FENPYROXIMATE (addendum)

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Explanation

Evaluation for an acute reference dose

Fenpyroximate is a phenoxypyrazole acaricide. Fenpyroximate was evaluated by the 1995 JMPR, when an acceptable daily intake (ADI) of 0–0.01 mg/kg bw was established based upon a no-observed-adverse-effect level (NOAEL) of 1 mg/kg bw per day in a 104-week study in rats and a safety factor of 100. The critical effect in that study was a reduction in body-weight gain. Fenpyroximate was re-evaluated by the present Meeting in order to determine an acute reference dose (ARfD).

1. Toxicological studies

1.1 Short-term studies of toxicity

Mice

A 4-week range-finding study in SPF ICR (Crj:CD-1) mice was undertaken. This was to determine the doses suitable for use in an 18-month study of carcinogenicity. Groups of nine males and nine females (aged 4 weeks) were given diets containing fenpyroximate (purity, 97.9%) at a concentration of 0, 20, 100 or 500 ppm, producing intakes of test material of 0, 2.58, 12.9 and 53.2 mg/kg bw per day for males and 0, 3.07, 14.5 and 66.7 mg/kg bw per day for females. The animals were observed daily. Food consumption was measured weekly. After 4 weeks, urine analysis was carried out. Blood was taken for haematological and clinical chemistry examination (including cholinesterase activity) after 4 weeks of treatment. At autopsy, the weights of selected organs were recorded. Pathological examination by microscopy was not carried out. No abnormal clinical signs were observed, and no deaths occurred. There was a decrease in body weight compared with that of the controls at weeks 1, 2 and 4 in the males and at week 4 in the females at 500 ppm. In the same group, food consumption was depressed in the males at weeks 1 and 4 and at week 1 at 100 ppm. The specific gravity of the urine was reduced in male mice at 100 and 500 ppm. Notable changes in haematological parameters were not seen. A decrease in

alanine aminotransferase activity was seen in male mice and an increase in blood urea nitrogen in female mice, both at the highest dietary concentration only. No test-material-related changes were noted in plasma or erythrocyte cholinesterase activities. No test-material related changes in gross pathology or organ weights were observed. The NOAEL for the study was 20 ppm (equal to 2.58 and 3.07 mg/kg bw per day in males and females respectively) on the basis of reduced food consumption at week 1 in males at 100 ppm (Takahashi, 1987).

Another 4-week range-finding study in SPF ICR (Crj:CD-1) mice was undertaken to determine the doses suitable for use in an 18-month study of carcinogenicity. A second range finding study was considered necessary, as few changes were found in the first (see above; Takahashi, 1987). Groups of nine males and nine females (aged 5 weeks) were given diets containing fenpyroximate (purity, 97.9%) at a concentration of 0, 80, 400 or 2000 ppm. These diets produced intakes of fenpyroximate of 0, 10.8, 48.4 and 182 mg/kg bw per day for males and 0, 11.7, 50.4 and 170 mg/kg bw per day for females. The animals were observed daily and the numbers of animals killed in extremis or found dead were recorded. Body weights were recorded weekly and food consumption was recorded over each period of 7 days. Urine analysis was performed on survivors at 4 weeks. Blood was taken for haematological and clinical chemistry examination (including cholinesterase activity) after 4 weeks of treatment. At autopsy, the weights of selected organs were recorded. Pathological examination by microscopy was not carried out. No deaths were seen and no clinical sign attributable to fenpyroximate was observed. At 2000 ppm, there was decreased body-weight gain and food consumption, while at 400 ppm in males there was decreased body-weight gain. Haematological examination showed decreases in erythrocyte volume fraction, haemoglobin concentration and total leukocyte count in males, and in haemoglobin concentration, erythrocyte count and mean corpuscular haemoglobin in females. An increase in aspartate aminotransferase activity was seen in both sexes and a decrease in total plasma protein was seen, also in both sexes. At 2000 ppm in males, absolute weights of the brain, pituitary, heart, thymus, kidney and testis were decreased. There was also, at this dietary concentration in the males, increases in the relative weights of the brain, thyroid, heart and adrenals and decreases in relative weights of the thymus and spleen. In the females at the highest dietary concentration, there were decreases in the absolute weight of the brain, pituitary, thyroid, heart, thymus, liver, kidney, spleen, adrenal and ovaries and an increase in the relative weight of the brain, heart and liver, and a decrease in the relative weight of the spleen and ovaries. At 400 ppm, the only finding of interest was a decrease in body-weight gain in males; on the basis of this finding, the NOAEL was 80 ppm, equal to 10.8 mg/kg bw per day for males and 11.7 mg/kg bw per day for females (Takahashi, 1988).

