

CYFLUTHRIN AND BETA-CYFLUTHRIN

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Explanation

Cyfluthrin, the International Organization of Standardization (ISO) approved common name for 3-(2,2-dichloro-vinyl)-2,2-dimethyl-cyclopropane-carboxylic acid cyano-(4-fluoro-3-phenoxy-phenyl)-methyl ester(*RS*), is a synthetic cyano-containing pyrethroid insecticide. It was evaluated by the JMPR in 1987, 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 50 ppm, equal to 2 mg/kg bw per day, which was identified on the basis of reduced body-weight gains in a 2-year study in rats and using a safety factor of 100. In 1997, the Joint FAO/WHO Expert Committee on Food Additives (JECFA) also established an ADI of 0–0.02 mg/kg bw.

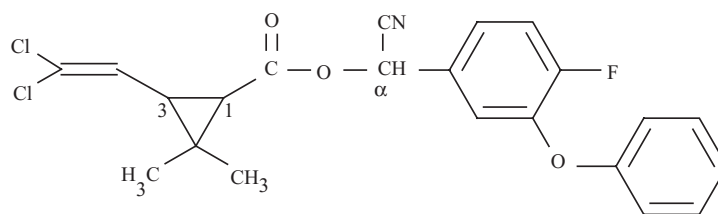
Technical-grade cyfluthrin consists of a mixture of four diastereomeric pairs of enantiomers (giving rise to eight optical isomers), consisting of two *cis* and two *trans* isomeric pairs. Beta-cyfluthrin consists of two diastereoisomeric pairs, which are the biologically active isomers of cyfluthrin. They are contained in cyfluthrin at a concentration of about 40%.

Cyfluthrin was re-evaluated by the present Meeting within the periodic review programme of the Codex Committee on Pesticide Residues (CCPR). Beta-cyfluthrin has not been evaluated previously. The Meeting reviewed new data on cyfluthrin and beta-cyfluthrin that had not been considered previously, and relevant data from the previous evaluation.

For cyfluthrin, the specifications were established by the FAO/WHO Joint Meeting on Pesticide Specifications (JMPS) and published as *WHO specifications and evaluations for public health pesticides: cyfluthrin* (2004).¹

Not all pivotal studies with cyfluthrin were certified as being compliant with good laboratory practice (GLP). These studies were carried out before the Organisation for Economic Co-operation and Development (OECD) guidelines on GLP were promulgated. However, the quality of these studies was considered to be acceptable.

Figure 1. Chemical structure of beta-cyfluthrin



¹ Available from http://www.who.int/whopes/quality/en/Cyfluthrin_spec_eval_WHO_Nov_2004.pdf

Table 1. Diastereoisomer pairs of cyfluthrin and beta-cyfluthrin

Pair No.	Cyfluthrin (FCR 1272)	Beta-cyfluthrin
I	1R - 3R - α R	—
	1S - 3S - α S	
II	1R - 3R - α S	—
	1S - 3S - α R	
III	1R - 3S - α R	Beta-cyfluthrin (FCR 4545)
	1S - 3R - α S	
IV	1R - 3S - α S	—
	1S - 3R - α R	

Evaluation for acceptable daily intake

Cyfluthrin

1. Biochemical aspects

1.1 Absorption, distribution and excretion

Rats

Groups of fasted male Wistar rats received cyfluthrin (purity unknown; FCR 1272, cyfluthrin isomer ratio: I, 26.6%; II, 19.1%; III, 33.7%; IV, 20.6%) as a single oral dose at 10 mg/kg bw, dissolved in either polyethylene glycol (PEG 400) or a Cremophor EL : water emulsion. Two rats per group were killed at 0.5, 1, 2, 4, 6, 16 and 24 h after treatment. The concentrations of the respective enantiomers of cyfluthrin were assessed in blood and the stomach.

Cyfluthrin in Cremophor EL : water emulsion was rapidly absorbed. The four enantiomers were already detectable in the blood after 30 min and peak concentrations in blood were reached after 1 h. The absorption of cyfluthrin in PEG 400 was slower; detectable concentrations in blood were found after 4 h and peak blood concentration was reached after 6 h. Peak concentrations with PEG 400 were five times lower than with the Cremophor EL : water emulsion. In the group receiving Cremophor EL : water emulsion, only small amounts of cyfluthrin were detected in the stomach 4 h after administration, while in the group receiving PEG 400 considerably higher amounts were detected in the stomach at this time. In both groups the *cis* : *trans* isomer ratio in the blood shifted in favour of the *cis*-enantiomer, indicating that the *trans*-enantiomer is broken down more rapidly than the *cis*-enantiomer (Eben et al., 1982).

Groups of five male and five female Mura:SPRA (SPF 68 Han) rats received ^{14}C -labelled cyfluthrin (radiochemical purity, 98%, labelled in the fluorobenzene moiety) either as single oral doses at 0.5 and 10 mg/kg bw, or as single intravenous doses at 0.5 mg/kg bw. A group of five male that were equipped with bile-duct cannula received cyfluthrin at a dose of 0.5 mg/kg bw intraduodenally. Additional groups of five male and five females received unlabelled cyfluthrin as 14 daily oral doses at 0.5 mg/kg bw, followed by ^{14}C -labelled cyfluthrin at the same dose. Samples of urine, faeces, organs, tissues and blood were collected at several time-points after dosing.

After oral administration of 0.5 or 10 mg/kg bw, about 90% was absorbed (in females in the group at 10 mg/kg bw, only 80%). The $t_{1/2}$ for absorption was about 30 min. About 98% of the radioactivity was excreted within 48 h, with a rapid ($t_{1/2}$ of 2–3 h) and slow phase ($t_{1/2}$ of 9–12 h). The urine : faeces ratio of excretion was higher in males (3 : 1) than in females (3 : 2). Less than 0.001% was excreted through expired air. No marked differences in kinetics between the groups at the lower and higher doses were observed.

After intravenous administration, biphasic elimination was found, with a $t_{1/2}$ of 2 h for the rapid phase and a $t_{1/2}$ of 20 h for the slow phase. Forty-eight hours after intravenous administration; 93–95% of the dose was excreted, again with a higher urine : faeces ratio in males than in females. In male rats with bile-duct cannulations, after an intraduodenal dose at 0.5 mg/kg bw, about 33% of radioactivity was excreted in the bile within 2 days, about half of which was excreted within 2 h.

The apparent volume of distribution was about 17%, which is consistent with distribution primarily in extracellular fluid. The highest concentrations were found in fat, ovaries, adrenal, liver and spleen. The lowest concentrations were found in the brain.

Daily dosing for 14 days with unlabelled cyfluthrin followed by a single dose of [^{14}C]-cyfluthrin on day 15 yielded results similar to those of the single-dose experiments (Klein et al., 1983)

Groups of male Mura:SPRA (SPF 68 Han) rats received oral doses of [^{14}C]-cyfluthrin (radiochemical purity, 98%, labelled in the fluorobenzene moiety) at 0.5 or 10 mg/kg bw, or 0.5 mg/kg bw via the intravenous or intraduodenal route. Rats treated intraduodenally were fitted with bile-duct cannula. In addition a group of female rats received a single oral dose of cyfluthrin at 0.5 mg/kg bw.

After oral administration, about 90% was absorbed, with a half-life of about 0.5 h. Maximum concentrations in blood were reached after 1.5 h. Thereafter, in the groups at the lower or higher dose, similar declines in plasma concentrations were observed. In female rats, plasma concentrations were 1.5 to 3 times higher than in male rats at the lower dose. Two and 10 days after the oral administration, respectively 1–2% and 0.2% remained in the body. At day 10, the highest concentrations were found in the fat. Low concentrations were detected in the spleen, testes, erythrocytes and plasma. Excretion through expiration was less than 0.001%. In rats with bile-duct cannula, after an intraduodenal dose of 0.5 mg/kg bw, about one third of the radioactivity was excreted in the bile within 2 days, 50% and 90% of which was excreted within 2 and 6 h respectively.

After intravenous administration, 94% of radioactivity was excreted within 48 h (70% in the urine, 24% in the faeces). The volume of distribution was 18% (Weber & Suwelack, 1983)

1.2 Biotransformation

The studies on the metabolism of cyfluthrin in animals using radioactively labelled material were restricted to the ^{14}C -phenyl- or ^{14}C -fluorophenyl-labelled parent compound. The metabolite 3-(2,2-dichlorovinyl)-2,2-dimethylcyclopropane carboxylic acid (DCVA) that would be released after the cleavage of the ester bond had been extensively investigated in mice, rats, cows and hens as a part of studies on other chemically similar synthetic pyrethroids. This acid portion has been reported to undergo hydroxylation at the methyl groups. DCVA and its hydroxylated derivative were found to form various conjugates in mammalian and avian systems (Casida et al., 1979; Miyamoto et al., 1981). The results can be extrapolated to cyfluthrin.

(i) *In vivo**Rats*

Four groups of five male and five female Sprague Dawley (SPF 68 Han) rats received [^{14}C]-cyfluthrin (radiochemical purity, 98%) either as an oral dose at 0.5 or 10 mg/kg bw or as an intravenous dose at 0.5 mg/kg bw. Another group received unlabelled cyfluthrin orally once per day for 14 consecutive days, followed by a single oral dose of [^{14}C]-cyfluthrin at 0.5 mg/kg bw. For identification of metabolites, samples of urine and faeces were collected at 8 h (urine only), 24 h and 48 h after dosing.

The initial step in the biotransformation of cyfluthrin was ester hydrolysis, giving a 3-phenoxy-4-fluorobenzyl alcohol intermediate and the permethric acid fraction. The metabolism of permethric acid has been well established in studies with chemically similar pyrethroids in rats. After ester hydrolysis, the 3-phenoxy-4-fluorobenzyl alcohol moiety was oxidized to the free metabolite 3-phenoxy-4-fluorobenzoic acid. This metabolite can then either be conjugated with glycine to form 3-phenoxy-4-fluorohippuric acid or hydroxylated to give 4'-hydroxy-3-phenoxy-4-fluorobenzoic acid (conjugates of which account for 41–50% of the total urinary radiolabel recovered from rats given one or multiple doses of cyfluthrin at 0.5 mg/kg bw). Females tended to excrete more of this metabolite as the free form in the faeces than did males. Males and females at the higher dose (10 mg/kg bw) excreted about 35% of the administered dose as conjugates of 4'-hydroxy-3-phenoxy-4-fluorobenzoic acid, while females excreted about 5% more than males as the free metabolite. After repeated oral doses at 0.5 mg/kg bw for 14 days, 12–16% of labelled metabolite was found in the faeces as cyfluthrin, while < 1% was found when single oral doses were administered. After a single high dose at 10 mg/kg bw, 17–19% of the administered dose was recovered in the faeces as parent compound. The authors concluded that the metabolism of cyfluthrin is slightly dose-dependent (Ecker, 1983).

Three male rats received ^{14}C -labelled cyfluthrin (radiochemical purity, 98%) at a dose of 10 mg/kg bw and urine was collected over 0–8 h and 8–24 h after administration. As an initial analysis by thin-layer chromatography (TLC) revealed no difference in metabolites between animals, samples of urine were pooled by collection time for identification of metabolite structures. It was found that about 60% of the administered radioactivity was excreted in the urine in a conjugated form (glucuronide or sulfate). Most of this was identified as conjugates of 4'-hydroxy-3-phenoxy-4-fluorobenzoic acid (50%). A second major metabolite was identified after hydrochloric acid hydrolysis as a conjugate of 3-phenoxy-4-fluorohippuric acid (40%). These metabolites represented 33% and 27% of the administered radiolabel, respectively. A glycine conjugate constituted 2.5% of the conjugated metabolites (Ecker, 1982).

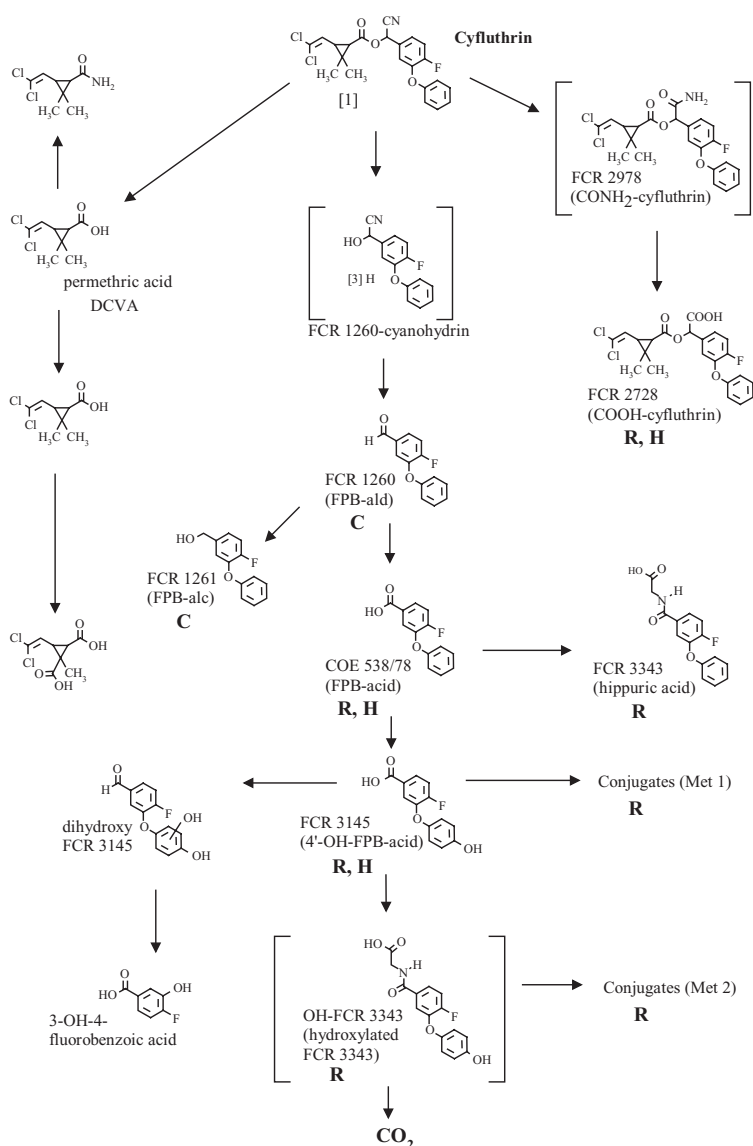
Groups of 10 male Wistar (TNO/W 74) albino rats were given cyfluthrin (purity, 95%) at a dose of 1, 5, 10, or 15 mg/kg bw by intraperitoneal (IP) injection, urine was collected for 3 days, for analysis of thiocyanate content. In addition, groups of 10 male and 10 female rats were exposed to cyfluthrin at a dose of 59, 93 or 180 $\mu\text{g/l}$ for 4 h through inhalation. Excretion of thiocyanate in urine was monitored over 92 h.

It was found that after IP administration, 24–42% of the alpha-cyano group of cyfluthrin was excreted via the kidneys in the thiocyanate form. After exposure by inhalation, 4–6% (male) or 2–6% (female) of the alpha-cyano group of cyfluthrin was excreted via the kidneys in the thiocyanate form (Eben & Thyssen, 1981).

The maximum concentration of radioactivity in the milk was 0.079 mg/l expressed as cyfluthrin equivalents 3 days after initial dosing; the level then declined steadily. Of the radiolabel found in milk, 98% was parent compound. The highest concentrations of residue were found in the liver (0.622 mg/kg), fat (0.195 mg/kg), and kidney (0.188 mg/kg); brain, skeletal muscle, and myocardium had the lowest concentrations, ranging from 0.015 to 0.040 mg/kg. Most of the radiolabel recovered in tissues was parent compound. Heart and kidney also contained a metabolite identified as 4-fluoro-3-phenoxybenzenemethanol, and liver also contained 4-fluoro-3-phenoxybenzaldehyde (Shaw et al., 1983).

The proposed metabolic pathway of cyfluthrin in rats is shown in Figure 2.

Figure 2. Proposed metabolic pathway of cyfluthrin in rats



2. Toxicological studies

2.1 Acute toxicity

The results of studies of acute toxicity with cyfluthrin are summarized in Table 2.

The observed clinical signs (increased salivation, uncoordinated movements, increased activity and vocalization, reduced, laboured breathing, apathy, straddle-legged gait (mostly in the rear legs), and reduced sensitivity to external stimuli) were typical of this class of pyrethroids.

