LAMBDA-CYHALOTHRIN

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Explanation

Lambda-cyhalothrin, the International Organization for Standardization (ISO) approved common name for (*R*)-cyano(3-phenoxyphenyl)methyl (1*S*,3*S*)-rel-3-[(1*Z*)-2-chloro-3,3,3-trifluoro-1-propenyl]-2,2-dimethylcyclopropanecarboxylate is a synthetic cyano-containing type II pyrethroid insecticide (Chemical Abstracts Service, CAS No. 91465-08-6).

Cyhalothrin (CAS No. 68085-85-8) was evaluated by the JMPR in 1984, when an acceptable daily intake (ADI) of 0–0.02 mg/kg bw was established based on a no-observed-adverse-effect level (NOAEL) of 20 ppm, equal to 2 mg/kg bw per day, identified on the basis of clinical signs in a 2-year study in mice; a NOAEL of 30 ppm, equal to 1.5 mg/kg bw per day, identified on the basis of decreased body-weight gain in a three-generation study in rats; and a NOAEL of 2.5 mg/kg bw per day, identified on the basis of neurotoxicity in a 6-month study in dogs, and using a safety factor of 100.

At its meeting in 2000, the Joint FAO/WHO Expert Committee on Food Additives (JECFA) established a temporary ADI of 0–0.002 mg/kg bw based on a lowest-observed-effect level (LOEL) of 1 mg/kg bw per day for induction of liquid faeces in dogs in a 26-week study, and using a safety factor of 500. The high safety factor was used to compensate for the absence of a no-observed-effect level (NOEL) in this study.

At its meeting in 2004, JECFA concluded that the toxicity of cyhalothrin is similar in rats and dogs. The Committee decided that the temporary ADI could be replaced by an ADI of 0–0.005 mg/kg bw, which was determined by dividing the LOEL of 1 mg/kg bw per day in dogs (also the NOEL for rats) by a safety factor of 200. The safety factor incorporated a factor of 2 to compensate for the absence of a NOEL in dogs.

Lambda-cyhalothrin consists of two of the four enantiomers (i.e. the *cis* 1*R*α*S* and *cis* 1*S*α*S* enantiomeric pair) of cyhalothrin. One of the two enantiomers of lambda-cyhalothrin is the insecticidally active gamma-cyhalothrin (CAS No. 76703-62-3). Cyhalothrin comprises about 50% lambda-cyhalothrin.

Lambda-cyhalothrin was evaluated by the present Meeting within the periodic review programme of the Codex Committee on Pesticide Residues (CCPR). For the present re-evaluation, studies with cyhalothrin and lambda-cyhalothrin were available.

For lambda-cyhalothrin, specifications were established by the FAO/WHO Joint Meeting on Pesticide Specifications (JMPS) and published as *WHO specifications and evaluations for public health pesticides: lambda-cyhalothrin*[1] (technical material, 2003). For other formulations, specifications also exist.

All pivotal studies with cyhalothrin and lambda-cyhalothrin were certified as being compliant with good laboratory practice (GLP).

Evaluation for acceptable daily intake

1. Biochemical aspects

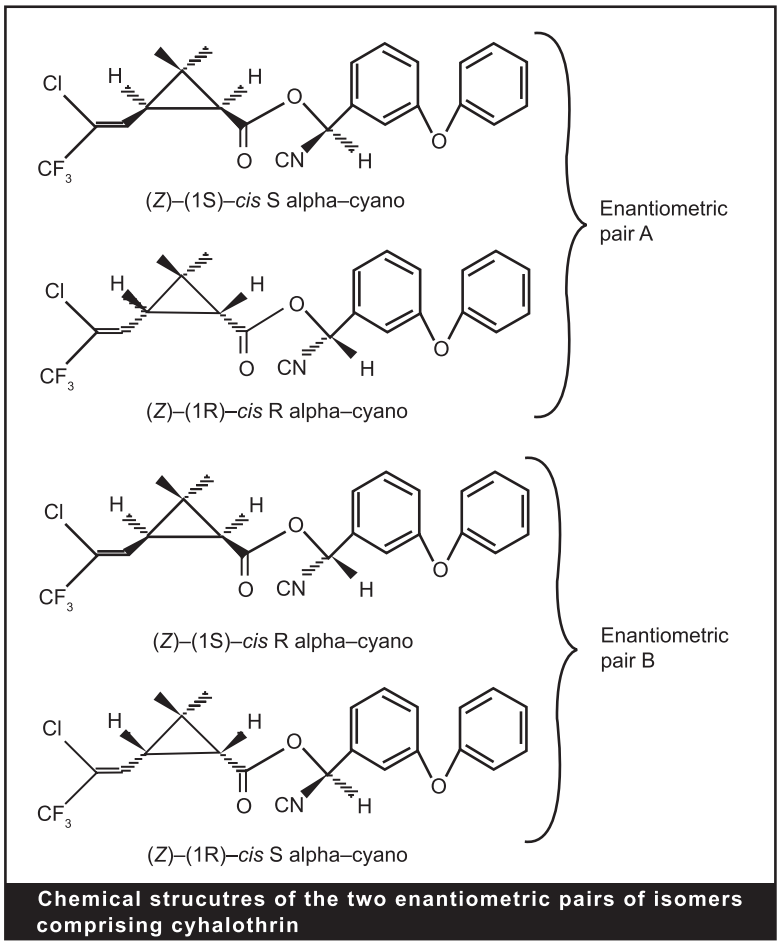
1.1 Absorption, distribution and excretion

Rats

Groups of six male and six female Alderley Park Wistar (Alpk/Ap) (SPF) rats were given a single dose of [^{14}C]cyhalothrin (purity, >99%) at 1 or 25 mg/kg bw in corn oil by gavage. Cyhalothrin was labelled either at the 3-phenoxybenzyl side-chain (i.e. the carbon to which the cyanide moiety is attached: ^{14}CHCN, or at the 1 position of the cyclopropyl moiety (see Figure 1). In a separate experiment, groups of three or four rats with bile-duct cannulae were given an oral dose of ^{14}C-benzyl-labelled cyhalothrin at 1 mg/kg bw. An additional group of five males and six females received ^{14}C-benzyl-labelled cyhalothrin as a subcutaneous dose at 1 mg/kg bw. In a repeated-dose experiment to study the excretion and tissue accumulation of cyhalothrin given at a dose of 1 mg/kg per day by gavage, groups of six male and six female rats received daily doses of ^{14}C-benzyl-labelled or ^{14}C-cyclopropyl-labelled cyhalothrin for 14 days. Excreta (urine, faeces and, in selected rats, expired air) were collected for up to 7 days after dosing and analysed for total radioactivity and metabolites by liquid scintillation counting (LSC) and thin-layer chromatography (TLC). Blood samples were also collected at various times up to 48 h and analysed for total radioactivity and unchanged cyhalothrin. Statements of adherence to quality assurance (QA) and GLP were included.

[1] Available from: http://www.who.int/whopes/quality/en/Lambda-cyhalothrin_eval_specs_WHO_2003.pdf

Figure 1. Chemical structures of the two pairs of enantiomeric pairs of isomers comprising lambda-cyhalothrin



From IPCS (1990)

Recovery of radioactivity was 81–91%. Approximately 30–40% and 40–60% of the orally administered ^{14}C-benzyl-labelled material was recovered in urine and faeces respectively. No $^{14}CO_2$ was detected in expired air. The proportions absorbed and the rate of excretion were similar at both doses, although excretion in faeces tended to be slower at the higher dose. Peak blood concentrations (approximately 0.6 and 6 µg/kg of cyhalothrin equivalents at 1 and 25 mg/kg bw, respectively) were reached 7 h after dosing. By 48 h, the blood concentrations had depleted to less than 10% of the peak value. In bile-duct cannulated rats, biliary excretion accounted for 4.8% of the total excretion in males and 8.9% in females. The extent of absorption in rats equipped with a biliary fistula was less than in intact rats, however absorption was increased in rats (four males) given replacement bile, indicating that cyhalothrin is absorbed along with the fats of the oil formulation. In the males treated with replacement bile, biliary excretion was 11.2%.

At the lower dose, 70% of the administered material was recovered within 24 h, and only 2–3% of the administered radiolabel remained in the carcass after 7 days. At this time-point, the radiolabel was distributed mainly in fat (11.5 µg/g at a dose of 25 mg/kg bw).

Elimination of radiolabel was slower after subcutaneous administration of ^{14}C-benzyl-labelled cyhalothrin than after oral dosing; 58% of the radiolabel was still present in the carcass 7 days after dosing. This was attributed to retention of the oil formulation in subcutaneous fat.

With cyclopropyl-labelled cyhalothrin, smaller proportions of the administered radiolabel were recovered in the urine (19–30%). Peak blood concentrations were achieved at 4–7 h, but these had declined to 10% of the peak values by 48 h. Only 1–3% of the administered dose remained in the carcass after 7 days.

In the repeated-dosing experiment, more than 90% of the cumulative dose was recovered in urine and faeces within 7 days of the last dose. The daily excretion reached a constant after the second dose. Comparison with the single-dose experiment showed that radioactivity accumulated in fat (Harrison & Case, 1981; Harrison, 1984a, 1984b).

A study was undertaken to explore the retention, in fat, of cyhalothrin and lambda-cyhalothrin in rats. Male rats (Alpk/AP) received ^{14}C-cyclopropyl-labelled cyhalothrin (purity, 92.2%) as daily oral doses at 1 mg/kg per day, for up to 119 days. Rats in the control group received vehicle (corn oil). At several time-points (approximately weekly), groups of three rats were killed 24 h after the last dosing, and the concentrations of radioactivity in the liver, kidney, fat, and blood were determined. In addition, the concentration in fat of lambda-cyhalothrin and its opposite enantiomer pair (enantiomer pair A) was measured by high-performance liquid chromatography (HPLC). Furthermore, the elimination of radioactivity from blood, liver, kidneys and fat was assessed for 7 weeks after cessation of treatment. Statements of adherence to QA and GLP were included.

Levels of radioactivity in the blood remained fairly constant and low (approximately 0.2 µg cyhalothrin equivalents per gram) throughout the dosing period. In the liver and kidney, the radioactivity reached a plateau after approximately 70 days, at a level corresponding to cyhalothrin equivalents of approximately 2.5 µg/g liver and 1.2 µg/g kidney. The concentration of radioactivity in fat continued to increase with time, corresponding to cyhalothrin levels of 10 µg/g fat at the end of the treatment period. After cessation of dosing, concentrations of radioactivity in the kidney and blood declined rapidly, and were barely detectable after 5 weeks. In fat, the levels declined more slowly with an elimination half-life of 30 days. Concentrations of radioactivity in the liver initially declined rapidly, while subsequent elimination paralleled that of the fat. The radioactive material in fat was unchanged cyhalothrin; the ratio of enantiomeric pairs, one of which was lambda-cyhalothrin, was not significantly different from that in the dosing solution, indicating that the rate of metabolism of lambda-cyhalothrin was the same as that of cyhalothrin and that there was no preferential accumulation of lambda-cyhalothrin (Prout, 1984).

