5.8 FENPROPIMORPH (188)

TOXICOLOGY

Fenpropimorph is the ISO-approved common name for (±)-*cis*-4-[3-(4-*tert*-butylphenyl)-2-methylpropyl]-2,6-dimethylmorpholine (IUPAC), with the CAS number 67564-91-4. Fenpropimorph belongs to the chemical class of morpholines; it acts by inhibition of two enzymes in the ergosterol biosynthetic pathway of fungi.

Fenpropimorph has been previously evaluated by JMPR in 1994, 2001 and 2004 and was reviewed by the present Meeting under the periodic review programme of CCPR. In 1994, JMPR established an ADI of 0–0.003 mg/kg bw on the basis of a NOAEL of 0.3 mg/kg bw per day in a 2-year study of toxicity and carcinogenicity in rats. In 2001, JMPR established an ARfD of 1 mg/kg bw on the basis of a NOAEL of 100 mg/kg bw in an acute neurotoxicity study in rats. In 2004, JMPR reviewed the data to determine the most appropriate end-point and NOAEL for establishing an ARfD and evaluated a new screening study of prenatal and postnatal developmental toxicity in rats; that Meeting established an ARfD of 0.2 mg/kg bw on the basis of an overall NOAEL of 15 mg/kg bw per day for embryo and fetal toxicity and teratogenicity in two studies of prenatal developmental toxicity in rabbits.

New studies on absorption, distribution, metabolism and excretion, acute toxicity, skin and eye irritation, skin sensitization, genotoxicity, multigeneration reproductive toxicity and developmental toxicity of the parent compound and genotoxicity studies on the rat and plant metabolite BF 421-10 were submitted. The current Meeting evaluated all previously submitted toxicological data in addition to new published and unpublished toxicological studies.

All critical studies contained statements of compliance with GLP and were conducted in accordance with relevant national or international test guidelines, unless otherwise specified.

Biochemical aspects

In oral gavage studies conducted in rats using [^{14}C-phenyl]fenpropimorph or [^{14}C-dimethylmorpholine]fenpropimorph at a dose of 1 or 15 mg/kg bw, absorption from the gastrointestinal tract was rapid. Following a single dose, an initial peak plasma concentration was followed by a second peak plasma concentration over 1–8 hours, with plasma half-lives of approximately 4–24 hours. The second plasma peak was more apparent in rats administered 15 mg/kg bw and was a consequence of enterohepatic circulation. From mass balance experiments together with a study conducted in bile duct–cannulated rats, absorption was calculated to be approximately 90% in males and 70% in females with the phenyl-labelled compound at 1 mg/kg bw. For the 15 mg/kg bw dose, absorption was complete in both sexes with the phenyl-labelled compound and almost complete in both sexes with the dimethylmorpholine-labelled compound. The higher absorption calculated for the 15 mg/kg bw dose compared with the 1 mg/kg bw dose may be due to enterohepatic circulation, which may lead to an overestimation of the sum of radioactivity excreted in urine in the mass balance experiment and in bile in the biliary excretion experiment. Following absorption, radioactive material was distributed to all organs and tissues, with the highest concentrations of radioactivity found in the gastrointestinal tract and liver.

The excretion of radioactivity was rapid, with approximately similar amounts excreted in the urine and faeces; biliary excretion was significant. For dimethylmorpholine-labelled fenpropimorph, elimination also occurred in exhaled carbon dioxide. Slightly higher excretion in the faeces and lower excretion in the urine were seen in females compared with males. There was no evidence of accumulation of radioactivity in any tissue.

The parent compound was extensively metabolized by several hydroxylation, oxidation, sulfoxylation and demethylation processes, combined with cleavage of the morpholine ring. Besides

biotransformation reactions, conjugation with glucuronic acid combined with further degradations and derivative processes occurred.

