

**BENTAZONE (addendum)**

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**Explanation**

Bentazone was first evaluated by the Joint Meeting in 1991 (Annex 1, reference 62), when an ADI of 0–0.1 mg/kg bw was allocated on the basis of a NOAEL of 9 mg/kg bw per day in a long-term study of toxicity in rats and a safety factor of 100. Further observations in humans, a 90-day feeding study in rats with 6-hydroxybentazone, and studies of genotoxicity with 6-hydroxybentazone were identified as valuable in the continued evaluation of the compound.

**Evaluation for Acceptable Daily Intake****1. Biochemical aspects***(a) Absorption, distribution, and excretion*

Male and female CD rats were given a single intravenous dose of 4 mg/kg bw of [phenyl-<sup>14</sup>C] bentazone as the sodium salt, a single oral dose of 4 or 200 mg/kg bw free acid, or a single oral dose of 4 mg/kg bw free acid after a 14-day pretreatment with unlabelled bentazone at approximately 4 mg/kg bw per day. Recovery of radiolabel in urine after oral dosing indicated extensive absorption from the gastrointestinal tract. By 24 h after the single oral dose, 83–94% of the radiolabel appeared in urine. Total recovery of radiolabel 120 h after dosing accounted for 90–97% of the dose in the animals treated orally and 90–95% of the dose in the animals treated intravenously. After oral administration, 88–96% of the dose was eliminated in urine and 0.8–2.3% in faeces over the 120-h collection period, most being eliminated within the first 24 h. No difference between the sexes or among dose groups was seen. Experiments with bile-duct-cannulated rats indicated that only 0.24–1.3% of the dose of 4 mg/kg bw and

0.3–1.8% of the dose of 200 mg/kg bw was eliminated in the bile over a 48-h collection period.

In a parallel series of studies, CD rats of each sex were given a single dose of 4 mg/kg bw [phenyl-U-<sup>14</sup>C]-bentazone (sodium salt) intravenously or an oral dose of 4 (free acid or sodium salt) or 200 mg/kg bw (free acid). The area under the curve (AUC) for radioabel in plasma per unit dose for animals that received the high dose was nearly double that of rats given the low dose, suggesting that a non-linear region in disposition was reached at the high dose. Additionally, the AUC values for females given the low dose were nearly one-half those of females dosed intravenously; the corresponding values for males were not significantly different. The biological significance of the difference in bioavailability in females is unclear in view of the similar, extensive absorption of the compound (about 90%) in both males and females, the limited metabolism of the compound, and the apparently similar rates of excretion in the two sexes. At sacrifice at 120 h, the total radiolabel in carcasses represented less than 0.69% of the dose in all groups. Whole-body autoradiography indicated steady disappearance of the label with time. Signed and dated statements of compliance with good laboratory practice (GLP) (40 CFR 160.35) and quality assurance were provided with the study. This study satisfies the FIFRA Subdivision F Guideline requirement for an 85-1 study of general metabolism (Hawkins et al., 1987).

#### *(b) Biotransformation*

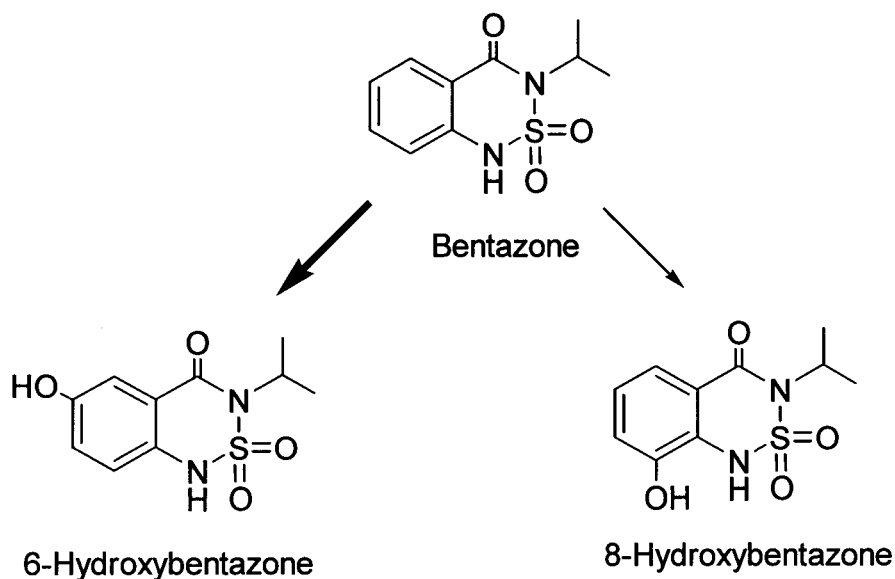
In the study of Hawkins et al. (1987), described above, parent bentazone was the major excretion product in the urine of treated rats during the 24-h collection period, representing 81–91% of the dose in males and 77–89% in females. 6-Hydroxybentazone represented up to 6.3% of the dose, and the isomeric 8-hydroxybentazone was present in trace amounts, 0–0.23% of the dose (Figure 1). Although slightly less parent bentazone was excreted in the urine of females and less 6-hydroxybentazone was excreted by rats treated intravenously (0.98% of the dose versus 2.4–6.3% in rats given the low oral dose), there were no major dose-dependent differences among the groups. Little or no glucuronide or sulfate conjugation was seen.

