5.9 CYCLOXYDIM (179)

TOXICOLOGY

Cycloxydim is the ISO approved name for (5RS)-2-[(EZ)-1-(ethoxyimino)butyl]-3-hydroxy-5-[(3RS)-thian-3-yl]cyclohex-2-en-1-one (IUPAC). The CAS chemical name for cycloxydim is 2-[1-(ethoxyimino)butyl]-3-hydroxy-5-(tetrahydro-2H-thiopyran-3-yl)-2-cyclohexen-1-one and the CAS No. is 101205-02-1. Cycloxydim is a cyclohexene oxime herbicide that is used for the control of grass weeds of many agricultural and horticultural broad-leaved crops.

Cycloxydim was evaluated previously by the JMPR in 1992 when an ADI of 0–0.07 mg/kg bw was established. Cycloxydim was reviewed by the present Meeting as part of the periodic re-evaluation programme of the CCPR. New studies evaluated by the Meeting included studies with repeated percutaneous doses, studies of acute toxicity and genotoxicity with various metabolites, and 28-day and 90-day studies of toxicity in rats given repeated oral doses of metabolites.

Cycloxydim was used in the free acid form in most of the toxicological studies. However, because of chemical instability of the acid in animal feed and because of its low solubility in water, the sodium salt of cycloxydim was used in those studies that required water or feed as vehicle. The name "cycloxydim" refers to the acid form unless otherwise indicated. All the pivotal studies met the basic requirements of the relevant OECD guidelines and certificates of compliance with GLP and QA were provided.

Biochemical aspects

Both the free acid and the sodium salt of cycloxydim are well absorbed; bioavailability was approximately 100%. The results of excretion-balance studies indicated that most (74–86%) of a single oral dose of the sodium salt of cycloxydim at 10 mg/kg bw per day is eliminated via the urine, most being excreted within 24 h. Biliary excretion (50–65% of the administered dose) and enterohepatic circulation play an important role in the elimination of cycloxydim. The highest concentrations of radiolabel were found in the liver and the kidneys. Quantities of radiolabel in all organs rapidly declined over time. There was no evidence for bioaccumulation of cycloxydim. The pattern of metabolites in the urine was similar for the free acid and the sodium salt of cycloxydim and AUC data indicated that elimination was saturable at higher doses. The major metabolite in the urine and bile was the sulfoxide of cycloxydim, BH 517-TSO. Additional metabolites identified were BH 517-T1SO (derived from N-de-ethoxylation of BH 517-TSO), BH 517-T1SO_2 and BH 517-T2SO. Only small amounts of unchanged parent compound were detected in the urine.

Toxicological data

Cycloxydim is of low acute toxicity when administered orally, dermally or by inhalation.

The oral LD_{50} of cycloxydim was 3940 mg/kg bw in rats and > 5000 mg/kg bw in mice. No specific clinical signs were observed. Macroscopic findings in rats that died after receiving high oral doses by gavage indicated irritation of the gastric mucosa. The dermal LD_{50} in rats was > 2000 mg/kg bw, a dose of 2000 mg/kg bw causing neither mortality nor systemic toxicity. No local skin reaction was observed at the application site. When cycloxydim is administered by inhalation, the LC_{50} is > 5.28 mg/L of air (4 h exposure). Cycloxydim was not an irritant in a study of ocular and dermal irritation in rabbits, nor a dermal sensitizer in the Magnussen & Kligman maximization test in guinea-pigs.

Short-term and long-term studies of oral toxicity in mice, rats and dogs were conducted using cycloxydim sodium salt or cycloxydim free acid. In all the studies described below, the dose or

dietary concentration of the test substance is expressed as cycloxydim free acid rather than its sodium salt.

The results of these studies are characterized by clinico-chemical changes, associated with changes in water and food consumption, and effects on the liver. Effects on erythrocytes were only seen in dogs at high doses. Where the test substance was administered in the drinking-water, the reduction in water consumption is regarded to be a palatability effect rather than a specific adverse effect.