Rats

A 13-week study in CD rats was undertaken to assist in determining the doses for a 2-year combined study of carcinogenicity and toxicity. Groups of 10 males and 10 females were given diets containing fenpyroximate (purity, 99.0%) at a concentration of 0, 20, 100 or 500 ppm (equal to 0, 1.30, 6.57 and 35.2 mg/kg bw per day for males and 0, 1.65, 8.29 and 38.6 mg/kg bw per day for females. The rats were examined twice daily and any clinical signs recorded. A more detailed physical examination was carried out weekly. Body weights were estimated weekly, as was food consumption. Ophthalmoscopy was carried out before the start of the experiment on all rats and at 13 weeks in the controls and in the rats fed fenpyroximate at the highest dietary concentration. Blood was taken at 13 weeks for haematological and clinical chemistry examination. Urine analysis was undertaken at 13 weeks. After the rats had been killed, selected organs were removed, weighed and processed

for microscopical examination. A total of three intercurrent mortalities occurred (two males at the highest dietary concentration, and one female at 20 ppm). None of these fatalities was believed to be related to the administration of the test material. No abnormal clinical signs were seen, but hair loss and encrustations/excoriations of the skin were seen in females at 500 ppm; a few males at this dose had encrustations of the muzzle. Body-weight gain in both sexes at 100 and 500 ppm was lower than that in controls (markedly so at 500 ppm). Food consumption was markedly lower in both sexes in rats receiving fenpyroximate at a dietary concentration of 500 ppm. No significant abnormality was found on ophthalmoscopy. At 500 ppm, there was an increase in erythrocyte volume fraction, haemoglobin concentration and erythrocyte count, as well as a decrease in total leukocyte count in males and an increase in erythrocyte volume fraction, haemoglobin concentration and erythrocyte count in females. At 100 ppm, there was a decrease in total leukocyte count in males. Lowered total protein was seen in both sexes at 500 ppm and in females at 100 ppm. Lower plasma butyrylcholinesterase activity was seen in females at 500 ppm. A rise in the activity of alkaline phosphatase was observed in females at 500 ppm. In rats treated with fenpyroximate at 500 ppm for 12 weeks, the volume and pH of the urine were decreased in males and the specific gravity was decreased in females. No treatment-related intergroup differences were seen in organ weights. At autopsy, facial hair loss was noted in females at 500 ppm. At microscopy, minimal hepatocyte hypertrophy was seen in both sexes at 100 ppm and 500 ppm. The NOAEL for the study was 20 ppm, equal to 1.30 mg/kg bw per day for males and 1.65 mg/kg bw per day for females, on the basis of minimal hepatocyte hypertrophy at the higher doses (Aughton, 1987).