In a previous study, adult male CD rats received <sup>14</sup>C-bentazone, presumably [phenyl-U-<sup>14</sup>C]-labelled, as a single oral dose of 4 mg/kg bw of the sodium salt (expressed as the free acid), and metabolites in the urine were analysed by thin-layer chromatography. Parent bentazone represented 65, 15, and 3.2% of the dose in urine collected 0–6, 6–12, and 12–24 h after dosing, respectively, for a total of 83% of the dose; 6-hydroxybentazone represented 1.7, 0.4, and 0.1% of the dose at those times. 8-Hydroxybentazone was not detected. Polar radioactive compounds at the origin represented 2.1% of the dose in the 0–24-h period (Hawkins et al., 1986).

## **2. Toxicological studies**

#### *(a) Acute toxicity*

Bentazone is more acutely toxic to rats by the oral route than its 6-hydroxy or 8-hydroxy metabolites. The LD<sub>50</sub> values for technical-grade bentazone (purity unspecified) suspended in aqueous carboxymethyl cellulose in Wistar rats were 1800 mg/kg bw for males, 1500 mg/kg bw for females, and 1600 mg/kg bw for males and females combined. The LD<sub>50</sub> value for males was estimated from deaths at four doses, with no statistical analysis; the values for females and for males and females combined were determined by probit analysis. Dyspnoea and apathy were noted at doses of 825 mg/kg bw and higher, and staggering occurred at the highest dose, 2610 mg/kg bw per day. Animals at this dose that died had bloody ulcerations in the stomach and intestinal contents mixed with blood (Hildebrand & Kirsch, 1982).

**Figure 1. Biotransformation of bentazone**

Both hydroxylated isomers are found rat and plant metabolites of bentazone

(b) *Short-term studies of toxicity*

*Rats*

Groups of 10 Wistar KFM-Han, outbred SPF quality rats of each sex received technical-grade bentazone (purity, 97.8%) at a dietary level of 0, 400, 1200, or 3600 ppm for 13 weeks, equal to doses of 0, 25, 78, and 240 mg/kg bw per day in males and 0, 29, 86, and 260 mg/kg bw per day in females. Twenty additional rats were used for a 28-day recovery experiment. Ten rats received 3600 ppm bentazone for 13 weeks and were then given regular diet and observed for an additional 28 days; 10 rats served as untreated controls in the recovery experiment. The animals were observed for clinical signs, deaths, body weight, and food consumption; ophthalmic, urinary, haematological, and clinical chemical parameters; organ weights; and gross and histopathological alterations.

One male and two females at the high dose died, one of the females under anesthesia; no signs of toxicity were reported. The body weights of females at this dose were statistically significantly lower than those of controls from week 10 onwards; there were no effects on the body weights of males, and no statistically significant differences in body weights were seen during the recovery period. The food consumption of males at the high dose was slightly increased and became statistically significantly greater than that of controls from week 7 onwards; the food consumption of females was generally not affected. No ophthalmological effects were reported. Statistically significant increases in prothrombin time and partial thromboplastin time were seen in males at the high dose, whereas females at all doses had statistically significantly depressed prothrombin time and the partial thromboplastin time was not affected. The values for certain clinical chemical parameters were statistically significantly different from those of controls in males at the high dose, but they were generally within the historical control values and returned to normal during the recovery period; the values for females were within the historical control range.