Toxicological data

The acute oral toxicity of fenpropimorph in rats and mice was low to moderate. The oral LD_{50} was greater than 500 mg/kg bw and equal to or less than 2000 mg/kg bw in female rats. The dermal LD_{50} in rats was greater than 5000 mg/kg bw. The 4-hour acute LC_{50} in rats was greater than 5.2 mg/L. Fenpropimorph was moderately irritating to the skin and slightly to moderately irritating to the eyes of rabbits. In guinea-pig maximization tests, no skin sensitization occurred.

In repeated-dose toxicity studies in mice, rats and dogs, the main adverse effects were liver toxicity and decreased body weight gain. Increased liver weight together with altered clinical chemistry parameters but without histopathological correlates was the most common finding in the short-term studies.

In a 28-day toxicity study in mice, which tested dietary concentrations of fenpropimorph of 0, 500, 1000, 2000 and 4000 ppm (equal to 0, 79.9, 169, 338 and 671 mg/kg bw per day for males and 0, 83.5, 203, 377 and 786 mg/kg bw per day for females, respectively), the NOAEL was 500 ppm (equal to 79.9 mg/kg bw per day), based on decreased body weight gain at 1000 ppm (equal to 169 mg/kg bw per day).

In a 42-day toxicity study in mice, which tested dietary concentrations of fenpropimorph of 0, 25, 50, 100 and 200 ppm, the 25 ppm concentration (for weeks 1–3) was increased to 400 ppm (for weeks 4–6). The achieved doses were equal to 0, 3.29/47.4, 6.64, 13.1 and 24.0 mg/kg bw per day for males and 0, 4.02/59.9, 8.00, 14.8 and 31.8 mg/kg bw per day for females, respectively. The NOAEL was 200 ppm (equal to 24.0 mg/kg bw per day), the highest dose tested for 42 days. No adverse effects were observed in the 25/400 ppm group.

In a 28-day toxicity study in rats, which tested dietary concentrations of fenpropimorph of 0, 100, 250, 625 and 1600 ppm (equal to 0, 10, 21, 62.5 and 148 mg/kg bw per day for males and 0, 10, 24, 60 and 154 mg/kg bw per day for females, respectively), the NOAEL was 100 ppm (equal to 10 mg/kg bw per day), based on increased bilirubin at 250 ppm (equal to 21 mg/kg bw per day).

In a 90-day toxicity study in rats, which tested dietary concentrations of fenpropimorph of 0, 6.25, 12.5 and 25 ppm (equal to 0, 0.39, 0.78 and 1.55 mg/kg bw per day for males and 0, 0.47, 0.93 and 1.82 mg/kg bw per day for females, respectively), the NOAEL was 25 ppm (equal to 1.55 mg/kg bw per day), the highest dose tested.

A combined subchronic toxicity and neurotoxicity study was also available in rats and is reported below.

In a 28-day toxicity study in dogs, which tested dietary concentrations of fenpropimorph of 0, 200, 400, 800 and 1600 ppm (equal to 0, 7, 12, 27 and 51 mg/kg bw per day for males and 0, 8, 15, 29 and 62 mg/kg bw per day for females, respectively), the NOAEL was 800 ppm (equal to 27 mg/kg bw per day), based on increased platelet count, increased absolute and relative liver weights and decreased absolute and relative testis weights at 1600 ppm (equal to 51 mg/kg bw per day).

In a 90-day toxicity study in dogs, which tested dietary concentrations of fenpropimorph of 0, 50, 100, 200 and 400 ppm (equal to 0, 1.5, 3.0, 6.5 and 11.6 mg/kg bw per day for males and 0, 1.9, 3.7, 7.8 and 14.8 mg/kg bw per day for females, respectively), the NOAEL was 200 ppm (equal to 6.5 mg/kg bw per day), based on increased alanine aminotransferase activity at 400 ppm (equal to 11.6 mg/kg bw per day).

In a 12-month toxicity study in dogs, which tested dietary concentrations of fenpropimorph of 0, 25, 100 and 400 ppm (equal to 0, 0.8, 3.2 and 12.7 mg/kg bw per day for males and females, respectively), the NOAEL was 25 ppm (equal to 0.8 mg/kg bw per day), based on increased alanine aminotransferase activity at 100 ppm (equal to 3.2 mg/kg bw per day).