Table 2. Results of studies of acute toxicity with cyfluthrin

Species	Strain	Sex	Route	Formulation	Purity (%)	LD ₅₀ (mg/kgbw)	LC ₅₀ (mg/l air)	Reference
Mouse	NMRI	Male	Oral ^b	PEG 400	83.6	291	—	Flucke & Thyssen (1980)
		Female				609		
Mouse	NR	Female	Oral ^b	Cremophor EL/DW	NR	< 100	—	Heimann (1982a)
Rat	Wistar	Male	Oral	PEG 400	83.6	869	—	Flucke & Thyssen (1980)
		Female				1271		
Rat	Wistar	Male	Oral ^b	PEG 400	83.6	590	—	Flucke & Thyssen (1980)
		Female				1189		
Rat	NR	Male	Oral ^b	Acetone/oil	NR	254	—	Heimann (1982a)
Rat	NR	Male	Oral ^b	DMSO	NR	396	—	Heimann (1982a)
Rat	NR	Male	Oral ^b	Cremophor EL/DW	NR	16.2	—	Heimann (1982a)
Rat	NR	Male	Oral ^b	N-methyl-pyrrolidone	NR	500–1000	—	Heimann (1982a)
Rat	NR	Male	Oral ^b	Isodecane	NR	505	—	Heimann (1983a)
Rat	NR	Male	Oral ^b	Xylene	NR	499	—	Heimann (1983b)
Rat	NR	Male	Oral ^b	PEG 400	NR	795	—	Heimann (1984b)
Rat	NR	Male	Oral ^b	Acetone/oil	93	155	—	Heimann (1987a) ^a
		Female				160		
Rat	Wistar	Male	Oral ^b	Cremophor EL/DW	95.1	15	—	Kroetlinger (1994) ^a
Rabbit	NZW	Male	Oral ^b	PEG 400	83.6	> 1000	—	Flucke & Thyssen (1980)
Dog	Beagle	Male	Oral ^b	NS	95	> 100	—	Hoffmann (1981a)
Dog	Beagle	Male	Oral	PEG 400	83.6	> 100 ^c	—	Flucke & Thyssen (1980)

Species	Strain	Sex	Route	Formulation	Purity (%)	LD ₅₀ (mg/kgbw)	LC ₅₀ (mg/l air)	Reference
Sheep	NR	Male & Female	Oral ^b	Water/tylose	NR	1000	—	Hoffmann (1981b)
Hen	White Leghorn	Female	Oral	PEG 400	84–94	5000	—	Thyssen et al. (1981)
Hen	White leghorn	Female	Oral	Cremophor EL/DW	NR	> 5000	—	Thyssen (1982)
Hen	White Leghorn	Female	Oral	Cremophor EL/DW	93.5	> 5000	—	Sachsse & Zbinden (1985a) ^a
Hen	White Leghorn	Female	Oral	PEG 400	93.5	4500	—	Sachsse & Zbinden (1985b) ^a
Rat	Wistar	Male Female	IP	Concentrated active substance	83.6	66 104	—	Flucke & Thyssen (1980)
Rat	NR	Male Female	IP	Cremophor EL/DW	NR	20 24	—	Heimann (1982a)
Rat	NR	Male Female	IP	NR	NR	34 94	—	Heimann (1982a)
Mouse	NMRI	Male emale	SC	PEG 400	83.6	> 2500 > 2500	—	Flucke & Thyssen (1980)
Rat	Wistar	Male Female	Dermal (24-h)	Cremophor EL/DW	83.6	> 5000 > 5000	—	Flucke & Thyssen (1980)
Rat	NR	Male Female	Dermal (24-h)	PEG 400	NR	> 5000 > 5000	—	Heimann (1982a)
Rat	NR	Male Female	Dermal (24-h)	NaCl	NR	> 5000 > 5000	—	Heimann (1982a)
Mouse	NMRI	Male Female	Inhalation (4-h)	Ethanol/PEG 400	93.9	—	± 0.141	Pauluhn (1989a) ^a
Rat	Wistar	Male & Female	Inhalation (1-h)	Ethanol/PEG 400	83.6	—	> 1.089	Flucke & Thyssen (1980)
Rat	Wistar	Male & Female	Inhalation (4-h)	Ethanol/PEG 400	83.6	—	> 0.469–0.592	Flucke & Thyssen (1980)
Rat	NR	Male & Female	Inhalation (4-h)	Ethanol/PEG 400	<i>cis</i> : <i>trans</i> 55 : 45	—	0.180–0.326	Flucke & Thyssen (1981)
Rat	Wistar	Male & Female	Inhalation	Ethanol/PEG 400	93	—	0.405	Pauluhn (1987a) ^a
Rat	Crj:CD	Male Female	Inhalation (4-h)	Ethanol/PEG 400	95	—	1.010 1.020	Watanabe et al. (1984)
Rat	NR	Male Female	Inhalation (4-h)	Cremophor EL/DW	95	—	> 0.735 0.200–0.735	Pauluhn & Thyssen (1982)

Species	Strain	Sex	Route	Formulation	Purity (%)	LD ₅₀ (mg/kgbw)	LC ₅₀ (mg/l air)	Reference
Rat	NR	Male Female	Inhalation (4-h)	DMSO/PEG 400	95	—	0.575 0.490	Pauluhn & Thyssen, (1982)
Rat	Wistar	Male & Female	Inhalation (5 × 6 h)	Ethanol/PEG 400	83.6	—	0.047– 0.196	Flucke & Thyssen (1980)
Hen	NR	Female	Inhalation (4-h)	Ethanol/PEG 400; Cremophor EL/DW	NR	—	> 0.596	Pauluhn & Kaliner (1983)

DMSO, dimethyl sulfoxide; DW, distilled water; IP, intraperitoneal; NR, not reported; NZW, New Zealand White; SC, subcutaneous.

^a Statements of adherence to quality assurance and good laboratory practice were included.

^b Fasted animals.

^c In the study in dogs, vomiting occurred at doses of 50 mg/kg bw and above.

(a) Dermal irritation

In a study of dermal irritation in NZW rabbits, performed in compliance with the United States Department of Agriculture guidelines (1973), six animals were exposed to cyfluthrin (purity, 83.6%) for 24 h on the intact and abraded skin. Irritation was scored at 24 h and 72 h.

No skin irritation was observed (Flucke & Thyssen, 1980).

In a study of dermal irritation in six female rabbits, 0.1 ml of cyfluthrin (purity, 95%) was applied under occlusion for 24 h on the intact or abraded skin of the inner ear. Irritation was scored at 24 h and 72 h.

No skin irritation was observed (Iyatomi et al., 1982).

(b) Ocular irritation

In a study of ocular irritation, performed in compliance with United States Department of Agriculture guidelines (1973), the eyes of New Zealand White rabbits were exposed to cyfluthrin (purity, 83.6%) for 5 min (five rabbits) or 24 h (three rabbits). The eyes were examined at 1 h and at 1, 2, 3 and 7 days.

Cyfluthrin induced moderate to severe redness and mild to moderate chemosis of the conjunctivae. The effects had almost completely resolved within 72 h (Flucke & Thyssen, 1980).

In a study of ocular irritation in female rabbits, 12 animals received 0.1 ml of cyfluthrin (purity, 95%) in the conjunctival sac of the left eye. The right eye served as control. In six of the animals, the eyes were rinsed after 30 s with 100 ml of tepid water. Eyes were examined at 1, 3, 6, 24, 48, 72 and 168 h.

Redness and chemosis of the conjunctiva was seen regardless of rinsing of the eye. The effects had almost completely reversed within 3 days. It was concluded that cyfluthrin has a minimal irritating effect on the eye (Iyatomi et al., 1982).

(c) Dermal sensitization

In a study of dermal sensitization, using the method reported by Draize, cyfluthrin (purity not reported) was tested using 15 male Pirbright White guinea-pigs. The control group consisted of 15 animals. The treatment regime involved induction of sensitization by 10 intracutaneous injections of

cyfluthrin (0.1% v/v) at a dose of 0.05 mg on day 1, 0.1 mg for the next nine treatments (three per week) and, after an interval of 14 days, 0.05 mg (challenge injection).

No signs of skin sensitization induced by cyfluthrin were observed (Mihail, 1981a).

In a study of dermal sensitization, conducted according to the Magnusson & Kligman method, cyfluthrin (purity not reported) was tested on 15 male Pirbright White W58 guinea-pigs. The control group consisted of 15 animals. In the induction phase, the animals received cyfluthrin by intradermal injection (1%) on day 1 followed by a topical administration (25% v/v) after 1 week and challenge by topical administration (25%) 3 weeks after the intracutaneous injection. The vehicle was PEG 400.

No signs of skin sensitization induced by cyfluthrin were observed (Mihail, 1981b).

The skin sensitization potential of cyfluthrin (purity, 96.2%) was tested in 20 male Hsd/Win:DH guinea-pigs, in a study conducted according to OECD guideline 406 using the Magnusson & Kligman maximization test. Ten animals served as controls. In the induction phase, the animals received cyfluthrin by intradermal injection (5%) on day 1 followed by a topical administration (50% w/v) after 1 week and challenge by topical administration (50% and 25%) 3 weeks after the intracutaneous injection. The vehicle was PEG 400. Statements of adherence to GLP and quality assurance (QA) were included.

After challenge with 50% cyfluthrin formulation, 5% of the animals showed reddening of the skin. No skin reactions were observed after challenge with 25% solution of cyfluthrin (Vohr, 1994a).

2.2 *Short-term studies of toxicity*

(a) *Oral administration*

Mice

Groups of 18 male and 18 female mice (strain unknown) received diets containing cyfluthrin (purity unknown) at a concentration of 0, 300, 1000 or 3000 ppm (equal to 0, 43.1, 136.3 and 406.9 mg/kg bw per day for males and 0, 50.4, 164.5 and 432.8 mg/kg bw per day for females). After 1 month, 12 males and 12 females in each group were killed. The remaining animals were allowed to recover for 4 weeks. Animals were observed for clinical signs at 6 h and daily after start of the treatment. Body weight, food and water consumption were measured weekly. Haematology and clinical chemistry were performed at weeks 4 and 8. At weeks 4 or 8, the mice were killed, organs were weighed and the animals were examined macroscopically and histologically.

In the group receiving the highest dose, mice developed ataxia, salivation, and/or emaciation, and one female died. Body-weight was reduced at 3000 ppm (15–21%). A slight reduction (8%) in body weight, observed only at week 3 in females receiving the intermediate dose was considered not toxicologically relevant. Slight increases in alkaline phosphatase activity (maximally 35%) and blood urea nitrogen (BUN) (maximally 12%) at 1000 and 3000 ppm were considered not biologically significant. In males and females at 3000 ppm, macroscopy at 4 weeks revealed dark-red livers in some mice, and increased relative weights of the submaxillary glands (17–20%) and kidneys (13%). Males at 3000 ppm also had significantly increased relative liver weights (25%). Histopathological examination revealed minimally increased chromatin in the nuclei of hepatocytes of males at 1000 ppm or more and in females at the highest dose. Mice at 1000 ppm or more had cytoplasmic swelling of the glandular epithelium of the submaxillary glands. All findings disappeared within the 4-week recovery period. On the basis of the histological changes in the liver (males only) and the submaxillary glands, the NOAEL was 300 ppm, equal to 43.1 mg/kg bw per day (Watanabe et al., 1982b).

Rat

Groups of 20 male and 20 female Wistar rats were given technical cyfluthrin (purity, approximately 85%) at a dose of 0, 5, 20, or 40 (80) mg/kg bw per day by gavage for 28 consecutive days. PEG 400 served as vehicle. The highest dose of 80 mg/kg bw per day was administered during weeks 1 and 3, while a dose of 40 mg/kg bw per day was given during weeks 2 and 4. The highest dose was lowered after the first week due to toxicity in treated males; however, as these symptoms disappeared after 1 week at the lower dose, the highest dose was again raised in week 3. However, owing to severe symptoms of toxicity, the dose had to be lowered again in week 4. A group of 10 males and 10 females from each group was maintained on control diet without additional treatment for 6 weeks in order to assess recovery. Rats were observed daily for clinical signs and mortality and body weights were recorded weekly. Haematology, clinical chemistry and urine analysis were conducted for five males and five females at each dose at the end of the 28-day treatment period and at the end of the 6-week recovery period. At the end of the treatment period, half of the surviving rats in each treatment group were killed, while the remaining animals were killed after the 6-week recovery period. Animals were examined macroscopically and histologically and selected organs were weighed.

In the group receiving the highest dose, six males and one female died. At this dose, rats displayed apathy, ruffled coat, dyspnoea, salivation, hyperkinesis, ataxia, and uncoordinated movements. The symptoms were described as being most severe during weeks 1 and 3 (when a highest dose of 80 mg/kg bw per day was administered), and minimal during weeks 2 and 4 (when the highest dose was lowered to 40 mg/kg bw per day). Body weight was decreased by about 10% in males at the highest dose, but not in females at this dose. Clinical chemistry demonstrated slightly increased activity (20% and 68% in males and females, respectively) of alanine aminotransferase (ALT) in the group at the highest dose. No effects on haematology and urine analysis were found. At necropsy in rats at the highest dose, increased absolute (15% and 19% in males and females, respectively) and relative (38% and 19% in males and females, respectively) adrenal weights were noted. In females at this dose, absolute and relative liver weight was increased by 24%. No toxicologically relevant macroscopic or histological changes were observed. All effects related to treatment with cyfluthrin returned to normal during the 6-week recovery period. On the basis of effects on mortality, clinical signs, body weight (males only) and effects on absolute and relative adrenal and liver weights, the NOAEL was 20 mg/kg bw per day (Flucke & Schilde, 1980).

Groups of 18 male and 18 female rats (strain unspecified) received diets containing cyfluthrin (purity unknown) at a concentration of 0, 100, 300, or 1000 ppm (equal to 0, 8.3, 24.7 and 78.9 mg/kg bw per day for males and 0, 8.4, 25.2 and 77.9 mg/kg bw per day for females) for 4 weeks, when 12 males and 12 females of each group were sacrificed. Six males and six females per group were allowed to recover for 4 weeks. Animals were observed for clinical signs at 6 h and daily after start of the treatment. Body weight, food and water consumption were measured weekly. Urine analysis, haematology and clinical chemistry were performed at week 4 and 8. At week 4 or week 8 animals were killed, organs were weighed and the animals were examined macroscopically and histologically.

No mortality was observed. Clinical signs in rats at the highest dose consisted of straddled-gait, salivation and/or nervousness during treatment. A decrease in body weight (up to 19%), food intake (up to 35%), and water consumption (up to 37%) was observed at 1000 ppm. Urine analysis indicated a higher incidence of urobilinogen and ketone bodies in rats at 1000 ppm. Haematology demonstrated a decrease in erythrocyte count, erythrocyte volume fraction, and haemoglobin content at 1000 ppm. Blood glucose concentrations were significantly decreased in both sexes at 1000 ppm (17–18%) and in males at 300 ppm (12%). No effects were seen on macroscopic examination. Histopathology revealed minimal degeneration of single fibres of the sciatic nerve and cytoplasmic swelling of the

glandular epithelium of the submaxillary glands at the highest dose. All observed changes induced by treatment with cyfluthrin returned completely to normal during the 4-week recovery period, except for the effects on total protein and blood glucose, which showed a partial recovery. On the basis of the reduced blood glucose concentrations in male rats at 300 ppm, the NOAEL was 100 ppm, equal to 8.3 mg/kg bw per day (Watanabe et al., 1982a).

Groups of 30 male and 30 female Wistar rats were fed diets containing cyfluthrin (purity, 84.2%, 50% diluted in a premix with Wessalon S) at a concentration of 0, 30, 100, or 300 ppm (equal to 0, 2.2, 7.4 and 22.5 mg/kg bw per day in males and 0, 2.7, 8.8 and 28.0 mg/kg bw per day in females) for 3 months. Rats were examined daily for mortality and clinical signs. Body weights and food consumption were recorded weekly. Clinical chemistry was conducted at months 1 and 3. In addition, five males and five females per group were killed after weeks 1 and 4 for interim examinations, including assays for induction of microsomal enzymes (*N*- and *O*-demethylase and cytochrome P450 content). At the end of the treatment period, the remaining rats were killed, macroscopically and histologically examined and organs were weighed.

No effects on mortality, clinical signs, body weight, food consumption, haematology, serum chemistry, urine analysis, macroscopy, histology and organ weights were observed. At week 1, a slight, dose-independent increase in *N*-demethylase activity was seen in all treated males and in *O*-demethylase activity in females at 100 and 300 ppm; the activity of enzymes of the cytochrome P450 system was significantly increased only in males at 300 ppm at this time. By 3 months, no differences were seen in the activities of the microsomal enzymes in any treated group.

On the basis of the absence of toxicologically relevant effects at 3 months, the NOAEL was 300 ppm, equal to 22.5 mg/kg bw per day (Loser & Schilde, 1980).

In a 3-month feeding study, groups of 28 male and 28 female Sprague-Dawley rats were fed diets containing technical cyfluthrin (purity, 95%, incorporated into the powdered diet on a 0.4% maximum clay carrier) at a concentration of 0, 100, 300, or 1000 ppm (equal to 0, 6.2, 19.0 and 61.0 mg/kg bw per day for males and 0, 7.3, 21.2 and 68.5 mg/kg bw per day for females). Twenty rats from each group were killed after 3 months of treatment, and the remaining eight rats from each group were maintained on control diets for one additional month. Rats were observed daily for clinical signs. Body weights were recorded weekly. Food consumption was measured three times per week. Clinical chemistry and urine analysis studies were conducted after 3 months of treatment, or after the 1-month recovery period. At termination, organs were weighed and the rats were examined macroscopically and histologically.

At the highest dose, rats displayed abnormal gait and excess salivation during the first weeks of treatment. The number of rats that displayed these symptoms decreased over the treatment period, so that by the end of 3 months, no abnormal symptoms were noted. Mortality rate was not affected by treatment. Body-weight gain and food consumption were reduced by about 16% in rats at the highest dose. In the females, but not the males of the recovery group, a partial rebound of body weight was noted. Haematology or urine analysis parameters were not affected by treatment. The slight increases (maximally 16%) in aspartate aminotransferase (AST) and BUN values observed in the groups at the intermediate and highest doses were considered to be not biologically significant. ALT activity appeared to be decreased in treated animals. Blood glucose concentrations were depressed in males at 300 (−15%) and 1000 ppm (−29%) and in females at 1000 ppm (−17%). No significant changes in serum chemistry values were apparent at the end of the recovery period. The observed reductions in absolute organ weight at termination were considered to be related to the reduced body weight. No treatment-related macroscopic changes were noted. Histological examinations revealed an increased incidence of single-fibre degeneration of the sciatic nerve in 5 out of 20 males at the highest dose and 3 out of 20 females at the highest dose, when compared with an incidence of zero in the control

group and in the groups at the lowest and intermediate doses. In the 1-month recovery group, the incidence of this finding was one out of eight in males at the highest dose, and zero out of eight in all other groups.