In a tissue-distribution time-course study, groups of 15 male and 15 female Alpk:AP$_f$SD Wistar-derived rats received [^{14}C]benzyl labelled cyhalothrin (radiochemical purity, > 97.5%) as a single oral dose at 1 or 25 mg/kg bw in corn oil (volume, 4 ml/kg). In the group receiving the lower dose, three males and three females were killed at intervals of 6.5, 11 (13 females), 24, 48 and 96 h after dosing. At the higher dose, groups of three male rats were killed at 10 h (time of peak plasma concentration), 17 h (half-life of elimination of radioactivity from blood) and at 24, 48 and 96 h. Also at this dose, groups of three female rats were killed at 7 h (time of peak plasma concentration), 21 h (half-life of elimination of radioactivity from blood) and at 30, 48 and 96 h. At these time-points, plasma, whole blood, liver, kidneys, lungs, spleen, bone, brain, heart, muscle, gonads, white and brown fat from each rat were analysed for radioactive content. Statements of adherence to QA and GLP were included.

Brown fat contained the highest concentrations of radioactivity (0.89–1.45 µg eq/g in rats at the lower dose and about 15 µg eq/g in rats at the higher dose). The concentration of radioactivity declined relatively quickly during the study in all tissues except white fat. The peak concentration of radioactivity in white fat increased in proportion to the dose. No marked sex differences in tissue distribution were noted. (Jones, 1989a, 1989b).

In a comparative study, the absorption, distribution, excretion, and metabolism of single oral doses of lambda-cyhalothrin (purity, 99.0%) and cyhalothrin (a 50 : 50 mixture of lambda-cyhalothrin and the opposite enantiomer pair A (see Figure 1); purity, 97.4%) was investigated in groups of four male rats (Alpk/AP). One group was given [^{14}C]cyclopropyl-labelled lambda-cyhalothrin (1 mg/kg bw), a second group was given [^{14}C]cyclopropyl-labelled lambda-cyhalothrin (1 mg/kg bw) plus the unlabelled enantiomeric pair A (1 mg/kg bw), and a third group was given [^{14}C]cyclopropyl-labelled cyhalothrin (1 mg/kg bw). The urinary and faecal excretion of radioactivity was monitored for 3 days and the residual radioactivity was then determined in selected tissues. The metabolite profile of the excreta was determined by TLC. Statements of adherence to QA and GLP were included.

The results of this study indicated that coadministration of enantiomer pair A with lambda-cyhalothrin had little or no effect upon the absorption, distribution, or tissue retention of radioactivity, and there was no effect upon the metabolite profile of lambda-cyhalothrin. Similarly, the absorption, distribution, excretion, and metabolism of cyhalothrin was indistinguishable from that of lambda-cyhalothrin (Prout & Howard, 1985).

Dogs

Groups of three male and three female beagle dogs received gelatin capsules containing either [^{14}C]cyclopropyl-labelled cyhalothrin or [^{14}C]benzyl-labelled cyhalothrin (purity, > 97%) as a single oral dose at 1 and 10 mg/kg bw dissolved in corn oil. The same dogs also received [^{14}C]benzyl- or [^{14}C]cyclopropyl-labelled material as a single intravenous injection at 0.1 mg/kg bw (in ethanol : 0.9% saline in a 3.2 : 1.2 ratio). There was an interval of at least 3 weeks between each dose. Blood samples and excreta were collected over 7 days after dosing and were analysed for radiolabel by liquid scintillation counting (LSC). Metabolites were measured by TLC, and the identities of selected metabolites were confirmed by mass spectrometry. Statements of adherence to QA and GLP were included.

Overall recovery ranged from 82% to 93%. After a single oral administration at a dose of 1 or 10 mg/kg bw, approximately 30% and 50% of the [^{14}C]benzyl-label was excreted in the urine and faeces respectively. In dogs that were dosed intravenously, 37% and 42% of [^{14}C]benzyl-label was excreted in the urine and faeces respectively. Excretion of radioactivity after both oral and intravenous dosing was initially rapid, with most of the administered radioactivity being excreted in the first 48 h after dosing. When [^{14}C]cyclopropyl-cyhalothrin was given orally, the proportion of residue in the urine was slightly lower (19%) and the amount in the faeces was higher (68%). The proportions of residue in the urine and in the faeces were approximately equal when the two radiolabelled forms of cyhalothrin were given intravenously. A large proportion (46–87%) of the faecal residue was in the form of unchanged cyhalothrin after oral dosing, but only small amounts of parent substance (1.4–1.5% of faecal radiolabel) were found in faeces after intravenous injection, suggesting that the oral dose of cyhalothrin was only partially absorbed from the gut lumen, leaving unabsorbed cyhalothrin in the faeces. No marked sex differences were observed (Harrison, 1984c).

1.2 Biotransformation

(a) In vivo

Rats

Groups of six male and six female Alderley Park Wistar (Alpk/Ap) (SPF) rats were given [^{14}C] cyhalothrin (purity, > 99%) as a single dose at 1 or 25 mg/kg bw in corn oil by gavage. Cyhalothrin was labelled either at the 3-phenoxybenzyl side-chain (i.e. the carbon to which the cyanide moiety is attached: ^{14}CHCN) or at the 1 position of the cyclopropyl moiety (for structure see Figure 1). Urine and faeces were collected for up to 7 days after dosing and analysed for metabolites by TLC. Bile samples were also collected at various times up to 48 h and analysed for metabolites.

The patterns of metabolites derived from the two ^{14}C-labelled forms of cyhalothrin were totally different, suggesting that metabolism involves initial cleavage of the ester bond. Two major urinary metabolites (not further identified), representing 75% and 17% of radioactivity in the urine, were derived from [^{14}C]benzyl-labelled cyhalothrin. Both were polar and resistant to glucuronidase. Of the urinary material derived from cyclopropyl-labelled cyhalothrin, 60% could be hydrolysed by glucuronidase. Three biliary metabolites (not further identified) were derived from [^{14}C]benzyl-labelled cyhalothrin, two of which (representing 12% and 67% of the radioactivity in bile) were different from the urinary metabolites. Urine and bile did not the contain parent compound. Faeces, on the other hand, contained mainly unchanged cyhalothrin, which was probably nonabsorbed material. In addition, the faeces contained three relatively non-polar metabolites which could be hydrolysis products of conjugates excreted in bile. Residues in fat probably represent unchanged cyhalothrin (Harrison & Case, 1981; Harrison, 1984a, 1984b).

In a study designed to identify the major pathways of cyhalothrin metabolism, groups of six male and six female Alpk:AP$_f$SD Wistar-derived rats were given [^{14}C]benzyl-labelled cyhalothrin at a dose of 12.5 mg/kg bw per day for 8 days until each rat had received approximately 25 mg of cyhalothrin. Urine and faeces were collected daily, after dosing and for up to 3 days after the last dose. A further six male and six female rats were each given fourteen consecutive daily doses of [^{14}C]cyclopropyl-labelled cyhalothrin at 1 mg/kg bw per day, and the urine was collected and combined. Metabolic profiles were determined by TLC, both before and after enzymic hydrolyses using aryl sulfatase and β-glucuronidase enzymes. Individual metabolites were purified by reverse-phase HPLC before analysis by gas chromatography-mass spectrometry (GC-MS), probe MS, fast atom-bombardment mass spectrometry (FAB-MS) and/or carbon nuclear magnetic resonance spectroscopy (^{13}C-NMR). Statements of adherence to QA and GLP were included.

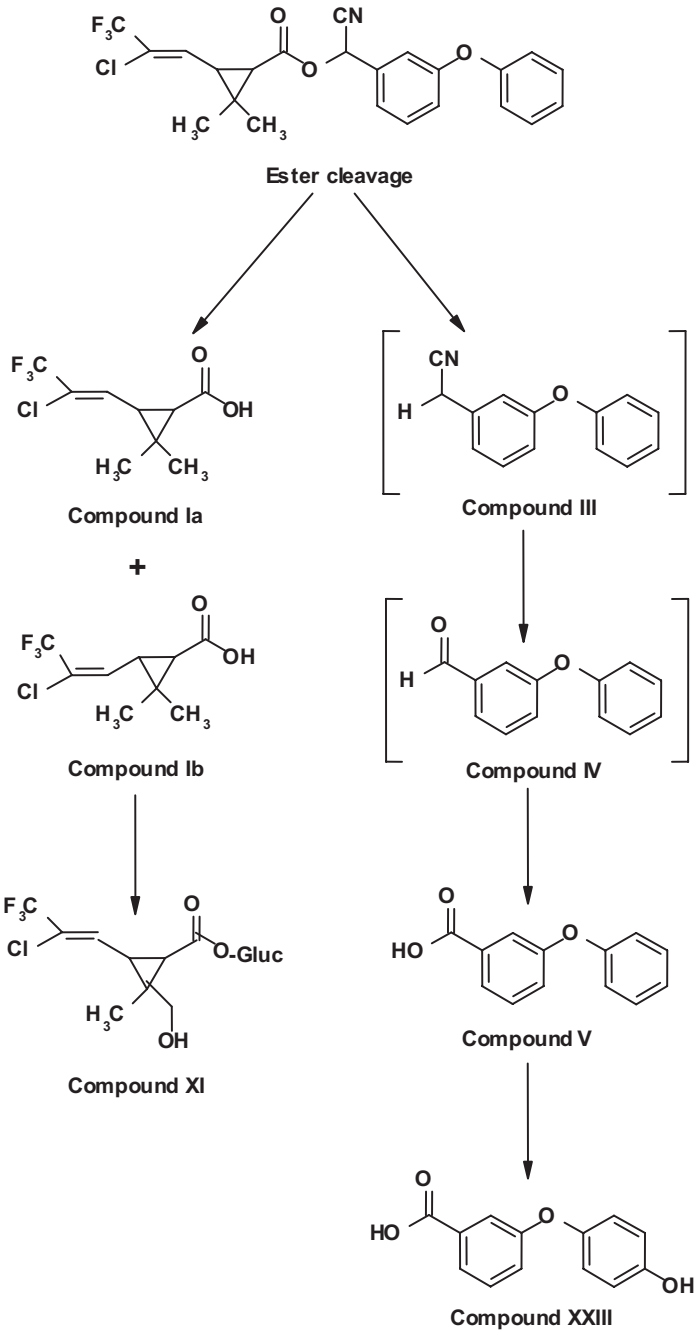
The major radioactive component in urine of rats dosed with [^{14}C]benzyl-labelled cyhalothrin was the sulfate conjugate of 3-(4'-hydroxyphenoxy) benzoic acid (compound XXIII). Unconjugated compound XXIII and 3-phenoxybenzoic acid (compound V) were minor metabolites. The major radioactive component in urine of rats dosed with [^{14}C]cyclopropyl labelled cyhalothrin was the glucuronide conjugate of (1*RS*)-*cis*-3-(2-chloro-3,3,3-trifluoropropenyl)-2,2-dimethylcyclopropanoic acid (compound Ia). One of the minor metabolites also appeared to be a glucuronide conjugate, which was tentatively identified as a hydroxylated analogue of acid (compound XI) (Harrison & Case, 1983).

