5.3 BENTAZONE (172)

TOXICOLOGY

Bentazone is the ISO-approved common name for 3-isopropyl-1H-2,1,3-benzothiadiazin-4(3H)-one-2,2-dioxide (International Union of Pure and Applied Chemistry [IUPAC]), with CAS number 25057-89-0. Bentazone is a post-emergence herbicide used for selective control of broadleaf weeds and sedges in beans, rice, corn, peanuts, mint and others. It acts by interfering with photosynthesis.

Bentazone was first evaluated by JMPR in 1991, when an ADI of 0–0.1 mg/kg bw was established on the basis of a NOAEL of 9 mg/kg bw per day (for increased clotting times and increased output of urine with decreased specific gravity) in a long-term study of toxicity in rats and using a safety factor of 100. In 1998, the Meeting re-evaluated bentazone and data on 6-hydroxybentazone, a metabolite of bentazone. The Meeting concluded that 6-hydroxybentazone was less toxic than bentazone and reaffirmed the ADI of 0–0.1 mg/kg bw. Because data were not evaluated to establish an ARfD, the Meeting in 2004 re-evaluated bentazone and concluded that the establishment of an ARfD was not necessary.

Bentazone is being reviewed at the present meeting as part of the periodic re-evaluation programme of CCPR.

Since the 2004 JMPR review, no relevant new studies have been provided. Two published literature studies on the effects of bentazone on spermatogenesis in mice and on litter size and postnatal growth in rats were submitted. Most of the studies do not comply with GLP, as they were generated before implementation of GLP.

Biochemical aspects

Toxicokinetic studies performed on mice, rats and rabbits indicate that bentazone is rapidly and almost completely absorbed via the oral route (> 99%), and maximum blood concentrations of radioactivity are achieved in approximately 15 minutes at low doses (4 mg/kg bw) and by 1 hour at high doses (200 mg/kg bw). Administration of bentazone either as the sodium salt or as the free acid did not result in any significant differences in absorption. There was no evidence of penetration into the central nervous system or spinal cord, and elimination from other tissues was rapid, with no indication of bioaccumulation.

Elimination was almost exclusively via the urine (approximately 91% within 24 hours); 5 days after dosing, less than 2% was found in faeces and less than 0.02% in expired air. Biliary excretion of radioactivity was minimal. No significant differences were found in absorption and elimination among the different species investigated (rat, rabbit, mouse).

Bentazone is minimally metabolized in vivo, with the parent compound being the predominant excretion product. Only small amounts of 6-hydroxybentazone (up to approximately 6% of the dose) and minimal amounts of 8-hydroxybentazone (less than approximately 0.2% of the dose) were detected in urine.

Toxicological data

Bentazone has moderate acute toxicity when administered orally to rats, guinea-pigs and rabbits and low toxicity when administered dermally or by inhalation to rats. In rats, the oral LD_{50} was greater than or equal to 850 mg/kg bw. The dermal LD_{50} in rats was greater than 5000 mg/kg bw. The inhalation LC_{50} was greater than 5.1 mg/L of air (4-hour exposure; nose only). Bentazone was moderately irritating to the eye but not irritating to the skin in rabbits. It was a dermal sensitizer in the Magnusson & Kligman maximization test and the Buehler test in guinea-pigs.

Repeated-dose toxicity studies (subchronic and chronic) in mice, rats and dogs indicate that effects on haematology and blood coagulation (e.g. prolongation of prothrombin time and partial thromboplastin time) were consistently observed.

Three short-term oral rat studies demonstrated an overall NOAEL of 400 ppm (equal to 25.3 mg/kg bw per day), with a lowest-observed-adverse-effect level (LOAEL) of 800 ppm (equal to 40 mg/kg bw per day) for decreased body weight gain, decreased feed consumption, increased serum total cholesterol levels, increased urine output and prolonged prothrombin time and partial thromboplastin time.

In 90-day and 1-year dog studies, clinical signs, anaemia and effects on blood coagulation were noted. In the 90-day study, the NOAEL was 300 ppm (equal to 12.0 mg/kg bw per day), on the basis of sedation and ulceration and alopecia on the leg of one dog at 1000 ppm (equal to 39.6 mg/kg bw per day). The NOAEL for the 1-year study was 400 ppm (equal to 13.1 mg/kg bw per day), on the basis of anaemia, altered blood coagulation parameters, clinical signs and weight loss at the highest dietary concentration of 1600 ppm (equal to 52.3 mg/kg bw per day).

In a 2-year dietary toxicity and carcinogenicity study in mice, the NOAEL was 100 ppm (equal to 12 mg/kg bw per day), based on prolongation of prothrombin time and an increased incidence of calcification of the testicular tunica albuginea and deferent canals in the males at 400 ppm (equal to 47 mg/kg bw per day). No carcinogenic effects were observed in this study.