On the basis of the reductions in blood glucose in males at the intermediate dose, the NOAEL was 100 ppm, equal to 6.2 mg/kg bw per day (Oikawa & Iyatomi, 1983).

Dogs

In a 6-month study, groups of six male and six female beagle dogs were fed diets containing technical cyfluthrin (purity, 90.8%) at a concentration of 0, 65, 200, or 600 ppm, equal to 0, 2.0, 6.5, and 19.9 mg/kg bw per day, respectively. Food consumption was measured daily. Body weights were determined weekly. Dogs were examined daily for clinical signs. Examinations of reflexes, pulse and body temperature, and haematology, clinical chemistry, urine analysis and ophthalmoscopy were performed before treatment initiation, and after 4, 7, 13, and 26 weeks. At termination, dogs were examined macroscopically and histologically, and organs were weighed.

No deaths occurred and reflexes and body temperature were not affected by treatment. At the highest dose, five out of six males and three out of six females showed signs of uncoordinated, stiff gait of the hindlimbs, persisting for several hours, on several occasions after week 21. Vomiting after dosing occurred slightly more often in animals at the highest dose than in the controls. Diarrhoea occurred in all groups, including the controls, but much more frequently in dogs at the highest dose, from the start of treatment. Body-weight gain was decreased in males at the intermediate dose but not at the highest dose. Therefore this reduction in body-weight gain in males was considered to be not related to treatment. In females at the highest dose, a reduction in body-weight gain was observed that may have been related to treatment. No effects were found on ophthalmoscopic, haematological, clinical chemistry, or urinary parameters or on organ weights. Macroscopical and histological examination revealed no treatment-related changes. No lesions of the nervous system were observed. On the basis of the clinical signs in both sexes and reduced body-weight gain in females at the highest dose, the NOAEL was 200 ppm, equal to 6.5 mg/kg bw per day (Hoffmann & Kaliner, 1981).

Groups of six male and six female beagle dogs were fed diets containing technical cyfluthrin (purity, 90.8%) at a concentration of 0, 40, 160, or 640 ppm, equal to about 0, 1.4, 5.1, and 22.9 mg/kg bw per day for both sexes, for 12 months. Food consumption and clinical signs were assessed daily. Body weights were determined weekly. A complete physical examination including reflexes and body temperature, haematology, clinical chemistry and urine analysis were carried out before treatment initiation, and after 6, 13, 26, 39 and 52 weeks of treatment. Ophthalmoscopy was conducted before treatment initiation, and after 5, 13, 29, 39 and 52 weeks of treatment. At termination, dogs were necropsied and organs and tissues from dogs in the control group and at the highest dose were histologically examined.

During weeks 36–37, two males at the highest dose displayed clumsy, stiff movements of the hindquarters and a reluctance to move. Males at the highest dose had higher incidences of vomiting and soft, pasty faeces, and decreased body weights (–10%). Food and water consumption, physical examination, body temperature, ophthalmoscopy, haematology, clinical chemistry or urine analysis parameters were not affected. No treatment-related macroscopic or histological changes (including the sciatic nerve) were noted. The absolute and relative weight of spleen was increased by about 70% in females at the highest dose.

On the basis of decreased body weight, soft faeces and disturbances in the gait in males and the increased spleen weight in females at the highest dose, the NOAEL was 160 ppm, equal to 5.1 mg/kg per day (Hoffmann & Schilde, 1983).

In a study performed according to OECD guideline 453, groups of four male and four female beagle dogs were given diets containing cyfluthrin (purity, 94.8–95.1%) at a concentration of 0, 50, 100, 360 and 640 ppm (equal to 0, 1.4, 2.4, 10.6 and 15.5 mg/kg bw per day for males and 0, 1.5, 3.6, 10.7, and 18.0 mg/kg bw per day for females) for 12 months. Since the group at the highest dose began to demonstrate severe neurological symptoms in the first few weeks of the study, the highest dose was reduced to 500 ppm, beginning on week 8 and for the remainder of the study. Food consumption and clinical signs were assessed daily. Body weights were determined weekly. A detailed neurological examination was performed before testing, at 6 months and at termination. An electrocardiogram (ECG) and blood pressure were measured before the start of the treatment and at termination. Haematology, clinical chemistry (including plasma cholinesterase activity) and urine analysis were carried out before treatment initiation, and after 3, 6, 9 and 12 months. At termination, organs were weighed and the dogs were examined macroscopically and histologically. Statements of adherence to GLP and QA were included.

Two dogs in the control group (one male, one female) died from asymptomatic idiopathic epilepsy. One female at the highest dose was killed for welfare reasons when it developed a severe neurological condition that was considered to be treatment-related. Neurological examination at 6 and 12 months demonstrated dose-dependent gait abnormalities (hypermetria, reluctance to walk) and postural reaction deficits (abnormal head placement during wheel barrowing and abnormal foot placement during backward stepping, abnormal foot placement during lateral hopping, abnormal hemistanding posture) in the groups at 360 and 640/500 ppm. One female at the highest dose displayed ptosis, deficits in direct and indirect pupillary responses and protrusion of the membrane nictitans. Food consumption was not affected. At the highest dose, body weight was decreased by 17% in males. Reductions in female body weights in all treatment groups could be attributed to the death of a small female in the control group. ECG, blood pressure, clinical chemistry, plasma cholinesterase, haematology or urine analysis were not affected. Reductions of absolute organ weight in the treatment groups were considered to be secondary to the reduced body weights. No treatment-related macroscopic or histological changes were found.

On the basis of the neurological effects, the NOAEL was 100 ppm, equal to 2.4 mg/kg bw per day (Jones & Hastings, 1997).

(b) Dermal administration

Rats

In a 7-day study from published literature, groups of five male albino rats received daily dermal applications of a 40% formulation of cyfluthrin at a dose (active ingredient) of 0, 80, 160, 240 or 320 mg/kg bw per day under occlusion. The animals were killed 24 h after the last application. An additional group of five males and five females received cyfluthrin as a daily dermal dose at 100 mg/kg bw per day for 7 days, and was subsequently allowed to recover for 20 days. Animals were observed for clinical signs. At the end of the treatment period, blood was sampled for determination of alkaline phosphatase (AP), ALT, AST, total bilirubin, total protein, albumin, β -globulin and acetylcholinesterase activity.

All animals at the two higher doses died within 4 days after initiation of the treatment. At all doses, increases in AP, ALT, AST, total bilirubin and β -globulin were observed. Total protein, albumin, total globulin and acetylcholinesterase activity were reduced. Apart from the bilirubin concentrations, all parameters returned to normal within 15 days after cessation of treatment (El-Elaimy, 1986).

In a study of dermal toxicity, performed according to OECD guideline 411, groups of eight male and eight female Sprague-Dawley rats were treated dermally for 21 days with technical-grade

cyfluthrin (purity, 95.5–95.9%) at a dose of 0, 100, 340 or 1000 mg/kg bw per day. Doses were administered with a moistened pad to the shaven skin on the back of the animal. An additional eight males and eight females were included with the control group and the group at the highest dose and were allowed to recover for 2 weeks after cessation of the treatment. Animals were checked daily for mortality and clinical signs. Body weight and food consumption were measured weekly. Ophthalmoscopy was performed before dosing and at the end of the treatment period. At termination, blood was sampled for haematology and clinical chemistry, organs were weighed and macroscopy and histology was performed. Statements of adherence to GLP and QA were included.

No mortality or ocular abnormalities were observed. Body weight was not affected. Food consumption at the highest dose was significantly reduced during the first week of treatment. At the highest dose, a red discharge from the nose and urine stains were observed. At the intermediate and highest dose, scabbing at the application site was found. Clinical chemistry or haematology parameters and organ weights were not affected by treatment. At the application site, macroscopy revealed crusty, discolored and/or raised zones, and histological examination showed extensive areas of moderate to marked ulceration with bordering epidermis thickened by acanthosis and hyperkeratosis. There was inflammatory cell infiltration in the exposed dermis underlying the ulceration at the intermediate and highest dose. An accompanying minimal to slight dermal fibrosis in two females at 1000 mg/kg bw per day was also noted. After a 2-week recovery period, the local skin lesions partially recovered. On the basis of the effects on food consumption during the first week and clinical signs, the NOAEL for systemic effects was 340 mg/kg bw per day (Warren et al., 1996).

Rabbits

In a 3-week study, groups of six male and six female New Zealand White rabbits were exposed to technical cyfluthrin (purity, 83.5%; dissolved in PEG 400) at a dose of 0, 50 or 250 mg/kg bw per day by dermal application. The skin of three males and three females in each group was abraded before application. Animals were exposed for 6 h each day for 5 days per week for 3 weeks. At the end of each 6-h application, the treated skin was washed. Rabbits were observed daily for changes in appearance or behaviour, and body weights were recorded weekly. The application site was examined for signs of skin irritation. Studies of clinical chemistry and urine analysis were conducted on all rabbits before the initiation of treatment and at study termination. At termination, the rabbits in each group were examined for gross lesions and changes in organ weights. A selected number of tissues from rabbits in the control group and at the highest dose, along with testes from rabbits at the intermediate dose, were examined histologically.

Examination of appearance, behaviour, body weight, haematology, clinical chemistry, urine analysis and organ weights showed no treatment-related effects. Gross and histopathological examination showed no effects attributable to treatment with cyfluthrin. The NOAEL was 250 mg/kg bw per day (Flucke & Vogel, 1980).

(c) Inhalation

In a short-term study of exposure by inhalation, two experiments were performed. In the first experiment, groups of 10 male and 10 female Wistar rats were exposed (head/nose only) to aerosols (90% of particles < 3 µm) of technical cyfluthrin (purity, 83.1–85.3%) at actual concentrations of 0, 2.3, 11.5 and 69.6 µg/l for 6 h each day for 5 days per week for 3 weeks (a total of 15 exposures). The solvent used in the generating system (and the control atmosphere) was a 1 : 1 mixture of ethanol and PEG 400. Rats were observed daily for clinical signs. Body weights were recorded weekly. Rectal body temperatures were measured before and after exposures 1, 5, 10 and 15. Clinical chemistry and urine analysis were performed on five males and five females at each dose after the last exposure. At

termination, the rats were killed, examined macroscopically and organs were weighed. Five males and five females from each group were examined microscopically.

A second experiment was performed with the same design as the first experiment except that clinical chemistry was not performed. In this experiment, rats were exposed to cyfluthrin at actual concentrations of 0, 0.4, 1.4 or 10.5 µg/l.

In the first experiment, animals at the intermediate and highest dose displayed signs of ungroomed coat, abnormal gait, and increased salivation. One female at the highest dose died. Body-weight gain was affected in all treatment groups, as treated rats either lost body weight or failed to gain weight during the treatment period. Rats in the control group showed normal weight gains. As compared to values measured before treatment, body temperatures were consistently lowered after treatment. Haematology, clinical chemistry and urine analysis studies did not reveal any significant effects. No evidence of induction of liver drug-metabolism enzymes was apparent. No macroscopic lesions and no toxicologically relevant effects on organ weight were noted. Histological examinations revealed treatment-related increases in inflammation of trachea and in the incidence of emphysema in rats at the highest dose. On the basis of the effects on body-weight gain in all treatment groups in this experiment, the lowest-observed-adverse-effect concentration (LOAEC) was 2.3 µg/l air.

In the second experiment, it was reported that behavioural changes (data not shown) were noted only in rats at the highest dose during the final week of treatment. Body-weight gain was decreased in rats at the highest dose, in particular during the first 2 weeks of treatment. At termination, no treatment-related gross lesions were noted. At the highest dose, absolute and relative spleen weight was slightly reduced (absolute, up to 18%; relative, up to 13%). Small reductions ($\leq 6\%$) in absolute and relative liver weights in rats at the intermediate and highest dose were considered to be not toxicologically relevant. No treatment-related lesions were noted after histological examinations.

Taking the data from both experiments together, the no-observed-adverse-effect concentration (NOAEC) was 1.4 µg/l air, on the basis of the retarded body-weight gain at 2.3 µg/l (Thyssen & Mohr, 1980).

In a short-term study of exposure by inhalation, performed in accordance with OECD 412, groups of 10 male and 10 female Wistar rats were exposed to cyfluthrin (purity, 93.8%) for 4 weeks (6 h each day, 5 days per week) at actual concentrations of 0, 0.44, 6.0, and 46.6 mg/m³ air (head/nose exposure). Mortality, clinical signs and body weights were assessed daily. Reflexes (cornea, pinna, light, startle, righting, myotactic), and lung function were assessed weekly. Rectal temperature was measured twice per week, 5–20 min after the end of exposure. Ophthalmoscopy, clinical chemistry, haematology and urine pH tests were performed on five males and five females in each group at the end of the study. In an additional five males and five females, arterial blood gases and acid-base status was determined. At termination, the rats were necropsied, organs were weighed and histologically examined. Statements of adherence to GLP and QA were included.

At the highest concentration, mild to moderate clinical signs of a non-specific nature (ruffled coat, hyperactivity, bradypnoea) were observed after the end of exposure. At concentrations of 6 mg/m³ and higher, a transient reflex bradypnoea was observed. At the same concentrations, a slight, transient reduction in body temperature, as well as a reduction in leukocyte counts, reduced absolute (up to 38%) and relative (up to 28%) thymus weights and (in the males only) decreased body weight (10%) were found. Slight acidification of the urine, observed at the highest dose was considered to be secondary to the reflexive bradypnoea. No other treatment-related effects were observed.

On the basis of transitory bradypnoea, slight transitory reduction of body temperature, leukocyte count, thymus weight (in both sexes), and growth retardation (only in males) the NOAEC was 0.44 mg/m³ (0.044 µg/l air) (Pauluhn, 1989b).

In a short-term study of exposure by inhalation, groups of 10 male and 10 female Wistar rats were exposed to cyfluthrin (purity, 94.9%) in aerosols (> 85% of particles were < 5µm) at actual concentrations of 0, 0.09, 0.71 and 4.52 µg/l for 6 h each day for 5 days per week for 13 weeks (a total of 63 exposures). The solvent used was a 1 : 1 mixture of ethanol and PEG 400. Rats were observed daily for clinical signs. Body weights were recorded weekly. Clinical chemistry and urine analysis studies were conducted on all rats after 6 and 13 weeks of treatment. At termination, the rats were killed, examined macroscopically and histologically and organs were weighed. Statements of adherence to GLP and QA were included.

Signs of non-specific behavioural disturbances were observed in all males at the highest dose and in all females at the intermediate and highest dose. Body weight (8–15%) was reduced at concentrations of 0.71 mg/m³ air and greater in the males, but only at 0.71 mg/m³ air in the females. No effects of treatment on haematology, clinical chemistry or urine analysis parameters were observed. Small (maximally 10%) but statistically significant reductions in relative liver weights were observed in rats at the intermediate and highest dose. Measurements of *N*-demethylase, *O*-demethylase and cytochrome P450 activities yielded no evidence of enzyme induction. Macroscopic and histological examinations did not reveal any evidence of specific organ damage.

On the basis of behavioural changes and reduced body weight, the NOAEC was 0.09 µg/l air (Pauluhn & Mohr, 1984).

Four male Sprague-Dawley rats with permanently implanted intra-arterial catheters were exposed nose-only for 4 h to aerosols containing cyfluthrin (purity, 96.2%) at analytical concentrations of 13.2 µg/l air. Body temperature, blood gas concentrations and blood pH were assessed. Statements of adherence to QA and GLP were included.

A distinct hypothermia developed during the 4-h exposure period. Furthermore, decreases in arterial partial pressure of carbon dioxide and a rise in arterial blood pH were demonstrated. These results corroborated the hypothesis that the reflex bradypnoea, which in turn has been induced by sensory irritation, induces secondary hypothermia and respiratory alkalosis. The study author suggested that these effects influenced embryonic development and cause dysmorphogenesis as observed by Holzum (1993) (Pauluhn, 1992).

2.3 Long-term studies of toxicity and carcinogenicity

Mice

Groups of 50 male and 50 female CF1/W74 mice received diets containing cyfluthrin (purity, 90.8%) at a concentration of 0, 50, 200, or 800 ppm (equal to 0, 11.6, 45.8 and 194.5 mg/kg bw per day in males and 0, 15.3, 63.0 and 259.9 mg/kg bw per day in females) in the form of a 50% premix with Wessalon S for 23 months. Animals were examined daily for mortality and clinical signs. Body weights and food consumption were determined weekly. Haematology, clinical chemistry and urine analysis were performed on 10 males and 10 females per group at 0, 6, 12, 18 and 23 months. The fluoride content of bones and teeth was determined for five males and five females in each group after 23 months of treatment. At termination, the remaining animals were examined macroscopically and histologically, and organs were weighed.

No treatment-related effects were observed on mortality, clinical signs, haematological parameters, fluoridation of bones or teeth, food intake, or water consumption. Body weight was reduced (up to 10% in males and 12% in females) at the highest dose, in particular during the second year of treatment. Plasma AP activity was increased in all treated males at 6, 12 and 18 months. However, at all doses the increases were small (36–74%, except for the measurements at 18 months in males at 50 ppm when the increase was 114%, and the measurement at 6 months in males at 800 ppm

when the increase was 232%), and the increases were not strictly dose-dependent. At termination, the highest levels of AP activity were found in males in the control group. In females, treatment with cyfluthrin had no observed effect on AP activity. Histological examination revealed no evidence of liver damage. ALT was slightly elevated in males at the highest dose after 6 and 18 months of treatment, but not after 12 months. No treatment-related macroscopic, histological or organ weight changes were seen. The incidences of non-neoplastic and neoplastic lesions were all within normal ranges.