Dogs

In a 13-week study, groups of four male and four female dogs received capsules containing fenpyroximate (purity, 98.4–98.6%) at a dose of 2, 10 or 50 mg/kg bw per day. Controls (four dogs of each sex per group) received the empty gelatin capsules. Dogs were inspected throughout the working day and daily observation of each animal was carried out. A more detailed weekly examination was also carried out. A detailed veterinary examination was carried out before the start of the study and after 4, 8 and 12 weeks of treatment. Ophthalmoscopic examination of the eyes was undertaken after 4, 8 and 12 weeks of treatment. Debilitated animals were carefully observed and those in extremis were killed, blood samples having been taken ante mortem. Body weight was measured at the start of the study, thence weekly and before death. Food consumption was measured daily. Water consumption was measured during 3 days in week 6. Electrocardiography was performed before the start of treatment and at weeks 6 and 12; at weeks 6 and 12, electrocardiography was performed both 2 h and 24 h after dosing. Before the start of treatment and after 6 and 12 weeks of dosing, blood was taken for haematological investigations and clinical chemistry studies; during the treatment period, samples were taken before dosing. Urine analysis was carried out before the start of the study and after 11 weeks of treatment. Surviving dogs were killed at 12 weeks and a detailed necropsy undertaken. Selected organs were removed and weighed. Samples of selected organs and any macroscopical abnormalities were processed for histopathological examination. Two females at the highest dose were killed in extremis during the study, because of severe weight loss and loss of appetite. Dogs in all treated groups had diarrhoea, and in the males this appeared to be dose-related and was apparent from week 1 (see Tables 1 and 2).

Emesis was seen in both sexes at 10 and 50 mg/kg bw per day. Emaciation was seen at 50 mg/kg bw per day (and in one female at 2 mg/kg bw per day). Torpor was seen in some females at 2 and 10 mg/kg bw per day, and in males and females at 50 mg/kg bw per

Table 1. The mean percentage[a] of dogs having diarrhoea after treatment with capsules containing fenpyroximate in a 13-week study

Sex	Dose (mg/kg bw per day)			
	0	2	10	50
Males	8.5	22.7	21.2	70.0
Females	5.0	30.8	50.0	48.0

From Broadmeadow (1989)

[a] The percentage of dogs having diarrhoea was recorded each day. The mean percentage of dogs having diarrhoea was calculated by adding the daily percentage for each group and dividing by the number of days on which observations had been carried out

Table 2. Data from individual animals[a] on diarrhoea observed before dosing and during week 1 of dosing

Individual	Dose (mg/kg bw per day)							
	Males				Females			
	0	2	10	50	0	2	10	50
1	0 (3)	0 (4)	0 (4)	0 (7)	0 (0)	0 (5)	0 (5)	0 (3)
2	0 (0)	0 (2)	0 (6)	0 (7)	0 (0)	1 (6)	0 (6)	1 (7)
3	0 (0)	0 (0)	1 (0)	0 (2)	3 (3)	0 (2)	0 (0)	0 (2)
4	0 (0)	0 (1)	0 (1)	0 (6)	0 (0)	0 (0)	0 (1)	0 (0)

From Broadmeadow (1989)

[a] The first figure is the number of days during the week before dosing that each beagle had diarrhoea; the figure in parentheses is the number of days during the first week of dosing that each beagle had diarrhoea

day. Weight loss was seen in week 1, in females receiving fenpyroximate at a dose of 10 mg/kg bw per day and in males and females at a dose of 50 mg/kg bw per day. Body-weight gain was clearly depressed at 50 mg/kg bw per day in males, and at 50 and 10 mg/kg bw per day in females, compared with that of the controls. Body-weight gain in females was marginally depressed, compared with that of the controls, in the group receiving fenpyroximate at 2 mg/kg bw per day. Food consumption was unaffected by treatment in males, but was reduced by treatment in a dose-related fashion in females. No treatment-related ocular lesions were noted. Slight bradycardia was seen in all treatment groups in both sexes, but especially in the groups receiving fenpyroximate at 10 and 50 mg/kg bw per day. There was no consistent difference between the measurements made 2 h after dosing and 24 h after dosing, and the bradycardia was not consistently present at 2 mg/kg bw per day. In males at all doses and in females at 2 and 10 mg/kg bw per day, no differences in haematological parameters were seen, compared with those of the concurrent controls. In females at 50 mg/kg bw per day, low total leukocyte counts at 6 weeks and 12 weeks, prolonged activated partial thromboplastin times at 6 weeks and high platelet counts at 12 weeks were recorded relative to these values for the concurrent controls. The two decedents (both females at 50 mg/kg bw per day) had low leukocyte counts. Raised blood urea nitrogen concentration was seen in females at 50 mg/kg bw per day at week 6, and at 2 and 50 mg/kg bw per day at week 12; it is unclear whether these effects were treatment-related as there was no clear dose–response relationship. Low concentrations of glucose were seen in males at 10 mg/kg bw per day and in both sexes at 50 mg/kg bw per day at weeks 6 and 12. The two decedents (both females at 50 mg/kg bw per day) had high blood urea concentrations and low plasma butyrylcholinesterase activities, and one of them had a low concentration of blood glucose. No intergoup differences were seen in the results of urine analysis. Slightly higher absolute and relative weights of the adrenals were observed in males at 50 mg/kg bw

