

CYPERMETHRIN (INCLUDING ALPHA- AND ZETA-CYPERMETHRIN)

*First draft prepared by
U. Mueller,¹ L. Lenton¹ & David Ray²*

¹ *Office of Chemical Safety, Therapeutic Goods Administration, Canberra, ACT, Australia*

² *Medical Research Council Applied Neuroscience Group, Biomedical Sciences,
University of Nottingham, Queens Medical Centre, Nottingham, England*

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Explanation

Cypermethrin is the International Organization of Standardization (ISO) approved common name for (*RS*)- α -cyano-3-phenoxybenzyl (1*RS*,3*RS*;1*RS*,3*SR*)-3-(2,2-dichlorovinyl)-2,2-dimethylcyclopropanecarboxylate. Cypermethrin is a synthetic pyrethroid insecticide containing three chiral centres, giving a racemic mixture of eight isomers comprising four diastereoisomeric pairs. The cypermethrins are alpha-cyano- or type II pyrethroids. Cypermethrin was first evaluated by the 1979 JMPR, when a temporary acceptable daily intake (ADI) was established. New toxicological data were evaluated by the 1981 JMPR and an ADI of 0–0.05 mg/kg bw per day was established. Cypermethrin was reviewed by the present Meeting within the periodic review programme of the Codex Committee on Pesticide Residues (CCPR); this review included alpha-cypermethrin and zeta-cypermethrin, which had not previously been considered by the JMPR.

Cypermethrin and alpha-cypermethrin were considered by the Joint FAO/WHO Expert Committee on Food Additives (JECFA) in 1996 and in 2002. In 2002, JECFA established a group ADI of 0–0.02 mg/kg bw, and recommended that JMPR should also consider this approach. The studies submitted to JECFA were available for consideration by the JMPR at its present meeting. Several studies on cypermethrin that were reviewed by JMPR in 1979 and 1981 were not available at the present meeting, but were considered in this evaluation on the basis of the JMPR summaries. The 2006 JMPR was made aware of a study of developmental neurotoxicity with zeta-cypermethrin that had not been submitted before the present meeting. This study was submitted during the meeting, but was not evaluated in detail; however, based on a brief review, the Meeting concluded that this study was not critical for its final conclusion.

For alpha-cypermethrin, 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: alpha-cypermethrin* (2006).¹

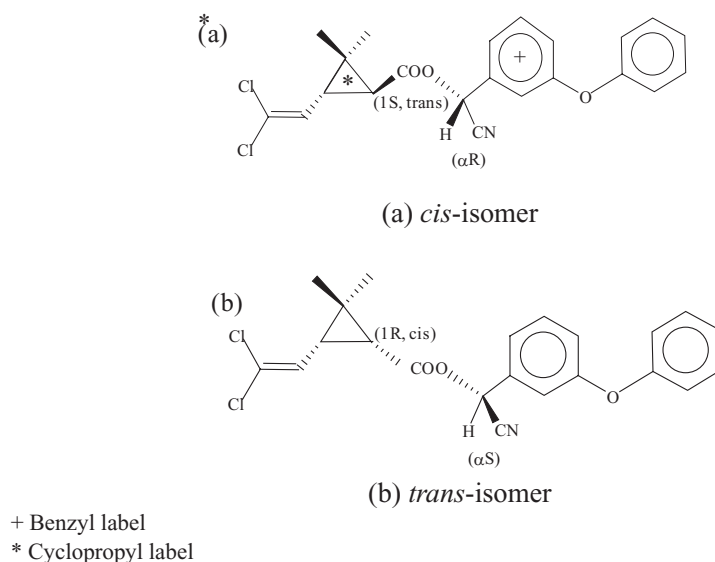
Most studies, excluding those described in previous JMPR monographs, were certified as having been performed in compliance with good laboratory practice (GLP) and in accordance with the relevant Organisation for Economic Co-operation and Development (OECD) test guidelines.

Pyrethroids are typically grouped into two general classes, called type I and type II, on the basis of a combination of toxicological and physical properties. Type II pyrethroids, such as cypermethrin, are those with a cyano group and are characterized by their ability to elicit sinuous writhing (choreoathetosis) and salivation in mammals. A common mode of action has been proposed for pyrethroids, on the basis of in-vitro studies; this includes alterations in the dynamics of sodium channels in tissues of the nervous system, consequent disturbance of membrane polarization, and abnormal discharge in targeted neurons.

As shown in Figure 1, the three chiral centres of cypermethrin are located at carbon positions 1 and 3 of the cyclopropane ring, and at the benzyl α -carbon. The *cis*- and *trans*-configurations each refer to two diastereoisomeric pairs in which the C-1 carboxyl group and the C-3 dichlorovinyl group are on the same, or opposite sides of the cyclopropane ring, respectively. The technical products commonly available contain more than 90% cypermethrin and the ratio of *cis*- to *trans*-isomers varies from 50 : 50 to 40 : 60.

