5.15 FENBUCONAZOLE (197)

TOXICOLOGY

Fenbuconazole is the ISO-approved common name for 4-(4-chlorophenyl)-2-phenyl-2-(1H-1,2,4-triazol-1-ylmethyl)butyronitrile (IUPAC), with the CAS number 119611-00-6. It is a triazole fungicide intended for agricultural and horticultural use for the control of a variety of fungal infections of crops.

JMPR evaluated fenbuconazole in 1997, when an ADI of 0–0.03 mg/kg bw was established on the basis of a NOAEL of 3 mg/kg bw per day in a chronic toxicity study in rats.

The present Meeting considered the requirement for an ARfD for fenbuconazole, on the basis of data from the previous evaluations and from one new developmental toxicity study in rabbits.

All critical studies complied with GLP.

Toxicological data

Fenbuconazole has low acute oral toxicity (LD_{50} > 2000 mg/kg bw in rats), and clinical signs observed after administration of high doses are generally nonspecific. In short-term studies of toxicity in mice, rats and dogs and in long-term studies of toxicity in mice and rats, fenbuconazole generally induced decreases in body weight gain and feed consumption, liver toxicity and changes in clinical chemistry. Less frequently, kidney, adrenal and thyroid toxicity and haematological effects were seen. The Meeting considered the observed effects in these repeated-dose studies as unlikely to be the result of a single (1 day) exposure to fenbuconazole.

In a previously evaluated two-generation study of reproductive toxicity in rats, the observed adverse effects were similar to those found in the repeated-dose studies. In addition, at 800 ppm (equivalent to 40 mg/kg bw per day), the number of F_0 and F_1 dams that delivered live young was reduced to 10 out of 25 and 4 out of 21, respectively, compared with 21/25 and 22/25 in F_0 and F_1 control dams, respectively, whereas the number of stillborn was increased at the same dose. Some F_0 (n = 4) and F_1 (n = 3) females at this dose level died while delivering their litters. The NOAEL was 80 ppm (equivalent to 4 mg/kg bw per day).

In this multigeneration study, it was reported that a considerable number of high-dose dams did not deliver. The Meeting considered the possible causes for this finding and concluded that it was unlikely to be the result of an acute (single day) exposure.

In a previously evaluated developmental toxicity study in rats, a reduction in body weight gain was observed from gestation day (GD) 6 to GD 8 at 75 mg/kg bw per day. Feed consumption was not measured. Also at this dose, the number of animals with scant faeces was increased, often from GD 7 or 8 onwards. At 150 mg/kg bw per day, an increased incidence of early, late and total resorptions was seen. No effects were observed at 30 mg/kg bw per day.

In a previously evaluated developmental toxicity study in rabbits, a dose-dependent reduction in feed consumption and increased incidences of soft or scant faeces were seen at 30 and 60 mg/kg bw per day. At the high dose, these effects were marked and occurred early after the start of treatment. Feed consumption was 172, 162, 148 and 99 g/dam on GDs 7–8 and 176, 153, 141 and 46 g/dam on GDs 8–9 at 0, 10, 30 and 60 mg/kg bw per day, respectively (these values were calculated by the present Meeting from the tables with individual data). In addition, body weight gain from GD 7 to GD 9 was dose dependently reduced: 1, −13, −43 and −174 g weight gain at 0, 10, 30 and 60 mg/kg bw per day, respectively, reaching statistical significance at 30 and 60 mg/kg bw per day (calculation of the mean body weight changes and statistical analysis performed by the present Meeting). At 60 mg/kg bw per day, only 1 out of 19 does produced a viable litter, whereas 10 does had litters that were totally resorbed and 6 does aborted. At this high dose, an increase in the number of early resorptions was observed (mean number 0.3, 0.2, 0.1 and 4.4 per dam at 0, 10, 30 and 60 mg/kg bw per day, respectively). The NOAEL for maternal toxicity was 10 mg/kg bw per day on the basis of a

decrease in feed consumption and body weight (gain) soon after the commencement of treatment and an increase in soft or scant faeces at 30 mg/kg bw per day. The NOAEL for developmental effects was 30 mg/kg bw per day, on the basis of early resorptions and abortions at 60 mg/kg bw per day.

A second oral developmental toxicity study in rabbits[1], which was not previously evaluated by JMPR, was performed according to OECD Test Guideline 414. Pregnant New Zealand White rabbits (21 per group) were exposed from GD 7 to GD 19 to fenbuconazole technical (lot no. 3-2508R FL-12L-656,748-038W002, purity 97.01%) by gavage at doses of 0, 15 or 45 mg/kg bw per day. All rabbits were observed daily for clinical signs. Body weights were recorded on GDs 0, 7, 9, 11, 14, 17, 20 and 29. Feed consumption was recorded daily from GD 2 to GD 29. Rabbits were killed on GD 29, and gross examination of thoracic and abdominal viscera was performed on all rabbits. The uterus was weighed, and numbers of corpora lutea, implantations, fetuses and early and late resorptions were counted. All live fetuses were weighed and examined for external and visceral alterations. Subsequently, the fetuses were stained with Alizarin Red S and examined for skeletal alterations.