per day and slightly higher relative weights of the adrenals in females at that dose. Relative weights of the liver were increased in both sexes at 50 mg/kg bw per day. Macroscopic examination post mortem showed emaciation in one surviving female at 50 mg/kg bw per day. The decedents showed emaciation. There was depleted hepatic glycogen and fine renal medullary cytoplasmic vacuolation in the two decedent females at the highest dose, as well as in one surviving female at 50 mg/kg bw per day. The lowest-observed-adverse-effect level (LOAEL) for the study was 2 mg/kg bw per day on the basis of clinical signs at that dose (diarrhoea in both sexes, and torpor in females) and reduced body-weight gain in females. This LOAEL is probably close to the NOAEL (Broadmeadow, 1989).

1.2 Reproductive toxicity

(a) Multigeneration studies

Rats

In a two-generation study of toxicity, groups of male and female CD rats were given diets containing fenpyroximate (purity, 97.3%) at a concentration of 0, 10, 30 or 100 ppm (equal to 0.67, 1.99 and 6.59 mg/kg bw per day for the F_o males and 0.83, 2.44 and 8.60 mg/kg bw per day for the F_o females, and 0.78, 2.33 and 8.45 mg/kg bw per day for the F_1 males and 0.96, 2.82 and 9.92 mg/kg bw per day for the F_1 females). In the F_o generation, there were 24 males and 24 females in each group and they received the test diets for 14 weeks before being paired to produce the F_1 litters; treatment of the F_o parents was continued throughout mating and until weaning of the F_1 offspring, at which time the F_0 males were killed, while the females were killed about 10 days later. At each dietary concentration, the size of these litters was reduced to eight (four males and four females where the numbers of each sex in the litter made this possible). Where the litter size was less than eight, culling was not carried out. Twenty-four males and 24 females were selected as the F_1 generation (if possible, one male and one female being selected from each litter. These animals were given diets containing fenpyroximate, as described above, for 14 weeks, after which they were paired to produce the F_2 litters. Treatment of the F_1 parents via the diet continued throughout mating and until weaning of the F_2 offspring, at which time the F_1 males and the F_2 offspring were killed, while the females were killed about 10 days later. All animals were examined daily throughout the study and any clinical signs were recorded. Animals found dead or killed in extremis were examined macroscopically and abnormal tissues retained. Males were weighed weekly throughout, while females were weighed weekly until mating was detected and thence on days 0, 6, 13 and 20 post coitum and on postnatal days 1, 4, 7, 14, 21 and 25. Food consumption was recorded weekly until pairing. The time between pairing and detection of mating was noted (precoital interval) and the time between detection of mating and commencement of parturition (i.e. the duration of gestation) was recorded. In each generation, on postnatal day 1 the number of offspring borne (alive or dead) was recorded, together with the individual weights and sex. The offspring were examined. Thereafter, daily records were kept of mortality of the offspring. The offspring were weighed on postnatal days 1 and 4 (i.e. before culling) and on postnatal days 7, 14, 21 and 25, and sexed on postnatal days 1 and 4 (before culling) and on postnatal days 14 and 25. Physical development was assessed by recording the time of unfolding of the pinna, growth of body hair, tooth eruption and eye opening. All parental animals were the subject of detailed necropsy and the reproductive organs were weighed (testis, seminal vesicles, prostate and epididymis in males, uterus and ovaries in females) and retained. In the females, the number of uterine implantation sites was recorded. Histopathological examination was carried out on the reproductive organs (testis, seminal vesicles, prostate and