Alpha-cypermethrin contains the most insecticidally active enantiomer pair of the four *cis*-isomers of cypermethrin as a racemic mixture comprising (*R*)- α -cyano-3-phenoxybenzyl (1*S*,3*S*)-3-(2,2-dichlorovinyl)-2,2-dimethylcyclopropanecarboxylate and (*S*)- α -cyano-3-phenoxybenzyl (1*R*,3*R*)-3-(2,2-dichlorovinyl)-2,2-dimethylcyclopropanecarboxylate (1*R*-*cis*-*S* and 1*S*-*cis*-*R*). In contrast, zeta-cypermethrin is a mixture of the stereoisomers (*S*)- α -cyano-3-phenoxybenzyl (1*R*,3*RS*;1*RS*,3*SR*)-3-(2,2-dichlorovinyl)-2,2-dimethyl cyclopropanecarboxylate, where the ratio of the (*S*);(1*RS*,3*RS*) isomeric pair to the (*S*);(1*RS*,3*SR*) isomeric pair lies in the range of 45–55 to 55–45 respectively.

Figure 1. Examples of *cis*- and *trans*- isomers of cypermethrin, also showing positions of radiolabels



¹ Available from http://www.who.int/whopes/quality/en/Alphacypermethrin_eval_april_2006.pdf

Evaluation for acceptable daily intake

Unless otherwise stated, the studies reported in this monograph, excluding those assessed in previous JMPR monographs, were certified as having been performed in compliance with good laboratory practice and in accordance with the relevant OECD test guidelines.

Cypermethrin

1. Biochemical aspects

1.1 Absorption, distribution and excretion

Mice

Groups of male mice were given the *cis*- or *trans*-isomers of cypermethrin dissolved in methoxytriglycol as a single oral dose at 7 mg/kg bw as [¹⁴C-cyclopropyl]cypermethrin or 8 mg/kg bw as [¹⁴C-benzyl]cypermethrin. Results suggest that the proportion of cypermethrin that was readily absorbed after oral dosing was rapidly eliminated in the urine in mice. Absorption from the gastrointestinal tract was more rapid with the *trans*-isomer than with the *cis*-isomer as shown by relatively high concentrations of radioactivity for the *cis*-isomers in the faeces within the first few days of the study. The rate of urinary excretion of cypermethrin isomers labelled in acid or alcohol portions of the molecule was very similar, with most of the radioactivity eliminated from the body within 3 days. Tissue residues after 3 days were low. Adipose tissue was found to retain small quantities of radioactivity in concentrations higher than those noted for most other tissues (Annex 1, references 32, 33; Hutson, 1978a).

To evaluate the elimination of cypermethrin and its metabolites from animal tissues after oral administration, groups of male mice were given cypermethrin at doses approximating 9 mg/kg bw as [¹⁴C-benzyl]cypermethrin. In contrast to data from other tissues, the rate of elimination of cypermethrin from adipose tissue of mice was relatively slow, with a half-life of approximately 10–20 days. Unchanged *cis*-cypermethrin was the only chemical residue identified in adipose tissue. There was little change in the residue during the last half of the 42-day trial after the relatively rapid elimination during the first 3 weeks, suggesting possible long-term storage and build up of residue in adipose tissue (Annex 1, references 32, 33; Crawford & Hutson, 1978a).

Rats

Groups of six male and six female Wistar rats were given cypermethrin (¹⁴C-benzyl, *cis*-isomer; radiochemical purity, 99.5%) in corn oil as a single oral dose at 2.4 mg/kg bw for females and 1.8 mg/kg bw for males. Animals and tissues were monitored for 8 days, with two animals of each sex being sacrificed at 24 h, 3 days and 8 days after dosing. Excretion was rapid for both sexes. There was a significant sex difference in the rate of excretion, with male rats excreting a substantially larger portion of the radioactivity in the urine (53%) than females (35%) over the first 24 h, with 19% and 35% of administered radioactivity excreted in the faeces of males and females, respectively, over this period. However, approximately 90% of administered radioactivity was excreted within 48 h in both sexes, with no substantial differences in the overall rate of elimination by males and females when data were evaluated over the total 8-day period of the test. The residues of radioactivity in the tissues of both males and females sacrificed at various periods over the 8 days showed a small residue in a variety of tissues. While the radioactivity in blood, liver, kidney, muscle and brain was rapidly

depleted over the test interval, concentrations of cypermethrin in adipose tissue were relatively stable over the 8 days (Annex 1, reference 33; Crawford, 1976a).

Groups of three male and three female Wistar rats were given cypermethrin (^{14}C -benzyl, *trans*-isomer) as a single oral dose at 2.4 mg/kg bw for males and 3.0 mg/kg bw for females in corn oil. Again, excretion was rapid in both sexes, with approximately 95% of the administered dose excreted within 48 h. In contrast to the *cis*-isomer, there appeared to be no sex differences in the routes of elimination of the *trans*-isomer. Residues in adipose tissue of females were two to three times higher than in the adipose tissue of males. However, residues in the tissues were lower than after dosing with the *cis*-isomer (Annex 1, reference 33; Crawford, 1976a). Concentrations in adipose tissue were approximately half those achieved after similar treatment with the *cis*-isomer, suggesting that the *trans*-isomer is metabolized faster than the *cis*-isomer. A low level of administered radioactivity (0.04%) was detected in expired air (Annex 1, reference 33; Crawford, 1976b).