In an 18-month toxicity and carcinogenicity study in mice, which tested dietary concentrations of fenpropimorph of 0, 5, 30, 150 and 1000 ppm (equal to 0, 0.5, 3.0, 16 and 106 mg/kg bw per day for males and 0, 0.5, 3.5, 17 and 118 mg/kg bw per day for females, respectively), the NOAEL for chronic toxicity was 150 ppm (equal to 16 mg/kg bw per day), based on decreased body weight gain and decreased haemoglobin (males) at 1000 ppm (equal to 106 mg/kg bw per day). No treatment-related increase in tumour incidence was observed in this study.

In a 2-year toxicity and carcinogenicity study in rats, which tested dietary concentrations of fenpropimorph of 0, 5, 10, 50 and 250 ppm (equal to 0, 0.2, 0.3, 1.7 and 8.8 mg/kg bw per day for males and 0, 0.2, 0.4, 2.1 and 11.2 mg/kg bw per day for females, respectively), the NOAEL for chronic toxicity was 10 ppm (equal to 0.4 mg/kg bw per day), based on decreased body weight and body weight gain in females at 50 ppm (equal to 2.1 mg/kg bw per day). No treatment-related increase in tumour incidence was observed in this study.

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

Fenpropimorph was tested for genotoxicity in an adequate range of in vitro and in vivo tests. No evidence of genotoxicity was found.

The Meeting concluded that fenpropimorph 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 fenpropimorph is unlikely to pose a carcinogenic risk to humans.

In a two-generation reproductive toxicity study in rats, which tested dietary concentrations of fenpropimorph of 0, 6.25, 12.6 and 25.0 ppm (equal to 0, 0.5, 1.0 and 2.0 mg/kg bw per day for males and 0, 0.7, 1.4 and 2.7 mg/kg bw per day for females, respectively), the NOAEL for reproductive, parental and offspring toxicity was 25.0 ppm (equal to 2.0 mg/kg bw per day for reproductive and parental toxicity and 2.7 mg/kg bw per day for offspring toxicity), the highest dose tested.

In a second two-generation reproductive toxicity study in rats, which tested dietary concentrations of fenpropimorph adjusted to achieve target doses of 0, 2, 4, 8 and 16 mg/kg bw per day, the NOAEL for reproductive toxicity was 16 mg/kg bw per day, the highest dose tested. The NOAEL for parental toxicity was 4 mg/kg bw per day, based on decreased body weight and body weight gain at 8 mg/kg bw per day. The NOAEL for offspring toxicity was 4 mg/kg bw per day, based on reduced pup body weight and body weight gain at 8 mg/kg bw per day.

In a non-standard prenatal/postnatal toxicity screening study in rats, which tested fenpropimorph doses of 0, 2.5, 10, 40 and 160 mg/kg bw per day administered by gavage from gestation day 15 until the end of lactation, the NOAEL for maternal toxicity was 2.5 mg/kg bw per day, based on marginally reduced body weight gain during lactation at 10 mg/kg bw per day. The NOAEL for embryo/fetal and offspring toxicity was 40 mg/kg bw per day, based on pup mortality, decreased body weight and body weight gain and delayed development (retardation of unfolding of the auricle and fur development and delayed opening of the eyes and auditory canal) at 160 mg/kg bw per day.

In a non-standard prenatal/postnatal toxicity screening study in rats, which tested dietary concentrations of fenpropimorph adjusted throughout gestation and lactation to achieve target doses of 0, 5, 10 and 15 mg/kg bw per day, the NOAEL for reproductive toxicity was 15 mg/kg bw per day, the highest dose tested. The NOAEL for maternal toxicity was 5 mg/kg bw per day, based on decreased body weight gain and feed consumption in dams at 10 mg/kg bw per day. The NOAEL for offspring toxicity was 10 mg/kg bw per day, based on decreased body weight and body weight gain in pups at 15 mg/kg bw per day.