On the basis of the effects on body weight, the NOAEL was 200 ppm, equal to 45.8 mg/kg bw per day (Suberg & Loser, 1983a).

Groups of 50 male and 50 female CD-1 mice were given diets containing technical cyfluthrin (purity, 93.9–95.1%) at a concentration of 0, 200, 750 or 1400/1600 (male/female) ppm (equal to 0, 31.9, 114.8 and 232.7 mg/kg bw per day for males and 0, 38.4, 140.6 and 309.7 mg/kg bw per day for females) for 2 years. Animals were examined daily for mortality and clinical signs. A detailed physical examination was performed weekly. Body weights and food consumption were recorded weekly. Ophthalmoscopy was performed before the start of treatment and at 12 and 24 months. Haematology was performed at 12 and 18 months on 10 males and 10 females per dose. At termination, animals were examined macroscopically and histologically and organs were weighed. Statements of adherence to GLP and QA were included.

Mortality was not affected by treatment. An increased incidence of rough coat was observed in both sexes at 1400/1600 ppm. At the highest dose, females displayed hunched back, and lesion redness and lesion scab, generally associated with the ear pinnae of one or both ears. Body weights were significantly reduced in males in the group at the highest dose (up to 10%) and in females at the intermediate and highest dose (10–20%). Food consumption and haematological parameters were not affected. Macroscopy revealed rough coat in males and females at 1400/1600 ppm, crusty zones of the skin of the ear in males at 750 ppm and males and females at 1400/1600 ppm, and wet/stained ventrum in males at 1400 ppm. Histological examinations revealed increased incidences of acanthosis, chronic active inflammation, inflammation (all types), ulcer, and debris of the skin of the ears of males at 750 ppm and males and females at 1400/1600 ppm. No evidence for a tumorigenic effect of cyfluthrin was found. Observed reductions in absolute organ weight were likely to be secondary to the reduced body weight, and were considered to be not toxicologically relevant.

On the basis of the reductions in body weight in the female mice and the macroscopic and histological effects in males, the NOAEL was 200 ppm, equal to 38.4 mg/kg bw per day (Wahle & Christenson, 1998).

Rats

Groups of 65 male and 65 female Wistar rats were fed diets containing technical cyfluthrin (purity, 90.8%) at a concentration of 0, 50, 150 or 450 ppm (equal to 0, 2.0, 6.2, and 19.2 mg/kg bw per day in males and 2.7, 8.2, and 25.5 mg/kg bw per day in females) for 2 years. Animals were examined daily for abnormalities of behaviour or appearance. Body weights were recorded weekly through study week 27, every other week from week 27 to week 74, and then weekly until study termination. Food consumption was measured weekly. Haematology, clinical chemistry and urine analysis were performed at 6, 12, 18, and 24 months on 10 males and 10 females per group. Serum protein electrophoresis was performed at 12 months. At day 7 of treatment, mixed function oxidase activities and liver cytochrome P450 content were assessed in five males and five females per group. After 12 and 24 months of treatment, the fluoride content of bones and teeth was determined.

Ten males and 10 females per group were killed after 12 months of treatment, of which five males and five females per group were perfused with 10% buffered formalin before gross examination

and dissection. At termination, animals were macroscopically and histologically examined and organs were weighed (except for animals perfused with formalin).

No treatment-related effects on mortality, clinical signs, food consumption, haematology or urine analysis were observed. Occasional changes in blood glucose, alpha-1-globulin and leukocyte count were considered to be not toxicologically relevant. Compared with controls, body weights were significantly decreased throughout the study by about 8–10% at the highest dose. The reduction in body-weight gain (about 5%) in males at the intermediate dose during the first year of treatment was considered to be not biologically significant. At day 7 of treatment, *N*-demethylase activity in the group at the highest dose was increased by 30% (males) and 70% (females). *O*-Demethylase activity and cytochrome P450 content were not affected. Fluoride content of bones of males at the intermediate and highest dose and females at the highest dose was increased at 24 months, but not at 12 months. Macroscopic and histological examination and organ weights revealed no toxicologically relevant effects. Treatment did not affect the total or specific incidence of tumours.

On the basis of decreases in body weight in the group at the highest dose, the NOAEL was 150 ppm, equal to 6.2 mg/kg bw per day (Suberg & Loser, 1983b).

Groups of 60–70 male and 60–70 female Fischer 344 rats were given diets containing technical cyfluthrin (purity, 93.9–95.1%) at a concentration of 0, 50, 225, or 450 ppm (equal to 0, 2.6, 11.6, and 22.8 mg/kg bw per day for males and 0, 3.3, 14.4, and 28.3 mg/kg bw per day for females) for 2 years. Animals were examined daily for mortality and clinical signs. A detailed physical examination was performed weekly. Body weights and food consumption were recorded weekly. Ophthalmoscopy was performed before the start of treatment and at 12 and 24 months. Haematology, clinical chemistry and urine analysis were performed at 3, 6, 12, 18, and 24 months on 20 males and 20 females per group. Twenty males and 20 females in the control group and the group at the highest dose and 10 males and 10 females at the lowest and intermediate doses were killed for interim examination after 12 months of treatment. At termination, animals were examined macroscopically and histologically and organs were weighed. Statements of adherence to GLP and QA were included.

Body weight was reduced by 11% in the group at the highest dose. The reduction in body-weight gain (about 6%) at the intermediate dose was considered to be not biologically significant. At the highest dose, an increased incidence of alopecia was observed. Clinical chemistry demonstrated a slight reduction in serum triglyceride concentration (and, to a lesser extent, serum cholesterol concentration) in males at the highest dose. Food consumption, survival, ophthalmology, haematology, and urine analysis were not affected by treatment. No treatment-related changes in macroscopic and histological parameters and no evidence for a tumorigenic effect of cyfluthrin were found. Observed reductions in absolute organ weight were considered to be secondary to the reduced body weight, and not toxicologically relevant.

On the basis of the reduced body weight and alopecia, the NOAEL was 225 ppm, equal to 11.6 mg/kg bw per day (Wahle & Christenson, 1997).

2.4 Genotoxicity

The results of tests for genotoxicity are summarized in [Table 3](#). The Meeting concluded that cyfluthrin is unlikely to be genotoxic.

Table 3. Results of studies of genotoxicity with cyfluthrin

End-point	Test object	Concentration ^a	Purity (%)	Results	Reference
<i>In vitro</i>					
Reverse mutation	<i>S. typhimurium</i> . strains TA98, TA100, TA1535 and TA1537	20–24 000 µg/plate (± S9)	83.6	Negative	Herbold (1980a)
Reverse mutation	<i>S. typhimurium</i> . strains TA98, TA100, TA1535, TA1537 and TA1538	5–5 000 µg/plate (± S9)	95.0	Negative	Nagane et al. (1982)
Reverse mutation	<i>S. typhimurium</i> . strains TA98, TA100, TA1535, TA1537 and TA 1538	10–25 000 µg/plate (± S9)	95.0	Negative	Ohta & Moriya (1982)
Reverse mutation	<i>E. coli</i> WP2uvrA	5–5 000 µg/plate (± S9)	95.0	Negative	Nagane et al. (1982)
Reverse mutation	<i>E. coli</i> WP2uvrA	10–25 000 µg/plate (± S9)	95.0	Negative	Ohta & Moriya (1982)
Reverse mutation	<i>S. cerevisiae</i> S138	312.5–10 000 µg/ml (± S9)	95.0	Negative	Brusick (1982a,b)
Reverse mutation	<i>S. cerevisiae</i> D7	625–10 000 µg /ml (± S9)	95.0	Negative	Brusick (1982c)
Gene mutation	CHO K1-BH4 cells, <i>Hprt</i> locus	3–10 µg/ml (± S9)	94.7	Negative	Yang & Louie (1985) ^b
Chromosomal aberrations	Chinese hamster lung cells	3.3×10^{-5} – 3.3×10^{-3} mol/l (± S9)	93.7	Negative	Sasaki et al. (1986) ^b
Chromosomal aberrations	Human lymphocytes	500–5 000 µl/ml (± S9)	95.1 –95.5	Negative	Herbold, (1988a)
Sister chromatid exchange	CHO cells	3–20 µg/ml (± S9)	Technical	Negative	Putnam (1985) ^b
DNA damage	<i>E. coli</i> pol A+ and pol A–	62.5–1 000 µg/plate (± S9)	95.0	Negative	Herbold (1981a)
DNA damage	<i>B. subtilis</i> H17, M45 rec–	200 µg/plate (+ S9)	95.0	Negative	Nagane et al. (1982)
DNA damage	<i>B. subtilis</i> H17, M45 rec–	100–10 000 µg/plate (+ S9)	95.0	Negative	Ohta & Moriya (1982)
Unscheduled DNA synthesis	Rat primary hepatocytes	17–5 000 µg/ml	94.7	Negative	Curren (1985) ^b
Mitotic gene conversion	<i>S. cerevisiae</i> D7	625–10 000 µg/ml (± S9)	95.0	Negative	Brusick (1982c)
Mitotic crossing over	<i>S. cerevisiae</i> D7	625–10 000 µg/ml (± S9)	95.0	Negative	Brusick (1982c)
<i>In vivo</i>					
Micronucleus formation	Mouse bone marrow	2 × 7.5 or 2 × 15 mg/kg bw (gavage, administration interval for 24 h)	83.6	Negative	Herbold (1980b)
Dominant lethal mutation	Mouse	30, 60 mg/kg bw, oral (gavage?) administration	83.6	Negative	Herbold (1981b)

^a Positive and negative (solvent) controls were included in all studies.^b Statements of adherence to good laboratory practice and quality assurance were included.

2.5 Reproductive toxicity

(a) Multigeneration studies

Rats

In a two-generation study of reproductive toxicity, groups of 10 male and 20 female Wistar (BOR:WISW) rats (age 5 to 6 weeks) received diets containing cyfluthrin (purity, 90.8%) at a concentration of 0, 50, 150, or 450 ppm (equal to 0, 3.8, 11.4 and 34.7 mg/kg bw per day for males and 0, 5.1, 14.0 and 46.9 mg/kg bw per day for females) as a 50% premix with Wessalon S. Treatment started 105 days before mating and continued throughout mating, gestation, and rearing of pups. Each male was mated with two females. The parameters measured included behaviour, body weight, food consumption, mortality, fertility, viability during gestation and lactation, development of the young, parental body-weight gain, and sex ratio. The study was conducted with two litters per generation. The parameters assessed included fertility, litter size, fetal birth weight, fetal variability, and parental weight gain. Macroscopy, histology and organ weight were examined for F_{2b} parental animals and F_{3b} pups.

Treatment had no effect on mortality and clinical signs. In the parental animals of the groups at the intermediate and highest dose, body-weight gain was decreased in a dose-dependent manner. Body-weight effects at the intermediate dose were mild (maximally 8% and 12% in males and females, respectively, only at a certain stage during the test period). No consistent treatment-related effects on fertility, sex ratio or the incidence of fetal abnormalities were observed. At the highest dose, birth weight was consistently reduced (7–10%). In the offspring of groups at the intermediate and highest dose, decreased body-weight gain during lactation and occasionally reductions in viability and lactation indices were observed. Adult reproductive parameters were not affected.

On the basis of the borderline reductions in body-weight gain at 150 ppm, the NOAEL for parental toxicity was 50 ppm, equal to 3.8 mg/kg bw per day. On the basis of the reduced body-weight gain during lactation and the occasional reductions in viability and lactation indices, the NOAEL for offspring toxicity was 50 ppm, equal to 5.1 mg/kg bw per day (based on the cyfluthrin intake of the dams). The NOAEL for reproductive toxicity was 450 ppm, equal to 34.7 mg/kg bw per day, i.e. the highest dose tested (Loser & Eiben, 1983).

In a two-generation study of reproductive toxicity, performed according to OECD 416, groups of 30 male and 30 female Sprague-Dawley CD rats received diets containing technical-grade cyfluthrin (purity, 94.6–96.2%) at a concentration of 0, 50, 125 or 400 ppm (equal to 0, 3, 9 and 29 mg/kg bw per day in males, 0, 4, 10 and 33 mg/kg bw per day in females during the premating period and gestation and 0, 7, 19 and 59 mg/kg bw per day for females during the lactation period). Animals were observed daily for mortality and clinical signs of toxicity. Body weights were determined weekly, and on days 0, 6, 13 and 20 of gestation and days 0, 4, 7, 14 and 21 of lactation. Food consumption was measured weekly, and twice per week during the first week of lactation. Estrous cycling, mating, fertility, duration of gestation, and litter size were assessed. In the offspring, sex ratio, pup viability, body-weight gain and clinical signs were determined. Macroscopy was performed on all adults and pups. Histopathological evaluation of reproductive organs, the pituitary, and gross lesions was performed on all parental and F₁ adults. Statements of adherence to QA and GLP were included.

Mortality was not affected by treatment. P and F₁ females at 400 ppm showed splaying of the hindlimbs during lactation. At 400 ppm, body weight was reduced (up to 14%) in the F₁ males, in the P females during gestation and in the P and F₁ females during lactation. The reduction in body

weight was accompanied by a decrease in food consumption. Adult reproductive parameters were not affected. In the F₁ and F₂ pups at 125 ppm and 400 ppm, coarse tremors were observed between day 5 and day 18 of lactation. No other treatment-related effects were observed in the pups. No treatment-related macroscopic and histological changes were observed in parental animals or offspring.

On the basis of effects on body weight and food consumption the NOAEL for parental toxicity was 125 ppm, equal to 9 mg/kg bw per day. On the basis of coarse tremors in the pups during lactation, the NOAEL for offspring toxicity was 50 ppm, equal to 7 mg/kg bw per day (based on the cyfluthrin intake of the dams during lactation). The NOAEL for reproductive effects was 400 ppm, equal to 29 mg/kg bw per day, i.e. the highest dose tested (Eigenberg & Elcock, 1996).

In a supplementary two-generation study of reproductive toxicity, performed according to OECD guideline 416, groups of 30 male and 30 female CD Sprague-Dawley rats received diets containing technical-grade cyfluthrin (purity, 95.5%–96.2%) at a concentration of 0, 25 or 50 ppm (equal to 0, 1.9 and 3.8 mg/kg bw per day in males, approximately 0, 2 and 4 mg/kg bw per day in females during the premating and gestation and 0, 4.1 and 8 mg/kg bw per day for females during lactation). Animals were observed daily for mortality and clinical signs of toxicity. Body weights were determined weekly, and on days 0, 6, 13 and 20 of gestation and days 0, 4, 7, 14 and 21 of lactation. Food consumption was measured weekly, and twice per week during the first week of lactation. Estrous cycling, mating, fertility, duration of gestation, and litter size were assessed. In the offspring, sex ratio, pup viability, body-weight gain and clinical signs were determined. Macroscopy was performed on all adults and pups. Histopathological evaluation of reproductive organs, the pituitary, and gross lesions was performed on all P and F₁ adults. Statements of adherence to QA and GLP were included.

No toxicologically relevant effects were observed on any of the parameters tested.

The NOAEL for reproductive effects, parental and offspring toxicity was 50 ppm, equal to 1.9 mg/kg bw per day, i.e. the highest dose tested (Eigenberg, 1997).

(b) *Developmental toxicity*

(i) *Oral administration*

Rats

Groups of 25 inseminated FB30 rats were treated with cyfluthrin (purity, about 85%) as daily oral doses at 0, 3, 10, and 30 mg/kg bw by gavage from day 6 to day 15 of gestation. Vehicle was PEG 400. Animals were observed for signs of toxicity and were weighed (time-points not specified). On day 20 of gestation, rats were killed and fetuses were examined for visceral and skeletal anomalies. The description of the methods and results was concise.

In the females receiving the intermediate or highest dose, a high-stepping gait was reported from the second week of treatment, and the females at the highest dose occasionally displayed ataxias and reduced motility (data not shown). Litter size, frequency of resorptions, and placental weights were not affected. Treatment did not affect mortality or maternal body-weight gain. No embryotoxic and/or teratogenic effects were found. Malformations were of a comparable type and frequency in all groups.

On the basis of the clinical signs, the NOAEL for maternal toxicity was 3 mg/kg bw per day. The NOAEL for embryo/fetotoxicity was 30 mg/kg bw per day, i.e. the highest dose tested (Schlüter, 1982).

Groups of 25 inseminated Wistar rats (KFM-HAN) were given technical-grade cyfluthrin (purity, 93.4%) as daily oral doses at 0, 1, 3, and 10 mg/kg bw by gavage from day 6 to day 15 of

gestation. The vehicle was 1% Cremophor EL/water. Rats were observed daily for mortality and signs of toxicity. Body weights were recorded daily, and food consumption was recorded on days 6, 11, 16 and 21 of gestation. On day 21 of gestation, dams were killed and ovaries and gravid uteri were removed by caesarean section for assessment of potential developmental effects. About one out of three of the live fetuses in each litter were fixed and examined for visceral changes, the remaining fetuses were examined for skeletal effects. Statements of adherence to GLP and QA were included.