Groups of three male and three female Wistar rats were given cypermethrin (1 : 1 *cis* : *trans*-isomer ratio, ^{14}C -cyclopropyl, in corn oil) as a single oral dose at a dose of 1 mg/kg bw for males and 2 mg/kg bw for females. The rats were killed after 3 days, and concentrations of radioactivity determined in selected tissues. Rapid elimination of cypermethrin was observed, with a substantial difference noted in 24-h urinary excretion in males and females. Females excreted considerably more radioactivity in the urine (55% of administered radioactivity) over the first 24 h relative to males (32%). After 72 h, total urinary and faecal excretion in both sexes was approximately the same. Small quantities of radioactivity were expired as $^{14}\text{CO}_2$ (approximately 0.1% of administered radioactivity), which suggested some metabolic breakdown of the cyclopropyl ring. After 3 days, tissue concentrations in liver, kidney, muscle, brain, blood, skin and remaining carcass were low, but concentrations of radioactivity in the livers of males was approximately threefold that in females, and radioactivity in adipose tissue of females was approximately twice that found in males. Radioactivity in the intestines was approximately three times higher in males than in females, averaging 9% of the administered dose. Otherwise, the highest residual radioactivity was in fat, but this was less than 1% of the administered radioactivity (Annex 1, reference 33; Crawford, 1977).

Administration of [^{14}C -benzyl]cypermethrin (*cis*-isomer) as a single oral dose at approximately 2.5 mg/kg bw to eight female Wistar rats resulted in a residue of approximately 0.3 ppm in the fat after 8 days. Further studies to 42 days after dosing were performed to evaluate the half-life of the *cis*-isomer in fat and the total elimination pattern. At the end of 42 days, residues were observed in fat which were approximately 10% of the concentrations noted at 8 days. There was a 90% loss of the material from fat over the 8–42 day interval during which timed samples were taken. From these data with rats, a half-life of approximately 20–25 days was estimated with respect to removal of residues from fat after a single oral dose. These half-life values were somewhat longer than those noted with mice (Annex 1, reference 33; Crawford & Hutson, 1978b).

The fate of orally administered *cis*- and *trans*-isomers of cypermethrin was studied in rats given radiolabelled cypermethrin as one of three forms, i.e. ^{14}C -benzyl; ^{14}C -cyclopropyl and ^{14}C -cyano at doses of 1 to 5 mg/kg bw. Radioactivity derived from the ^{14}C -benzyl and ^{14}C -cyclopropyl labelling was rapidly eliminated, mostly in the urine. Tissue residues were generally very low, e.g. 0.01 $\mu\text{g/g}$ in brain, with the exception of fat (about 1 $\mu\text{g/g}$). Residues derived from the *cis*-isomer tended to be higher than those derived from the *trans*-isomer. The rate of depletion of the residues derived from [^{14}C -benzyl]*cis*-cypermethrin was rapid ($t_{1/2}$, less than about 1 day) from all tissues except fat ($t_{1/2}$, 11–12 days). This residue consisted largely of unchanged *cis*-cypermethrin. The rapid elimination of cypermethrin from rats is due primarily to the efficient cleavage of the ester bond giving rise to

polar metabolites, which are further oxidized and conjugated before excretion (Annex 1, reference 37; Crawford et al., 1981).

The kinetics of cypermethrin in the blood of groups of five to seven male and female Wistar rats given ^{14}C -benzyl- or ^{14}C -cyclopropyl-labelled cypermethrin (50 : 50 of *cis* : *trans*) as single oral doses at 2 mg/kg bw or 200 mg/kg bw were described in two studies. At the lowest dose (2 mg/kg bw), the half-lives for the elimination of radioactivity from the blood of rats given an oral dose of ^{14}C -labelled cypermethrin were: ^{14}C -benzyl label: males, 2.78 h; females 4.36 h; and ^{14}C -cyclopropyl label: males, 4.3 h; females, 4.74 h. The mean peak blood concentrations of cypermethrin equivalents derived from the benzyl label were 1.8 and 1.4 $\mu\text{g/ml}$ at about 3 h after dosing for male and female rats respectively. The equivalent figures for the cyclopropyl label were 0.7 and 0.6 $\mu\text{g/ml}$ at about 3 and 3–4 h after dosing, respectively. This difference could be attributed to a rapid clearance of the cyclopropyl-labelled chemical from the body or to interanimal variation. The mean peak plasma concentrations of benzyl-labelled cypermethrin were 0.19 and 0.18 $\mu\text{g/ml}$ for male and female rats respectively. The equivalent figures for the cyclopropyl label were 0.04 and 0.02 $\mu\text{g/ml}$. The difference between the two studies can only be accounted for by interanimal variation with respect to the absorption of cypermethrin.