In a developmental toxicity study in rats, which tested fenpropimorph doses of 0, 2.5, 10, 40 and 160 mg/kg bw per day administered by gavage, the NOAEL for maternal toxicity was 10 mg/kg bw per day, based on vaginal bleeding and decreased body weight gain at 40 mg/kg bw per day. The NOAEL for embryo/fetal toxicity was 40 mg/kg bw per day, based on total litter losses, early

resorptions, a decrease in fetal weight and length, and an increase in variations/retardations, particularly cleft palate and asymmetrical sternebrae, in fetuses at 160 mg/kg bw per day.

In a second developmental toxicity study in rats, which tested fenpropimorph doses of 0, 4, 16 and 40 mg/kg bw per day administered by gavage, the NOAEL for maternal toxicity was 4 mg/kg bw per day, based on decreased body weight gain, feed consumption and clinical chemistry parameters that might suggest disturbance of liver function at 16 mg/kg bw per day. The NOAEL for embryo/fetal toxicity was 40 mg/kg bw per day, the highest dose tested.

In a developmental toxicity study in rabbits, which tested fenpropimorph doses of 0, 2.4, 12, 36 and 60 mg/kg bw per day administered by gavage, the NOAEL for maternal toxicity was 12 mg/kg bw per day, based on lethality, abortions, diarrhoea, salivation and inflammation of the vaginal region at 36 mg/kg bw per day. The NOAEL for embryo/fetal toxicity was 12 mg/kg bw per day, based on a slight increase in post-implantation loss and pseudoankylosis in fetuses at 36 mg/kg bw per day, a maternally toxic dose.

In a developmental toxicity study in rabbits, which tested fenpropimorph doses of 0, 7.5, 15 and 30 mg/kg bw per day administered by gavage, the NOAEL for maternal toxicity was 15 mg/kg bw per day, based on swelling of the anus and reduced feed consumption, body weight gain and gravid uterus weight at 30 mg/kg bw per day. The NOAEL for embryo/fetal toxicity was 15 mg/kg bw per day, based on reduced body weight, cleft palate, shortened bones of the forelimbs and hindlimbs along with position anomaly of these limbs and fused sternebrae at 30 mg/kg bw per day.

An overall NOAEL for maternal toxicity in the developmental toxicity studies in rabbits was 15 mg/kg bw per day, and an overall NOAEL for embryo and fetal toxicity was 15 mg/kg bw per day.

Fenpropimorph demonstrated only very low binding affinity to recombinant human androgen receptor in a cell-free in vitro system. Fenpropimorph did not show any estrogenic receptor–mediated activity in the in vitro E-screen assay.

The Meeting concluded that fenpropimorph is teratogenic in rats and rabbits at maternally toxic doses, exceedingly so in rats.

In an acute neurotoxicity study in rats, which tested fenpropimorph doses of 0, 100, 500 and 1500 mg/kg bw administered by gavage, the NOAEL for neurotoxicity was 1500 mg/kg bw, the highest dose tested. The NOAEL for systemic toxicity was 100 mg/kg bw, based on piloerection, behavioural signs and decreased body weight gain at 500 mg/kg bw.

In an acute study primarily investigating effects on cholinesterase activity in rats, which tested fenpropimorph doses of 0, 420, 1240 and 2290 mg/kg bw administered by gavage, no consistent effects on brain cholinesterase activity were observed, and erythrocyte cholinesterase activity was not affected.

In a combined 13-week toxicity and neurotoxicity study in rats, which tested dietary concentrations of fenpropimorph of 0, 1, 10, 100 and 1000 ppm (equal to 0, 0.1, 0.7, 7.1 and 71.0 mg/kg bw per day for males and 0, 0.1, 0.8, 8.5 and 77.7 mg/kg bw per day for females, respectively), the NOAEL for systemic toxicity was 10 ppm (equal to 0.7 mg/kg bw per day), based on decreased body weight gain, decreased landing foot splay and increased relative liver weight at 100 ppm (equal to 7.1 mg/kg bw per day); the observed change in landing foot splay was considered a secondary consequence of systemic toxicity. The NOAEL for neurotoxicity was 1000 ppm (equal to 71.0 mg/kg bw per day) the highest dose tested.