Dogs

Groups of three male and three female beagle dogs received gelatin capsules containing either [^{14}C]cyclopropyl-labelled or [^{14}C]benzyl-labelled cyhalothrin (purity, > 97%) as a single oral dose at 1 or 10 mg/kg bw dissolved in corn oil. The same dogs received a single intravenous injection of [^{14}C]cyclopropyl-labelled or [^{14}C]benzyl-labelled cyhalothrin at a dose of 0.1 mg/kg bw (in ethanol : 0.9% saline in a 3.2 : 1.2 ratio). The doses were separated by an interval of at least 3 weeks. Blood samples and excreta were collected for 7 days after dosing and were analysed for radiolabel by LSC. Metabolites were measured by TLC, and the identities of selected metabolites were confirmed by MS. Statements of adherence to QA and GLP were included.

Metabolism occurred initially by cleavage of the ester bond to give a phenoxybenzyl moiety and a cyclopropanoic acid moiety. Further metabolism of the phenoxybenzyl moiety produced *N*-(3-phenoxybenzoyl) glycine, 3-(4'-hydroxyphenoxy)benzoic acid (compound XXIII) and its sulfate conjugate, 3-phenoxybenzoyl glucuronide, small amounts of various other conjugates of these compounds, and a little free phenoxybenzoic acid. The cyclopropanoic acid moiety was extensively metabolized to at least 11 further metabolites, including 45% as the glucuronide of the cyclopropanoic acid and up to 23% as the free cyclopropanoic acid (i.e. 3-(*Z*-2-chloro-3,3,3-trifluoropropenyl)-2,2-dimethylcyclopropanoic acid; see Fig. 2) (Harrison, 1984c).

Figure 2. Main pathways of biotransformation of cyhalothrin in mammals



Compound Ia	(1*RS*)-*cis*-3-(*Z*-2-chloro-3,3,3-trifluoroprop-1-enyl)-2,2-dimethylcyclopropanoic acid
Compound Ib	(1*RS*)-*trans*-3-(*Z*-2-chloro-3,3,3-trifluoroprop-1-enyl)-2,2-dimethylcyclopropanoic acid
Compound III	(*RS*)-α-cyano-3-phenoxybenzyl alcohol,Mixture of R and S isomers
Compound IV	3-phenoxybenzaldehyde
Compound V	3-phenoxy benzoic acid
Compound XI	*EZ*)-1-(*RS*)-2-*trans*-3-*cis*-3-(2-chloro-3,3,3-trifluoromethylpropenyl)-2-hydroxymethyl-2-methylcyclopropanoic acid
Compound XXIII	3-(4'-hydroxyphenoxy) benzoic acid

2. Toxicological studies

2.1 Acute toxicity

(i) Lethal doses

The results of studies of acute toxicity with lambda-cyhalothrin are summarized in Table 1. It is noteworthy that lambda-cyhalothrin and cyhalothrin are unusual among pyrethroids in that these compounds cause lethality via the dermal route.

The observed clinical signs (ataxia, decreased activity, tiptoe gait, splayed gait, loss of stability, dehydration, urinary incontinence, hunched posture, piloerection, salivation, ungroomed appearance and pinched-in sides) were typical of this class of pyrethroids.

(ii) Dermal irritation

In a study of dermal irritation in female New Zealand White (NZW) rabbits, six rabbits were exposed to cyhalothrin (purity, 92.9%) or lambda-cyhalothrin (purity, 96.5%) for 4 h on the intact skin. Irritation was scored at 1, 20, 44 and 68 h, and 5, 7, 9 and 14 days after the removal of the occlusive dressing. Statements of adherence to QA and GLP were included.

In the rabbits treated with cyhalothrin, no erythema was observed. Very slight oedema was observed at 1 and 20 h, but not at other time-points after application. In the rabbits treated with lambda-cyhalothrin, no erythema was observed. Very slight oedema was observed only at 1 h, but not at other time-points after application (Pritchard, 1985a).

(iii) Ocular irritation

In a study of ocular irritation, the eyes of six male NZW rabbits were exposed to lambda-cyhalothrin (purity, 96.5%). The eyes were examined at 1–2 h and at 1, 2, 3, 4 and 7 days in all rabbits, and on days10, 11, 13, 14 and 17 in one to three rabbits. Statements of adherence to QA and GLP were included.

Lambda-cyhalothrin induced slight to moderate redness, slight or mild chemosis of the conjunctivae, and slight or severe discharge at 1 h after application. At day 2 after application, slight or moderate redness, slight chemosis and slight discharge were observed. In four rabbits, the effects had completely resolved within 4 days, while the other two rabbits had recovered at day 10. All rabbits appeared very agitated, flicking their heads, blinking and pawing at the treated eye during the first 24 h. This was attributed to paresthaesia effects. Also, additional irritation effects observed during the study may have been caused by rubbing of the eyes as a result of paresthaesia (Pritchard, 1985b).

Table 1. Results of studies of acute toxicity with lambda-cyhalothrin

Species	Strain	Sex	Route	Vehicle	Purity (%)	LD_{50} (mg/kg bw)	LC_{50} (mg/l)	Reference
Mouse	NS	Male Female	Oral	Corn oil	96.5	19.9 19.9	—	Southwood (1984)[a]
Rat	NS	Male Female	Oral	Corn oil	92.6-96	79 56	—	Southwood (1985)[a]
Rat	NS	Male Female	Dermal (24-h)	Propylene glycol	92.6	632 696	—	Barber (1985)[a]
Rat	Wistar	Male & Female	Inhalation (4-h)	NS	NS	—	0.06	Hext (1987)[a]

NS, not stated.

[a] Statements of adherence to QA were included.

(iv) Dermal sensitization

In a study of dermal sensitization using the Magnusson & Kligman maximization test, lambda-cyhalothrin (purity, 96.5%) was tested on 20 Dunkin Hartley guinea-pigs. The control group consisted of 10 guinea-pigs. In the induction phase, guinea-pigs received three intracutaneous injections: lambda-cyhalothrin (5% w/v in corn oil), Freund complete adjuvant and corn oil (1 : 1), and lambda cyhalothrin (5% w/v in Freund complete adjuvant and corn oil (1 : 1). One week later, this was followed by a topical application (48 h) of lambda-cyhalothrin (1% w/v) in corn oil. Two weeks after the topical application the guinea-pigs received the challenge dose of lambda-cyhalothrin (1% w/v in corn oil, 0.05 ml) for 24 h under occlusion. Skin reactions were examined immediately and 1 and 2 days after removal of the occlusive dressing. Statements of adherence to QA and GLP were included.

No response to the challenge dose was observed (Pritchard, 1984).

In deviation from what is required in the OECD 406 testing guideline, no skin irritation was observed in the induction phase. The skin was not treated with sodium lauryl sulfate before the topical application in the induction phase. Therefore the test was not been properly performed and no conclusion can be drawn as to the skin sensitizing properties of lambda-cyhalothrin.

In the IPCS Environmental Health Criteria 99 (IPCS, 1990) document on cyhalothrin it is reported that cyhalothrin induced skin sensitization in a Buehler test in guinea-pigs. In guinea-pigs previously induced with undiluted technical cyhalothrin, a moderate sensitization response was elicited in a Magnusson & Kligman maximization test.

2.2 Short-term studies of toxicity

Rats

In a limited 28-day study in Wistar rats, which included a recovery period, the toxicity of cyhalothrin for the liver was investigated. Groups of 32 male rats received diets containing cyhalothrin (purity, 89.2%) at a concentration of 0 or 250 ppm (equivalent to 12.5 mg/kg bw per day). Rats were checked daily for clinical signs. Body weights were measured at the start of treatment and weekly thereafter. After 28 days, eight rats from each group were killed. The remaining rats were maintained on a control diet and eight rats per group were killed after 7, 14 or 28 days. Livers from all rats were weighed and examined histologically and byelectron microscopy and hepatic aminopyrine-*N*-demethylase activity was measured. A statement of adherence to quality assurance (QA) was included.

The body-weight gain of the rats fed cyhalothrin decreased during treatment and remained decreased until the day of sacrifice. Although there was a tendency for a slight reduction of the absolute liver weights of the treated rats, relative liver weights were not affected. At the end of the 28-day treatment period, electron microscopy showed significant proliferation of smooth endoplasmic reticulum in only five rats of the group exposed to cyhalothrin. Such proliferation was no longer apparent in rats allowed a 7-day recovery. Hepatic aminopyrine-*N*-demethylase activity was elevated by 66% after 28 days feeding at 250 ppm, but had reverted to control levels 7 days after cessation of exposure (Lindsay et al., 1982).

In a 90-day study, groups of 20 male and 20 female Wistar derived Alderley Park rats were fed diets containing technical-grade cyhalothrin (purity, 89.2%; total pyrethroid content, 92.2%, of which 96.8% was cyhalothrin) at a concentration of 0, 10, 50, or 250 ppm (equal to 0, 0.56, 2.6, and 14 mg/kg bw per day for males and 0, 0.57, 3.2, and 15 mg/kg bw per day for females). Rats were checked daily for clinical signs. Detailed clinical examinations and body weights were assessed at the start of treatment and weekly thereafter. Food consumption was measured weekly. Haematology was performed on 10 males and 10 females per group at the start of the study and after 1 and 3

months of treatment. At the same time-points, clinical chemistry and urine analysis was performed on the 10 males and 10 females per group not designated for haematology. In addition, bone-marrow smears taken at 3 months were examined. During the last week of treatment, ophthalomoscopy was performed on all rats in the control group and those at the highest dose. At termination, the rats were killed and necropsied. Selected organs were weighed. An extensive range of tissues from rats in the control group and those at the highest dose, and the testes, epididymes, prostate, seminal vesicles, liver, kidneys, heart, spleen and abnormal tissues of all rats were histologically examined. Livers from six males and six females per group were examined by electron microscopy. Hepatic aminopyrine-*N*-demethylase activity was measured in liver samples from 10 males and 10 females per group. Statements of adherence to QA and GLP were included.

No effects of treatment on mortality, clinical signs, ophthalmoscopy and relative organ weights were observed. Minor effects on haematological parameters were considered not to be toxicologically relevant. The body-weight gain of males at the highest dose was consistently reduced (±10%) throughout the study. Food consumption was reduced in males at 50 and 250 ppm by 12% and 13%, respectively. At 13 weeks, plasma triglyceride concentrations were reduced (42% and 59%, respectively). Urinary glucose concentration was increased (49% and 69%) in males at 50 and 250 ppm, respectively. However, since the increases were small and similar increases in urine glucose concentrations were observed before treatment (54% and 79% at 50 and 250 ppm, respectively) this effect was not considered to be treatment-related. The results of gross examinations were not reported. No treatment-related changes were revealed by optical microscopy of organs. Electron microscopy of the liver showed mild proliferation of smooth endoplasmic reticulum in the hepatocytes of three males in the groups at 50 ppm and 250 ppm. Hepatic aminopyrine-*N*-demethylase activity was increased in males at 50 or 250 ppm by 34% and 68%, respectively, and in females at 250 ppm by 46%.