Bentazone had a diuretic effect in animals of each sex. In both males and females, the urine volume was increased in a dose-related manner, becoming significantly different from that of controls at 3600 ppm. The specific gravity was decreased in animals of each sex; the decrease was dose-related in males and was statistically significantly different from that of controls at the high dose; in females, the decrease was significantly different from that of controls at all doses but did not decrease monotonically. The mean absolute and relative kidney weights were statistically significantly greater than those of controls in males at 3600 ppm; in females, although both the mean absolute and relative kidney weights were greater than those of controls, the values reached statistical significance only for absolute weights. The only change in liver weights was a statistically significant increase in relative liver weight in females at 3600 ppm. Gross examination revealed lung thrombi in 1/10 controls and 3/10 females at the high dose and dilated uterine horns in 1/10 controls and 3/9 females at the high dose. No statistically significant histopathological findings were made. The NOAEL for systemic toxicity was 1200 ppm, equal to 78 mg/kg bw per day, and the LOAEL was 3600 ppm, equal to 240 mg/kg bw per day, on the basis of statistically significant decreased body weights of females throughout the latter part of treatment, increased prothrombin time and partial thromboplastin time in males, increased urinary output with decreased specific gravity in animals of each sex, and some degree of kidney hypertrophy in both males and females (Tennekes et al., 1987).

Groups of five male and five female New Zealand white rabbits received repeated dermal applications of bentazone (purity, 97.6%) in Tylose CB in 0.5% aqueous suspension under semioclusion for 6 h once a day for 21 days at a dose of 0, 250, 500, or 1000 mg/kg bw per day. No deaths or clinical signs were seen in animals of either sex at any dose, and no adverse effects were seen on treated skin. The NOAEL was 1000 mg/kg bw per day, the highest dose tested (Kirsch, 1993).

(c) *Genotoxicity*

Bentazone was considered not to be genotoxic *in vitro* or *in vivo* in the previous evaluation. It has been tested only as a compound of 96.7% purity for reverse mutation in *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537, and TA1538, at concentrations of 20–5000 µg per plate, in the presence and absence of an exogenous metabolic activation system. Negative results were obtained (Gelbke & Engelhardt, 1983).

(d) *Developmental toxicity*

*Rats*

In a study of developmental toxicity, pregnant Wistar/HAN rats (Kfm: WIST, outbred, SPF quality) received technical-grade bentazone (purity, 97.8%) mixed with 4% carboxymethyl cellulose in distilled water by gavage at a dose of 0, 40, 100, or 250 mg/kg bw per day on days 6–15 of gestation. The dams were observed for mortality, clinical signs, body weight, and food consumption; *post mortem*, the uterus was removed, weighed, and opened for internal examination. The fetuses were examined for sex, weight, and gross external abnormalities, and underwent visceral (slice technique) and skeletal examinations. No signs or symptoms of compound-related toxicity were reported, and there were no effects on body weight, body-weight gain, or food consumption. The litter incidence of fetal resorptions was increased in dams at 250 mg/kg bw per day as compared with controls, and the difference in total number was statistically significant (0 in controls and 44 at the high dose). There was a small but statistically significant decrease in mean fetal weight at the high dose (4.8 g in controls versus 4.3 g). The rate of ossification in the phalangeal nuclei of fore- and hindlimb digits, the fifth sternebra, and cervical vertebrae was decreased, and the litter incidence of phalangeal nuclei with delayed ossification was statistically significant at the high dose ( $\chi^2$ ,  $p < 0.05$ ). The NOAEL for maternal toxicity was 250 mg/kg bw per day, the highest dose tested, and that for developmental toxicity was 100 mg/kg bw per day on the basis of statistically significantly

decreased mean fetal weights and delays in tissue ossification at the high dose (Becker et al., 1986).

### 3. Studies of metabolites

#### (a) Acute toxicity

The acute oral LD<sub>50</sub> values for 6-hydroxy- and 8-hydroxybentazone suspended in aqueous carboxymethyl cellulose in male and female Wistar rats were  $\geq 5000$  mg/kg bw. The 6-hydroxy compound was  $> 98\%$ , and the 8-hydroxy compound was  $> 98.5\%$  pure. Two males that received 5000 mg/kg bw 8-hydroxybentazone died, but no deaths occurred among females at any dose (2150, 3830, or 5000 mg/kg bw) or among any of the animals given the 6-hydroxy metabolite. Necropsy of the rats that died after intake of 5000 mg/kg bw 8-hydroxybentazone showed general congestion (Kirsch & Kieczka, 1987). No lesions were found at necropsy in animals given 5000 mg/kg bw 6-hydroxy-bentazone (Kirsch & Kieczka, 1986).