No treatment-related signs or mortalities were observed. No treatment-related effect on body-weight gain (with or without gravid uterine weight) was observed. Necropsy revealed no effect of treatment on pre- or postimplantation loss, litter size, fetal viability or fetal body weight. Furthermore the incidences of malformations and fetal variations were not affected by treatment.

The NOAEL for maternal and embryo/fetotoxicity was 10 mg/kg bw per day, i.e. the highest dose tested (Becker, 1983).

Rabbits

Groups of 15 inseminated female Himalayan rabbits (strain CHBB:HM) were given technical-grade cyfluthrin (purity, 95.0%) at a dose of 0, 5, 15 or 45 mg/kg bw per day by gavage on days 6–18 of gestation. The vehicle was 0.5% Cremophor EL. Rabbits were observed for clinical signs of toxicity, and were weighed periodically during gestation. On day 29 of gestation, rabbits were killed and uteri were examined to assess the effects of treatment on fetal development. Fetuses were weighed and examined for visceral and skeletal abnormalities. The description of the study was concise.

No effects on mortality, behaviour, appearance, insemination rate, or maternal weight gain were observed. At the highest dose, two rabbits aborted on days 25 and 28 of gestation, and one rabbit completely resorbed its implants. Fetal body weight, placental weights or litter size were not affected by treatment. No effect of treatment on the incidences of visceral or skeletal abnormalities was observed. Arthrogryposis was seen in rabbits of all treatment groups. However, the incidence was not dose-dependent and this malformation was reported by the study authors to be one of the most common spontaneous malformations in this strain, with an incidence of 0.76%. Therefore, the occurrence of arthrogryposis was considered to be spontaneous.

On the basis of the two abortions and a single case of complete resorption, the NOAEL for maternal and embryo/fetotoxicity was 15 mg/kg bw per day (Roetz, 1983).

In a study of developmental toxicity that was performed according to OECD guideline 414, groups of 16 pregnant Chinchilla rabbits (Chb:CH hybrids, SPF) received cyfluthrin (purity, 96.0–96.1%) at a dose of 0, 20, 60, or 180 mg/kg bw per day by gavage on days 6–18 of gestation. Mortality, clinical signs and body weight were assessed daily. Food consumption was measured during days 0–6, 6–11, 11–15, 15–19, 19–24 and 24–28 of gestation. The dams were killed 28 days after mating and necropsied. Fetuses were examined for visceral and skeletal anomalies. Statements of adherence to GLP and QA were included.

Mortality and clinical signs were not affected by treatment. Food consumption and body weight were reduced in animals at 60 and 180 mg/kg bw per day, and were increased 24–28 days after mating. When compared with does in the control group, food consumption during the treatment period was decreased by 7, 26 and 40% in the groups at the lowest, intermediate and highest dose, respectively. When compared with their body weight on day 6, the does in the groups at the intermediate and highest dose showed a body-weight loss of 4% and 5%, respectively, during treatment, while in the control group and the group at the lowest dose, body-weight loss was only 0.5% during the same period. A dose-related, statistically significant increase in postimplantation loss, due to increased embryonic resorptions, was observed in rabbits at the intermediate and

highest dose. Necropsy revealed no significant alteration attributable to treatment. Sex ratio and fetal body weights were unaffected by treatment, and no significant alterations were found in fetal heads or brains. The observed skeletal alterations (delayed ossification of vertebrae, sternebrae, and ribs) were considered to be within the normal range for spontaneous occurrence. There was no indication of a teratogenic effect.

On the basis of the reduced food consumption and body-weight loss, the NOAEL for maternal toxicity was 20 mg/kg bw per day. On the basis of the increased postimplantation loss, the NOAEL for embryo/fetotoxicity was 20 mg/kg bw per day (Becker & Biedermann, 1992).

(ii) *Exposure by inhalation*

Rats

Two separate studies were performed in which groups of 30 inseminated Wistar rats (bor:WISW) received cyfluthrin (purity, 92.9%) at actual concentrations of 0, 1.1, 4.7, and 23.7 mg/m³ air (first experiment) or 0, 0.09, 0.25, and 0.59 mg/m³ air (second experiment) from day 6 to day 15 of gestation. Exposure was nose-only for 6 h per day under dynamic conditions. Oxygen substitution (30% oxygen) was carried out in a further group exposed at 4.16 mg/m³ air. Rats were observed daily for mortality and signs of toxicity. Body weights were recorded on days 0, 9, 12, 15 and 20 of gestation. On day 20 of gestation, dams were killed and ovaries and gravid uteri were removed by caesarean section for assessment of potential developmental effects. About one third of the live fetuses in each litter were fixed and examined for visceral changes, the remaining fetuses were examined for skeletal effects. Statements of adherence to GLP and QA were included.

No mortality was observed in the dams. At concentrations of 4.16 mg/m³ air and higher, reduced motility, ruffled unkempt fur, irritation of the visible mucous membranes and laboured breathing were observed. In the group at the highest concentration, these signs were already observed during the exposure period, while in the groups at 4.16 and 4.7 mg/m³ air they first appeared at the end of the exposure period. During the treatment period, body-weight gain of dams was significantly reduced at concentrations of 1.1 mg/m³ air and higher. At concentrations of 1.1 mg/m³ air and higher, significant reductions in fetal weights and a higher number of foetuses with retarded ossification were observed. In the group exposed at 4.16 µg/l air substituted with 30% oxygen, reductions in maternal body-weight gain, fetal weight and fetal ossification were much less pronounced. Therefore, the maternal and fetal effects were interpreted as signs of a non-specific retardation of embryonic development and were attributed to a maternal hypoxia induced by the treatment. No evidence of teratogenic effects was observed at any dose.

On the basis of the reduced body-weight gain, the NOAEC for maternal toxicity was 0.59 µg/l air. On the basis of the reduced body weight and the retarded ossification the NOAEC for embryo/fetotoxicity was 0.59 µg/l air. The NOAEC for teratogenicity was 23.7 µg/l air, i.e. the highest concentration tested. (Renhof & Pauluhn, 1988).

In a study of developmental toxicity performed according to OECD guideline 414, groups of 25 inseminated (Bor:WISW) Wistar rats were exposed nose-only to cyfluthrin (purity, 94.7–96.2%) at actual concentrations of 0, 0.46, 2.55 or 11.9 µg/l air, on days 6–15 of gestation. The vehicle was PEG 400. An additional group was exposed to cyfluthrin at 12.8 µg/l air, supplemented with 40% oxygen. Animals were checked daily for mortality and clinical signs. Body weight was assessed on day 0 of gestation, daily from day 6 to day 15 of gestation, and on day 20 of gestation. Food consumption was measured during days 0–6, 6–11, 11–16 and 16–20 of gestation. At day 20 of gestation, the dams were killed and necropsied, and fetuses were examined for visceral and skeletal abnormalities. For every group, a satellite group of five

females was exposed during days 6–13 of gestation for determination of mortality, clinical signs, body weight, food intake (daily on days 6–13 of gestation), lung function (day 6 of gestation only), reflexes and rectal temperature (day 6 and day 12 of gestation), plasma concentrations of cyfluthrin (day 13 of gestation) and pathology (day 13 of gestation). Statements of adherence to GLP and QA were included.

At concentrations of 0.46 µg/l and above, food intake and body-weight gain were decreased. At 2.55 µg/l and above, bloody snout, unkempt fur and piloerection were observed. At 11.9 µg/l and 12.8 µg/l (+40% oxygen) dams displayed respiratory disturbances and hypoactivity. In addition, in the group at 11.9 µg/l, dams displayed high-stepping and salivation. In the satellite groups, hypothermia and bradypnoea were found at concentrations of 0.46 µg/l and above.

No macroscopic findings were reported. At concentrations of 2.55 µg/l and above decreased placental weights (7–23%), fetal weights (11–29%) and retarded ossification of the phalanges, metacarpals, metatarsals, vertebrae, pelvis and skull, and an increased incidence of malformations were found. The nature of the malformations, with one exception (supernumerary and fused rib), were comparable to those observed in the rats in the control group in this study and in historical controls. There was no indication of a specific teratogenic potency of cyfluthrin. In the group with oxygen supplementation the embryo/fetotoxic effects were less pronounced. Therefore, the embryo/fetotoxicity of cyfluthrin after exposure by inhalation was considered to be caused by a physiological maternal compensation mechanism (hypothermia with respiratory alkalosis) after reflex bradypnoea following sensory irritation (see Pauluhn, 1992). Detectable amounts of cyfluthrin in plasma were only found in the group at the highest dose. The concentrations of cyfluthrin were low and not affected by supplementation with oxygen.

On the basis of reduced food consumption and body-weight gain, the LOAEC for maternal toxicity was 0.46 µg/l. On the basis of reduced placental and fetal weights, retardation of development and increased incidence of malformations of fetuses, the NOAEC for embryo/fetotoxicity was 0.46 µg/l air (Holzum, 1993; Schmidt, 1993).

2.6 *Special studies*

(a) *Neurotoxicity*

Hens

Cyfluthrin was tested for acute delayed neurotoxicity in White Leghorn hens in several experiments. In these experiments, symptoms of excitation and behavioural disorders, and mortality were observed in birds given single or multiple oral doses at as high as 5000 mg/kg bw. Systematic histological examinations did not reveal any evidence of treatment-related lesions to nerve tissues, nor was any effect on neuropathic target esterase (NTE) activity noted. Exposures by inhalation or by dermal application also failed to produce evidence of delayed neurotoxicity (Thyssen et al., 1981a and 1981b, 1985; Hixson, 1981; Thyssen & Kaliner 1982; Pauluhn & Kaliner, 1983; Flucke & Eben, 1985; Sacchse, 1986).

Rats

The acute oral neurotoxicity of cyfluthrin (purity, 96.1%) was assessed in an inclined plane test in groups of 5 or 10 female Wistar (Hsu Cpb: WU) rats treated by gavage. The vehicle was an aqueous Cremophor EL suspension. In the first experiment, groups of five rats received doses of 0, 0.015, 0.05, 0.1, 0.15, 0.3, 0.45, 0.5, 1, 2.5, 3, 7.5 or 9 mg/kg bw. In the second experiment, groups of 10 rats received doses of 0, 1, 2.5 or 7.5 mg/kg bw. The ability of the rats to retain their grip on a

tilted plane was assessed at several time-points between 30 min and 24 h after treatment. In addition, the rats were checked for clinical signs several times on the day of treatment. Rats from the second experiment were macroscopically examined 2 weeks after treatment. Statements of adherence to GLP and QA were included.

The slip angle was significantly reduced only in rats in the group at 9 mg/kg bw and only 2 h, but not 1 h or 6 h after administration. A dose of 7.5 mg/kg bw resulted in a marginal, statistically non-significant effect. A clinical sign of toxicity, i.e. shaking, was observed at doses of 2.5 and 3 mg/kg bw, in one and two animals respectively. The effect occurred about 2 h after administration and lasted for 1–2 h. At higher doses reduced motility, laboured breathing, increased salivation, uncoordinated gait, sternal recumbency, rolling over, narrowed palpebral fissures, digging and preening movements, diarrhoea and vocalization were also observed. The number and intensity of clinical signs increased with dose.

The NOAEL for clinical signs was 1 mg/kg bw. The NOAEL with regard to changes in slip angle was 7.5 mg/kg bw (Andrews, 1999).

Fifty male Sprague-Dawley rats received technical-grade cyfluthrin (purity, 95%) at a dose of 80 mg/kg bw per day as a 1.6% solution in PEG 400 by gavage on five consecutive days. Due to the onset of mild to severe symptoms of toxicity, the dose was reduced to 40 mg/kg bw per day on days 6–14. Twenty-five male rats were treated with vehicle only. The rats were observed for appearance and behaviour throughout treatment and a recovery period of 3 months. Ten treated and five control rats were killed, and their tissues examined histologically on the days 1 and 5 of treatment and 1, 2, and 3 months after cessation of treatment. At each time-point, tissues from two treated males and one control male were also examined by electron microscopy.

The treated rats showed clinical signs of intoxication (abnormal, straddled gait, slow leg movements, and excess salivation) throughout the dosing period. No symptoms were observed 5 days after cessation of treatment. Body-weight gain was reduced throughout treatment but recovered during the recovery period. Histologically, a minimal degree of axonal degeneration (swelling and demyelination) was observed in single fibres of the sciatic nerve in six out of eight rats at the first examination, in three out of eight rats 5 days to 1 month after treatment, and in two out of nine rats 2 months after treatment. A similar lesion was reported in the femoral nerve of one treated male examined on the fifth day after treatment, but was no longer seen at the end of the 3-month recovery period. No alterations were reported in any other nervous tissue or skeletal muscle examined. Electron microscopy revealed dilatation of neurotubules, accompanied by proliferation of neurofilaments and degeneration of mitochondria, which was maximal 1 month after treatment but was not seen after 3 months (Oikawa et al., 1983).

Groups of five male and five female Wistar (SPF-Cpb) rats received cyfluthrin (purity, 96.5%) at a dose of 0 or 60 mg/kg bw per day by gavage for 2 weeks. A supplementary group of male rats received doses of 0 or 50 mg/kg bw per day. Behaviour, appearance and body weights were recorded over the treatment period. At the end of treatment, rats were killed, perfused with 10% formalin and autopsied. Brain, spinal column, sciatic nerve and femoral muscle were histologically examined.

From the second day of treatment onwards, clinical signs of toxicity (tremor, altered gait, and increased vocalization) were observed in all treated animals. Four males at 60 mg/kg bw per day died between treatment days 5 and 8, but macroscopic examination revealed no specific alterations. The body-weight gain of females was not affected by treatment, but decreased by about 11% for males at 50 or 60 mg/kg bw per day. Small, fresh brain haemorrhages were seen in all four males that died. The authors concluded that the “most likely explanation is that these are the result of a terminal cardiovascular disorder with necrosis of the vascular walls”. However, since these haemorrhages

were not seen in rats in the control group, a treatment-related effect could not be ruled out (Heimann & Kaliner, 1983).

Groups of 15 male and 15 female Wistar TNO/W74 rats received cyfluthrin (purity, 83.3%) emulsified in PEG 400 by gavage daily for 35 weeks. The doses administered ranged from 30 to 80 mg/kg bw per day. The dose was varied intermittently with the purpose of inducing symptoms of acute toxicity after each dose. For the most part, doses of 60 or 80 mg/kg were given. The rats were observed daily for clinical signs. Body weights were recorded weekly. At termination clinical chemistry was performed and mixed function oxidase (MFO) activity of the liver was determined. Animals were examined macroscopically, organ weights were recorded and liver, kidney, adrenal gland, brain, spinal cord, and sciatic nerve tissues from five treated and five control rats of each sex were examined microscopically.

In the treatment group, eight males and two females died, while in the control group two males and two females died. Throughout the study treated animals displayed signs of acute toxicity (apathy, ruffled coat, and respiratory disturbances, and in some rats, increased salivation, tremor, and uncoordinated gait). No paralysis of the extremities was observed. Body-weight gain was reduced by 20–25% in males, but not in females. Clinical chemistry parameters or MFO activity were not affected by treatment. Reductions in liver and kidney weight in treated males are considered secondary to the decreased body weight. Macroscopic and histological examination revealed no treatment-related changes. However, rats that died during the treatment period were not examined (Thyssen & Vogel, 1982).

In a concisely reported study to assess the effect of treatment on neuromuscular function, groups of 10 male Wistar rats received cyfluthrin (purity, 94.5%) as a single oral dose (method of administration not specified) at 0, 0.1, 0.3 or 1.0 mg/kg bw in the first experiment and 0, 0.01, 0.03 or 0.1 mg/kg bw in the second experiment. Diazepam (5 mg/kg bw) was administered as a positive control. Cypermethrin (0.1–1.0 mg/kg bw) was used as a reference compound. The ability of the rats to retain their grip on a tilted plane was assessed at 30 min and at 2, 5 and 7 h after treatment. The experimental variable was the angle of the plane at which rats lost their grip.

Statistically significant decreases in the angle at which rats lost their grip were noted after treatment with cyfluthrin. This effect was maximal after 5 h. The effect was observed at doses of 0.03 mg/kg bw and higher. The positive control diazepam and reference chemical cypermethrin produced similar results (Polacek, 1984).

The present Meeting noted that the effects, although statistically significant (by Student t-test), were small and not strictly time- or dose-dependent. Furthermore, individual data were not presented and appropriate statistical analysis was not performed. Therefore the Meeting considered this study to be inappropriate for assessing neurotoxicity.

In a concisely reported study, the neurotoxic effects (i.e. analgesia, catalepsy, traction, orientation motility, spontaneous activity, lingomandibular reflex and neuromuscular transmission, effects on hexobarbital-induced sleep and, pentylenetetrazole-induced convulsions) of single oral doses of cyfluthrin (purity unknown) at 3, 10 and 30 mg/kg bw were assessed in groups of 5–10 male CF1 mice and male Wistar rats. The vehicle was PEG 400.

Cyfluthrin at a dose of 30 mg/kg bw followed by hexobarbital at a dose of 100 mg/kg bw (subcutaneous), induced 60% mortality in mice. No potentiation of hexobarbital-induced sleep was observed with cyfluthrin at doses of 3 and 10 mg/kg bw. Cyfluthrin at doses of 3 and 10 mg/kg bw had no muscle-relaxant, analgesic or anticonvulsive properties, and did not affect central coordination or spontaneous and orientation motility in male CF1 mice. Also in mice, a dose of 30 mg/kg bw lead to the disappearance of the righting reflex, the inability to grip the support, and prostration, but caused

no catalepsy. In rats, doses of up to and including 30 mg/kg bw caused no catalepsy and did not affect reflexes or neuromuscular transmission in male Wistar rats (Polacek, 1985).