On the basis of reduced body-weight gain and food consumption in males at 250 ppm, the NOAEL was 50 ppm, equal to 2.6 mg/kg bw per day (Lindsay et al., 1981). The Meeting noted that the 1984 JMPR had stated that a NOEL could not be established owing to haematological effects in all treatment groups. However, the effects were very small (generally < 3%, and 6% for mean cell volume at 250 ppm).

In a 3-month feeding study, groups of 20 male and 20 female Alderley Park (Alpk/AP) rats were fed diets containing lambda-cyhalothrin (P321; purity, 96.5%) at a concentration of 0, 10, 50, or 250 ppm (equivalent to 0, 0.5, 2.5 and 12.5 mg/kg bw per day). The rats were checked daily for clinical signs. Detailed clinical examinations and body weights were assessed at the start of treatment and weekly thereafter. Food consumption was measured weekly. Haematology was performed on 10 males and 10 females per group at the start, and at 1 and 3 months of treatment. At the same time-points, clinical chemistry and urine analysis was performed on the 10 males and 10 females per group not designated for haematology. During the last week of treatment, ophthalomoscopy was performed on all rats in the control group and at the highest dose. After 13 weeks, the rats were killed and necropsied. Selected organs were weighed. A selection of tissues from rats in the control group and at the highest dose, and the liver, kidneys, lungs and abnormal tissues of all rats were examined histologically. Hepatic aminopyrine-*N*-demethylase activity was measured in liver samples of six males and six females per group. Statements of adherence to QA and GLP were included.

No toxicologically relevant effects on clinical signs, ophthalmoscopy, haematology, clinical chemistry and urine analysis were observed. Body-weight gain and food consumption were reduced in the group at the highest dose (males, 11%; females, 7–9%). Blood triglyceride concentrations, measured after 1 and 3 months of treatment, were reduced by 28–32% in males at the highest dose and by 15–17% in males at the intermediate dose. A slight increase in relative liver weight (8%) was

observed in rats at the highest dose. Slight increases in hepatic aminopyrine-*N*-demethylase activity were observed in males (17%) and females (27%) at the highest dose. These were not accompanied by histopathological changes in the liver.

On the basis of the reduction in body-weight gain and food consumption in males at the highest dose, the NOAEL was 50 ppm, equivalent to 2.5 mg/kg bw per day (Hart, 1985).

Dogs

In a pilot study, groups of one male and one female beagle dog received gelatin capsules contaning lambda-cyhalothrin (purity, 87.7%; as a solution in corn oil) at a dose of 0, 0.75, 1.5, 3.0 or 4.0 mg/kg bw per day for 6 weeks. The test compound was given 2 h after feeding. the dogs were checked daily for clinical signs. Food consumption was measured daily and the dogs were weighed weekly. Ophthalmoscopy was performed before the start of treatment and before termination. Haematology and clinical chemistry was performed before the start of treatment and during weeks 1, 3 and 6. At the end of the treatment period, the dogs were killed, examined macroscopically and histologically and selected organs were weighed. Statements of adherence to QA and GLP were included.

Both dogs at 4.0 mg/kg bw per day were killed for humane reasons on day 15, after inappetence and body-weight loss that were observed from the start of dosing. Before this, occasionally slightly decreased activity, thin appearance, fluid faeces and regurgitation/vomiting was observed. In the groups at 1.5 and 3.0 mg/kg bw per day, occasional transient signs of minor neurological disturbance (e.g. decreased activity, slight tremors and unsteady gait) vomit and/or regurgitation were seen. Fluid faeces were observed in all treatment groups (Horner, 1996).

Groups of six male and six female beagle dogs received gelatin capsules containing cyhalothrin (purity unknown; as a solution in corn oil) at 0, 1.0, 2.5 or 10 mg/kg bw per day for 26 weeks. The test compound was given 1 h before feeding.

Clinical signs, body weight and food consumption were assessed daily. Water consumption was recorded before dosing and during weeks 1–3, 5–7, 9–11, 13–15, 17–19 and 21–24. Ophthalmoscopy was performed before the start of treatment and during weeks 6, 12 and 24. A neurological examination, investigating the cranial nerves, the segmental reflexes and the postural reactions, was carried out on all dogs in the control group and on dogs at 10 mg/kg bw per day before the start of treatment and during week 6 at approximately 1 h after administration. Haematological and clinical chemistry was performed before dosing started and during weeks 4, 8, 12, 16, 20 and 25. Urine analysis was performed before dosing and during weeks 8, 16, and 25.

On the day before autopsy, bone marrow was obtained by sternal puncture and a smear was prepared for examination. At the end of the treatment period, the dogs were killed and macroscopied, selected organs were weighed and a range of tissues microscopically examined. Statements of adherence to QA and GLP were included.

In the group at the highest dose, clinical signs indicative of a disturbance of the nervous system (e.g. unsteadiness, marked lack of coordination, collapse and occasionally muscular spasms) and vomiting were seen, from the first week of treatment onwards. The signs in general appeared within a few hours after administration. These observations were not accompanied by histological changes in nervous tissue. From the first week of treatment onwards, there was a dose-related increase in the passage of liquid faeces, observed in all treatment groups. Other pyrethroids produce this effect, which may represent a consequence of the gastrointestinal equivalent of paresthaesia in the skin (Ray & Fry, 2006). No compound-related changes in body weight were seen apart from a transient loss in weight for one male at 10.0 mg/kg bw per day that also showed transient reductions in food consumption. In the group at the highest dose, a transient increase in water consumption during the first half

of the dosing period and a reduction in food consumption may have been treatment-related. No other treatment-related effects were observed.

On the basis of the neurotoxic effects observed at 10 mg/kg bw per day, the NOAEL for systemic effects was 2.5 mg/kg bw per day. On the basis of the increased incidence of liquid faeces the lowest-observed-adverse-effect level (LOAEL) for local gastrointestinal effects was 1.0 mg/kg bw per day (Chesterman, 1981).

Groups of six male and six female beagle dogs received capsules containing lambda cyhalothrin (purity, 96.5%; as a solution in corn oil) at a dose of 0, 0.1, 0.5 or 3.5 mg/kg bw per day, for 52 weeks. The test compound was given by capsule 1 h before feeding. Clinical signs and food consumption were recorded daily. Body weight was measured weekly. Haematology and clinical chemistry were performed before treatment and at weeks 4, 13, 26, 39 and 52. At week 52 the dogs were killed and examined macrosopically and histologically. A selection of organs was weighed. Statements of adherence to QA and GLP were included.

At the highest dose, ataxia and muscle tremors with the occasional instance of convulsions, as well as vomiting were observed on several occasions throughout the study. The signs were observed from the first week of treatment onwards and usually occurred within 3–7 h after dosing. In general, males showed a higher frequency and severity of observations and one dog in this group was killed for humane reasons during week 46. The clinical signs were not accompanied by histopathological lesions of the nervous system. From the start of treatment, a dose-dependent increased incidence in liquid faeces was observed in the groups at 0.5 and 3.5 mg/kg bw per day. The passing of fluid faeces was not accompanied by histopathological lesions of the alimentary tract. Other pyrethroids produce this effect, which may represent a consequence of the gastrointestinal equivalent of paraesthesia in the skin (Ray & Fry, 2006). Body weight and food consumption were not affected by treatment. There were no toxicologically significant effects on haematological and clinical chemistry parameters. Slight increases in relative liver weight (up to 17%) at the highest dose were not accompanied by increases in liver enzyme activity in plasma or histopathological changes and were not considered to be toxicologically significant.

On the basis of the neurotoxic effects observed at 3.5 mg/kg bw per day, the NOAEL for systemic effects was 0.5 mg/kg bw per day. On the basis of the increased incidence of liquid faeces the NOAEL for local gastrointestinal effects was 0.1 mg/kg bw per day (Hext et al. 1986).

2.3 Long-term studies of toxicity and carcinogenicity

Mice

In a 2-year dietary study, 52 male and 52 female CD-1 mice received cyhalothrin (purity unspecified) at a concentration of 0, 20, 100, or 500 ppm (equal to 0, 1.8, 9.2, and 53 mg/kg bw per day for males and 0, 2.0, 11, and 51 mg/kg bw per day for females). Satellite groups of 12 males and 12 females were given the same diets for 52 weeks and then killed. All mice were checked daily for mortality. Clinical observations were carried out daily for the first 4 weeks and then weekly for the remainder of the study. All mice were palpated weekly for masses. Food consumption per cage of mice (four per cage) and body weights were recorded weekly. Before the 1-year interim and terminal kills, samples of blood and urine were obtained for haematology, clinical chemistry and urine analysis.

At the termination of the study, all surviving mice were killed and macroscopied. Adrenals, brain, heart, kidneys, liver, lungs, ovaries, spleen and testes were weighed and a range of tissues, including any abnormal tissues, were examined histologically. Statements of adherence to QA and GLP were included.

Mortality was not affected by treatment. In both sexes at the highest dose and in males at 100 ppm, piloerection and hunched posture were observed. Males at 500 ppm also showed emaciation, pallor, hyperactivity, increased fighting activity, reduced food efficiency and reduced body-weight gain, especially during the first 13 weeks. Water consumption was also slightly increased in males at 500 ppm. Changes in haematological parameters were not consistent or dose-related and therefore considered not toxicologically relevant. Urine analysis revealed no significant differences from control values. The serum glucose concentration was slightly reduced (9–12%) in mice at 500 ppm. Increases (41–70%) in aspartate aminotransferase (AST) and alanine aminotransferase (ALT) activity were observed in males and females at 100 or 500 ppm at week 100, but not at week 50. Since the magnitude of the increases in AST were not dose-related, and not accompanied by histological changes in the liver, they are considered not toxicologically significant.

Macroscopic and histological evaluation and organ weights of the interim group revealed no treatment-related effects. In the main group, at the end of the study a number of findings, e.g. thickening of the forestomach, decreased ovarian weight and non-neoplastic lesions were not dose-related and were considered to be not related to treatment.

An increase in the incidence of mammary adenocarcinomas was seen in females in the main group (1 out of 52 in controls, 0 out of 52 at 20 ppm, 7 out of 52 (13%) at 100 ppm and 6 out of 52 (12%) at 500ppm). Data for historical controls from 17 studies from the same laboratory for 1980–1982 ranged from 2% to 12%. No preneoplastic changes were found in the mammary glands of mice in the main or satellite groups. Since the highest incidence of mammary adenocarcinoma in any group was only slightly above the range of historical controls and as there was no clear dose–response relationship, it was considered to be unlikely that these tumours were caused by treatment with cyhalothrin. On the basis of the clinical signs (piloerection and hunched posture) in males at 100 ppm, the NOAEL was 20 ppm, equal to 1.8 mg/kg bw per day (Colley et al., 1984).