#### (b) Short-term studies of toxicity

Groups of 10 Wistar rats of each sex received 8-hydroxybentazone (99.9% active ingredient) in the diet at 0, 400, 1200, or 3600 ppm for three months, equal to doses of 0, 28, 85, and 260 mg/kg bw for males and 0, 34, 100, and 300 for females. No compound-related effects were seen on mortality, clinical signs, body weight, food consumption, haematological, clinical chemical, or urinary parameters, organ weights, or gross or histopathological appearance. In particular, there was no significant effect on thromboplastin time at 45 or 94 days. The NOAEL was 3600 ppm, equal to 260 mg/kg bw per day, the highest dose tested (Mellert et al., 1993).

#### (c) Genotoxicity

Studies on the genotoxicity of metabolites of bentazone are summarized in Table 1. The 6- and 8-hydroxy isomers of bentazone also gave negative results in assays for reverse mutation, with and without microsomal activation (Gelbke & Engelhardt, 1987a,b). 8-Hydroxybentazone gave negative results in an assay for gene mutation at the *hprt* locus in Chinese hamster V79 cells, with and without metabolic activation (Mullerschön, 1992) and in an assay for micronucleus formation in mice treated *in vivo* (Gelbke, 1993).

**Table 1. Results of assays for the genotoxicity of the 6-hydroxy and 8-hydroxy metabolites of bentazone**

End-point	Test object	Concentration	Purity (%)	Results	Reference
<b>6-Hydroxybentazone</b>					
Reverse mutation	<i>S. typhimurium</i> TA98, TA100, TA1535, TA1537	20–5000 $\mu\text{g}/\text{plate}$ $\pm$ S9	$> 98$	Negative	Gelbke & Engelhardt (1987a)
<b>8-Hydroxybentazone</b>					
Reverse mutation	<i>S. typhimurium</i> TA98, TA100, TA1535, TA1537	20–5000 $\mu\text{g}/\text{plate}$ $\pm$ S9	$> 98.5$	Negative	Gelbke & Engelhardt (1987b)
Gene mutation	Chinese hamster V79 cells, <i>hprt</i> locus	Trial 1: 55–2002 $\mu\text{g}/\text{ml}$ –S9 495–5005 $\mu\text{g}/\text{ml}$ +S9 Trial 2: 300–3000 $\mu\text{g}/\text{ml}$ –S9 500–5000 $\mu\text{g}/\text{ml}$ +S9	99.9	Negative	Mullerschön (1992)
Micronucleus formation	NMRI mouse <i>in vivo</i>	625, 1250, 2500 mg/kg bw	99.9	Negative	Gelbke (1993)

*(d) Developmental toxicity*

In a range-finding study for developmental toxicity, groups of nine or 10 pregnant Wistar (Chbb:THOM SPF) rats received 8-hydroxybentazone (purity unspecified) in 0.5% aqueous carboxymethyl cellulose (Tylose CB 30 000) at a dose of 0 or 300 mg/kg bw per day on days 6–15 of gestation. Maternal toxicity was observed, consisting of significant decreases in body-weight gain (89%) and food consumption during days 6–8 of gestation. The frequency of post-implantation loss (12.6%) was greater than that in concurrent controls (4.6%), but this finding was within the range for historical controls (4.5–15.7%) (BASF, 1992).

In a study of developmental toxicity, groups of 25 pregnant Wistar (Chbb:THOM SPF) rats received 8-hydroxybentazone (purity, 99.9%) in 0.5% aqueous carboxymethyl cellulose (Tylose CB 30,000) at a dose of 0, 40, 100, or 250 mg/kg bw per day on days 6–15 of gestation. The dams were observed for deaths, clinical signs, body weight, and food consumption; *post mortem*, the uterus was removed, weighed, and opened for internal examination. The fetuses were observed for sex, weight, and gross external abnormalities, and underwent visceral (slice technique) and skeletal examinations. There was no maternal or developmental toxicity. The NOAEL for both maternal and developmental toxicity was 250 mg/kg bw per day, the highest dose tested (Hellwig & Hildebrand, 1993).