The effects of single oral doses of cyfluthrin (purity, 94.9%) at 0, 0.1, 0.3 or 1.0 mg/kg bw (administered by gavage in Cremophor EL/water) on analgesia, traction, catalepsy, anticonvulsive properties, orientation motility, spontaneous activity and hexobarbital-induced sleep was assessed in groups of 5–10 mice and rats.

The duration and depth of hexobarbital-induced sleep in the mouse were slightly increased by cyfluthrin at 1 mg/kg bw. Lower doses had no effect. In mice, cyfluthrin exhibited no analgesic or anticonvulsant properties, and had no effect on central coordination and no protective effect against pentetrazole-induced convulsions. Cyfluthrin also had no cataleptic effect in rats and mice and did not inhibit the traction capacity of mice to any significant degree. At all doses tested (0.1–1.0 mg/kg bw), cyfluthrin induced weak, non-dose-dependent stimulation of spontaneous motility. Inhibition of the linguomandibular reflex and of neuromuscular transmission in rats was not observed (Polacek, 1982).

In a study from published literature it was reported that male Long Evans Hooded rats aged 8 weeks that had received cyfluthrin as oral doses at 0, 12.5, 25 or 50 mg/kg bw in 1 ml of corn oil 1.5 h before testing exhibited a dose-dependent reduction in spontaneous motility.

In the acoustic startle-response test, cyfluthrin (at doses of 12.5–75 mg/kg bw) reduced the amplitude of the effect and the sensitivity to background noise and increased the latent period preceding the onset of the reaction. The effects of cyfluthrin in these experiments were comparable to those of other type-II pyrethroids (Crofton & Reiter, 1988).

(b) Supplemental studies

In order to test the influence of cyfluthrin on body temperature, male Wistar rats (Bor:WISW) received single oral doses of cyfluthrin (purity, 95.3%) at 0, 125, 250 or 500 mg/kg bw by gavage. PEG 400 was used as the vehicle. Body temperature was measured at 5, 15 and 30 min and 1, 2, 2.5, 3, 3.5, 5, 5.5, 6, 6.5, 7 and 24 h after treatment. For 14 days after treatment, rats were checked daily for clinical signs. Body weight was measured at days 4, 8 and 15. At termination all animals were necropsied. Statements of adherence to GLP and QA were included.

No effect on body temperature was observed. Clinical signs (including apathy, periodic shaking, staggering gait, laboured breathing, salivation, uncoordinated movements) were observed at all doses. One animal in the group at the highest dose died (Bomann, 1991).

Studies on combination toxicity of cyfluthrin with triflumuron, methamidophos, propoxur, dichlorvos or imidacloprid did not reveal any evidence of synergism. The effects were either additive or sub-additive (Heimann, 1982b, 1983c, 1983d; Flucke, 1984a, 1984b; Krötlinger, 1994). A slight potentiation was observed on oral administration simultaneously with omethoate (Krötlinger, 1988).

In a study from published literature, a cell communication test with V79 fibroblasts, designed to indicate tumour-promoting potential, was performed. Cyfluthrin was found not to inhibit intracellular communication at non-cytotoxic concentrations (5–15 µmol/l) (Waerngard & Flodstroem, 1989).

3. Observations in humans

The effect of inhalatory exposure to cyfluthrin was assessed in 10 human subjects. In a first experiment, five men were exposed for 1 h to cyfluthrin (insecticide spray FCR 1272 0.04AE) at actual concentrations of about 2 µg/l (four subjects) or 0.09 µg/l (one subject). A second group of five

men was exposed for 1 h to actual concentrations of cyfluthrin of about 0.75 µg/l. Vital signs were recorded before, immediately after and 1.5, 2 and 3 h after the start of the exposure. In addition, in the first experiment vital signs were also recorded at 12 and 24 h after the start of the exposure, and in the second group 10 h after the start of the exposure. Electrocardiograms (ECGs) were recorded immediately before and after exposure and at 24 h (first experiment) or at 10 h (second experiment) after the start of exposure. The mucous membranes of the nose, oropharynx and eyes were examined immediately before and after exposure. For haematology and clinical chemistry, blood was sampled just before the start and 24 h (first experiment) or 10 h (second experiment) after the start of the exposure. Urine analysis was performed before and 24 h (first experiment) and 10 h (second experiment) after the start of the experiment. Statements of adherence to GLP and QA were included.

There were no clinically significant or drug-related abnormalities in vital signs, ECGs or clinical laboratory tests after either exposure session. In the first experiment, only two of the subjects tolerated exposure for the defined period of 1 h, mild to moderate irritation of the mucous membranes of the nose, upper respiratory tract, throat and eyes and mild hyperaemia of the nasal mucosa being observed. The effects resolved within 1 h after treatment.

In the second experiment, all subjects tolerated exposure for the defined period of 1 h. Mild irritation of the mucous membranes of the nose and throat and mild hyperaemia of the nasal mucosa were reported. The effects resolved within 1 h after treatment (Ruddy et al., 1998).

Cyfluthrin caused a topical skin effect, characterized by a stinging sensation in the affected areas in laboratory workers. Areas most commonly affected were the face, and mucosal tissues (e.g. prepuce). Since this chemical adheres strongly to skin and is not washed off by soap and water, it is possible to contaminate various parts of the body with cyfluthrin present on the hands (Flucke & Lorke, 1979; Miksche, 1979; Faul, 1984; Faul & Krauthausen, 1995). Yearly medical examinations of factory workers revealed no effects on body weights, haematological and urine analysis parameters, ALT and gamma glutamyl transferase (GGT) activities and thoracic organs, as examined by X-rays (Faul, 1988; Kollert, 1988; Faul & Krauthausen, 1995).

Beta-cyfluthrin

4. Toxicological studies

4.1 Acute toxicity

The results of studies of acute toxicity with beta-cyfluthrin are summarized in Table 4. The observed clinical signs (increased salivation, uncoordinated movements, increased activity and vocalization, and reduced, laboured breathing, apathy, straddle-legged gait (mostly in the rear legs), and reduced sensitivity to external stimuli) were typical of this class of pyrethroids.

Table 4. Results of studies of acute toxicity with beta-cyfluthrin

Species	Strain	Sex	Route	Formulation	LD ₅₀ (mg/kg bw;)	LC ₅₀ (µg/l)	Purity (%)	Reference
Mouse	NMRI	Male	Oral	PEG 400	91 ^a	—	99.1	Heimann (1987b) ^b
		Female			165 ^a			

Rat	Wistar	Male	Oral	PEG 400	380 ^a	—	99.1	Heimann (1987c) ^b
		Female			651 ^a			
		Male			655			
		Female			1369			
Rat	Wistar	Male	Oral	Xylene	211 ^a	—	99.1	Heimann (1987d) ^b
		Female			336 ^a			
		Male			307			
		Female			343			
Rat	Wistar	Male	Oral	Acetone/oil 1 : 10	84 ^a	—	99.1	Heimann (1987e) ^b
		Female			77 ^a			
		Male			141			
		Female			108			
Rat	??	Male	Oral	Water/Cremophor EL	16 ^a	—	NS	Heimann (1984c)
		Male						
Rat	??	Male	Oral	Water/Cremophor EL	11 ^a	—	NS	Heimann (1986a)
		Male						
Dog	Beagle	Male	Oral	Tylose	> 5000	—	98.5	Von Keutz (1985)
		Female			(emesis) ^c			
					> 5000			
Hen	White Leghorn	Female	Oral	Water/Cremophor EL	> 5000	—	98.5	Flucke (1985a) ^b
Rat	Wistar	Male	Dermal	PEG400	> 5000	—	98.7–99.1	Heimann (1987f) ^b
		Female			> 5000			
Rat	Wistar	Male	Dermal	Xylene	> 5000	—	98.7–99.1	Heimann (1987g) ^b
		Female			> 5000			
Rat	Wistar	Male	Inhalation (4 h)	Ethanol/PEG 400	—	90	98.5	Pauluhn (1985a)
		Female				100		
Rat	Wistar	Male	Inhalation (4 h)	Ethanol/PEG 400	—	82	97.9	Pauluhn (1988a) ^b
		Female				81		
Rat	Wistar	Male	Inhalation (4 h)	Dust	—	967	98.5	Pauluhn (1985a)
		Female				695		
Rat	Wistar	Male/ Female	Inhalation (4 h)	Dust	—	532	97.9	Pauluhn (1988a) ^b
Dog	Beagle	Male	Intravenous	Tylose	5	—	98.5	Von Keutz (1985)
		Female						
Mouse	NMRI	Male	Intraperitoneal	PEG400	18	—	98.0	Krötlinger (1988) ^b
Rat	Wistar	Male	Intraperitoneal	PEG400	917	—	99.1	Heimann (1987h) ^b
		Female						

NS, not stated.

^a Fasted animals.

^b Statements of adherence to QA and GLP were included.

^c In the study in dogs, vomiting occurred at both doses (2500 and 5000 mg/kg bw) shortly after administration.

(a) Dermal absorption

The rate and extent of dermal absorption of radioactivity was investigated after topical application of [¹⁴C]beta-cyfluthrin (radiochemical purity, > 99%) at a concentration of 125 g/l or

40 g/l, in a flowable concentrate for seed treatment (FS) formulation, to male Sprague-Dawley CD rats. The animals were exposed for 8 h. Groups of five rats were killed at 8, 24, 72 and 144 h after the start of the exposure. Statements of adherence to GLP and QA were included.

During the 8-h exposure period, 0.37% and 0.48% of the applied radioactivity at the highest and lowest dose respectively were detected in excreta, carcasses (including whole blood) and untreated skin (including skin surrounding the dose site). After removal of the dose from the skin at the end of the 8-h exposure period, in the groups at the lowest and highest dose totals of 1.29% and 0.8% respectively were absorbed at 144 h (Kemp, 2004).

In a study of dermal absorption *in vitro*, the rate and extent of absorption was investigated after topical application of [^{14}C]beta-cyfluthrin (radiochemical purity, > 99%) at concentrations of 40 or 125 g/l to excised human and rat skin in an FS formulation. The skin samples were exposed to the test material for 8 h, after which the remaining dose was washed off the skin. Statements of adherence to GLP and QA were included.

At 24 h, the total amounts of applied radioactivity absorbed at the highest dose were 0.071% and 0.406% and at the lowest dose were 0.039% and 0.611% in human and rat skin, respectively.

The results show that rat skin is about 6 and 16 times more permeable than human skin at the highest and lowest doses used, respectively (Cage, 2004).

(b) Dermal irritation

In a study of dermal irritation, performed according to OECD guideline 404, three New Zealand White rabbits (two males, one female) received a dermal application of 0.5 g of beta-cyfluthrin (purity, 98.5%) for 4 h. Irritation was assessed according to the Draize method at 1, 24, 48, 72 and 168 h.

Very slight erythema was observed at 24 and 48 h, but not at 72 h and 168 h (Pauluhn, 1985b).

(c) Ocular irritation

In a study of eye irritation, performed according to OECD guideline 405, three male New Zealand White rabbits received 0.1 ml of beta-cyfluthrin (purity, 98.5%) in the conjunctival sac of the eye. The eyes were rinsed with saline after 24 h. Irritation was assessed according to the Draize method at 1, 24, 48, 72 and 168 h.

Slight irritation of the conjunctivae was observed at 24 and 48 h, but not at 72 and 168 h (Pauluhn, 1985b).

(d) Dermal sensitization

In a study of dermal sensitization conducted according to OECD guideline 406 and using the Magnusson & Kligman maximization test, beta-cyfluthrin (purity, 98.5%) was tested in 20 male Bor:DHWP/SPF guinea-pigs. Ten animals served as controls. In the induction phase, the animals received beta-cyfluthrin by intradermal injection (1%) on day 1 followed by a topical administration (25% w/v) after 1 week and challenge by topical administration (25%) 3 weeks after the intracutaneous injection. The vehicle was 2% Cremophor EL/saline. Statements of adherence to GLP and QA were included.

After challenge with 25% beta-cyfluthrin formulation, 10% of the animals from both the induction group and 10% of the control animals showed a slight reddening of the skin, which disappeared after 48 h (Heimann, 1986b).

In a study of dermal sensitization conducted according to OECD guideline 406 and using the Magnusson & Kligman maximization test, beta-cyfluthrin (purity, 98.6%) was tested in 20 male Hsd/Win:DH guinea-pigs. Ten animals served as controls. In the induction phase, the animals received beta-cyfluthrin by intradermal injection (5%) on day 1 followed by a topical administration (50% w/v) after 1 week and challenge by topical administration (25 or 50%) 3 weeks after the intracutaneous injection. The vehicle was 2% Cremophor EL/saline. Statements of adherence to GLP and QA were included.

No dermal reactions were observed in either the induction or the control group (Vohr, 1994b).

4.2 *Short-term studies of toxicity*

(a) *Oral administration*

Rats

In a 4-week study of toxicity performed according to OECD guideline 407, groups of 15 male and 15 female Wistar rats were treated orally with beta-cyfluthrin (purity, 98.6%) at a dose of 0, 0.25, 1, 4 or 16 mg/kg bw per day by gavage. Additional groups of 15 males and 15 females were treated for 4 weeks and then kept untreated for a 4-week recovery period. Rats were observed daily for clinical signs and mortality and body weights were recorded weekly. Haematology, clinical chemistry, urine analysis and measurements of enzyme levels (*N*-demethylase, *O*-demethylase, cytochrome P450) in the liver were conducted on five males and five females per dose at the end of the 28-day treatment interval, and at the end of the 4-week recovery period. At termination, 10 males and 10 females per dose were macroscopically examined and organs were weighed. Histology was performed on organs and tissues, including nervous tissue, of five males and five females per dose. Statements of adherence to GLP and QA were included.

At the highest dose, 11 males and 12 females died. At 4 mg/kg bw per day, rats displayed increased motility and grooming and digging movements throughout the treatment period, starting on the first day of treatment. These symptoms occurred 30–80 min after application and lasted for about 4 h. In this group, salivation was also observed. At 16 mg/kg bw per day, ataxia, straddled-gait, dyspnoea, apathy and dacryohemorrhoea were also observed. No effects of treatment on body weight, clinical chemistry, haematology, urine analysis and liver enzymes were observed. Relative liver, adrenal and testis weights were increased in males of the group at the highest dose. In females of the group at the highest dose, relative lung weight was increased. Macroscopic and histopathological examinations and special histopathological studies of nervous tissues did not indicate treatment-related effects. At the end of the 4-week recovery period, no effects were observed.

On the basis of the clinical signs, the NOAEL was 1 mg/kg bw per day (Heimann & Majeed, 1988).

Groups of 15 males and 15 female Wistar rats received diets containing beta-cyfluthrin (purity, 99.7%) at a concentration of 0, 30, 125, or 500 ppm (equal to 0, 2.3, 9.5 and 38.9 mg/kg bw per day in males and 0, 2.5, 10.9 and 42.9 mg/kg bw per day in females) for 13 weeks. In addition, groups of 15 males and 15 females were fed diets containing beta-cyfluthrin at a concentration of 0 or 500 ppm (equal to 0 and 37.0 mg/kg bw per day in males and 0 and 43.0 mg/kg bw per day in females) for 13 weeks and were then kept on control diet for an additional 4 weeks. Rats were examined daily for mortality and clinical signs. Body weights and food and water consumption were recorded weekly. Clinical chemistry, haematology and urine analysis were conducted after 1 and 3 months and at the end of the recovery period. After 13 weeks and at the end of the recovery period, a tooth and femur

were removed from five males and five females per dose for determination of fluoride content. In addition, the activity of microsomal enzymes in liver was determined in these rats. Ophthalmoscopy was performed at weeks 1 and 11 during treatment, and at week 15 in rats in the recovery groups. At the end of the treatment or recovery period, the rats were killed, macroscopically and histologically (including bone-marrow smears) examined and organs were weighed. Statements of adherence to GLP and QA were included.

No effect of treatment on mortality, clinical signs, food and water consumption and body-weight gain were observed at doses of up to and including 125 ppm. At 500 ppm, rats exhibited an uncoordinated gait and impaired general condition. Food ($\pm 12\%$) and water consumption ($\pm 18\%$) and body weight ($\pm 8\%$) were reduced during the first week of treatment. No treatment-related effects were observed on any of the other parameters tested.

On the basis of the clinical signs and reductions in food and water consumption and body-weight gain of rats during the first week of treatment, the NOAEL was 125 ppm, equal to 9.5 mg/kg bw per day (Suberg & Wood, 1988).

Dogs

In a 13-week dietary study, groups of four male and four female beagle dogs received beta-cyfluthrin (purity, 99.2%) at a concentration of 0, 10, 60 or 360 ppm (equivalent to 0, 0.3, 1.3 and 9 mg/kg bw per day). Clinical signs and food consumption were recorded daily. Body weights were assessed weekly. Measurements of reflexes, body temperature and pulse rate, haematology, clinical chemistry and urine analysis were performed before testing and during weeks 4, 7 and 13 of treatment. Ophthalmoscopy was performed before testing and during weeks 7 and 13. At the end of the treatment or recovery period, the dogs were killed, macroscopically and histologically examined (including bone-marrow smears) and organs were weighed. In addition the activity of microsomal enzymes in liver and the fluoride content in bones and teeth were determined. Statements of adherence to GLP and QA were included.

The treatment induced no mortalities. Animals of the group at the highest dose occasionally displayed unsteady, staggering gait, intermittent buckling of the hind legs, vomiting and diarrhoea for short periods after feeding. Body weight was slightly decreased (7%) in females of the group at the highest dose. No other treatment-related effects were observed.