Rats

Groups of 62 male and 62 female Alpk/AP rats were fed diets containing cyhalothrin (purity, 98.2%) at a concentration of 0, 10, 50 or 250 ppm (equal to about 0, 0.47, 2.3 and 12 mg/kg bw per day for males and 0, 0.55, 2.7, and 14 mg/kg bw per day for females) for 2 years. Additional groups of 10 males and 10 females were designated for interim sacrifice after 52 weeks. The rats were examined daily for clinical signs. A detailed clinical examination was carried out weekly. Body weights were recorded weekly for the first 12 weeks and every 2 weeks thereafter. Food consumption per cage of four rats was recorded weekly for the first 12 weeks and every fourth week thereafter. Haematology was performed on 10 males and 10 females per group before testing, at 4 and 13 weeks and subsequently at 13 week intervals. At termination, femoral bone-marrow smears were prepared from all rats submitted for haematological examination. Clinical chemistry and urine analysis were performed on a different group of 12 males and 12 females per dose before testing, at 4 and 13 weeks and subsequently at 13-week intervals. At week 52 and before termination, the eyes of 20 males and 20 females from the control group and the group at 250 ppm were examined.

The rats designated to the interim-kill group and the rats surviving to termination were killed and macroscopically examined. Gonads, spleen, heart, kidneys, adrenals, liver, lungs (with trachea) and brain were weighed. A range of tissues was examined histologically. Statements of adherence to QA and GLP were included.

There were no treatment-related effects on mortality and clinical signs. Compared with controls, body weights in the group at 250 ppm were decreased throughout treatment (up to 11%). The decreased body-weight gain was accompanied by a small decrease in food consumption during the first 12 weeks of the study. There were minor changes in blood biochemistry at this dose, consistent with reduced growth rate, i.e. reduced concentrations of plasma glucose (up to 9%), cholesterol

(up to 26%) and triglycerides (up to 39%). No toxicologically relevant changes in haematology and ophthalmoscopy were observed.

Increased relative liver weight (up to 17%) was seen in male and female rats at 250 ppm at the interim sacrifice, but not at termination. Since these effects were not accompanied by histological lesions, these effects were considered to be not toxicologically significant. An unusual incidence of palatine fistulation and rhinitis observed from week 64 onwards was unrelated to treatment with cyhalothrin and appeared to be caused by long pointed fibres of cereal origin in the food as a consequence of a change in diet formulation. This may have contributed to a relatively high mortality rate in this study. Survival was highest in the group at 250 ppm. No significant treatment-related increase in the incidence of any tumour type was observed.

On the basis of the reduction in body-weight gain, the NOAEL was 50 ppm, equal to 2.3 mg/kg bw per day (Pigott et al., 1984).

2.4 Reproductive toxicity

(a) Multigeneration studies

Rats

In a dietary study of reproductive toxicity, groups of 15 male and 30 female Alpk/AP Wistar-derived rats were given diets containing cyhalothrin (purity, 89.2%) at a concentration of 0, 10, 30 or 100 ppm (equivalent to 0, 0.67, 2.0 and 6.7 mg/kg bw per day) for three successive generations. The parental rats produced two litters (F_{1a}, F_{1b}). The breeding programme was repeated with F_1 parents selected from the F_{1b} offspring and F_2 parents selected from the F_{2b} offspring. The rats were observed daily for clinical signs. Detailed examination and body-weight measurements were recorded After the premating period, the male rats were weighed at approximately 4-week intervals until termination and the females were weighed on days 1, 8, 15 and 22 of pregnancy (day 1 of pregnancy determined by the presence of sperm in a vaginal smear). Food consumption was recorded weekly throughout the premating period.

Litters were examined at least once daily and dead or grossly abnormal pups removed for soft tissue examination. The body weight, sex of the pups and any clinical abnormalities were recorded within 24 h of parturition and on days 5, 11, 22 and 29 after birth. All grossly abnormal pups, and those found dead at up to and including age 18 days were removed and examined by free-hand sectioning. Any pup aged more than 18 days found dead or moribund was removed for pathological examination and a range of tissues was taken and submitted for histopathological examination. On day 36, pups from 'a' litters were killed and approximately half of these were examined macroscopically and any abnormal tissues were histologically examined. All pups from 'b' litters except those selected to be parents of the following generation were killed on day 36 after birth and approximately five males and five females per group from the F_{1b} and F_{2b} litters and 10 males and 10 females per group from the F_{3b} litters were examined post mortem and a range of tissues taken and submitted for histopathological examination. Approximately half of the remaining rats were examined post mortem and only abnormal tissue submitted for examination. The F_0, F_1 and F_2 parents were killed and examined macroscopically and a range of tissues was taken and submitted for histopathological examination. Statements of adherence to QA and GLP were included.

A mild reduction in body-weight gain (up to 9%) was consistently found in parental rats at the highest dose, particularly males. A slight reduction in body-weight gain (7%) at 30 ppm cyhalothrin seen only in females of the F_1 generation, was considered to be not toxicologically significant. There were no treatment-related effects on food consumption, fertility rate, duration of pre-coital period or duration of gestation. No neurological effects were seen in parents or offspring. Small reductions in litter size in the group at 100 ppm were considered to be not toxicologically significant. In

the group at 100 ppm, reductions in pup weight gain during lactation (up to −17%) were found in all generations except for the F_2a generation. At autopsy, no treatment-related effects were found on pathological or histopathological examination.

The NOAEL for parental toxicity was 30 ppm, equivalent to 2.0 mg/kg bw per day, on the basis of a reduction in body-weight gain. The NOAEL for offspring toxicity was 30 ppm, equivalent to 2.0 mg/kg bw per day, on the basis of a reduced body-weight gain during lactation. The NOAEL for reproductive toxicity was 100 ppm, equivalent to 6.7 mg/kg bw per day, i.e. the highest dose tested (Milburn et al., 1984).

(b) Developmental toxicity

Rats

Groups of 24 time-mated (two females per male) CD rats were given cyhalothrin (purity, 98.2%) at a dose of 0, 5, 10 or 15 mg/kg bw per day by gavage on days 6–15 of gestation. The rats were checked daily for clinical signs. Body weight of the dams was recorded on days 0, 6–15, 18 and 20 of gestation. Food intake was recorded on days 3, 6, 9, 12, 15, 18 and 20. On day 20 of gestation, the rats were killed and examined macroscopically. The ovaries and uterus were removed and the fetuses were weighed and examined for visceral and skeletal abnormalities. A statement of adherence to QA was included.

No mortality was observed. At 15 mg/kg bw per day, two rats showed loss of limb coordination. At the highest dose, the dams initially lost weight and overall body-weight gain on days 6–20 was reduced by 12%. The effect on body weight was accompanied by a 7% reduction in food intake. There was no effect of treatment on the incidence of pregnancy, number, size, weight and sex of the fetuses and pre- and postimplantation loss. Gravid uterus weights were comparable between the groups. There was no treatment-related effect on external, visceral and skeletal development. Abnormalities in one litter at 10 mg/kg bw per day, in which 5 out of 17 fetuses had major defects (four bilateral agenesis of the kidneys; three skeletal malformations of the vertebral centrae, sternebrae, and/or metacarpals) were considered to be incidental and not related to treatment.

On the basis of reduction in body weight and the loss of limb coordination, the NOAEL for maternal toxicity was 10 mg/kg bw per day. The NOAEL for developmental toxicity was 15 mg/kg bw per day, i.e. the highest dose tested (Killick, 1981a).

Rabbits

Groups of 18–22 time-mated female New Zealand White rabbits received cyhalothrin (purity, 89.2%) at a dose of 0, 3, 10 or 30 mg/kg bw per day by gavage from day 6 to day 18 of gestation. All rabbits were examined daily for clinical signs. Body weight was recorded on days 0, 6–19, 24 and 28 of gestation. Food intake was recorded on days 3, 6, 9, 12, 15, 18, 21, 24 and 28. On day 28 of gestation, the rats were killed and examined macroscopically. The ovaries and uterus were removed and the fetuses were weighed and examined for visceral and skeletal abnormalities. A statement of adherence to QA was included.

The incidence of deaths was 1, 2, 6 and 2 in the groups at 0, 3, 10 and 30 mg/kg bw per day respectively. In the majority of rabbits, the deaths (three of which occurred before treatment had started) were attributed to pulmonary disorders, and were considered to be not related to treatment. In the surviving does, no treatment-related clinical signs and no macroscopic changes were observed.

At the highest dose, the does showed body-weight loss and reduced food consumption from days 6–9 of gestation. After that, body-weight gain of the dose at the highest dose was comparable to that of the other groups. No toxicologically relevant effects of treatment on incidence of pregnancy, gravid uterus weights, pre and postimplantation losses, number and sex of fetuses, litter weight, fetal

weight or fetal crown/rump length were observed. Treatment with cyhalothrin did not affect the incidences of skeletal or visceral malformations or variations.

On the basis of the reduced body weight and food intake at the start of treatment, the NOAEL for maternal toxicity was 10 mg/kg bew per day. The NOAEL for developmental toxicity was 30 mg/kg bw per day, i.e. the highest dose tested (Killick, 1981b)

2.5 Genotoxicity

Lambda-cyhalothrin was tested for genotoxicity in a range of guideline-compliant assays, both in vitro and in vivo. No evidence for genotoxicity was observed in any test. A number of published studies, largely from the same laboratory, have reported significant increases in DNA damage in vitro (comet assay) and chromosomal aberrations in vitro and in vivo (Celik et al., 2003; Celik et al., 2005a, 2005b; Naravaneni & Jamil, 2005). Since the materials tested in these studies were either commercial formulations of unknown composition or were inadequately described, these studies were not further considered.

The results of tests for genotoxicity are summarized in Table 2. is the Meeting concluded that lambda-cyhalothrin is unlikely to be genotoxic.

2.6 Special studies: neurotoxicity

In a study of acute neurotoxicity that was performed according to OECD guideline 424, groups of 10 male and 10 female Alpk:AP$_f$SD (Wistar-derived) rats were given lambda-cyhalothrin (purity, 87.7%) at a dose of 0, 2.5, 10 or 35 mg/kg bw by gavage in corn oil. The rats were observed daily for clinical signs. Detailed clinical observations, including landing foot splay, sensory perception and muscle weakness and locomotor activity were recorded before treatment and on days 1, 8 and 15. Body weight and food consumption were measured weekly. Two weeks after dosing, five males

Table 2. Results of studies of genotoxicity with lambda-cyhalothrin

End-point	Test object	Concentration[a]	Lambda-cyhalothrin content (%)	Result	Reference
In vitro					
Reverse mutation	*S. typhimurium.* strains TA98, TA100, TA1535, TA1537 and TA1538	1.6–5000 µg/plate (±S9)	96.5	Negative	Callander (1984) [b]
Gene mutation	Mouse lymphoma L5178Y*Tk*$^{+/-}$	125-4000 µg/ml (±S9)	96.6	Negative	Cross (1985)[b]
Chromosomal aberration	Human lymphocytes	10^{-9}–10^{-2} mol/l (±S9)	96.5	Negative	Sheldon et al. (1985) [b]
Unscheduled DNA synthesis	Rat primary hepatocytes	17–5000 µg/ml	96.6	Negative	Trueman (1989) [b]
In vivo					
Micronucleus formation	Mouse bone marrow	22 and 35 mg/kg bw (intraperitoneal)	96.5	Negative	Sheldon et al. (1984) [b,c]

[a]Positive and negative (solvent) controls were included in all studies.