In a 2-year combined toxicity and carcinogenicity study in rats, the NOAEL was 200 ppm (equal to 9 mg/kg bw per day), based on clinical chemistry changes indicative of effects on liver and kidney and effects on blood coagulation parameters at 800 ppm (equal to 35 mg/kg bw per day). No carcinogenic effects were observed in this study.

The Meeting concluded that bentazone was not carcinogenic in rats or mice.

Bentazone was tested for genotoxicity in an adequate range of assays, both in vitro and in vivo. It showed no evidence of genotoxicity.

The Meeting concluded that bentazone is unlikely to be genotoxic.

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

In a two-generation dietary reproduction study in rats, the NOAEL for parental and offspring toxicity was 200 ppm (equal to 14 mg/kg bw per day), on the basis of reduced parental feed consumption and body weight gain and reduced pup body weight resulting from parental toxicity at 800 ppm (equal to 59 mg/kg bw per day). There were no effects on reproduction at 3200 ppm (240 mg/kg bw per day), the highest dose tested.

In two studies of developmental toxicity in rats treated by gavage, the overall NOAEL for maternal toxicity was 250 mg/kg bw per day, the highest dose tested. The developmental NOAEL was 200 mg/kg bw per day, on the basis of increased post-implantation loss, reduced weight of fetuses surviving to day 21 and skeletal anomalies at the next higher dose of 250 mg/kg bw per day.

In a third study of developmental toxicity, in which rats were given diets containing bentazone from day 0 to day 21, the NOAEL for maternal toxicity was 2000 ppm (equal to 162 mg/kg bw per day), on the basis of increased water consumption at 4000 ppm (equal to 324 mg/kg bw per day). The developmental NOAEL was 4000 ppm (equal to 324 mg/kg bw per day), on the basis of decreased fetal weight gain and reduced ossification of cervical vertebrae at 8000 ppm (equal to 631 mg/kg bw per day).

In two gavage studies of developmental toxicity in rabbits, the overall NOAEL for maternal and developmental toxicity was 150 mg/kg bw per day, on the basis of a reduction in maternal feed consumption and increased post-implantation losses at 375 mg/kg bw per day.

The Meeting concluded that bentazone was not teratogenic in rats or rabbits.

In a subchronic neurotoxicity study, there was no indication of neurotoxicity at doses up to 3500 ppm (equal to 258 mg/kg bw per day), the highest dose tested.

6-Hydroxybentazone and 8-hydroxybentazone are major plant metabolites of bentazone. Both were less acutely toxic than the parent compound. Neither of the metabolites induced mutations in

bacterial tests, and 8-hydroxybentazone was also not genotoxic in an in vitro mammalian forward mutation test and an in vivo mouse micronucleus test. In a subchronic dietary toxicity study and a developmental toxicity study in rats with 8-hydroxybentazone, the NOAEL was approximately 250 mg/kg bw per day, the highest dose tested.

No adverse health effects or poisoning in manufacturing plant personnel or in operators and workers exposed to bentazone have been reported.

Several case reports of suicide attempts due to ingestion of bentazone formulations have been reported in the literature, including four cases resulting in death. The range of doses ingested that resulted in death was 35–250 g of bentazone. The poisoning symptoms and signs included nausea, vomiting, abdominal pain, rhabdomyolysis, hepatorenal damage and cardiac failure.

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

Toxicological evaluation

The Meeting established an ADI of 0–0.09 mg/kg bw derived from a NOAEL of 9 mg/kg bw per day from the 2-year study of toxicity and carcinogenicity in rats, on the basis of prolonged blood coagulation and clinical chemistry changes indicative of effects on liver and kidney at 35 mg/kg bw per day. A safety factor of 100 was applied. This ADI was supported by the NOAEL of 13.1 mg/kg bw per day observed in the 1-year study in dogs for anaemia, altered blood coagulation parameters, clinical signs and weight loss seen at the highest dose of 52.3 mg/kg bw per day; by the NOAEL of 14 mg/kg bw per day in the two-generation study in rats, on the basis of reduced parental feed consumption and body weight gain and reduced pup body weight resulting from parental toxicity at 59 mg/kg bw per day; and by the NOAEL of 12 mg/kg bw per day in a 2-year toxicity and carcinogenicity study in mice, based on prolongation of prothrombin time and an increased incidence of testicular calcification at 47 mg/kg bw per day.

The Meeting reaffirmed its previous conclusion that no ARfD is necessary. It considered that the post-implantation loss seen in the rat developmental study was not caused by a single dose and that no other effects were observed in repeated-dose studies that could be due to a single dose.

A toxicological monograph was prepared.