On the basis of clinical signs in both sexes, the NOAEL was 60 ppm, equivalent to 1.3 mg/kg bw per day (Von Keutz, 1987).

(b) Exposure by inhalation

Rats

In a dose range-finding study, groups of 10 male and 10 female Wistar rats were exposed to aerosols containing beta-cyfluthrin (purity, 98%) at actual concentrations of 0, 0.3, 3.8 or 28.0 $\mu\text{g/l}$ air by nose-only inhalation for 6 h per day for five consecutive days, followed by a 2-week recovery period. The rats were observed daily for clinical signs, but not during exposure. Body weights were assessed before testing, on days 5 and 8 and once per week thereafter. At the end of the recovery period, the rats were necropsied. Statements of adherence to GLP and QA were included.

At a concentration of 3.8 $\mu\text{g/l}$ air, transient clinical signs (unkempt fur and piloerection) were noted. Rats in the group at the highest dose still exhibited these signs in the morning before they were again exposed. During the exposure period, body-weight gain in the rats at the highest dose was reduced (7%). On the basis of the clinical signs, the NOAEC was 0.3 $\mu\text{g/l}$ air (Pauluhn, 1988b).

Groups of 10 male and 10 female Wistar rats were exposed to aerosols containing beta-cyfluthrin (purity, 97.9%) at actual concentrations of 0, 0.2, 2.7 or 23.5 $\mu\text{g/l}$ air by nose-only

inhalation for 6 h per day for five consecutive days. The rats were observed daily for clinical signs, but not during exposure. Body weights were assessed weekly. Ophthalmoscopy was performed before testing and towards the end of the study. In the last third of the study, five male rats of each group were subjected to lung function tests. Clinical chemistry, haematology and urine analysis were performed at the end of the study. At termination, the rats were necropsied, selected organs were weighed and a wide range of organs were examined histologically. At termination liver tissue was also sampled for determination of cytochrome P450, *N*-demethylase and *O*-demethylase activity and triglyceride concentrations. Statements of adherence to GLP and QA were included.

At the highest concentration, animals displayed slight to moderate clinical signs (unkempt fur, piloerection, hyperactivity or, partially, hypoactivity). At concentrations of 2.7 µg/l air and higher, body-weight gains were reduced in both sexes (7–11%). At 23.5 µg/l, air the rats had reduced absolute and relative thymus and spleen weights, and reduced leukocyte and lymphocyte counts. No other toxicologically relevant effects were observed.

On the basis of reduced body-weight gains in both sexes, the NOAEC was 0.2 µg/l air (Pauluhn, 1989c).

4.3 Genotoxicity

The results of tests for genotoxicity with beta-cyfluthrin are summarized in Table 5. The Meeting concluded that beta-cyfluthrin is unlikely to be genotoxic.

Table 5. Results of studies of genotoxicity with beta-cyfluthrin

End-point	Test object	Concentration ^a	Cyfluthrin content (%)	Results	Reference ^b
<i>In vitro</i>					
Reverse mutation	<i>S. typhimurium</i> strains TA98, TA100, TA1535 and TA1537	20–12 500 µg/plate (± S9)	98.5	Negative	Herbold (1986)
Gene mutation	CHO K1-BH4 cells, <i>Hprt</i> locus	20–100 µg/ml (± S9)	99.6	Negative	Lehn (1988)
Chromosomal aberration	Human lymphocytes	500–5 000 µl/ml (± S9)	98.8	Negative	Herbold (1988b)
Unscheduled DNA synthesis	Rat primary hepatocytes	1.01–1 010 µg/ml	99.5	Negative	Cifone (1987)
<i>In vivo</i>					
Micronucleus formation	Mouse bone marrow	80 mg/kg bw, oral	99.6	Negative	Herbold (1988c)

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

^b Statements of adherence to GLP and QA were included in all studies.

4.4 Reproductive toxicity: developmental toxicity

Rats

In a study of developmental toxicity, inseminated Wistar rats were given technical-grade beta-cyfluthrin (purity, 96.5%–97.3%) at a dose of 0, 2.7, 9.4, and 42.0 mg/kg bw per day by oral gavage on days 6 to 15 of gestation. The animals were observed daily for mortality and clinical signs. Body

weights and food consumption were recorded on days 0 (body weight only), 2, 4, 6–16, 18 and 20 of gestation. On day 20 of gestation, dams were killed and necropsied and ovaries and gravid uteri were examined. About one half the live fetuses in each litter were examined for visceral changes, the other half for skeletal effects. Statements of adherence to GLP and QA were included.

Severe maternal toxicity, including mortality, was observed in the group at the highest dose. Clinical signs included hypoactivity, locomotor incoordination, and salivation. In the group at the highest dose, body-weight gain (–55%) and food consumption were decreased. The statistically non-significant reduction in body-weight gain in females at the intermediate dose (–9%) was considered to be not biologically significant. In the group at the highest dose, a statistically significant decrease (9%) in fetal weight was observed. In these fetuses from the group at the highest dose, incompletely ossified frontal bones, sacral arches, metacarpals, and second sternbrae, unossified caudal arches, fifth sternbrae, and xiphoid and enlarged anterior fontanelle were also found, which were considered to be secondary to maternal toxicity at this dose. No other treatment-related effects on reproductive or developmental endpoints, including pre/postimplantation loss, resorptions and visceral development were observed.

On the basis of increased mortality, clinical signs, decreased body-weight gain and food consumption, the NOAEL for maternal toxicity was 9.4 mg/kg bw per day. On the basis of the reduced fetal weight and the retarded ossification of the bones, the NOAEL for embryo/fetotoxicity was 9.4 mg/kg bw per day (Astroff, 1996).

4.5 *Special studies: neurotoxicity*

Rats

Groups of 12 male and 12 female fasted Fischer 344 rats were given technical-grade beta-cyfluthrin (purity, 96.9–97.3%) as a single dose at 0, 0.5, 2 or 10 mg/kg bw by gavage. The vehicle was 1% Cremophor EL in deionized water. The rats were observed daily for clinical signs and mortality. Body weight was measured weekly. The animals were tested in a functional observational battery (FOB) and motor activity test 1 week before testing and 2 h and 7 days and 14 days after treatment. At termination on day 15, all rats were necropsied and brains were weighed. Six males and six females per dose were selected for perfusion and tissue collection. Skeletal muscle, peripheral nerves, eyes (with optic nerves) and tissues from the central nervous system of the rats in the control group and at the highest dose were examined histologically. Statements of adherence to GLP and QA were included.

No deaths occurred. Beta-cyfluthrin at a dose of 2 mg/kg bw, induced perianal staining during the first 5 days after treatment. At 10 mg/kg bw, perianal, oral and urine stains were observed. Body weight was not affected by treatment. In the FOB, 2 h after treatment, rats at the intermediate dose displayed a decreased approach response (both sexes), oral stains (males only) and a decreased activity (females only). In the group at the highest dose, rats displayed uncoordinated gait, decreased activity, flattened posture, repetitive pawing motion, decreased approach and touch responses, impaired righting, salivation and oral, urine and perianal stains. In addition, in males a decreased body temperature, writhing behaviour, decreased tail pinch response and prolapsed penis was observed while females displayed slight muscle fasciculations. Motor and locomotor activities were decreased on day 0 in males at 10 mg/kg bw and in females at 2 and 10 mg/kg bw. All signs of toxicity had resolved on day 7. No effects of treatment on brain weight, macroscopic and histological parameters were observed.

On the basis of the perianal staining and the effects in the FOB and motor activity tests, the NOAEL for beta-cyfluthrin was 0.5 mg/kg bw (Sheets et al., 1997).

Groups of 12 male and 12 female Fischer 344 rats were given diets containing beta-cyfluthrin (purity, 96.5–97.3%) at a concentration of 0, 30, 125 or 400 ppm (equal to 0, 2.0, 8.9 and 26.8 mg/kg bw per day for males and 0, 2.3, 9.4 and 30.8 mg/kg bw per day for females) for 13 weeks. The rats were checked daily for clinical signs and mortality. A detailed clinical examination was performed once per week. Body weight and food consumption were determined weekly. The animals were tested in a FOB and a test for motor activity 1 week before and 4, 8 and 13 weeks after the start of treatment. Ophthalmoscopy was performed before treatment and in week 12. After 13 weeks of treatment, all rats were killed and examined macroscopically. Six male and six females per group were selected for perfusion and tissue collection. From these rats, the brain, spinal cord, eyes, sciatic, tibial and sural nerves, gasserian ganglion, and gastrocnemius muscle were collected for histological examination. The brains of these animals were weighed. These tissues from rats in the control group and at the highest dose were examined histologically. Statements of adherence to GLP and QA were included.

No mortality occurred. Beta-cyfluthrin induced clinical signs throughout the treatment period in males at 125 ppm and in both sexes at 400 ppm. In males of the group at 125 ppm, self-induced lesions from scratching were observed. These were considered to be the consequence of paresthesias after absorption of beta-cyfluthrin through the skin. At the highest dose, clinical signs consisted of ataxia and repetitive chewing movements in males and ataxia, repetitive pawing, increased reactivity, increased activity and red nasal stains in females. Body-weight gain was reduced in males of the group at 400 ppm (–31%) and in females of the groups at 125 ppm (–21%) and 400 ppm (–39%). In these groups, food consumption was also decreased. At 400 ppm, FOB testing revealed repetitive chewing, uncoordinated gait, decreased fore- and hindlimb grip strength in both sexes, and additionally increased reactivity, a slightly exaggerated auditory response, a slight decrease in body temperature and an uncoordinated righting response in females. Motor and locomotor activities were not affected by treatment at any dietary concentration. There were no treatment-related ophthalmic findings. No effects of beta-cyfluthrin on brain weight and macroscopic or histological parameters were found.

On the basis of the decreased body-weight gain and food consumption in females of the group at 125 ppm, the NOAEL was 30 ppm, equal to 2.3 mg/kg bw per day (Sheets & Hamilton, 1997).

In a study of developmental neurotoxicity, groups of 30 mated female Wistar rats were given diets containing technical-grade beta-cyfluthrin (purity, 95.1–97.6%) at a concentration of 0, 29, 133 or 215 ppm (equal to 0, 2.4, 11.0 and 17.8 mg/kg bw per day during gestation and 0, 5.9, 25.4 and 40.9 mg/kg bw per day during lactation) from day 0 of gestation until day 21 of lactation. The dams were subjected daily to a detailed examination for clinical signs. All rats were tested in a detailed observational battery (in the home cage, during handling and in an open field) on day 6 and day 21 of gestation, while the same test was performed on 10 rats per group on day 11 and day 21 of lactation. Body weight and food consumption were assessed on days 0, 6, 13 and 20 of gestation and days 0, 4 (body weight only), 7, 14 and 21 of lactation. At postnatal day 4, litters were culled to eight pups. The pups were examined daily for clinical signs and selected pups (about 16 males and 16 females per group) were subjected to a detailed observational battery on postnatal days 4, 11, 21, 35, 45 and 60. Body temperature was assessed in the dams and selected pups on postnatal days 10, 15, 18 and 21. In the pups, body weight (from postnatal day 0) and food consumption (from postnatal day 28) were assessed weekly. In addition preputial separation or vaginal patency, motor activity (postnatal days 13, 17, 21 and 60), acoustic startle habituation (postnatal days 22, 38 and 60) learning and memory (postnatal days 22, 29, 60) were assessed. Ophthalmoscopy was performed in pups at age 7–8 weeks. Neural tissues were collected on postnatal day 21 and at study termination for microscopic examination and morphometry. Statements of adherence to GLP and QA were included.

In females at the highest dose, body-weight gain was reduced during the first week of gestation (–56%) and during the first 2 weeks of lactation (–18%). In this group food consumption was reduced (9–11%) during the second and third week of lactation. No other treatment-related effects were observed.

In the offspring, a reduced body-weight gain was found in males at the highest dose and females from postnatal days 4 to 11. Acoustic startle habituation was reduced in males at the highest dose at postnatal day 22. No treatment-related effects on the other parameters were observed.

On the basis of the reduced body-weight gain and food consumption in the dams, the NOAEL for maternal toxicity was 133 ppm, equal to 11.0 mg/kg bw per day. On the basis of the reduced body weight during lactation and the reduced startle habituation at postnatal day 22, observed in the pups at the highest dose, the NOAEL for offspring toxicity was 133 ppm. Although the reduced startle habituation in the pups was observed during or just after the lactation period, when the compound intake of the dams was higher, it could be excluded that the observed effects were the result of exposure during gestation. Therefore, the NOAEL of 133 ppm for offspring toxicity was considered to be equal to 11.0 mg/kg bw per day (Sheets & Lake, 2003).

5. Studies on metabolites

The results of studies of acute toxicity and genotoxicity are summarized in Table 6. The LD₅₀ studies were performed in fasted rats and in non-fasted mice.

Table 6. Results of studies of acute toxicity and genotoxicity with metabolites of cyfluthrin

Metabolite	Species	LD ₅₀ (mg/kg bw)		Result of <i>S.typhimurium</i> test (reverse mutation) ^f	References
		Males	Females		
3-Phenoxy-4-fluoro-benzyl alcohol	Rat	1589	1600–1800	Negative	Krötlinger (1987a); Herbold (1987a)
3-Phenoxy-4-fluoro-benzaldehyde	Rat	1248	1040	Negative	Thyssen (1981); Herbold (1985)
3-Phenoxy-4-fluorobenzoic acid	Rat	> 5000	> 5000	—	Krötlinger (1986a)
3(4'-Hydroxyphenoxy)-4-fluorobenzoic acid	Rat	> 1000	> 1000	Negative	Krötlinger (1987b); Herbold (1987b)
3-Phenoxy-4-fluorobenzoic acid amide	Rat	> 5000	> 5000	Negative	Krötlinger (1986b); Herbold (1988e)
Metabolite 1 ^a	Rat	> 2500	> 2500	Negative	Krötlinger (1986c); Herbold (1988d)
Metabolite 2 ^b	Rat	> 2500	> 2500	—	Krötlinger (1986d)
Metabolite 3 ^c	Mouse	370 ^e	—	—	Gaughan et al. (1977)
Metabolite 4 ^d	Mouse	210 ^e	—	—	Gaughan et al. (1977)

^a Metabolite 1: +,–(R,S)-α-Carboxy-[3-phenoxy-4-fluoro]benzyl-1-(R,S)-trans-3-(2',2'-dichloroethen-1'-yl)-2,2-dimethylcyclo-propanecarboxylic acid ester

^b Metabolite 2: +,–(R,S)-α-Carboxamido-[3-phenoxy-4-fluoro]benzyl-1-(R,S)-trans-3-(2,2-dichloroethen-1-yl)-2,2-dimethyl-cyclopropanecarboxylic acid ester

^c Metabolite 3: *cis*-3-(2',2'-Dichloroethen-1'-yl)-2,2-dimethyl-cyclopropanecarboxylic acid

^d Metabolite 4: *trans*-3-(2',2'-Dichloroethen-1'-yl)-2,2-dimethyl-cyclopropanecarboxylic acid

^e Administered intraperitoneally administration in 20–50 µl of methoxytriglycol to Swiss mice.

^f Salmonella/microsome test for mutagenic activity.

The metabolites of cyfluthrin studied (both confirmed and hypothetical) exhibit weak to moderate toxicity after oral administration to the rat and after intraperitoneal administration to the mouse. The data indicate that their acute toxicity is lower than that of the parent compound (see [Table 2](#)). No evidence of mutagenic potential was found for any of the metabolites studied.

Comments

Biochemical aspects

In rats, cyfluthrin is rapidly absorbed and distributed. Peak concentrations in the blood were reached after 1 or 6 h, depending on the vehicle used. About 98% of the radiolabel was eliminated in the urine and faeces within 48 h after oral administration, with an initial half-life of about 3 h. Similar amounts were eliminated after intravenous administration. The ratio of excretion in urine : faeces was higher in males (3 : 1) than in females (3 : 2). About one third of the administered dose was excreted in bile. The highest concentrations of radiolabel were found in fat, ovaries, adrenal, liver and spleen. Repeat-dosing experiments yielded similar results. In rats, the major metabolic transformation is ester hydrolysis to a 3-phenoxy-4-fluorobenzyl alcohol intermediate and a permethric acid moiety. After ester hydrolysis, the benzyl alcohol moiety is oxidized to the free 3-phenoxy-4-fluorobenzoic acid metabolite, which can either be conjugated with glycine or oxidized to give 4'-hydroxy-3-phenoxy-4-fluorobenzoic acid.

Toxicological data

The acute oral LD₅₀ values of cyfluthrin and beta-cyfluthrin in rats ranged from 11 to > 1000 mg/kg bw, depending on the vehicle used and the feeding status of the animals. The observed clinical signs (increased salivation, uncoordinated movements, increased activity and vocalization, and reduced, laboured breathing, apathy, straddle-legged gait (mostly in the rear legs), and reduced sensitivity to external stimuli) are typical of this class of pyrethroids. In rats, the inhalation LC₅₀ values ranged from 0.047 to > 1 mg/l, and the dermal LD₅₀ values were > 5000 mg/kg bw. Cyfluthrin is not irritating to the skin, is slightly irritating to the eyes and is not a skin sensitizer.

The critical end-points induced by cyfluthrin and beta-cyfluthrin are neurotoxicity and reduction in body weight.