epididymis in males, ovaries, uterus, vagina in females and pituitary in both sexes) and also on any tissue noted at macroscopic examination to be abnormal. Additionally, in those females with litter loss, the mammary glands were examined histopathologically. Offspring found dead, culled at postnatal day 4, F_1 weanlings not selected for continuation of the study (that were killed at age 29–32 days) and F_2 weanlings (that were killed at age 25–27 days) were examined externally and internally for macroscopic abnormalities. In the offspring, any tissue noted at macroscopic examination to be abnormal was examined histopathologically.

In the F_o generation, no intergroup differences in clinical signs were observed. One female in the F_o generation, receiving fenpyroximate at 30 ppm, was killed in extremis, its poor condition apparently being due to difficulties with parturition, this event occurring on the 23rd day post coitum. Although there were some minor intergroup differences in body-weight gain in the males of the F_o generation, these were not dose-related. In the females at 100 ppm, weight gain was reduced in the period up to pairing and during gestation. In the F_o females at 30 ppm, there was slightly reduced body-weight gain during gestation. In the F_o males at 100 ppm, there was slightly reduced food consumption compared with that of the controls, but food consumption was not reduced in males receiving fenpyroximate at at lower dietary concentration nor in any group of females. Estrus cycles, mating performance, gestation length and gestation index were not affected by treatment. At 100 ppm in the F_o generation, the conception rate and fertility index were slightly reduced. Litter size at birth and viability up until the time of weaning were not affected by treatment. The initial body weights of the offspring were similar in all groups, but weight gain until weaning of the F_1 offspring in the group receiving fenpyroximate at 100 ppm was reduced. Physical development in the groups was similar. There was no indication of a treatment-related effect on sex ratio. Necropsy of adult F_o rats, of F_1 offspring which died before weaning, and of F_1 offspring, which were culled on postnatal day 4 or which were not selected to be F_1 parents, did not show treatment-related macroscopic abnormalities. Absolute and relative weights of the reproductive organs in all groups were similar. No treatment-related effect was apparent on histopathological examination of the organs of reproduction.

One female in the F_1 generation receiving fenpyroximate at 100 ppm was killed in extremis on day 24 post coitum and was found to have a ruptured uterus. Intergroup differences in clinical signs were seen in neither sex. At 100 ppm, there was a reduction in body-weight gain in males of the F_1 generation. In females at 100 ppm, body-weight gain was reduced in the period up to pairing and during gestation, but recovered during lactation. Reduced body-weight gain was not seen at lower dietary concentrations in either sex. In the F_1 males at 100 ppm, food consumption was slightly reduced compared with that of the controls, but food consumption was not reduced in males receiving fenpyroximate at lower dietary concentrations, nor in any group of females. Estrus cycles, mating performance, gestation length and gestation index were not affected by treatment. Notably, at 100 ppm in the F_1 generation, the conception rate and fertility index were not reduced. Litter size at birth and viability up until the time of weaning were not affected by treatment. The initial body weights of the offspring were similar in all groups, but weight gain until weaning of the F_2 offspring in the group at 100 ppm was reduced. Physical development in the groups was similar. No intergroup differences in sex ratio, that were attributable to treatment, were seen. Necropsy of adult F_1 rats, of F_2 offspring that died before weaning and of F_1 offspring that were culled on postnatal day 4 or that were killed at termination after weaning did not show any treatment-related macroscopic abnormalities. In the F_1 males, the absolute weights