The Meeting concluded that fenpropimorph is not neurotoxic.

A 14-day dietary study investigating hepatic drug metabolizing enzyme activities in male rats indicates that fenpropimorph is an inducer of a number of hepatic P450 enzymes.

Toxicological data on metabolites and/or degradates

BF 421-10 (*cis*-2,6-dimethylmorpholine), a major metabolite in rats (and in plants), was tested in an adequate range of in vitro and in vivo genotoxicity tests. No evidence of genotoxicity was found.

BF 421-14 (fenpropimorph *N*-oxide), a reported plant metabolite and in vitro degradate/metabolite seen following incubation of fenpropimorph with rat, mouse, dog or human liver microsomes, was evaluated in silico with the structure–activity relationship models OASIS TIMES and VEGA. No structural alerts indicating genotoxicity were identified, with the limitation that BF 421-14 was out of the prediction domain.

Human data

No information was provided on the health of workers involved in the manufacture or use of fenpropimorph. No information on accidental or intentional poisoning in humans is available.

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

Toxicological evaluation

The Meeting established an ADI of 0–0.004 mg/kg bw, based on a NOAEL of 0.4 mg/kg bw per day for decreased body weight and body weight gain in females in a 2-year combined toxicity and carcinogenicity study in rats, with the application of a 100-fold safety factor.

The previous ADI of 0–0.003 mg/kg bw was withdrawn.

The Meeting established an ARfD of 0.1 mg/kg bw, based on an overall NOAEL of 15 mg/kg bw per day for embryo and fetal toxicity and teratogenicity in two prenatal developmental toxicity studies in rabbits, with application of a 100-fold safety factor and rounding down to one significant figure in view of the severity of the effects at the lowest-observed-adverse-effect level (LOAEL), thus providing a margin of 300 between the ARfD and the LOAEL for teratogenicity. This ARfD applies to women of child-bearing age only.

The Meeting also established an ARfD of 0.4 mg/kg bw, based on decreased body weight and feed consumption observed in pregnant dams in a developmental toxicity study in rabbits at 60 mg/kg bw per day, which could not be excluded as being due to a single dose. These acute effects were not seen at 36 mg/kg bw per day. A safety factor of 100 was applied. This ARfD applies to the general population.

The Meeting withdrew the previous ARfD of 0.2 mg/kg bw.

A toxicological monograph was prepared.

Levels relevant to risk assessment of fenpropimorph

Species	Study	Effect	NOAEL	LOAEL
Mouse	Eighteen-month study of toxicity and carcinogenicity[a]	Toxicity	150 ppm, equal to 16 mg/kg bw per day	1 000 ppm, equal to 106 mg/kg bw per day
		Carcinogenicity	1 000 ppm, equal to 106 mg/kg bw per day[b]	–
Rat	Ninety-day study of toxicity/neurotoxicity[a]	Toxicity	10 ppm, equal to 0.7 mg/kg bw per day	100 ppm, equal to 7.1 mg/kg bw per day
		Neurotoxicity	1 000 ppm, equal to	–

Species	Study	Effect	NOAEL	LOAEL
			71.0 mg/kg bw per day[b]	
	Two-year study of toxicity and carcinogenicity[a]	Toxicity	10 ppm, equal to 0.4 mg/kg bw per day	50 ppm, equal to 2.1 mg/kg bw per day
		Carcinogenicity	250 ppm, equal to 8.8 mg/kg bw per day[b]	–
	Two-generation study of reproductive toxicity[a]	Reproductive toxicity	16 mg/kg bw per day[b]	–
		Parental toxicity	4 mg/kg bw per day	8 mg/kg bw per day
		Offspring toxicity	4 mg/kg bw per day	8 mg/kg bw per day
	Developmental toxicity study[c]	Maternal toxicity	4 mg/kg bw per day	16 mg/kg bw per day
		Embryo and fetal toxicity	40 mg/kg bw per day[b]	–
Rabbit	Developmental toxicity studies[c,d]	Maternal toxicity	15 mg/kg bw per day	30 mg/kg bw per day
		Embryo and fetal toxicity	15 mg/kg bw per day	30 mg/kg bw per day
Dog	One-year study of toxicity[a]	Toxicity	25 ppm, equal to 0.8 mg/kg bw per day	100 ppm, equal to 3.2 mg/kg bw per day

[a] Dietary administration.