Levels relevant to risk assessment

Species	Study	Effect	NOAEL	LOAEL
Mouse	Two-year study of toxicity and carcinogenicity[a]	Toxicity	100 ppm, equal to 12 mg/kg bw per day	400 ppm, equal to 47 mg/kg bw per day
		Carcinogenicity	2000 ppm, equal to 275 mg/kg bw per day[b]	—
Rat	Short-term studies of toxicity[c]	Toxicity	400 ppm, equal to 25.3 mg/kg bw per day	800 ppm, equal to 40 mg/kg bw per day
	Two-year studies of toxicity and carcinogenicity[a,c]	Toxicity	200 ppm, equal to 9 mg/kg bw per day	800 ppm, equal to 35 mg/kg bw per day
		Carcinogenicity	4000 ppm, equal to 274 mg/kg bw per day[b]	—
	Two-generation study of reproductive toxicity[a]	Reproductive toxicity	3200 ppm, equal to 240 mg/kg bw per day[b]	—
		Parental toxicity	200 ppm, equal to 14 mg/kg bw per day	800 ppm, equal to 59 mg/kg bw per day

Species	Study	Effect	NOAEL	LOAEL
		Offspring toxicity	200 ppm, equal to 14 mg/kg bw per day	800 ppm, equal to 59 mg/kg bw per day
	Developmental toxicity study[c,d]	Maternal toxicity	250 mg/kg bw per day[b]	—
		Embryo and fetal toxicity	200 mg/kg bw per day	250 mg/kg bw per day
Rabbit	Developmental toxicity study[d]	Maternal toxicity	150 mg/kg bw per day	375 mg/kg bw per day
		Embryo and fetal toxicity	150 mg/kg bw per day	375 mg/kg bw per day
Dog	Ninety-day and 1-year studies of toxicity[a,c]	Toxicity	400 ppm, equal to 13.1 mg/kg bw per day	1000 ppm, equal to 39.6 mg/kg bw per day

[a] Dietary administration.

[b] Highest dose tested.

[c] Two or more studies combined.

[d] Gavage administration.

Estimate of acceptable daily intake for humans

0–0.09 mg/kg bw

Estimate of acute reference dose

Unnecessary

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 bentazone

Absorption, distribution, excretion and metabolism in mammals	
Rate and extent of oral absorption	Rapid and almost completely absorbed (> 90%)
Dermal absorption	Poorly absorbed (1–2%)
Distribution	Widely distributed
Potential for accumulation	None
Rate and extent of excretion	Rapid, more than 90% within 24 h, mainly via urine
Metabolism in animals	Minimal
Toxicologically significant compounds in animals, plants and the environment	Parent compound
Acute toxicity	
Rat, LD_{50}, oral	≥ 850 mg/kg bw
Rat, LD_{50}, dermal	> 5000 mg/kg bw
Rat, LC_{50}, inhalation	> 5.1 mg/L of air
Rabbit, dermal irritation	Not irritating
Rabbit, ocular irritation	Irritating
Dermal sensitization	Sensitizer (Magnusson & Kligman test)
Short-term studies of toxicity	
Target/critical effect	Blood coagulation
Lowest relevant oral NOAEL	12 mg/kg bw per day (dogs)
Lowest relevant dermal NOAEL	1000 mg/kg bw per day (highest dose tested) (rabbits)
Lowest relevant inhalation NOAEC	No data
Long-term studies of toxicity and carcinogenicity	
Target/critical effect	Blood coagulation, liver and kidney effects
Lowest relevant NOAEL	9 mg/kg bw per day (rats)
Carcinogenicity	Not carcinogenic in rats or mice

Genotoxicity	
	Not genotoxic
Reproductive toxicity	
Target/critical effect	No reproductive effects
Lowest relevant parental NOAEL	14 mg/kg bw per day (rat)
Lowest relevant offspring NOAEL	14 mg/kg bw per day (rat)
Lowest relevant reproductive NOAEL	240 mg/kg bw per day (highest dose tested) (rat)
Developmental toxicity	
Target/critical effect	Post-implantation loss, reduced fetal weight and skeletal anomalies
Lowest relevant maternal NOAEL	150 mg/kg bw per day (rabbit)
Lowest relevant embryo/fetal NOAEL	150 mg/kg bw per day (rabbit)
Neurotoxicity	
Subchronic neurotoxicity	No effect up to 258 mg/kg bw per day (highest dose tested)
Medical data	
	No significant health effects in manufacturing personnel. Three cases of intentional poisoning have been reported with various critical symptoms.

Summary

	Value	**Study**	**Safety factor**
ADI	0–0.09 mg/kg bw	2-year chronic toxicity and carcinogenicity study (rats)	100
ARfD	Unnecessary	—	—