With the few available parameters measured in two 4-week range-finding studies in mice, an overall NOAEL was set at 1000 ppm, equal to 189 mg/kg bw per day, on the basis of a significant increase in relative liver weights at concentrations of 3000 ppm and 9000 ppm in combination with altered clinico-chemical parameters, and the occurrence of hydropic vacuolar parenchymal degeneration of hepatocytes in the first study.

In rats, a 90-day study of oral toxicity indicated that the target organs were the kidney and liver on the basis of increases in concentrations of creatinine, urea and cholesterol in females, and increases in the activity of alanine aminotransferase in males and females at 900 ppm. The NOAEL was 300 ppm, equal to 22 mg/kg bw per day.

In the 4-week study of oral toxicity in dogs, the NOAEL was 40 mg/kg bw per day in males on the basis of effects on the liver. The results of a 3-month study of oral toxicity in dogs showed changes in haematological parameters and liver effects, with a NOAEL of 1500 ppm, equal to 50 mg/kg bw per day. In a 1-year study of toxicity in dogs, the NOAEL was 400 ppm, equal to 12 mg/kg bw per day, on the basis of effects on erythrocytes and the liver and altered clinico-chemical parameters.

The 2-year study of carcinogenicity in mice did not demonstrate any substance-related change at any dietary concentration and the NOAEL was 240 ppm, equal to 32 mg/kg bw per day, i.e., the highest dose tested. The study was not adequate for the evaluation of carcinogenicity as the doses delivered were not sufficiently high; the highest dose used was much less than the NOAEL of 1000 ppm identified in the dose range-finding studies.

In an 18-month study in rats, there was a statistically significant reduction in body weight, body-weight gain and triglyceride concentrations at dietary concentrations of 400 ppm and above, with a NOAEL of 100 ppm, equal to 7.0 mg/kg bw per day. In a 2-year study of carcinogenicity in rats, administration of drinking-water containing cycloxydim at concentrations of 400 ppm and 1600 ppm resulted in a reduction in body weight. Consumption of drinking-water was reduced in the group at 1600 ppm. In female rats, there was a reduction in concentrations of triglycerides. The NOAEL was 100 ppm, equal to 7 mg/kg bw per day, on the basis of a reduction in body weights and a a reduction in concentrations of triglycerides in rats given drinking-water containing cycloxydim at concentrations of 400 ppm and above.

The Meeting concluded that cycloxydim was not carcinogenic in rats but had not been adequately tested in mice.

Cycloxydim was tested for genotoxicity in an adequate range of assays, both in vitro and in vivo. Cycloxydim acid and the sodium salt gave negative results throughout, except at cytotoxic concentrations in studies of chromosomal aberration in vitro.

The Meeting concluded that cycloxydim is unlikely to be genotoxic.

Although the carcinogenic study in mice was not adequate, it was still possible to reach a conclusion on carcinogenicity to humans, in view of the lack of genotoxicity and the absence of carcinogenicity in rats. The Meeting concluded that cycloxydim is unlikely to pose a carcinogenic risk to humans.

In a multigeneration study in rats, the NOAEL for offspring toxicity was 400 ppm, equal to 38 mg/kg bw per day, on the basis of reduced survival, growth and developmental retardation in pups

at 1600 ppm, equal to 129 mg/kg bw per day, the highest dose tested. Reproductive toxicity was not affected by treatment at dietary concentrations of up to 1600 ppm. The NOAEL for parental toxicity was 100 ppm, equal to 9.7 mg/kg bw per day, on the basis of reductions in feed consumption, body weight and body-weight gain in dams at 400 ppm.

