related tumours were observed.

Tebuconazole was not genotoxic in an adequate range of in vitro and in vivo genotoxicity tests.

The Meeting concluded that tebuconazole is unlikely to be genotoxic.

In view of the absence of genotoxic potential, the absence of carcinogenicity in rats and no carcinogenicity in mice relevant to human dietary exposure levels, the Meeting concluded that tebuconazole is unlikely to pose a carcinogenic risk to humans.

In a two-generation study of reproductive toxicity in rats, the reproductive parameters were not affected at doses up to 1000 ppm (equal to 72.3 mg/kg bw per day), the highest dose tested. The NOAEL for parental systemic toxicity and offspring toxicity was 300 ppm (equal to 21.6 mg/kg bw per day), based on reduced food consumption and decreased body weights in parental animals and pups seen at 1000 ppm (equal to 72.3 mg/kg bw per day).

Several developmental toxicity studies in mice, rats and rabbits using gavage administration were submitted. The overall NOAEL for maternal toxicity in the oral gavage studies in mice, rats and rabbits was 30 mg/kg bw per day, mainly based on decreases in body weights and body weight gains (during the early treatment period) at 100 mg/kg bw per day. Marginal effects in studies in mice (haematological effects) and rats (reduced body weight gains) were not considered as adverse. Selected liver parameters (enzymes, weights and clinical chemistry) were evaluated in developmental toxicity studies in mice and rats. Changes in the liver parameters in these studies were considered an adaptive response and not considered as adverse. In one study in mice, there was an increase in the number of small fetuses (runts) at doses of 30 mg/kg bw per day and above. These small fetuses, defined on the basis of low body weights, were considered unlikely to be due to a single exposure or a small number of exposures. The NOAEL for developmental toxicity in mice was 10 mg/kg bw per day. In other studies in mice, rats and rabbits, developmental effects included increased resorptions, a decreased number of live fetuses, decreased fetal weights, incomplete ossification and visceral and skeletal anomalies. In addition, post-implantation loss was observed in mice. These developmental effects were observed consistently at doses above 30 mg/kg bw per day and in the presence of maternal toxicity in all studies. The overall NOAEL for developmental toxicity was 30 mg/kg bw per day in rats and rabbits.

The Meeting concluded that tebuconazole caused developmental toxicity and teratogenic effects at doses that were maternally toxic in rats and rabbits.

In a study of acute neurotoxicity in rats with tebuconazole, the NOAEL was 50 mg/kg bw based on increased motor activity in male and female rats and decreased footsplay in female rats at 100 mg/kg bw. In a 90-day study of neurotoxicity in rats, no systemic or neurotoxic effects were seen at doses up to 1600 ppm (equal to 107 mg/kg bw per day), the highest dose tested. In a developmental neurotoxicity study in rats with dietary administration, the maternal NOAEL was 300 ppm (equal to 22 mg/kg bw per day), based on decreased body weights, body weight gains and food consumption, prolonged gestation with mortality, and an increased number of dead fetuses at 1000 ppm (equal to 65 mg/kg bw per day). The offspring toxicity NOAEL was 300 ppm (equal to 22 mg/kg bw per day), based on decreased pup viability, decreases in body weights and absolute brain weights, brain measurements and evidence of developmental delays seen at 1000 ppm (equal to 65 mg/kg bw per day), the highest dose tested. Tebuconazole did not produce neurobehavioural or neuropathological changes.

Workers did not report any adverse effects while handling tebuconazole in a production facility. The workers were monitored by routine physical examination and clinical chemistry measurements.

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

Toxicological evaluation

The Meeting reaffirmed the ADI of 0–0.03 mg/kg bw on the basis of an overall NOAEL of 2.9 mg/kg bw per day in two 1-year dietary toxicity studies in dogs, based on histopathological alterations in the adrenals seen at the LOAEL of 4.4 mg/kg bw per day, and using a safety factor of 100.

The Meeting established an acute reference dose (ARfD) of 0.3 mg/kg bw on the basis of a maternal and developmental toxicity NOAEL of 30 mg/kg bw per day in studies of developmental toxicity in rats and rabbits based on maternal toxicity manifested as decreases in body weight gains in the early treatment period and visceral and skeletal anomalies seen at higher doses. The increased

incidence of the number of small fetuses, defined on the basis of low body weights, was considered unlikely to be due to a single exposure or a small number of exposures. The ARfD is supported by the NOAEL of 30 mg/kg bw per day observed in a 28-day oral (gavage) toxicity study in rats based on changes in haematological parameters seen at the LOAEL of 100 mg/kg bw per day, which might be produced by a single dose.

A toxicological monograph was prepared.