In studies using the highest dose of 200 mg/kg bw (50 : 50 of *cis* : *trans*), there was a high degree of interanimal variation. Each animal behaved differently from the others, both with respect to the toxic effect of the compound and to the amount of labelled chemical in the blood at any given time. The mean peak blood concentrations of cypermethrin equivalents from the benzyl label were 41.9 and 39.7 $\mu\text{g/ml}$ at about 16 and 23 h after dosing for female and male rats, respectively. The equivalent figures for the cyclopropyl label were 6.7 and 10.3 $\mu\text{g/ml}$ blood at about 8 and 24 h, respectively. The peak plasma concentration of cypermethrin equivalents for the cyclopropyl label for female rats, however, occurred at 24 h and not at 8 h after dosing. The mean peak plasma concentration of cypermethrin for the benzyl label was 5.4 $\mu\text{g/ml}$ for both male and female rats. The equivalent figures for the cyclopropyl label were 0.43 and 0.42 $\mu\text{g/ml}$ for male and female rats respectively (Annex 1, reference 37; Climie, 1980).

The elimination of radioactivity after a high (200 mg/kg bw) single oral dose of either ^{14}C -benzyl- or ^{14}C -cyclopropyl-labelled cypermethrin (50 : 50 of *cis* : *trans*; purity, > 99%) was studied in groups of male and female rats. The purity of the unlabelled cypermethrin used was 98.4% (also 50 : 50 *cis* : *trans*). The overall excretion of cypermethrin and its metabolites was very rapid, with more than 75% and 85% of the administered dose in the case of males and females, respectively, being eliminated within 3 days. The residues in the tissues at 7 days were low with, on average, less than 1% of the total dose being retained in the whole body. The residues in fat were the highest of all tissues (21 to 14 $\mu\text{g/g}$), but they were considerably less than 100 times more than the residues found in fat when rats were dosed at about 2 mg/kg bw (Crawford, 1977), suggesting that an appreciable portion of the dose was not absorbed. The presence of a large proportion of the dose as untransformed cypermethrin in the faeces, 26–51%, is a further indication of the poor absorption of this insecticide at this dose (Annex 1, reference 37; Logan, 1980).

The bioaccumulation of radioactivity was investigated in rats given ^{14}C -benzyl-labelled cypermethrin (50 : 50 of *cis* : *trans*) as 28 consecutive daily oral doses at 2 mg/kg bw per day. Twenty-four hours after the 28th daily dose, the tissue distribution of radioactivity was similar in males and females. The highest mean concentrations of radioactivity were found in fat (4100 and 5100 ng equivalents of ^{14}C -cypermethrin/g tissue in males and females respectively), skin (636 and 712 ng equivalents/g of tissue), gastrointestinal tract (547 and 578 ng equivalents/g tissue), liver (566 and 672 ng equivalents/g tissue), kidney (495 and 535 ng equivalents/g tissue), adrenal glands (913 and 665 ng equivalents/g tissue) and ovaries (710 ng equivalents/g tissue). Low mean concentrations were found

in the heart (67.6 and 88.7 ng equivalents/g tissue in males and females respectively), spleen (64.2 and 63.6 ng equivalents/g tissue), muscle (35.2 and 51.7 ng equivalents/g tissue) and bone (72.8 and 44.4 ng equivalents/g tissue). There was no detectable radioactivity in the brain of female rats and only a very low concentration was detected in brains in males (mean, 13.4 ng equivalents/g tissue). Of the individual organs examined, the highest residual radioactivity was found in the gastrointestinal tract (mean, 6405 ng equivalents), liver (mean, 5820 ng equivalents) and kidney (mean, 795 ng equivalents). The high concentration of radioactivity found in fat, skin, ovaries and adrenal glands is consistent with the lipophilic nature of cypermethrin. The pyrethroid group of insecticides is known to undergo extensive metabolism in mammals (Casida & Ruza, 1980), resulting in metabolites of a less lipophilic nature that will therefore be more rapidly excreted than the parent compound. The accumulation of radioactivity in the liver and kidney found in this study was consistent with these processes of metabolism and excretion. High concentrations of radioactivity were also found in the gastrointestinal tract, reflecting its role in absorption. Less radioactivity was accumulated in the remaining tissues studied, the lowest concentrations being located in the brain (Annex 1, reference 37; Hall et al., 1980).

A study of bioaccumulation was undertaken to establish the rate and extent of accumulation of cypermethrin-derived ^{14}C label in a selected range of tissues during a daily oral dosing regime and also the rate of elimination of ^{14}C residues after the attainment of steady-state tissue concentrations. Sixty female rats were dosed orally with ^{14}C -benzyl-labelled cypermethrin (50 : 50 of *cis* : *trans*), at a dose of 2 mg/kg (2 $\mu\text{Ci/kg}$) bw in maize oil (2 ml/kg bw) for up to 70 consecutive days. A group of treated (three) and untreated (one) animals was sacrificed at prescribed intervals during the dosing regime in order to monitor the rate and extent of bioaccumulation of ^{14}C in liver, kidney, adipose tissue, blood (whole blood and plasma), skin and ovaries. The elimination of radioactivity from fat demonstrated biphasic characteristics. This was associated with a rapid elimination of residues of *trans*-cypermethrin coupled with a slower elimination of the *cis*-isomer. These elimination characteristics did not allow a simple half-life value to be calculated for elimination of radioactivity from fat. However, as the relative proportions of *cis*- and *trans*-isomers in fat were monitored from day 70 of the study, it was possible to determine the independent half-lives for both isomers. At the termination of dosing, the relative proportions of *cis*- and *trans*-isomers in fat were 88.25% to 11.75%. The half-lives of elimination of *cis*- and *trans*-cypermethrin from fat were calculated by linear regression analysis to be 18.24 and 3.43 days respectively.