Studies of developmental toxicity have been carried out in rats and rabbits. In the study of developmental toxicity in rats, the NOAEL for maternal toxicity and embryo/fetotoxicity was 200 mg/kg bw per day. Increased numbers of fetuses/litters with retardations and a statistically significant increase in the frequency of anomalies of the vertebral column and the sternebrae with involvement of the cartilage and incomplete ossification were observed. Maternal toxicity and fetal effects were also observed in two subsequent supplementary studies. In the study of developmental toxicity in rabbits, the NOAEL for maternal toxicity was 100 mg/kg bw per day. The maternal toxicity observed at doses of 200 and 400 mg/kg bw per day occurred late in the study, indicating that repeated dosing over several days was required to elicit the effect. At 400 mg/kg bw per day, the percentage of viable implantations per dam was decreased and the incidence of several skeletal anomalies, e.g. asymmetrical sternebra(e) and fused sternebrae, was increased above the range for the historical controls. The NOAEL for embryo/fetotoxicity was 200 mg/kg bw per day. The Meeting concluded that cycloxydim causes maternal toxicity that occurred at a late stage during the study. The dose that caused maternal toxicity also caused embryo/fetotoxicity. The Meeting concluded that cycloxydim was not teratogenic.

Some toxicological studies and studies of genotoxicity have been undertaken for four compounds that are either present as impurities in technical cycloxydim or are metabolites in plants and not in animals.

BH 517-5-OH-TSO is of low acute oral toxicity in rats; no mortality or clinical symptoms were observed at the limit dose of 2000 mg/kg bw. Repeated exposure to diets containing BH 517-5-OH-TSO for 90 days did not cause any adverse effects at a dose of 50 mg/kg bw per day. In a 28-day study in rats, the NOAEL for BH 517-$TGSO_2$ was greater than 440.5 mg/kg bw per day.

BH 517-5-OH-TSO, BH 517-TGSO, BH 517-$TGSO_2$ and BH 517-TSO were tested for genotoxicity in vitro. All gave negative results.

No reports of adverse health effects or poisoning in manufacturing-plant personnel or in operators and workers exposed to cycloxydim were available except for three cases of eye irritation that occurred during production/filling of an old formulation “Focus ultra”; after replacement of this formulation by a new formulation, no more such cases have occurred.

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

Toxicological evaluation

The Meeting established an ADI of 0–0.07 mg/kg bw based on the NOAEL of 7 mg/kg bw per day identified on the basis of a reduction in body weights and a reduction in concentrations of serum triglycerides at concentrations of 400 ppm and above in the long-term dietary study in rats and using a safety factor of 100.

An ARfD of 2 mg/kg bw was established for women of childbearing age, based on a NOAEL of 200 mg/kg bw per day identified on the basis of certain skeletal anomalies at 400 mg/kg bw per day in the studies of developmental toxicity in rats and rabbits, and with a safety factor of 100. The Meeting could not exclude the possibility that these skeletal anomalies were the result of a single exposure.

The Meeting concluded that the establishment of an ARfD for the general population was not necessary on the basis of the low acute toxicity of cycloxydim, the lack of evidence for any acute neurotoxicity and absence of any other toxicologically relevant effect that might be attributable to a single dose.

A toxicological monograph was prepared.

Levels relevant to risk assessment

Species	Study	Effects	NOAEL	LOAEL
Mouse	Two-year study of carcinogenicity[d]	Carcinogenicity	240 ppm, equal to 32 mg/kg bw per day [c]	—
Rat	18-month study of toxicity [d]	Toxicity	100 ppm, equal to 7 mg/kg bw per day	400 ppm, equal to 28 mg/kg bw per day
	Two-year study of toxicity [d]	Carcinogenicity	1600 ppm, equal to 99 mg/kg bw per day [c]	—
	Two-generation study of reproductive toxicity[d]	Offspring toxicity	400 ppm, equal to 38 mg/kg bw per day	1600 ppm, equal to 129 mg/kg bw per day
		Reproductive toxicity	1600 ppm equal to 129mg/kg bw per day [c]	—
		Parental toxicity	100 ppm, equal to 9.7 mg/kg bw per day	400 ppm, equal to 38 mg/kg bw per day
	Developmental toxicity [b]	Maternal toxicity	200 mg/kg bw per day	400 mg/kg bw per day
		Embryo/fetotoxicity	200 mg/kg bw per day	400 mg/kg bw per day
Rabbit	Developmental toxicity [b]	Maternal toxicity	100 mg/kg bw per day	200 mg/kg bw per day
		Embryo/fetotoxicity	200 mg/kg bw per day	400 mg/kg bw per day
Dog	One-year study of toxicity [a]	Toxicity	400 ppm, equal to 12 mg/kg bw per day	1600 ppm, equal to 49 mg/kg bw per day