Levels relevant to risk assessment

Species	Study	Effect	NOAEL	LOAEL
Mouse	Twenty-one-month study of toxicity and carcinogenicity[a,b]	Toxicity	20 ppm, equal to 5.9 mg/kg bw per day	60 ppm, equal to 18 mg/kg bw per day
		Carcinogenicity	180 ppm, equal to 53 mg/kg bw per day	500 ppm, equal to 85 mg/kg bw per day
	Developmental toxicity[c]	Maternal toxicity	30 mg/kg bw per day	100 mg/kg bw per day
		Embryo and fetal toxicity	10 mg/kg bw per day	30 mg/kg bw per day
Rat	Twenty-eight-day study of toxicity[c]	Toxicity	30 mg/kg bw per day	100 mg/kg bw per day
	Two-year study of toxicity and carcinogenicity[b]	Toxicity	300 ppm, equal to 15.9 mg/kg bw per day	1000 ppm, equal to 55 mg/kg bw per day
		Carcinogenicity	1000 ppm, equal to 55 mg/kg bw per day[d]	—
	Two-generation study of reproductive toxicity[a]	Parental toxicity	300 ppm, equal to 21.6 mg/kg bw per day	1000 ppm, equal to 72.3 mg/kg bw per day[d]
		Offspring toxicity	300 ppm, equal to 21.6 mg/kg bw per day	1000 ppm, equal to 72.3 mg/kg bw per day[d]
		Reproductive toxicity	1000 ppm, equal to 72.3 mg/kg bw per day[d]	—
	Developmental toxicity[c]	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[c]	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
Dog	Two 1-year studies of toxicity[a,b]	Toxicity	100 ppm, equal to 2.9 mg/kg bw per day	150 ppm, equal to 4.4 mg/kg bw per day

[a] Dietary administration.

[b] Two or more studies combined.

[c] Gavage administration.

[d] Highest dose tested.

Estimate of acceptable daily intake for humans

0–0.03 mg/kg bw

Estimate of acute reference dose

0.3 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 tebuconazole

Absorption, distribution, excretion and metabolism in mammals	
Rate and extent of oral absorption	Complete and rapid
Dermal absorption	Not available
Distribution	Extensive
Potential for accumulation	None
Rate and extent of excretion	Rapid and extensive
Metabolism in animals	Extensive; metabolic pathways include hydrolysis, oxidation and conjugation
Toxicologically significant compounds in animals, plants and the environment	Tebuconazole and 1,2,4-triazole
Acute toxicity	
Rat, LD_{50}, oral	1700 mg/kg bw
Rat, LD_{50}, dermal	> 2000 mg/kg bw
Rat, LC_{50}, inhalation	> 0.82 mg/L, dust (4 h exposure, nose only)
Rabbit, dermal irritation	Non-irritating
Rabbit, ocular irritation	Non-irritating
Guinea-pig, dermal sensitization	Not a sensitizer (Magnusson and Kligman and Buehler tests)
Short-term studies of toxicity	
Target/critical effect	Adrenals/hypertrophy of zona fasciculata cells (dogs)
	Liver, blood system and adrenals (rats)
Lowest relevant oral NOAEL	2.9 mg/kg bw per day (overall from two 1-year toxicity studies in dogs)
Lowest relevant dermal NOAEL	1000 mg/kg bw per day (rats)
Lowest relevant inhalation NOAEC	0.5 mg/L
Long-term studies of toxicity and carcinogenicity	
Target/critical effect	Liver toxicity (mice and rats)
Lowest relevant NOAEL	5.9 mg/kg bw per day (carcinogenicity study in mice)
Carcinogenicity	Not carcinogenic in rats, but hepatocarcinogenic in mice; unlikely to pose a carcinogenic risk at human dietary exposure levels
Genotoxicity	
	Not genotoxic

Reproductive toxicity	
Reproduction target/critical effect	No reproductive effects
Lowest relevant reproductive NOAEL	1000 ppm, equal to 72.3 mg/kg bw per day, highest dose tested (rats)
Developmental target/critical effect	Developmental toxicity, including teratogenicity, only at maternally toxic doses in rats and rabbits
Lowest relevant developmental NOAEL	30 mg/kg bw per day (rats, rabbits); 10 mg/kg bw per day (mice; runts)
Neurotoxicity/delayed neurotoxicity	
Acute neurotoxicity	Increased motor activity in rats
Subchronic neurotoxicity	No neurotoxicity in rats
Developmental neurotoxicity	No neurodevelopmental toxicity in rats
Other toxicological studies	
	None
Medical data	
	No adverse effects reported

Summary

	Value	**Study**	**Safety factor**
ADI	0–0.03 mg/kg bw	Two 1-year toxicity studies in dogs	100
ARfD	0.3 mg/kg bw	Developmental toxicity studies in rats and rabbits, supported by a 28-day study of toxicity in rats (gavage)	100