After daily dosing for 70 consecutive days, the extent of bioaccumulation of radioactivity in each tissue analysed was shown to reach a plateau. The extent of accumulation, expressed as μg equivalents of cypermethrin per gram of tissue (as mean $\pm$ standard deviation [SD] values from a group of three rats), was: liver, 0.97 ± 0.31 ; kidneys, 0.65 ± 0.24 ; fat, 3.91 ± 0.25 ; blood, 0.35 ± 0.13 ; plasma, 0.64 ± 0.28 ; skin, 1.86 ± 0.14 ; and for each ovary, 0.03 ± 0.01 μg equivalents. Such concentrations of radioactivity in ovaries were similar to background values. In addition, the degree of accumulation of ^{14}C -label in the sciatic nerve was determined by analysing nerves isolated from treated animals given cypermethrin as 56 to 70 daily doses. The extent of accumulation of radioactivity did not exceed 0.05 μg equivalents of cypermethrin per nerve, representing a level of radioactivity similar to the background value. After the termination of dosing, the remaining groups of treated and untreated rats were sacrificed at prescribed intervals for 50 days. Tissue residue concentrations of radioactivity were monitored and the rate of elimination of ^{14}C -label from each tissue was determined. After the cessation of dosing, the liver, kidney and blood ^{14}C -residue concentrations fell rapidly and reached control background levels within 29, 8 and 15 days respectively. With regard to skin, a much slower elimination of radioactivity was observed, with half of the radioactivity being eliminated by 18.7 days after dosing (Annex 1, reference 37; Jones, 1981).

Male and female Wistar rats were given oral doses of ^{14}C -benzyl cypermethrin or ^{14}C -cyclopropyl cypermethrin in corn oil as a single dose of 200 mg/kg bw or repeated doses of 2 mg/kg bw per day

for up to 70 days. Signs typical of pyrethroid toxicity were observed in rats dosed with 200 mg/kg bw, comprising salivation, hunched back, splayed gait, ataxia, convulsions and hypersensitivity, with the usual time of onset 1.5–2 h after dosing. At 200 mg/kg bw, minimal amounts of $^{14}\text{CO}_2$ were detected in the expired air. For males/females treated with 200 mg/kg bw cypermethrin, recovery of administered radioactivity in the urine and faeces, respectively, was 29/33% and 55/59% for the ^{14}C -benzyl label, and 41/56% and 46/34% for the ^{14}C -cyclopropyl label, suggesting that 29–56% of the dose was absorbed in most instances, as most of the ^{14}C in the faeces was present as unchanged cypermethrin. Less than 1% of the administered radioactivity remained in the animals 7 days after dosing. The distribution of radioactivity in the tissues was similar at 7 days after a single dose of 200 mg/kg bw cypermethrin labelled at either position, and 24 h after 28 daily doses of 2 mg/kg bw per day ^{14}C -benzyl-labelled cypermethrin, and was also similar in males and females. The highest concentrations of radioactivity occurred in fat, followed by skin, liver, and kidney, with the concentrations in female gonads also relatively high after either treatment regime, and in the adrenals after repeated dosing at 2 mg/kg bw per day. Seven days after the single dose of ^{14}C -cyclopropyl cypermethrin at 200 mg/kg bw, radioactivity in the liver and intestines of males was approximately three times that of females, and an extremely high level in the spleens of males was not explained (not determined in other groups). In a study of bioaccumulation and elimination in female rats dosed with ^{14}C -benzyl cypermethrin at 2 mg/kg bw per day, radioactivity accumulated rapidly in the liver, kidney, fat, blood, skin and ovaries in the first week of dosing, followed by a slow increase that continued throughout the next 9 weeks of treatment. The concentrations of radioactivity in the plasma, liver and kidneys approximately doubled between 4 and 10 weeks of treatment, but concentrations in fat and skin did not change markedly in this interval (Rhodes et al., 1984).

The distribution, kinetics and excretion of ^{14}C -phenyl cypermethrin at a dose of 3.0 mg/kg bw, diluted with unlabelled alpha-cypermethrin (purity, > 98%), were evaluated in female HAN-Ibm Wistar rats after intravenous administration via the tail vein. Radioactivity excreted in the urine and faeces within 120 h of treatment amounted to 89.7% of the administered dose, comprising 61.3% in the urine and 28.4% biliary excretion into the faeces, with approximately 80% of administered radioactivity excreted in the first 48 h. The half-life of radioactivity in the blood was 5.9 h, with similar half-lives of 4.8–9.9 h in most organs and tissues, the exceptions being fat (half-life, > 24 h) and the skin from the back region (half-life, 12.8 h). After 120 h, liver, ovaries, kidneys, sciatic nerve and skin from the back region retained higher concentrations of radioactivity than blood, but concentrations in these tissues (0.04–0.1 µg/g) were much less than the concentration in fat (1.45 µg/g) (Van Dijk & Burri, 1993).