[a] Dietary administration.

[b] Gavage administration.

[c] Highest dose tested.

[d] Administration in drinking-water.

Estimate of acceptable daily intake for humans

0–0.07 mg/kg bw

Estimate of acute reference dose

2 mg/kg bw for women of childbearing age

Unnecessary for the general population

Information that would be useful for the continued evaluation of the compound

Results from epidemiological, occupational health and other observational studies of human exposure

Critical end-points for setting guidance values for exposure to cycloxydim

Absorption, distribution, excretion and metabolism in mammals	
Rate and extent of oral absorption	Rapid and almost completely absorbed (> 90%) within 24 h
Distribution	Widely distributed; highest concentration in liver and kidney
Potential for accumulation	No evidence for accumulation
Rate and extent of excretion	About 78–85% of the administered dose is eliminated via the urine within 5 days. Faeces contained approximately 12–25%; enterohepatic recirculation occurred.
Metabolism in animals	Extensive. The major metabolite was the sulfoxide (TSO)
Toxicologically significant compounds (animals, plants and the environment)	Cycloxydim
Acute toxicity	
Rat, LD_{50}, oral	3940 mg/kg bw
Rat, LD_{50}, dermal	> 2000 mg/kg bw
Rat, LC_{50}, inhalation	> 5.28 mg/L air
Rabbit, dermal irritation	Not an irritant
Rabbit, ocular irritation	Not an irritant
Guinea-pig, dermal sensitization (test method used)	Not a sensitizer (Magnussen &Kligman test)
Short-term studies of toxicity	
Target/critical effect	Body weight and liver
Lowest relevant oral NOAEL	1000 ppm (189 mg/kg bw per day) (4-week study in mice)
	300 ppm (22 mg/kg bw per day) (3-month study in rats)
	400 ppm (12 mg/kg bw per day) (1-year study in dogs)
Lowest relevant dermal NOAEL	300 mg/kg bw per day (28-day study in rats)
Genotoxicity	
	Not genotoxic
Long-term studies of toxicity and carcinogenicity	
Target/critical effect	Body weight
Lowest relevant NOAEL	100ppm (7 mg/kg bw per day), (rat)
Carcinogenicity	No carcinogenic potential
Reproductive toxicity	
Reproduction target/critical effect	Reduced survival growth and development in pups at parentally toxic doses
Lowest relevant reproductive NOAEL	400 ppm (38 mg/kg bw per day)

Developmental target/critical effect	Increase in the number of skeletal anomalies at maternally toxic doses
Lowest relevant developmental NOAEL	200 bw per day (rats and rabbits)
Neurotoxicity/delayed neurotoxicity	
	No data; no concerns raised by other studies
Medical data	
	No significant health effects were reported among manufacturing personnel.

Summary

	Value	**Study**	**Safety factor**
ADI	0–0.07mg/kg bw	Rat, 2-year study	100
ARfD*	2 mg/kg bw	Rat and rabbit; study of developmental toxicity	100

*For women of childbearing age, unnecessary for the general population.

DIETARY RISK ASSESSMENT

Deferred to 2010, when residue re-evaluation is scheduled.