[b] Statements of adherence to GLP and QA were included

[c] Doses were 44% and 70% of the median lethal dose at 7 days (based on mortality observed within 7 days after a singleintraperitoneal injection of lambda cyhalothrin). A reduction in the polychromatic erythrocytes-normochromatic erythrocytes (PCE/NCE) ratio indicated that lambda-cyhalothrin had reached the bone marrow.

and five females per group were killed and examined macroscopically. Selected nervous tissues were removed, processed and examined microscopically. Statements of adherence to QA and GLP were included.

In the group at the highest dose, clinical signs, including decreased activity, ataxia, increased breathing rate, reduced stability and/or tiptoe gait, upward curvature of the spine, piloerection, occurred about 7 h after dosing, and were also observed in some rats on days 2–4. There was a statistically significant reduction in landing-foot splay in males and a statistically significant increase in tail-flick response in females on day 1. Motor activity was reduced in both sexes on day 1. Increased breathing rate in five females and urinary incontinence, salivation and/or reduced response to sound in one to two rats were observed at 10 mg/kg bw. At this dose, no changes were seen in the functional observational battery (FOB). A slightly reduced hindlimb-grip strength, observed in the groups at the lowest and highest dose, showed no dose–response relationship and was attributed to slightly higher values for the controls. At the highest dose, food consumption (both sexes) and body weights (males only) were reduced during the first week of the study. At termination, no treatment-related macroscopic and histological changes were observed.

On the basis of signs of neurotoxicity in the groups at the intermediate and highest dose, the NOAEL was 2.5 mg/kg bw (Brammer, 1999).

In a study of acute neurotoxicity from published literature, groups of male Long Evans rats received lambda-cyhalothrin (purity, 87.7%), and a number of other pyrethroids, by gavage in corn oil to male Long Evans rats. It was reported that 8–18 rats per group, and 6–11 doses per compound were tested (not further specified for lambda-cyhalothrin).

Motor activity was assessed in an automated figure-eight maze. The data were analysed using a nonlinear exponential threshold model. The model was used to determine the dose associated with a 30% decrease in motor activity (ED_{30}) and the threshold dose (estimate of highest no-effect dose at which the rats would not display any decrease in motor activity) and the 95% confidence limits (CL).

Lambda-cyhalothrin induced a decrease in motor activity with an ED_{30} of 1.32 ± 0.13 mg/kg bw (lower 95% CL, 1.06 mg/kg bw) and a threshold dose of 0.52 ± 0.13 mg/kg bw (lower 95% CL, 0.28 mg/kg bw). The NOAEL was 0.5 mg/kg bw (Wolansky et al., 2006)

In a 90-day study of neurotoxicity that was performed according to OECD guideline 424, groups of 12 male and 12 female Alpk:APfSD (Wistar-derived) rats were fed diets containing lambda-cyhalothrin (purity, 87.7%) at a concentration of 0, 25, 60 or 150 ppm (equal to 0, 2.0, 4.6 and 11.4 mg/kg bw per day for males and 0, 2.2, 5.2 and 12.5 mg/kg bw per day for females). All rats were observed daily for clinical signs. Detailed clinical observations, including quantitative assessments of landing-foot splay, sensory perception (tail-flick test) and muscle weakness (fore-and hindlimb grip strength), and tests for locomotor activity were performed in weeks −1, 2, 4, 9 and 14. Body weights and food consumption were measured weekly. The eyes of rats at the highest dose and in the control groups were examined pre-study and in week 12. At the end of the 13 weeks, five males and five females were killed, brains were weighed and selected nervous system tissues were removed, processed and examined microscopically. Statements of adherence to QA and GLP were included.

No treatment-related clinical signs were reported. At 150 ppm, body-weight gain was slightly reduced in males (5–7%). At this dose, food consumption was decreased by 14–17% during the first week of treatment, and remained less than that of controls during the first half of the study. Food consumption was also decreased in the other treatment groups during the first week of treatment. This was considered to be due to the reduced palatability of the food. Ophthalmoscopy and the comprehensive battery of neurobehavioural and neuropathological examinations revealed no effects of

treatment with lambda-cyhalothrin up to the highest dose tested. A statistically significant reduction in hindlimb grip strength in males at the highest dose during week 9 only was considered to be incidental and not related to treatment.

The reduction in body-weight gain at 150 ppm was slight, not progressive and occurred only in the first week of exposure and hence it is reasonable to attribute it to unpalatability of the diet. Therefore, the NOAEL was 150 ppm, equal to 11 mg/kg bw per day, i.e. the highest dose tested (Brammer, 2001).

In a study of developmental neurotoxicity, groups of 30 time-mated female Alpk:AP$_f$SD (Wistar-derived) rats received diets containing lambda cyhalothrin (purity, 87.7%) at a concentration of 0, 25, 60 or 150 ppm (equal to 0, 2.1, 4.9 and 11.4 mg/kg bw per day during gestation and 0, 4.6, 10.7 and 26.3 mg/kg bw per day during lactation) from day 7 of gestation through parturition and lactation to day 23 after birth. Pups were allocated to the F_1 phase of the study on postnatal day 5, separated from the dam on day 29 and allowed to grow to adulthood.

The dams were checked daily for clinical signs. Body weight and detailed clinical observations were recorded before administration on day 7, on days 15 and 22 of gestation and on days 1, 5, 8, 12, 15 and 22 after birth and on the day of termination. Food consumption was recorded weekly. On days 10 and 17 of gestation and on days 2 and 9 of lactation, the females were subjected to FOB. Each litter was examined as soon as possible after parturition on day one. On postnatal days 1 and, the sex, weight and clinical condition of each pup was recorded. Litters were checked daily for dead or abnormal pups. On postnatal day 5, litters were standardized to eight (four males and four females) randomly selected pups where possible. Litters of seven or eight pups with at least three of each sex were used for selection of the F_1 generation. F_1 rats were examined daily for mortality and clinical signs of toxicity. From postnatal day 5, detailed clinical observations were recorded at the same time as the rats were weighed which was on days 5, 12, 18, 22, 29, 36, 43, 50 and 57 and before termination on day 63. The F_1 females were examined daily from day 29 to determine the day of vaginal opening. The selected F_1 males were examined daily from day 41 to determine the day of preputial separation. Body weight was recorded on the day the landmark was achieved. For the FOB, at least 10 males and females per group were observed on days 5, 12, 22, 36, 46 and 61. One male and one female from each litter were assigned to tests for auditory startle reflex (days 23 and 61), locomotor activity (days 14, 18, 22 and 60) or a learning and memory (Y-shaped water maze, on days 21 or 59 followed 3 days later by retesting).

Parent females were killed on postnatal day 29 and were not examined. Any intercurrent death F_1 rats and those not selected and killed on postnatal day 5 were not examined. At scheduled termination on days 12 and 63, one male and one female from each litter was killed, and brains were weighed. On day 63, a further 10 males and females per group were killed, brains were weighed and selected nervous system tissues were collected. The brains and other selected nervous tissues of the rats in the control group and at the highest dose were examined microscopically. Statements of adherence to QA and GLP were included.

There were no treatment-related effects in parental females on clinical observations or in the FOB. During days 7–15 of gestation, body-weight gain of females at the highest dose was reduced by 51% when compared with that of controls. From day 15 of gestation, body-weight gain of the group at the highest dose was comparable to that of the other groups, although the body weights of these rats remained lower throughout the rest of the study. The reduction in body-weight gain was accompanied by a reduction in food consumption.

There were no treatment-related effects on reproduction parameters. In the group at 150 ppm, survival to day 5 was slightly lower than that of controls. Pup weights at birth were similar to those of controls. Individual pup weights and total litter weights in the group at 150 ppm were lower (up to

10–12%) than those of controls from days 5–22 after birth. There were no treatment-related clinical observations in F_1 rats.

In F_1 males at 150 ppm, the mean age of preputial separation was slightly but statistically significantly greater than that in controls (45.8 days vs 45 days), and accompanied by a slightly lower body weight. This probably reflects the poorer pup growth in this group. Time of vaginal opening was not affected by treatment.

There were no treatment-related effects on motor activity, auditory startle response or learning and memory. Also, no treatment-related macroscopic findings, effects on brain weight, changes in brain morphometry or microscopic findings were observed. There was an increased incidence of demyelination in the proximal sciatic and distal tibial nerves of males at 150 ppm on day 63. This is a common spontaneous finding in this age and strain of rat, and the increased incidences were within the ranges for historical controls and therefore was considered to be incidental.

On the basis of the reduction in body-weight gain during gestation, the NOAEL for maternal toxicity was 60 ppm, equal to 4.9 mg/kg bw per day. On the basis of the reduction in body-weight gain during lactation the NOAEL for offspring toxicity was 60 ppm, equal to 10.7 mg/kg bw per day (based on maternal lambda-cyhalothrin intake). No evidence for developmental neurotoxicity was found at doses up to and including 150 ppm, equal to 11.4 mg/kg bw per day (Milburn, 2004).

3. Observations in humans

Six male volunteers were each given a single oral dose of 5 mg of lambda-cyhalothrin as a solution in corn oil (25 mg/g) in a gelatin capsule, followed by 150 ml of water. A group of five volunteers received a dermal dose of 20 mg/800 cm^2. Blood samples were taken from an in-dwelling cannula before dosing and at 0.5, 1, 2 ,3, 4, 5, 6, 8, 10 and 12 h after dosing and by venepuncture at approximately 24, 31 and 48 h. Complete urine collections were made at 2-h intervals up to 14 h, then 14–24 h followed by 12-h periods up to 120 h. Faeces were collected daily (oral dose only).

Samples of blood and excreta, including hydrolysed samples, were extracted with solvent that was analysed for the test substance and for three specific metabolites, i.e. 3-(2-chloro-3,3,3,-trifluoroprop-1-enyl)-2,2-dimethylcyclopropanoic acid (TFMCVA, also known as compound Ia, see Fig. 1), 3-phenoxybenzoic acid (3PBA, also known as compound V) and 3-(4-hydroxyphenoxy)benzoic acid (4-OH-3PBA, also known as compound XXIII). These metabolites were analysed as pentafluoropropionyl derivatives by GC-MS. Statements of adherence to QA and GLP were included.