of the testes were increased in all treatment groups and the relative weights of the testes at 100 ppm. Epididymal weights (both relative and absolute) were increased at 100 ppm. Absolute and relative weights of other reproductive organs were not altered in a treatment-related fashion. No treatment-related effects were seen on histopathological examination of the organs of reproduction. The NOAELs for parental, offspring and reproductive toxicity were all 30 ppm (equal to 1.99 mg/kg bw per day for F_0 males, 2.44 mg/kg bw per day for F_0 females, 2.33 mg/kg bw per day for F_1 males and 2.82 mg/kg bw per day for F_1 females). The NOAEL for parental toxicity was identified on the basis of reduced body-weight gain and food consumption at 100 ppm, together with increased testicular and epididymal weights in males at 100 ppm. The NOAEL for offspring toxicity was identified on the basis of reduced body-weight gain in the offspring at 100 ppm, while that for reproductive performance was identified on the basis of reduction in conception rate and fertility index in the F_0 generation only (Higgins, 1989a).

(b) Developmental toxicity

Rats

In a study of developmental toxicity, groups of 22 pregnant CD rats were given fenpyroximate (purity, 97.6%) at a dose of 1, 5 or 25 mg/kg bw per day by gavage from day 6 to day 15 of gestation. A control group of rats received vehicle only. The rats were examined daily during the study and animals found dead were examined macroscopically. The rats were weighed on days 0, 3, 6 to 16, 18 and 20 of gestation. Food consumption and water consumption were recorded over days 0–2, 3–5, 6–8, 9–11, 12–15, 16–17 and 18–19 of gestation. The surviving rats were killed on day 20 of gestation for examination macroscopically and for examination of their uterine contents. The numbers of corpora lutea per ovary, implantation sites, resorption sites and number of live and dead fetuses were recorded. The fetuses were weighed, sexed and examined for external abnormalities. Approximately two thirds of the animals in each litter were processed and stained (with alizarin red) for skeletal examination and the remaining one third were fixed in Bouin's fixative and serially sectioned. Three deaths occurred on day 12 of gestation in the group receiving the intermediate dose (5 mg/kg bw per day) and none in the other groups; the cause of death could not determined, but because deaths were not observed in the group receiving the highest dose, the effect was not considered to be related to the test material. No intergroup differences in clinical condition were seen. At 25 mg/kg bw per day, there was initial weight loss and although weight gain thereafter was similar to that in the other groups, body weights in this group were persistently low compared with those of the controls. No intergroup differences in body weight or body-weight gain were seen in the other groups. Food intake at 25 mg/kg bw per day was initially reduced and water intake increased, but intergroup differences in food intake and water intake were not seen in the other groups. Necropsy at day 20 showed no treatment-related macroscopic abnormalities. The numbers of implantations, viable young and resorptions and the extent of pre- and postimplantation losses were not affected by treatment. Fetal and placental weights were unaffected by treatment. All treated groups showed increases in the number of thoracic ribs, which was greatest at 25 mg/kg bw per day. At the lower doses, there was no clear dose–response relationship. The NOAEL was accordingly 5 mg/kg bw per day on the basis of maternal weight loss, initially reduced maternal food consumption and increased maternal water intake. The NOAEL for embryo/fetal toxicity was also 5 mg/kg bw per day on the basis of increases in the number of thoracic ribs (Higgins, 1989b).

Rabbits

In a preliminary study of developmental toxicity, groups of four pregnant New Zealand white rabbits were given fenpyroximate (purity, 98.4%) at a dose of 2.5 or 5.0 mg/kg bw per day by gavage from day 6 to day 19 of gestation. An additional group of four pregnant rabbits received the vehicle only, and a group of three pregnant rabbits received fenpyroximate at a dose of 1.0 mg/kg bw per day by gavage. Animals were examined and weighed daily and adverse effects were recorded. Food and water intake was recorded over days 1–5, 6–12, 13–19, 20–23 and 24–28 of gestation. On day 29, the rabbits were killed, examined macroscopically and abnormal tissues were retained and fixed. The reproductive tract was dissected out and the number of corpora lutea in each ovary and the number of implantation sites and resorption sites were determined. Also, the number and distribution of live and dead fetuses were determined. The weight of each fetus and placenta was determined, and any external abnormalities of fetuses and placentas were recorded. The fetuses were eviscerated and one third were decapitated. Adverse effects were only seen at 5.0 mg/kg bw per day. These were depression of maternal body-weight gain and reduced food and water intake. Increased postimplantation loss, reduced fetal weight and anomalies were observed. The NOAELs for maternal and fetal toxicity were both 2.5 mg/kg bw per day (Bailey, 1989).