[b] Highest dose tested.

[c] Gavage administration.

[d] Two or more studies combined.

Acceptable daily intake (ADI)

0–0.004 mg/kg bw

Acute reference dose (ARfD)

0.1 mg/kg bw (applies to women of child-bearing age only)

0.4 mg/kg bw (applies to the general population)

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 fenpropimorph

Absorption, distribution, excretion and metabolism in mammals	
Rate and extent of oral absorption	Rapid, with 70–100% absorption

Distribution	Rapid and extensive distribution
Potential for accumulation	No potential for accumulation
Rate and extent of excretion	Rapid and nearly complete excretion within 96 h
Metabolism in animals	Extensively metabolized
Toxicologically significant compounds in animals and plants	Fenpropimorph
Acute toxicity	
Rat, LD_{50}, oral	> 500 and < 2 000 mg/kg bw
Rat, LD_{50}, dermal	> 5 000 mg/kg bw
Rat, LC_{50}, inhalation	5.2 mg/L
Rabbit, dermal irritation	Moderately irritating
Rabbit, ocular irritation	Slightly to moderately irritating
Guinea pig, dermal sensitization	Non-sensitizing (maximization test)
Short-term studies of toxicity	
Target/critical effect	Decreased body weight gain
Lowest relevant oral NOAEL	0.7 mg/kg bw per day (rat)
Lowest relevant dermal NOAEL	2.0 mg/kg bw per day (rat)
Lowest relevant inhalation NOAEC	2.6 mg/kg bw per day (0.01 mg/L; rat)
Long-term studies of toxicity and carcinogenicity	
Target/critical effect	Decreased body weight and body weight gain
Lowest relevant NOAEL	0.4 mg/kg bw per day (rat)
Carcinogenicity	Not carcinogenic in mice or rats[a]
Genotoxicity	
	No evidence of genotoxicity[a]
Reproductive toxicity	
Reproduction target/critical effect	No evidence of reproductive toxicity; decreased body weight and body weight gain in dams and pups (rat)
Lowest relevant parental NOAEL	4 mg/kg bw per day (rat)
Lowest relevant offspring NOAEL	4 mg/kg bw per day (rat)
Lowest relevant reproduction NOAEL	16 mg/kg bw per day, highest dose tested (rat)
Developmental toxicity	
Developmental target/critical effect	Litter loss, early resorptions, decreased fetal weight and length and increase in variations, retardations and malformations (rat); post-implantation loss, decreased fetal weight, malformations (cleft palate) and skeletal anomalies (rabbit)
Lowest maternal NOAEL	4 mg/kg bw per day (rat)
Lowest embryo and fetal NOAEL	15 mg/kg bw per day (rabbit)
Neurotoxicity	
Acute neurotoxicity	1 500 mg/kg bw, highest dose tested (rat)

Subchronic neurotoxicity	71.0 mg/kg bw per day, highest dose tested (rat)
Developmental neurotoxicity	No data
Other toxicological studies	
Immunotoxicity	No data
Human data	
	No data

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

Summary

	Value	**Studies**	**Safety factor**
ADI	0–0.004 mg/kg bw	Two-year toxicity and carcinogenicity study (rat)	100
ARfD	0.1[a]	Developmental toxicity studies (rabbit)	100
ARfD	0.4[b]	Developmental toxicity studies (rabbit)	100

[a] Applies to women of child-bearing age.

[b] Applies to the general population.