Approximately equal amounts of TFMCVA (56.7% of administered dose), and 3PBA (25.1% of administered dose) + 4-OH-3PBA (25.2% of administered dose) were excreted in the urine, with peak excretion rates of between 2 h and 14 h after dosing. No parent compound was detected in the urine. Based upon TFMCVA measurements in urine, the estimated amount of test substance absorbed ranged from 50% to 64%.

The presence of intact test substance in plasma showed that lambda-cyhalothrin can be absorbed unchanged; however, the observation that the highest plasma concentrations of TFMCVA and 3PBA occurred soon after dosing indicates possible pre-systemic hydrolysis and/or rapid hydrolysis of the test substance in the liver and blood. Unabsorbed test substance and TFMCVA were detected in the faeces, but, with the exception of one subject, accounted for less than 1.5% of the dose. It was stated in the report that other metabolites in faeces could not be estimated due to matrix interference.

After dermal administration, concentrations of metabolites in the urine were very low. On the basis of TFMCVA excretion in urine it was estimated that 0.12% of the administered dose of lambda-cyhalothrin was absorbed through the skin. Total recovery of radioactivity ranged from 56% to 90%. Radioactivity was still excreted in urine at the end of the 120-h sampling period. In view of the amount of radioactivity that was not recovered and the urinary excretion of radioactivity at the end of the study, dermal absorption was likely to be greater than 0.12%, albeit still low (Marsh et al, 1994).

No other data on human observations were available for the present evaluation. Observations in humans were described by the World Health Organization (WHO) in 1999 and by JECFA in 2000. The text below is copied from the JECFA 2000 evaluation.

> No clinical or haematological effects were observed in six volunteers given a single dose of 5 mg of lambda-cyhalothrin in corn oil (equal to 0.05–0.07 mg/kg bw) (European Medicines Evaluation Agency, 1999). The route of administration was not reported, but it seems likely to have been oral.
>
> In the study of Pakistani pesticide workers described in section 2.2, the average exposure of the workers to lambda-cyhalothrin was estimated to be 54 µg/person per day (extrapolated from measured metabolites in urine). Transient signs of toxicity, lasting up to 24 h, were reported by the workers, which included skin paraesthesia, feeling hot, feeling cold, numbness, irritation of the skin, red eyes, coughing, and sneezing. Medical examination revealed one case of face rash that lasted 2 days (Chester et al., 1992).
>
> In a study carried out in a village in the United Republic of Tanzania, a lambda-cyhalothrin-based insecticide was sprayed inside houses and shelters at a coverage of approximately 25 mg/m^2. The insecticide was supplied as a water-dispersible powder in a soluble sachet. Every day for 6 days, 12 spraymen and 3 squad leaders were interviewed about symptoms. Each sprayman used up to 62 g of lambda-cyhalothrin over 2.7–5.1 h each day. The spraymen wore personal protective equipment (rubber boots and gloves, cotton overalls, caps, and gauze nose-mouth masks) which left much of the face exposed. One sprayman also used a face shield for 3 days.
>
> All the spraymen complained at least once of symptoms related to exposure to lambda-cyhalothrin. The commonest symptoms were itching and burning of the face and nose and throat irritation, frequently accompanied by sneezing or coughing. Facial symptoms occurred only on unprotected areas, and the worker who wore a face shield was free of facial symptoms. All the symptoms had disappeared by the morning after the spraying. The number of subjects affected and the duration of facial symptoms were proportional to the amount of compound sprayed. These parameters were not affected by use of lambda-cyhalothrin in the previous 6 months. A sample of occupants was interviewed 1 and 5–6 days after their houses had been sprayed. One woman who entered her house 30 min after the end of spraying complained of periorbicular itching, but this lasted only a few minutes. The other inhabitants of sprayed houses reported no other insecticide-related adverse effects. Furthermore, a squad leader who entered almost every house a few minutes after spraying reported no symptoms (Moretto, 1991)
>
> As part of a field trial conducted in South India, electrophysiological tests were conducted on 15 spraymen aged 19–48 years, before and after exposure to lambda-cyhalothrin (formulation and purity unspecified). The tests performed on the subjects comprised conduction of the right median, common peroneal, and facial motor nerves; conduction of the right median and sural sensory nerves; blink response with stimulation of the right supra-orbital nerve and recording of R1 and R2 responses from the right orbicularis oculi muscle with a pair of surface electrodes; concentric needle electromyography of the tibialis anterior; repetitive stimulation of the right median nerve at the wrist at 3 and 20 Hz and recording of the responses from the abductor pollicis brevis; and multi-modality visual, brainstem, auditory and somatosensory evoked potentials. The evoked potentials were measured in only six of the subjects, but the other measurements were made in all 15 subjects.
>
> Clinical observation revealed no changes, and facial nerve conduction, blink response, responses to repetitive stimulation, and visual, auditory, and somatosensory evoked potentials were all normal. Six of the 15 subjects had mild changes in peripheral nerve conduction parameters (paired t test: $p < 0.05$), but comparison of the mean values for the various nerve conduction parameters before and after exposure showed no significant difference except for prolongation of distal motor latency of the median nerve. Studies of nerve conduction 12–16 months later in three subjects who had shown abnormalities immediately after exposure showed normal rates. The authors concluded that occupational exposure to lambda-cyhalothrin can produce transient, subclinical electrophysiological changes in the nerves of the upper limbs (Arunodaya et al., 1997).

Comments

Biochemical aspects

Oral doses of cyhalothrin were readily but incompletely absorbed (30–40% of radiolabel was recovered in urine) in rats and dogs. Peak blood concentrations were reached after 4–7 h. In male rats treated with replacement bile obtained from treatment-naive rats, biliary excretion was about 11%. At a low dose, most (70%) of the administered material was excreted in the faeces and urine within 24 h. After 7 days, 2–3% of the cyhalothrin administered persisted as unchanged residue in fat. Metabolism in rats and dogs was similar, involving initial cleavage of the molecule at the ester bond. In rats dosed with cyhalothrin, major metabolites identified in urine were the sulfate conjugate of 3-(4'-hydroxyphenoxy) benzoic acid (compound XXIII) glucuronide conjugate of (1*RS*)-*cis*-3-(2-chloro-3,3,3-trifluoropropenyl)-2,2-dimethylcyclopropanoic acid (i.e. the compound 1a glucuronide). Minor metabolites identified were unconjugated compound XXIII and 3-phenoxybenzoic acid (compound V).

In volunteers given a single dose of lambda-cyhalothrin in capsules, serum and urine contained the metabolites compound XXIII, compound V and compound 1a ((1*RS*)-*cis*-3-(*Z*-2-chloro-3,3,3-trifluoroprop-1-enyl)-2,2-dimethylcyclopropanoic acid, TMFVCA). Their presence suggests that the initial metabolism of this compound in humans is similar to that in rats and dogs.

Toxicological data

The acute oral LD_{50} of lambda-cyhalothrin in rats was 79 mg/kg bw in males and 56 mg/kg bw in females. The observed clinical signs (ataxia, decreased activity, tiptoe gait, splayed gait, loss of stability, dehydration, urinary incontinence, hunched posture, piloerection, salivation, ungroomed appearance and pinched-in sides) were typical of this class of pyrethroids.

In studies with lambda-cyhalothrin in rats, the inhalation LC_{50} value was 60 mg/m^3 (0.06 mg/l), and the dermal LD_{50} was 632 mg/kg bw in males and 696 mg/kg bw in females. Lambda-cyhalothrin was not irritating to the skin and only slightly irritating to the eyes. With respect to dermal sensitization, the results of a maximization test with lambda-cyhalothrin in guinea-pigs were inconclusive. Technical-grade cyhalothrin has been reported to cause skin sensitization in a Buehler test and a maximization test in guinea-pigs.

In a 90-day feeding study in rats given cyhalothrin, the NOAEL was 50 ppm, equal to 2.6 mg/kg bw per day, on the basis of reduced body-weight gain and food consumption. In a 90-day feeding study in rats given lambda-cyhalothrin, the NOAEL was 50 ppm, equivalent to 2.5 mg/kg bw per day, on the basis of reduced body-weight gain and food consumption. In a 26-week study in dogs fed capsules containing cyhalothrin and a 1-year study in dogs fed capsules containing lambda-cyhalothrin, increased incidences of liquid faeces was observed, with an overall NOAEL of 0.1 mg/kg bw per day. The increased incidences of liquid faeces were observed from the first week of treatment. Other pyrethroids produce this effect, which may be the consequence of the local gastrointestinal equivalent of paraesthesia in the skin. In the two studies in dogs, signs of systemic neurotoxicity (ataxia, tremors, and occasionally convulsions) were observed, with an overall NOAEL of 0.5 mg/kg bw per day. Signs of systemic neurotoxicity were observed from the first week and generally occurred within a few hours after treatment.

In a 2-year dietary study with cyhalothrin in mice, the NOAEL was 20 ppm, equal to 1.8 mg/kg bw per day, on the basis of clinical signs (piloerection and hunched posture) in males. An increase in the incidence of mammary adenocarcinomas in the groups receiving the intermediate or highest dose was at the upper limit of the range for historical controls and was not dose-related. The Meeting therefore considered that it was unlikely that these tumours were caused by treatment with cyhalothrin.

In a 2-year dietary study with cyhalothrin in rats, the NOAEL was 50 ppm, equal to 2.3 mg/kg bw per day, on the basis of a reduction in body-weight gain. No treatment-related changes in tumour incidence were observed in this study.

The Meeting concluded that cyhalothrin is not carcinogenic in rodents.

Lambda-cyhalothrin was tested for genotoxicity in an adequate range of assays, both in vitro and in vivo. No evidence for genotoxicity was observed in any test. A number of published studies, largely from the same laboratory, have reported significant increases in DNA damage in vitro (Comet assay) and chromosomal aberrations in vitro and in vivo. The materials tested in these studies were either commercial formulations of unknown composition or were inadequately described. In view of the uniform finding of a lack of genotoxicity in those studies in which lambda-cyhalothrin was adequately characterized, the Meeting concluded that lambda-cyhalothrin is unlikely to be genotoxic.

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

In a multigeneration dietary study with cyhalothrin in rats, the NOAEL for parental toxicity was 30 ppm, equivalent to 2.0 mg/kg bw per day, on the basis of a reduction in body-weight gain. The NOAEL for offspring toxicity was 30 ppm, equivalent to 2 mg/kg bw per day, on the basis of reduced body-weight gain during lactation. The NOAEL for reproductive toxicity was 100 ppm, equivalent to 6.7 mg/kg bw per day, i.e. the highest dose tested.

The effect of oral exposure to cyhalothrin on prenatal development was investigated in rats and rabbits. In a study of developmental toxicity in rats treated by gavage, the NOAEL for maternal toxicity was 10 mg/kg bw per day on the basis of a reduction in body weight and loss of limb coordination. The NOAEL for fetal toxicity was 15 mg/kg bw per day, i.e. the highest dose tested. In a study of developmental toxicity in rabbits treated by gavage, the NOAEL for maternal toxicity was 10 mg/kg bw per day on the basis of reduced body-weight gain and food consumption. The NOAEL for fetotoxicity was 30 mg/kg bw per day, i.e. the highest dose tested.