Groups of male beagle dogs were given ^{14}C -benzyl cypermethrin or the individual ^{14}C -benzyl labelled *cis*- and *trans*-isomers of cypermethrin, orally, at a dose of 2 mg/kg bw. Elimination of radioactivity from all animals was rapid, although differences in data from individual dogs precluded a complete evaluation of the rate of elimination. Differences in the rates of elimination of the individual dogs in the study may have been due to differences in absorption, as cypermethrin was given orally in a capsule with no solvent. Tissue residues observed 4 days after oral administration of cypermethrin were extremely low. Most of the excreted material was found in the faeces (80%) with urine containing only 11% of the administered dose. As with other species, residues of cypermethrin were observed in fat, approximating 2% of the administered dose (this residue was estimated to be 0.3 ppm based upon total adipose tissue of the dog) (Annex 1, reference 33; Crawford, 1979b).

In a study of excretion in humans, cypermethrin (purity, 98.1–98.5%; *cis* : *trans* 1 : 1) was administered to four male subjects as a single oral dose at 0.25–1.5 mg in corn oil contained in a capsule. The urinary excretion of 3-(2,2-dichlorovinyl)-2,2-dimethylcyclopropanecarboxylic acid

(DCVA) was rapid and confined to the first 24 h after dosing. On the basis of the assumption that no *cis* to *trans* isomerization occurs, 78% of the *trans*-isomer and 49% of the *cis*-isomer was excreted as free and conjugated DCVA, and the amounts excreted were dose-related. This study confirmed that, as in other mammals, ester cleavage and elimination of the cyclopropanecarboxylic acid moieties is a major route of cypermethrin metabolism in humans (Eadsforth & Baldwin, 1983).

A study of human absorption and excretion was conducted in which cypermethrin was administered by the oral or dermal route to six human volunteers. Metabolites were measured in the urine that was collected for up to 5 days after dosing. In the oral study, 3.3 mg of cypermethrin (purity, 98.9–99.4%, *cis* : *trans* 1 : 1) was administered undiluted as a single oral dose. Metabolites *cis*- and *trans*-3-(2,2-dichlorovinyl)-2,2-dimethylcyclopropanecarboxylic acid (DCVA) were recovered in the urine in the ratio of 1 : 2, along with slightly less 3-phenoxybenzoic acid and 3-(4'-hydroxyphenoxy) benzoic acid combined (3PBA + 4OH3PBA). Excretion of DCVA peaked within 4 h of dosing, with derivatives of the phenoxybenzyl moiety peaking later at 4–24 h. The mean elimination half-life of total metabolites was 16.5 h. As estimated from the DCVA recovered, mean oral absorption was 36%. In the dermal study, 31 mg of technical-grade cypermethrin (purity, 91.5%, *cis* : *trans* 56 : 44), mixed with surfactants and wetting agents, and finally diluted to 26 mg/ml in soya bean oil, was applied over a skin area of 800 cm² on the backs of the volunteers. A large proportion of the dose was recovered in the wash (approximately 41%, 8 h after application) and from tee-shirts worn overnight (approximately 24%). In contrast to the oral study, the *cis* : *trans* ratio for DCVA in the urine was 1.2 : 1, and the amount of 3PBA + 4OH3PBA was approximately fourfold that of DCVA. Urinary excretion of cypermethrin metabolites peaked in the 12–36 h after dosing, with an elimination half-life of approximately 13 h. An estimate of the amount of cypermethrin absorbed dermally based on the total DCVA recovered was approximately 0.3%, considerably less than the estimate of approximately 1.2% based on the phenoxybenzyl derivatives. This demonstrates that the use of urinary DCVA in biological monitoring may underestimate dermal absorption (Woollen et al., 1992).

1.2 Biotransformation

The metabolic fate of cypermethrin was investigated in a variety of mammalian species and was determined to be relatively similar in the different species. Studies on the metabolic fate of both *cis*- and *trans*-cypermethrin administered orally to rats have shown that cypermethrin is rapidly cleaved at the ester bond to yield the cyclopropanecarboxylic acid and the 3-phenoxybenzyl alcohol moiety. The latter is rapidly oxidized to 3-phenoxybenzoic acid and conjugated before elimination. Major reactions occurring with the cyclopropanecarboxylic acid include, in part, oxidation at the methyl groups and apparent lactone rearrangement before conjugation and elimination. Hydroxylation of the phenoxybenzoyl moiety has been noted to occur in at least two positions before conjugation and elimination. Rats and mice metabolized cypermethrin in a similar fashion. In mice, a substantial portion of the phenoxybenzoic acid was conjugated with taurine as well as with glucuronic acid (Annex 1, reference 33; Hutson, 1977).

Oxidation has been noted to occur in the 4'-position of phenoxybenzoic acid. After oxidation, the molecule is conjugated as a sulfate and excreted. A portion of unconjugated hydroxylated phenoxybenzoic acid was also excreted. Hydroxylated cypermethrin was observed in the faeces in mice, suggesting that hydroxylation may occur before ester cleavage (Annex 1, reference 33; Hutson, 1978b).

Shono et al. (1978), using microsomal preparations from mouse liver, showed that hydroxylation of the phenoxybenzyl moiety at positions other than the 4'-position can occur. Small amounts of the 5- and 6-hydroxy phenoxybenzyl derivatives were also observed. Both *cis*- and *trans*-isomers were

rapidly metabolized by cleavage of the ester bond and aromatic hydroxylation at the 4'- position of the 3-phenoxybenzyl alcohol moiety.