Several short-term studies of oral toxicity with cyfluthrin were available for mice, rats and dogs. In a 4-week study in mice, the NOAEL was 300 ppm (equal to 43.1 mg/kg bw per day) on the basis of histological changes in the liver and the submaxillary gland. In one 4-week dietary study and two 3-month dietary studies, the overall NOAEL was 100 ppm (equal to 8.3 mg/kg bw per day) on the basis of a reduction in blood glucose concentration. In a 4-week gavage study, the NOAEL was 20 mg/kg bw per day on the basis of mortality, reduced body weight, increased liver and adrenal weight and clinical signs. In one 6-month study and two 12-month studies in dogs, the overall NOAEL was 200 ppm (equal to 6.5 mg/kg bw per day) on the basis of clinical signs and reductions in body-weight gain.

The effects of short-term oral exposure to beta-cyfluthrin were assessed in rats and dogs. In a 4-week gavage study in rats, the NOAEL was 1 mg/kg bw per day on the basis of clinical signs (increased motility, grooming and digging movements) at 4 mg/kg bw per day, which had already been observed on the first day of administration. In a 13-week dietary study in rats, the NOAEL was 125 ppm (equal to 9.5 mg/kg bw per day) on the basis of clinical signs, and reductions in body-weight gain, food and water consumption. In a 13-week dietary study in dogs, the NOAEL was 60 ppm (equal to 1.3 mg/kg bw per day) on the basis of clinical signs.

The dermal toxicity of cyfluthrin was assessed in 3-week studies in rats and rabbits. In rats, the NOAEL of 340 mg/kg bw per day was identified on the basis of a reduction in food consumption and clinical signs. In rabbits, no toxicologically relevant effects were observed at doses of up to and including 250 mg/kg bw per day, i.e. the highest dose tested.

In short-term studies of toxicity after inhalation of cyfluthrin and beta-cyfluthrin in rats, with a duration ranging from 5 days to 13 weeks, the overall NOAEC of 0.09 µg/l (equivalent to an inhalational dose of about 0.02 mg/kg bw per day²) was identified on the basis of reduced body-weight gain and behavioural changes. The high toxicity of cyfluthrin administered by inhalation, compared with oral exposure, was considered to be caused by the local effects of cyfluthrin on the respiratory system.

In long-term studies of toxicity and carcinogenicity, mice and rats were treated with cyfluthrin at dietary concentrations of up to 1400 and 450 ppm respectively. Statistically significant reductions in body-weight gain (> 10%), which were not related to reductions in food consumption, were consistently found in all studies. In two studies in mice, an overall NOAEL of 200 ppm, equal to 38.4 mg/kg bw per day was identified on the basis of reductions in body-weight gain in females, and macroscopic (crusty zones of the skin of the ear) and histological changes (acanthosis, chronic active inflammation, ulcer, debris of the skin of the ear) in males. The macroscopic and histological effects in the ear are likely to be due to the scratching of the skin by the animals in reaction to local paraesthesia, which is a characteristic of this class of compounds. In two studies in rats, the overall NOAEL was 150 ppm (equal to 6.2 mg/kg bw per day) on the basis of decreases in body-weight gain. The small reductions in body-weight gain (5–6%) observed at lower doses in both studies were not considered to be biologically significant. No evidence for a tumorigenic effect of cyfluthrin was found.

The Meeting concluded that cyfluthrin is not carcinogenic in rodents.

Cyfluthrin and beta-cyfluthrin gave negative results in an adequate range of tests for genotoxicity in vitro and in vivo. The Meeting concluded that cyfluthrin and beta-cyfluthrin are unlikely to be genotoxic.

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

In three multigeneration dietary studies with cyfluthrin in rats, the overall NOAEL for parental toxicity was 125 ppm (equal to 9 mg/kg bw per day) on the basis of reductions in body-weight gain at 400 ppm (equal to 29 mg/kg bw per day), and a borderline reduction in body-weight gain at 150 ppm (equal to 11.4 mg/kg bw per day). The overall NOAEL for offspring toxicity was 50 ppm (equal to 7 mg/kg bw per day) on the basis of coarse tremors in pups during lactation. The overall NOAEL for reproductive effects was 450 ppm, equal to 34.7 mg/kg bw per day, the highest dose tested.

The effect of oral exposure to cyfluthrin on prenatal development was investigated in rats and rabbits. In two studies of developmental toxicity in rats treated by gavage, the overall NOAEL for maternal toxicity was 3 mg/kg bw per day on the basis of clinical signs. The overall NOAEL for fetal toxicity was 30 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 and embryo/fetotoxicity was 15 mg/kg bw per day, on the basis of two abortions and one case of complete resorption in the group of 15 dams treated with cyfluthrin at a dose of 45 mg/kg bw per day. In a second study in rabbits, the NOAEL for maternal toxicity was 20 mg/kg bw per day on the basis of reduced food consumption and body-weight gain. The NOAEL for fetotoxicity was 20 mg/kg bw per day on the basis of increased post-implantation loss.

² Exposure was 6 h per day. Twenty-four hour respiratory volume for rats is 0.96 ml/kg bw (Zielhuis & Van der Kreek, 1979).

The increased incidence of malformations observed in a study of developmental toxicity in rats treated with cyfluthrin by inhalation was considered to be secondary to effects on pulmonary function.

In a study of developmental toxicity in rats treated with beta-cyfluthrin by gavage, the NOAEL for maternal toxicity was 9.4 mg/kg bw per day on the basis of a reduction in body-weight gain, clinical signs and mortality. The NOAEL for embryo/fetotoxicity was 9.4 mg/kg bw per day on the basis of reduced fetal weight and retarded ossification.

Cyfluthrin did not cause delayed neurotoxicity in hens. In a study of acute neurotoxicity in rats treated by gavage, the NOAEL was 1 mg/kg bw per day on the basis of mild clinical signs of toxicity (shaking) observed in one and two animals at 2.5 and 3 mg/kg bw, respectively. A range of additional studies of neurotoxicity with repeated high doses of cyfluthrin (30–80 mg/kg bw per day) administered by gavage also demonstrated clinical signs of (neuro-) toxicity, including disturbed gait, salivation, tremor and apathy.

Occasionally, in some of the short-term studies of toxicity and studies of neurotoxicity in rats, marked acute toxicity induced by high doses of cyfluthrin was accompanied by limited swelling and fragmentation of myelin, which was reversed within 1–3 months after cessation of treatment. The Meeting concluded that cyfluthrin does not cause irreversible neurological damage.

The (developmental) neurotoxicity of beta-cyfluthrin was investigated in rats. In a study in which single doses were administered by gavage, the NOAEL was 0.5 mg/kg bw per day on the basis of perianal staining, effects in the functional observational battery (decreased approach response in both sexes, oral staining in males and a decreased activity in females) and decreased motor and locomotor activities in females. In a 13-week dietary study, the NOAEL was 30 ppm (equal to 2.3 mg/kg bw per day) on the basis of reductions in body-weight gain and food consumption in females.

In a study of developmental neurotoxicity in rats, the NOAEL for maternal toxicity was 133 ppm (equal to 11 mg/kg bw per day) on the basis of reduced body weight and food consumption. The NOAEL for offspring toxicity was 133 ppm (equal to 11 mg/kg bw per day) on the basis of reduced body-weight gain during lactation and reduced startle habituation at postnatal day 22.

A number of pharmacological studies with cyfluthrin were considered not to be useful for the purpose of dietary risk assessment.

A limited number of studies of acute toxicity and genotoxicity with some metabolites³ of cyfluthrin were performed. The acute toxicity of the metabolites studied was lower than that of the parent compound. No evidence of mutagenic potential was found for any of the metabolites investigated.

Cyfluthrin caused a topical skin effect, characterized by a stinging sensation in the affected areas in laboratory workers. The areas most commonly affected were the face and mucosal tissues. Annual medical examinations of factory workers revealed no effects on body weights, haematological and urine analysis parameters, ALT and GGT activities and thoracic organs, as examined by X-rays.

³ Metabolite 1: +, -(R,S)- α -Carboxy-[3-phenoxy-4-fluoro]benzyl-1-(R,S)-*trans*-3-(2',2'-dichloroethen-1'-yl)-2,2-dimethylcyclo-propanecarboxylic acid ester

Metabolite 2: +, -(R,S)- α -Carboxamido-[3-phenoxy-4-fluoro]benzyl-1-(R,S)-*trans*-3-(2,2-dichloroethen-1-yl)-2,2-dimethyl-cyclopropanecarboxylic acid ester

Metabolite 3: *cis*-3-(2',2'-Dichloroethen-1'-yl)-2,2-dimethyl-cyclopropanecarboxylic acid

Metabolite 4: *trans*-3-(2',2'-Dichloroethen-1'-yl)-2,2-dimethyl-cyclopropanecarboxylic acid

The Meeting concluded that the present database was adequate to characterize the potential hazard of cyfluthrin and beta-cyfluthrin to fetuses, infants and children.

Evaluation of the available data showed that the toxicological profiles of cyfluthrin and beta-cyfluthrin appeared to be qualitatively similar. With respect to neurotoxicity, beta-cyfluthrin, being the biologically active component of cyfluthrin, was more potent than cyfluthrin. The Meeting concluded that the database for cyfluthrin was adequate to apply to beta-cyfluthrin. Therefore no additional studies on beta-cyfluthrin were necessary.

Toxicological evaluation

The Meeting considered establishing a group ADI of 0–0.06 mg/kg bw on the basis of an overall NOAEL of 6.2 mg/kg bw per day for reductions in body-weight gain observed in a 2-year dietary study with cyfluthrin in rats, and using a safety factor of 100. The overall LOAEL for this effect was 9.4 mg/kg bw per day, observed in a 13-week dietary study with beta-cyfluthrin in rats. Since the mode of action for reduction in body-weight gain was unknown, the Meeting considered it appropriate to apply the default 100-fold safety factor for this end-point. This was considered to be adequately protective against the neurotoxic effects of beta-cyfluthrin in dietary studies.

The Meeting established a group ARfD for cyfluthrin and beta-cyfluthrin of 0.04 mg/kg bw based on a NOAEL of 1 mg/kg bw for findings of acute neurotoxicity observed in a 4-week study with beta-cyfluthrin administered by gavage, and using a safety factor of 25. This overall NOAEL was supported by the NOAEL of 0.5 mg/kg bw identified on the basis of slight neurotoxic effects at 2 mg/kg bw in a study of neurotoxicity in rats given single doses of beta-cyfluthrin by gavage, and the NOAEL of 1 mg/kg bw identified on the basis of slight clinical effects at 2.5 mg/kg bw in a study in rats given single doses of cyfluthrin by gavage. Furthermore, this overall NOAEL is in line with the threshold dose of 0.9 mg/kg bw for acute effects of beta-cyfluthrin on motor activity (Wolansky et al., 2006). Since the neurotoxicity induced by (beta-) cyfluthrin is dependent on the C_{max} and is reversible, the Meeting considered it appropriate to apply a chemical-specific adjustment factor of 25 for this end-point.

The Meeting noted that the proposed ADI based on body-weight effects in studies with repeated doses was higher than the ARfD. Therefore, the ADI was established at 0–0.04 mg/kg bw, i.e. the same value as the ARfD.

Levels relevant for risk assessment

(a) Cyfluthrin

Species	Study	Effect	NOAEL	LOAEL
Rat	Two-year study of toxicity and carcinogenicity ^a	Toxicity	150 ppm, equal to 6.2 mg/kg bw per day	450 ppm, equal to 19.2 mg/kg bw per day ^c
		Carcinogenicity	450 ppm, equal to 19.2 mg/kg bw per day ^c	
	Two-generation study of reproductive toxicity ^a	Parental	50 ppm, equal to 3.8 mg/kg bw per day	150 ppm, equal to 11.4 mg/kg bw per day ^d

		Offspring toxicity	50 ppm, equal to 5.1 mg/kg bw per day	150 ppm, equal to 14.0 mg/kg bw per day
		Reproductive toxicity	450 ppm, equal to 34.7 mg/kg bw per day ^c	— ^c
	Two-generation study of reproductive toxicity ^a	Parental	125 ppm, equal to 9 mg/kg bw per day	400 ppm, equal to 29 mg/kg bw per day
		Offspring toxicity	50 ppm, equal to 7 mg/kg bw per day	150 ppm, equal to 19 mg/kg bw per day
		Reproductive toxicity	400 ppm, equal to 29 mg/kg bw per day ^c	— ^c
	Developmental toxicity ^b	Maternal toxicity	10 mg/kg bw per day	— ^c
		Fetotoxicity	10 mg/kg bw per day	— ^c
	Acute neurotoxicity ^b	Neurotoxicity	1 mg/kg bw	2.5 mg/kg bw
Dog	6-month study of toxicity ^a	Toxicity	200 ppm, equal to 6.5 mg/kg bw per day	600 ppm, equal to 19.9 mg/kg bw per day

^a Dietary administration.

^b Gavage administration.

^c Highest dose tested.

^d Actual NOAEL is likely higher given that the effects were borderline at the LOAEL.

(b) Beta-cyfluthrin

Species	Study	Effect	NOAEL	LOAEL
Rat	4-week study of toxicity ^b	Toxicity	1 mg/kg bw per day	4 mg/kg bw per day
	Developmental toxicity ^b	Maternal toxicity	9.4 mg/kg bw per day	42 mg/kg bw per day
		Fetotoxicity	9.4 mg/kg bw per day	42 mg/kg bw per day
	Acute neurotoxicity ^b	Neurotoxicity	0.5 mg/kg bw	2 mg/kg bw
	13-week study of neurotoxicity ^a	Neurotoxicity	30 ppm, equal to 2.3 mg/kg bw per day	125 ppm, equal to 9.4 mg/kg bw per day
	Developmental neurotoxicity ^a	Maternal toxicity	133 ppm, equal to 11 mg/kg bw per day	215 ppm, equal to 17.8 mg/kg bw per day
		Fetotoxicity	133 ppm, equal to 11 mg/kg bw per day	215 ppm, equal to 17.8 mg/kg bw per day
Dog	3-month study of toxicity ^a	Toxicity	60 ppm, equal to 1.3 mg/kg bw per day	360 ppm, equal to 9 mg/kg bw per day

^a Dietary administration.

^b Gavage administration.

^c Highest dose tested.

Estimate of acceptable daily intake for humans

0–0.04 mg/kg bw

Estimate of acute reference dose

0.04 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 cyfluthrin or beta-cyfluthrin

<i>Absorption, distribution, excretion and metabolism in animals</i>	
Rate and extent of absorption	Rapid and extensive (rats)
Distribution	Highest concentrations in liver, kidney, adrenals, spleen (rats)
Potential for accumulation	Low
Rate and extent of excretion	Rapid (75–91% in urine within 24 h in rats)
Metabolism in animals	Major metabolites: 3-(2,2-dichlorovinyl)-2,2-dimethylcyclopropane carboxylic acid (DCVA), 3-phenoxy-4-fluorobenzoic acid, 4'-hydroxy-3-phenoxy-4-fluorobenzoic acid (rats)
Toxicologically significant compounds (plants, animals and the environment)	Cyfluthrin, beta-cyfluthrin

<i>Acute toxicity</i>	
Rat, LD ₅₀ , oral	11 to > 1000 mg/kg bw
Rat, LD ₅₀ , dermal	> 5000 mg/kg bw
Rat, LC ₅₀ , inhalation	0.081 to > 1.0 mg/l of air
Rabbit, skin irritation	Not an irritant
Rabbit, eye irritation	Slightly irritating
Guinea-pig, skin sensitization	Not sensitizing (maximization test)

<i>Short-term studies of toxicity</i>	
Target/critical effect	Reduced body weight, clinical signs (rats, dogs)
Lowest relevant oral NOAEL	1 mg/kg bw per day (beta-cyfluthrin, rats) 60 ppm, equal to 1.3 mg/kg bw per day (beta-cyfluthrin, dogs)
Lowest relevant dermal NOAEL	340 mg/kg bw per day (cyfluthrin, rats)
Lowest relevant inhalatory NOAEC	0.09 µg/l (cyfluthrin, rats)

<i>Long-term studies of toxicity and carcinogenicity</i>	
Target/critical effect	Reduced body weight (rats)
Lowest relevant NOAEL	150 ppm, equal to 6.2 mg/kg bw per day (cyfluthrin, rats)
Carcinogenicity	Not carcinogenic (mice, rats)

<i>Genotoxicity</i>	
	Not genotoxic in vitro or in vivo

<i>Reproductive toxicity</i>	
Reproduction target/critical effect	No reproductive effects (rats)
Lowest relevant reproductive NOAEL	450 ppm, equal to 34.7 mg/kg bw per day, i.e. highest dose tested (cyfluthrin, rats)

Developmental target	delayed ossification (rats); increased post-implantation loss (rabbits)
Lowest relevant developmental NOAEL	9.4 mg/kg bw per day (beta-cyfluthrin, rats)
<i>Neurotoxicity/delayed neurotoxicity</i>	
Neurotoxicity	Behavioural effects (increased motility, grooming and digging movements)
Lowest relevant oral NOAEL	1 mg/kg bw (single and repeated dose by gavage, beta-cyfluthrin and cyfluthrin, rats)
<i>Other toxicological studies</i>	
	No data
<i>Medical data</i>	
	Topical skin effect, characterized by a stinging sensation in the affected areas in laboratory workers. Areas most commonly affected were the face, and mucosal tissues.

Summary for cyfluthrin and beta-cyfluthrin

	Value	Study	Safety factor
Group ADI	0–0.04 mg/kg bw	Based on the ARfD	25
Group ARfD	0.04 mg/kg bw	Rat, acute neurotoxicity, beta-cyfluthrin	25

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