In a study of developmental toxicity, groups of 15 pregnant New Zealand white rabbits received fenpyroximate (purity, 97.6%) at a dose of 1.0, 2.5 or 5.0 mg/kg bw per day by gavage from day 6 to day 19 of gestation. An additional group of 15 pregnant rabbits received the vehicle only. The rabbits were observed daily throughout the study and any that were observed to be in extremis or that had aborted were killed, macroscopic examination being carried out. The rabbits were weighed daily and food and water intake was recorded for days 1–5, 6–12, 13–19, 20–23 and 24–28 days of gestation. On day 29 of gestation, the animals were killed and examined macroscopically. The reproductive tract, including the ovaries, were examined and the numbers of corpora lutea, implantation sites, resorption sites and live and dead fetuses were determined. The fetuses and placentas were weighed and examined for external abnormalities. Approximately two thirds of the animals in each litter were processed and stained (with alizarin red) for skeletal examination and the remaining one third were fixed in Bouin's fixative and serially sectioned. Two rabbits at 2.5 mg/kg bw per day group were killed in extremis. One appeared to have a respiratory infection and the other a gastrointestinal disturbance. There was a reduced level of faecal output in all the test groups, particularly in the group receiving the highest dose. Loss of body weight early in the treatment period followed by recovery was observed at 2.5 and 5.0 mg/kg bw per day. No effect on body weight was seen at 1.0 mg/kg bw per day. A reduction in food consumption was noted at 2.5 and 5.0 mg/kg bw per day and the reduction was marked at 5.0 mg/kg bw per day. A reduction in water consumption was seen at 5.0 mg/kg bw per day early in the study. One female in each of the groups receiving fenpyroximate at a dose of 2.5 or 5.0 mg/kg bw per day had complete litter resorption. The prevalence of complete litter loss was within the range for historical controls at the testing facility. One female receiving fenpyroximate at 5.0 mg/kg bw per day aborted. There were no intergroup differences in numbers of implantations, viable young, pre- and postimplantation loss and fetal and placental weights. A higher incidence of unilateral and bilateral slightly folded retinas was observed in the group at 5.0 mg/kg bw per day compared with the concurrent controls: the frequency of these findings was just within the ranges for controls at that testing facility (see Table 3). The biological significance of the higher incidence of unilateral and bilateral slightly folded retinas was unclear.

Table 3. Incidence (%) of slightly folded retina in fetuses and litters[a]

	Dose (mg/kg bw)			
	0	1	2.5	5
Unilateral	8.1 (3)	6.1 (2)	5.9 (2)	25.8 (6)
Bilateral	10.8 (3)	6.1 (2)	14.7 (4)	16.1 (5)

From King (1989)

[a] The first value is the percentage incidence in fetuses; the value in parentheses is the litter data

A single fetus at the highest dose had abnormalities of the heart and great vessels. The NOAEL for maternal toxicity was 1 mg/kg bw per day on the basis of reduced body weight and food consumption. The NOAEL for fetotoxicity was 2.5 mg/kg bw per day on the basis of unilateral and bilateral slightly folded retinas at 5 mg/kg bw per day. These NOAELs are consistent with those idientified in the preliminary study (King, 1989).

Comments

The acute oral LD_{50} of fenpyroximate was 245 and 480 mg/kg bw in male and female rats respectively.