No treatment-related deaths were observed. One low-dose doe died due to an intubation error. One high-dose female that aborted on GD 26 was killed. Scant or no faeces were noted in several does at 45 mg/kg bw per day, but generally only after several days of treatment. Body weight gain in the treatment groups was reduced, not statistically significantly, from GD 7 to GD 9 (does gained 25, −4 and 1 g at 0, 15 and 45 mg/kg bw per day, respectively). Daily feed consumption was not affected during this period (feed consumption was 293, 189 and 297 g at 0, 15 and 45 mg/kg bw per day, respectively). No treatment-related effect on body weight gain of the does over the entire treatment period (GDs 7–19) was noted. Feed consumption was slightly decreased at the high dose from GD 7 to GD 19 (feed consumption was 147, 146 and 136 g/day at 0, 15 and 45 mg/kg bw per day, respectively). No treatment-related effects on gravid uterine weight were noted at any dose level. Necropsy revealed no treatment-related gross lesions in does at any dose level. No treatment-related effects were noted in the number of viable litters, mean numbers of resorptions, live fetuses or dead fetuses or sex ratio per litter at any dose level. A treatment-related decrease (9%) in combined (male and female) fetal body weight was noted in pups at 45 mg/kg bw per day. The difference was not statistically significant when males and females were compared separately. No treatment-related increases were detected in the type or incidence of external, visceral or skeletal variations or malformations at any dose level.

The NOAEL for maternal toxicity was 15 mg/kg bw per day, on the basis of a decrease in feed consumption during the entire treatment period and an increase in scant or no faeces at 45 mg/kg bw per day.

The NOAEL for developmental effects in this study was 15 mg/kg bw per day, based on a reduction in combined male and female fetal body weight.

The overall NOAEL for maternal toxicity in the rabbit was 15 mg/kg bw per day, based on a reduction in body weight (gain) soon after the commencement of treatment at 30 mg/kg bw per day. The overall NOAEL for developmental toxicity in the rabbit was 30 mg/kg bw per day, based on reduced fetal body weight at 45 mg/kg bw per day and early resorptions and abortions at 60 mg/kg bw per day.

The Meeting concluded that the existing database on fenbuconazole was adequate to characterize the potential acute hazard to fetuses, infants and children.

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[1] Inman-Wood SL, Craig LP, Danberry TL (2000). Fenbuconazole (RH-7592 technical): oral (gavage) developmental toxicity study in rabbits. Unpublished report no. 00R-017 from R&H Spring House Research, Spring House, PA, USA. Submitted to WHO by Dow AgroScience Gmbh, Munich, Germany.

Toxicological evaluation

The Meeting established an ARfD of 0.2 mg/kg bw on the basis of an overall NOAEL of 15 mg/kg bw per day, based on the reductions in body weight, body weight gain and feed consumption observed in developmental toxicity studies in the rabbit and application of a safety factor of 100. The ARfD is supported by the overall NOAEL for developmental toxicity in the rabbit of 30 mg/kg bw per day, based on the increased incidence of early resorptions observed at 60 mg/kg bw per day early after treatment commenced, and a NOAEL of 30 mg/kg bw per day for maternal toxicity in the rat, based on reduced body weight gain at 75 mg/kg bw per day.

A toxicological monograph was not prepared.

Levels relevant to risk assessment

Species	Study	Effect	NOAEL	LOAEL
Rat	Developmental toxicity study[a]	Maternal toxicity Embryo and fetal toxicity	30 mg/kg bw per day 75 g/kg bw per day	75 mg/kg bw per day 150 mg/kg bw per day
Rabbit	Developmental toxicity studies[a,b]	Maternal toxicity Embryo and fetal toxicity	15 mg/kg bw per day 30 mg/kg bw per day	30 mg/kg bw per day 45 mg/kg bw per day

[a] Gavage administration.

[b] Several studies combined.

DIETARY RISK ASSESSMENT

Short-term intake

ARfD for fenbuconazole is 0.2 mg/kg bw. The International Estimated Short-Term Intake (IESTI) for fenbuconazole was calculated for the plant commodities for which STMR and HR levels were estimated by the 2009 JMPR and for which consumption data were available. The results are shown in Annex 4. The IESTI represented a maximum of 10% of the ARfD. The Meeting concluded that the short-term intake of fenbuconazole residues from uses considered by the current Meeting was unlikely to present a public health concern.