**Comments**

After oral administration to rats, [phenyl- $U$ - $^{14}C$ ]-bentazone was extensively absorbed and rapidly excreted in the urine. In rats given a single dose, 83–94% appeared in the urine by 24 h and 90–97% by 120 h after dosing, with less than 0.7% in the residual carcass. Biliary excretion of the compound amounted to less than 2% of the dose. Bentazone undergoes very limited biotransformation in rats. Bentazone was the major compound identified in urine, representing 81–91% of the dose in males and 77–89% in females. 6-Hydroxybentazone was present in amounts up to 6.3% of the dose, and isomeric 8-hydroxybentazone was present in trace amounts (0–0.23% of the dose). There were no major differences among the groups. Glucuronide or sulfate conjugation was either negligible or nonexistent; 6- and 8-hydroxybentazone are also metabolites of bentazone in plants.

Bentazone is more acutely toxic to rats than are its two hydroxylated metabolites when given by the oral route. The acute oral  $LD_{50}$  of technical-grade bentazone was estimated to be 1800 mg/kg bw in males and 1500 mg/kg bw in females. The acute oral  $LD_{50}$  value for 6- and 8-hydroxybentazone was 5000 mg/kg bw.

WHO has classified bentazone as slightly hazardous (WHO, 1996).

The two studies described below indicate that 8-hydroxybentazone does not have the anticoagulant and diuretic effects of bentazone at the doses tested and has less systemic toxicity than the parent compound under the test conditions. No data were available on the short-term toxicity of 6-hydroxybentazone.

Rats received technical-grade bentazone in the diet at concentrations of 0, 400, 1200, or 3600 ppm for 13 weeks. The body weights of females were decreased and were statistically significantly different from those of controls at 3600 ppm from week 10 onward. Examination of haematological parameters indicated statistically significant increases in prothrombin time and partial thromboplastin time in males at 3600 ppm in comparison with controls. Bentazone had a diuretic effect in animals of each sex, reaching statistical significance at 3600 ppm. The NOAEL for systemic toxicity was 1200 ppm (equal to 78 mg/kg bw per day) on the basis of statistically significant decreased body weights in females throughout the latter part of the treatment, increased prothrombin time and partial thromboplastin time in males, increased output of urine with decreased specific gravity in animals of each sex, and some degree of kidney hypertrophy in both males and females at 3600 ppm, equal to 240 mg/kg bw per day.

Rats received 8-hydroxybentazone in the diet at concentrations of 0, 400, 1200, or 3600 ppm for three months. No compound-related effects were observed on body weights, clinical signs,

food consumption, haematological, clinical chemical, or urinary parameters, clotting time, organ weights, or gross or histopathological appearance. The NOAEL was 3600 ppm (equal to 260 mg/kg bw per day), the highest dose tested.

The following two studies of developmental toxicity indicate that bentazone has effects at doses below a maternally toxic dose, whereas 8-hydroxybentazone had no developmental or maternal toxicity at any of the doses tested.

Pregnant rats received technical-grade bentazone by gavage at 0, 40, 100, or 250 mg/kg bw per day on days 6–15 of gestation. The NOAEL for maternal toxicity was 250 mg/kg bw per day, the highest dose tested. The NOAEL for developmental toxicity was 100 mg/kg bw per day on the basis of significantly decreased mean fetal weights and delays in tissue ossification, which reached statistical significance on a litter basis at the highest dose.

No developmental toxicity was observed in pregnant rats that received 8-hydroxybentazone by gavage at 0, 40, 100, or 250 mg/kg bw per day on days 6–15 of gestation. The NOAEL for developmental toxicity was 250 mg/kg bw per day, the highest dose tested.

Bentazone, 6-hydroxybentazone, and 8-hydroxybentazone did not induce reverse mutation in bacteria, and 8-hydroxybentazone did not induce gene mutation in mammalian cells or micronucleus formation in mice *in vivo*. The Meeting concluded that neither bentazone nor its metabolites are genotoxic.

8-Hydroxybentazone was less toxic than the parent compound, and, on the basis of the structural similarities between the 6- and 8-hydroxy isomers, the Meeting concluded that the 6-hydroxy isomer is also less toxic than the parent. Therefore, the Meeting maintained the ADI of 0–0.1 mg/kg bw for bentazone.