The toxic effects of fenpyroximate include diarrhoea, failure to gain weight and haematological and clinical chemistry changes. In short-term (range-finding) dietary studies in mice, the effects of fenpyroximate were mainly limited to decreases in food consumption and reduced body-weight gain. The NOAELs for the two studies were 20 ppm (equal to 2.58 and 3.07 mg/kg bw per day in males and females, respectively) and 80 ppm (equal to 10.8 mg/kg bw per day in males and 11.7 mg/kg bw per day in females). In a 13-week dietary study in rats, effects were seen on body-weight gain, food consumption and haematological and clinical chemistry parameters. The NOAEL for the study was 20 ppm (equal to 1.30 mg/kg bw per day in males and 1.65 mg/kg bw per day in females). In a 13-week study in dogs given capsules containing fenpyroximate, weight loss or decreased weight gain, decreased food consumption and diarrhoea were seen. No NOAEL was identified in this study and the LOAEL was 2 mg/kg bw per day on the basis of diarrhoea occurring at all doses. This was considered to be a minimal effect level, and occurred from the beginning of the study. In a dietary study of reproductive toxicity in rats, parental toxicity comprised reduced body-weight gain and food consumption in both sexes, and increased testicular and epididymal weights in males. Offspring toxicity consisted of reduced body-weight gain. A reduction in conception rate and fertility index was observed in one generation only. The NOAELs for parental, offspring and reproductive toxicity were all 30 ppm (equal to 1.99 mg/kg bw per day in F_0 males, 2.44 mg/kg bw per day in F_0 females, 2.33 mg/kg bw per day in F_1 males and 2.82 mg/kg bw per day in F_1 females). In a study of developmental toxicity in rats treated by gavage, effects were seen on maternal body weight, while increases in the number of thoracic ribs were found in fetuses. The NOAEL for both effects was 5 mg/kg bw per day. In preliminary and substantive studies of the developmental toxicity of fenpyroximate in rabbits treated by gavage, reduced maternal body weight and food consumption was seen at the higher doses. These effects were not considered relevant for establishing an ARfD. The NOAEL for maternal toxicity was 1 mg/kg bw day. Significant elevations in the frequency of unilateral and bilateral slightly folded retinas were observed in fetuses at 5 mg/kg bw per day. No other significant evidence of fetotoxicity was observed and the biological significance of this finding is unclear.

Toxicological evaluation

The Meeting established an ARfD of 0.01 mg/kg bw on the basis of the a minimal LOAEL of 2 mg/kg bw per day for the induction of diarrhoea at the beginning of a 13-week study of toxicity in dogs. It was unclear whether the diarrhoea was the result of a direct irritant or pharmacological effect of fenpyroximate. A safety factor of 200 was used since no NOAEL was identified. This ARfD is probably conservative and could be refined using the results of an appropriately designed study.

Estimate of acute reference dose

0.01 mg/kg bw

Studies that would provide information useful for continued evaluation of the compound

Appropriately designed single-dose study

Levels relevant to risk assessment

Species	Study	Effect	NOAEL	LOAEL
Rat	Two-generation study of reproductive toxicity[a]	Parental toxicity	30 ppm, equal to 1.99 mg/kg bw per day	100 ppm, equal to 6.59 mg/kg bw per day
		Reproductive toxicity	30 ppm, equal to 1.99 mg/kg bw per day	100 ppm, equal to 6.59 mg/kg bw per day
	Developmental toxicity[b]	Maternal toxicity	5 mg/kg bw per day	25 mg/kg bw per day
		Embryo and feto-toxicity	5 mg/kg bw per day	25 mg/kg bw per day
Rabbit	Developmental toxicity[b]	Maternal toxicity	1 mg/kg bw per day	2.5 mg/kg bw per day
		Embryo and feto-toxicity	2.5 mg/kg bw per day	5 mg/kg bw per day
Dog	13-week study of toxicity[c,d]	Toxicity	—	2 mg/kg bw per day[e]

[a] Diet
[b] Gavage
[c] Capsules
[d] Effects evident within 1 week
[e] Lowest dose tested

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