In rats, approximately half of the administered cypermethrin was excreted as sulfate conjugates of the hydroxylated phenoxybenzoic acid. Phenoxybenzoic acid was also excreted free and conjugated with glycine in contrast to the conjugate pattern noted in mice (Annex 1, reference 33; Crawford & Hutson, 1977, 1978c).

In studies with cyclopropanecarboxylic acid-labelled cypermethrin, hydroxylation of the methyl groups on the cyclopropane ring occurred to a limited extent. Oxidation was believed to have occurred after ester cleavage. While most of the radioactive metabolites were found in the urine, a small quantity of hydroxylated metabolites were eliminated via the biliary-intestinal-faecal route suggesting absorption and redistribution through the bile to the faeces (Annex 1, reference 33; Crawford & Hutson, 1978c).

In mice, rats and other species, ester cleavage is rapid. There is quantitative and qualitative evidence to suggest that the *cis*-isomer is more stable, yielding a larger variety of hydroxylated products before ester cleavage, while the *trans*-isomer yields a wider variety of hydrolytic products which in part are oxidized after the ester cleavage. The acid fragment is conjugated predominantly with glucuronic acid as a β -glucuronide. Conjugated cyclopropanecarboxylic acid derivatives in urine identified as glucuronides have a relative resistance to the action of β -glucuronidase. β -Glucuronides formed from these acids are generally of the ester type readily cleaved by mild acid hydrolysis. Thus, treatment of urine with methanol and sulfuric acid will convert both the free acid and the acid glucuronide into a methyl ester. The methyl ester of the carboxylic acid has been shown to be volatile and analytical losses may occur with this compound. The alcohol fragment, the α -cyano-3-phenoxybenzyl alcohol, is readily oxidized metabolically to the benzoic acid, conjugated and excreted. Alcohol conjugates with glucuronic acid are generally ether derivatives, stable to acid and enzymatically hydrolysable. The phenoxybenzyl moiety of cypermethrin has been found to form both ester and ether β -glucuronides. Thus, the results of the studies with both rats and mice suggest that most of the excreted metabolites of cypermethrin are hydrolysis products, although hydroxylation of the intact ester has been reported. Hydroxylation of the methyl groups attached to the cyclopropane ring has also been reported. There was no evidence of metabolism at the 2,2-dichlorovinyl moiety. Evidence exists that the *cis*-isomer is somewhat more resistant than the *trans*-isomer to hydrolysis. In all cases, only small amounts of hydroxylated metabolites with the intact ester bond were observed with the cypermethrin.

After administration of a single oral dose of radiolabelled cypermethrin (50 : 50 of *cis* : *trans*) to groups of male and female rats at 200 mg/kg bw, cypermethrin was partially absorbed and rapidly cleaved at the ester bond to produce 2,2-dimethyl-3-(2',2'-dichlorovinyl) cyclopropanecarboxylic acid and a 3-phenoxy-benzoyl moiety that was mostly further metabolized by oxidation at the 4'- position. The resultant phenol was almost totally conjugated with sulfate, the identical result to that observed in studies at the lowest dose (Crawford & Hutson, 1977). The 4'-hydroxy sulfate forms the major aryl metabolite (16% of the dose) with 3-phenoxybenzoic acid as the second most important (5%). The other identified aryl metabolites are 3-(4-hydroxyphenoxy) benzoic acid (1%) and the glycine conjugate, *N*-(3-phenoxybenzoyl) glycine (1%). The cyclopropyl acid is almost exclusively conjugated as the ester glucuronide (30% of the dose in males, 47% in females) with some free acid (twice as much *trans*- as *cis*-) being found in the urine (4%) together with traces of the *trans*-hydroxymethyl cyclopropyl acids (2%) (Logan, 1980).

Thus, the results of the studies with both rats and mice suggest that most of the excreted metabolites of cypermethrin are hydrolysis products, although hydroxylation of the intact ester has been reported. Hydroxylation of the methyl groups attached to the cyclopropane ring has also been reported. There was no evidence of metabolism at the 2,2-dichlorovinyl moiety. Evidence exists that the *cis*-isomer is somewhat more resistant than the *trans*-isomer to hydrolysis. In all cases, only small amounts of hydroxylated metabolites with the intact ester bond were observed with the cypermethrin.

The metabolic fate of cypermethrin in dogs was qualitatively similar to that observed with other species with the exception being conjugation reactions of several metabolites. As with other species, cypermethrin is rapidly metabolized by cleavage of the ester bond and by hydroxylation of the phenoxybenzyl moiety at the 4'-position. Sulfate conjugation of the hydroxylated benzoic acid was reported. Additionally, a major urinary metabolite was identified as the 3-phenoxybenzyl glycine. Studies on the metabolic fate of 3-phenoxybenzoic acid in dogs revealed a metabolic pattern of oxidation and conjugation similar to that noted with cypermethrin (Annex 1, reference 33; Crawford, 1979a, 1979c).