In a study of acute neurotoxicity in rats given lambda-cyhalothrin by gavage, the NOAEL was 2.5 mg/kg bw per day on the basis of signs of neurotoxicity (increased breathing rate, urinary incontinence, salivation, reduced response to sound).

In a comparative study on the acute effects of pyrethroids in rats treated by oral gavage, in which the data were analysed using a nonlinear exponential threshold model, lambda-cyhalothrin showed decreased motor activity with a benchmark threshold dose (estimate of the highest no-effect level at which the rats would not display any decrease in motor activity) of 0.5 mg/kg bw. In a 90-day dietary study, the NOAEL was 150 ppm (equal to 11 mg/kg bw per day), i.e. the highest dose tested.

In a study of developmental neurotoxicity in rats, the NOAEL for maternal toxicity was 60 ppm, equal to 4.9 mg/kg bw per day, on the basis of reduced body-weight gain during gestation. The NOAEL for offspring toxicity was 60 ppm, equal to 10.7 mg/kg bw per day, based on maternal lambda-cyhalothrin intake, on the basis of reduced body-weight gain during lactation. No evidence for developmental neurotoxicity was observed.

In case reports in humans, no systemic effects were reported. In most cases exposure was by the dermal and inhalation routes. Predominant signs were skin paraesthesia, numbness, irritation of the skin, red eyes, coughing and sneezing.

No toxicological studies on metabolites of cyhalothrin were available. However, the Meeting considered it likely that the metabolites would be less neurotoxic than cyhalothrin, as none contains an intact pyrethroid structure.

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

Toxicological evaluation

Although increased incidences of liquid faeces were observed in dogs given lambda-cyhalothrin/cyhalothrin, which may represent a consequence of a local gastrointestinal equivalent of paraesthesia in the skin, the Meeting considered that it was not appropriate to base the ADI and acute reference dose (ARfD) on local effects on the gastrointestinal tract, observed after bolus administration.

The most sensitive systemic effect of lambda-cyhalothrin/cyhalothrin was neurotoxicity (decreased motor activity), which was observed in a study of acute toxicity in rats given lambda-cyhalothrin orally, with a threshold dose of 0.5 mg/kg bw, and in repeat-dose studies with cyhalothrin and lambda-cyhalothrin in dogs treated orally (ataxia, tremors, occasionally convulsions) with a NOAEL of 0.5 mg/kg bw per day. On the basis of these effects, the Meeting established a group ADI for cyhalothrin and lambda cyhalothrin of 0–0.02 mg/kg bw, using a safety factor of 25. Because lambda-cyhalothrin is relatively rapidly absorbed and excreted and the neurotoxic effects are rapidly reversible and dependent on C_{max}, the Meeting considered it appropriate to adjust the safety factor for the reduced variability in C_{max} compared with AUC. The Meeting considered that the ADI of 0.02 mg/kg bw is adequately protective against the other, non-neurotoxic effects of lambda-cyhalothrin/cyhalothrin observed in short- and long-term studies with repeated doses, and in studies of reproductive and developmental toxicity, where the use of a safety factor of 100 would be appropriate.

The Meeting established a group ARfD for cyhalothrin and lambda-cyhalothrin of 0.02 mg/kg bw on the basis of systemic neurotoxicity (decreased motor activity) observed in a study of acute toxicity in rats given lambda-cyhalothrin orally with a threshold dose of 0.5 mg/kg bw per day, and in repeat-dose studies with cyhalothrin and lambda-cyhalothrin in dogs treated orally, in which neurotoxic effects (ataxia, tremors, occasionally convulsions) occurred during the first week, within a few hours after treatment, with an overall NOAEL of 0.5 mg/kg bw per day, and using a safety factor of 25. For the same reasons as described above, the Meeting considered it appropriate to adjust the safety factor for the reduced variability in C_{max} compared with AUC.

Levels relevant for risk assessment

(a) Cyhalothrin

Species	Study	Effect	NOAEL	LOAEL
Mouse	Two-year study of toxicity and carcinogenicity[a]	Toxicity	20 ppm, equal to 1.8 mg/kg bw per day	100 ppm, equal to 9.2 mg/kg bw per day
		Carcinogenicity	500 ppm, equal to 51 mg/kg bw per day[c]	—
Rat	Ninety-day study of toxicity[a]	Toxicity	50 ppm, equal to 2.6 mg/kg bw per day	250 ppm, equal to 14 mg/kg bw per day
	Two-year study of toxicity and carcinogenicity[a]	Toxicity	50 ppm, equal to 2.3 mg/kg bw per day	250 ppm, equal to 12 mg/kg bw per day
		Carcinogenicity	250 ppm, equal to 12 mg/kg bw per day[c]	—
	Two-generation study of reproductive toxicity[a]	Parental toxicity	30 ppm, equivalent to 2.0 mg/kg bw per day	100 ppm, equivalent to 6.7 mg/kg bw per day[d]
		Offspring toxicity	30 ppm, equivalent to 2.0 mg/kg bw per day	100 ppm, equivalent to 6.7 mg/kg bw per day[d]
		Reproductive toxicity	100 ppm, equivalent to 6.7 mg/kg bw per day[c]	—

	Developmental toxicity[b]	Maternal toxicity	10 mg/kg bw per day	15 mg/kg bw per day
		Fetotoxicity	15 mg/kg bw per day[c]	—
Rabbit	Developmental toxicity[b]	Maternal toxicity	10 mg/kg bw per day	30 mg/kg bw per day
		Fetotoxicity	30 mg/kg bw per day[c]	—
Dog	Twenty-six-week study[b]	Toxicity	2.5 mg/kg bw per day	10 mg/kg bw per day

[a] Dietary administration.
[b] Gavage administration.
[c] Highest dose tested.

(b) Lambda-cyhalothrin

Species	Study	Effect	NOAEL	LOAEL
Rat	Ninety-day study of toxicity[a]	Toxicity	50 ppm, equivalent to 2.5 mg/kg bw per day	250 ppm, equivalent to 12.5 mg/kg bw per day
	Acute neurotoxicity[b]	Neurotoxicity	0.5 mg/kg bw[e]	1.3 mg/kg bw[f]
	Ninety-day study of neurotoxicity[a]	Neurotoxicity	150 ppm, equal to 11 mg/kg bwper day[c]	—
	Developmental neurotoxicity[a]	Maternal toxicity	60 ppm, equal to 4.9 mg/kg bw per day	150 ppm, equal to 11.4 mg/kg bw per day
		Offspring toxicity	60 ppm, equivalent to 10.7 mg/kg bw per day[d]	150 ppm, equivalent to 26.3 mg/kg bw per day[d]
		Developmental (neuro)-toxicity	150 ppm, equivalent to 11.4 mg/kg bw per day[c]	—
Dog	One-year study[b]	(Neuro)toxicity	0.5 mg/kg bw per day	3.5 mg/kg bw per day

[a] Dietary administration.
[b] Gavage administration.
[c] Highest dose tested.
[d] Based on maternal intake of lambda-cyhalothrin during lactation.
[e] Threshold dose obtained using a nonlinear exponential threshold model.
[f] ED_{30} (dose associated with a 30% decrease in motor activity) obtained using a nonlinear exponential threshold model.

Estimate of acceptable daily intake for humans

0–0.02 mg/kg bw

Estimate of acute reference dose

0.02 mg/kg bw

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

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

Critical end-points for setting guidance values for exposure to cyhalothrin/lambda-cyhalothrin

Absorption, distribution, excretion and metabolism in animals	
Rate and extent of absorption	Rapid, incomplete absorption (about 40–50% in rats)
Distribution	Highest concentrations in fat, followed by liver and kidney (rats)
Potential for accumulation	Low
Rate and extent of excretion	Rapid (70% in faeces and urine within 24 h in rats)

Metabolism in animals	Sulfate conjugate of 3-(4'-hydroxyphenoxy) benzoic acid (compound XXIII) and glucuronide conjugate of (1RS)-cis-3-(2-chloro-3,3,3-trifluoropropenyl)-2,2-dimethylcyclopropane carboxylic acid. Unconjugated compound XXIII and 3-phenoxybenzoic acid (compound V) were minor metabolites.
Toxicologically significant compounds in animals, plants and the environment	Cyhalothrin, lambda-cyhalothrin
Acute toxicity	
Rat, LD_{50}, oral	56 mg/kg bw
Rat, LD_{50}, dermal	632 mg/kg bw
Rat, LC_{50}, inhalation	0.060 mg/l
Rabbit, skin irritation	Not an irritant (cyhalothrin)
Rabbit, eye irritation	Slightly irritating (lambda-cyhalothrin)
Guinea-pig, skin sensitization	Sensitizing (cyhalothrin, Buehler test and Magnusson & Kligman)
Short-term studies of toxicity	
Target/critical effect	Neurotoxicity, i.e. ataxia, tremors, occasionally convulsions (dogs)
Lowest relevant oral NOAEL	0.5 mg/kg bw per day (lambda-cyhalothrin, dogs)
Lowest relevant dermal NOAEL	No data
Lowest relevant inhalation NOAEC	No data
Long-term studies of toxicity and carcinogenicity	
Target/critical effect	Decreased body-weight gain (rats)
Lowest relevant NOAEL	50 ppm, equal to 2.3 mg/kg bw per day (cyhalothrin, rats)
Carcinogenicity	Not carcinogenic (cyhalothrin, mice, rats)
Genotoxicity	
	Not genotoxic (lambda-cyhalothrin)
Reproductive toxicity	
Reproduction target/critical effect	No reproductive effects (rats)
Lowest relevant reproductive NOAEL	100 ppm, equal to 6.7 mg/kg bw per day, i.e. highest dose tested (cyhalothrin, rats)
Developmental target	No developmental effects (rabbits)
Lowest relevant developmental NOAEL	30 mg/kg bw per day (lambda-cyhalothrin, rabbits)
Neurotoxicity/delayed neurotoxicity	
Neurotoxicity	Type II pyrethroid toxicity (choreoathetosis/salivation syndrome)
Lowest relevant oral NOAEL	0.5 mg/kg bw (lambda-cyhalothrin, rats, dogs)
Other toxicological studies	
	No data
Medical data	
	No systemic poisoning reported. Skin paraesthesia, numbness, irritation of the skin, red eyes, coughing and sneezing.

Summary for cyhalothrin and lambda-cyhalothrin

	Value	Study	Safety factor
Group ADI	0–0.02 mg/kg bw	Rat, acute neurotoxicity, lambda-cyhalothrin;[a] dog, 1-year, lambda-cyhalothrin	25
Group ARfD	0.02 mg/kg bw	Rat, acute neurotoxicity, lambda-cyhalothrin; dog, 1-year, lambda-cyhalothrin[b]	25

[a] The lowest NOAEL for the primary action of the chemical and considered to be protective of other non-neurotoxic effects from studies of repeated doses.

[b] Neurotoxicity occurred a few hours after dosing during the first week of treatment.

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