Because this was a limited review, data were not evaluated that would permit the establishment of an acute reference dose.

## Toxicological Evaluation

### *Levels that cause no toxic effect*

#### ***Bentazone***

- Mouse: 100 ppm, equal to 12 mg/kg bw per day (toxicity in a two-year study of toxicity and carcinogenicity)
- Rat: 200 ppm, equal to 9 mg/kg bw per day (toxicity in a two-year study of toxicity and carcinogenicity)  
1200 ppm, equal to 78 mg/kg bw per day (13-week study of toxicity)  
250 mg/kg bw per day (maternal toxicity in a study of developmental toxicity)  
100 mg/kg bw per day (developmental toxicity)
- Dog: 400 ppm, equal to 13 mg/kg bw per day (one-year study of toxicity)

#### ***8-Hydroxybentazone***

- Rat: 3600 ppm, equal to 260 mg/kg bw per day (three-month study of toxicity)  
250 mg/kg bw per day (maternal and developmental toxicity in study of developmental toxicity)

### *Estimate of acceptable daily intake for humans*

0–0.1 mg/kg bw

### *Estimate of acute reference dose*

Not considered

**List of end-points relevant for comparing the toxicities of bentazone, 6-hydroxybentazone and 8-hydroxybentazone**

<i>Absorption, distribution, excretion and metabolism in mammals</i>	
Rate and extent of oral absorption	83–94% rapidly absorbed (bentazone)
Dermal absorption	No data
Distribution	Extensive
Potential for accumulation	Little or none for bentazone; no data on metabolites
Rate and extent of excretion	Rapid excretion: 83–94% of a dose excreted in urine within 24 h (bentazone)
Metabolism in animals	Very little biotransformation: 81–91% of a dose excreted untransformed. Metabolites are 6-hydroxybentazone (6.3% of dose) and 8-hydroxybentazone (0–0.23% of dose)
Toxicologically significant compounds (animals, plants and environment)	Bentazone
<i>Acute toxicity</i>	
Rat LD <sub>50</sub> oral	Bentazone: 1500 mg/kg bw 6-Hydroxybentazone: > 5000 mg/kg bw 8-Hydroxybentazone: > 5000 mg/kg bw
<i>Short-term toxicity</i>	
Target/critical effect	Bentazone: decreased body weights in females, increased clotting times (prothrombin time and partial thromboplastin time) and increased output of urine with decreased specific gravity 6-Hydroxybentazone: no data 8-Hydroxybentazone: no effect up to highest dose tested
Lowest relevant oral NOAEL	Rat: Bentazone: 90 days, 78 mg/kg bw per day 6-Hydroxybentazone: no data Rat: 8-Hydroxybentazone: 260 mg/kg bw per day, highest dose tested
Lowest relevant dermal NOAEL	Bentazone: 1000 mg/kg bw per day (highest dose tested) 6-Hydroxybentazone: no data 8-Hydroxybentazone: no data
Lowest relevant inhalation NOAEL	No data
<i>Genotoxicity</i>	
Bentazone and its metabolites are not genotoxic	
<i>Long-term toxicity and carcinogenicity</i>	
Target/critical effect	No data
Lowest relevant NOAEL	No data
Carcinogenicity	Bentazone: no carcinogenicity 6-Hydroxybentazone: no data 8-Hydroxybentazone: no data
<i>Reproductive toxicity</i>	
Reproduction target/critical effect	No data
Lowest relevant reproductive NOAEL	No data
Developmental target/critical effect	Bentazone: developmental effects (decreased fetal weights and delayed ossification) below maternally toxic dose 6-Hydroxybentazone: no data 8-Hydroxybentazone: no developmental toxicity at highest dose tested
Lowest relevant developmental NOAEL	Rat: Bentazone: 100 mg/kg bw per day 6-Hydroxybentazone: no data Rat: 8-Hydroxybentazone: 250 mg/kg bw per day
<i>Neurotoxicity / Delayed neurotoxicity</i>	
No data	

*Other toxicological studies* No data

*Medical data* No data

<i>Summary</i>	<i>Value</i>	<i>Study</i>	<i>Safety factor</i>
ADI	0–0.1 mg/kg bw	Long-term toxicity, rats	100
Acute reference dose	Not considered		

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