3-Phenoxybenzoic acid has been observed as a major metabolite of cypermethrin in all species studied. Residues of cypermethrin in rat skin (< 3% of the dose) were noted after oral administration. Further studies to define the skin residue were performed using ¹⁴C-3-phenoxybenzoic acid administered orally to rats as seven consecutive daily doses. The radioactive metabolites in skin were identified as predominately 3-phenoxybenzoic acid and a small quantity of glyceryl dipalmitate esters of 3-phenoxybenzoic acid (Annex 1, reference 33; Crawford & Hutson, 1979).

The metabolic fate of cypermethrin in dogs was qualitatively similar to that observed with other species, the exception being conjugation reactions of several metabolites. As with other species, cypermethrin is rapidly metabolized by cleavage of the ester bond and by hydroxylation of the phenoxybenzyl moiety at the 4'-position. Sulfate conjugation of the hydroxylated benzoic acid was reported. Additionally, a major urinary metabolite was identified as 3-phenoxybenzyl glycine. Studies on the metabolic fate of 3-phenoxybenzoic acid in dogs revealed a metabolic pattern of oxidation and conjugation similar to that noted with cypermethrin (Annex 1, reference 33; Crawford, 1979a, 1979c).

The metabolites derived from a single oral dose of (¹⁴C-cyclopropyl) cypermethrin (1 : 1 *cis* : *trans*-WL 43467), administered orally to two male beagle dogs, have been studied. The rapid elimination of cypermethrin in dogs was due to the efficient cleavage of the ester linkage of both the *cis*- and *trans*-isomers and the urinary excretion of the cyclopropanecarboxylic acid moiety, largely as its glucuronic acid conjugate. This metabolite comprised 18% and 51% of the respective doses administered to dog Nos 1 and 2. Absorption of the orally administered cypermethrin was not complete, i.e. 65.6% of the dose was excreted as unchanged cypermethrin in the faeces of dog 1 and 32.1% in the faeces of dog 2. The results of this study confirmed those derived from a similar study in which dogs were dosed with (¹⁴C-aryl) cypermethrin, in that most of the excreted metabolites were ester-cleavage products of cypermethrin. While the 3-phenoxybenzyl moiety was mostly hydroxylated in the 4'-position before excretion, most of the cyclopropanecarboxylic acids (*cis*- and *trans*-) were excreted without further metabolism other than glucuronide conjugation. The results of these studies show that the metabolic fate of cypermethrin in dogs is similar to that in rats and mice, but hydroxylation reaction(s) do not occur as readily in dogs as in rats and mice (Annex 1, reference 37; Crawford & Croucher, 1979).

2. Toxicological studies

2.1 Acute toxicity

(a) Oral, dermal and inhalational toxicity

The acute toxicity of cypermethrin is summarized in Tables 1 and 2.

Cypermethrin-induced signs of toxicity were typical of cyano-containing pyrethroid intoxication. After oral administration, signs of intoxication included sedation, subdued behaviour, ataxia, splayed gait, unsteady gait, tip-toe walking, abasia, diarrhoea, excessive salivation, piloerection, with occasional tremors and clonic convulsions. These signs of toxicity appeared within a few hours after dosing. Survivors generally recovered within several days (Coombs et al., 1976; Freeman, 1987), although clinical signs persisted in some rats throughout the 2-week period of observation after oral or dermal dosing in one study (Henderson & Parkinson, 1980). Acute toxicity after dermal administration is low (Coombs et al., 1976; Jaggars, 1979; Henderson & Parkinson, 1980), with few overt signs of toxicity reported. Immediately after exposure by inhalation, salivation, lachrimation, reduced reflexes, reduced activity, slow deep breathing, shaking and reduced stability were reported, followed by splayed or tiptoe gait and tail erection (Brammer, 1989). In dogs, signs of acute intoxication noted at extremely high doses included nervousness, inappetence, diarrhoea, vomiting, tremors and exaggerated ataxia while walking (Coombs et al., 1976). Studies that indicate that the *cis*-isomer of cypermethrin is more acutely toxic via the oral route in rats than the *trans*-isomer are summarized in Table 2.

Table 1. Results of studies of acute toxicity with cypermethrin^a

Species	Sex	Strain	Route	Vehicle/comments	LD ₅₀ (mg/kg bw)/ LC ₅₀ (mg/m ³)	Reference
Mouse	M, F	NS	Oral	5% in corn oil	82	Coombs et al. (1976)
Mouse	M, F	CD	Oral	5% in corn oil ^c	88	Rose (1982)
Mouse	M, F	NS	Oral	DMSO	138	Coombs et al. (1976)
Mouse	M, F	CD	Oral	40% in DMSO ^c	1126	Rose (1982)
Mouse	M, F	NS	Oral	Aqueous suspension	779 ^b	Jaggars (1979)
Mouse	M, F	CD	Oral	50% aqueous suspension ^c	657	Rose (1982)
Mouse	M, F	CD	Dermal	5% in corn oil ^c	> 100	Rose (1982)
Mouse	M, F	NS	Intraperitoneal	Corn oil	485	Coombs et al. (1976)
Rat	M, F	NS	Oral	Corn oil	251–992	Coombs et al. (1976)
Rat	MF	Alderley Park	Oral	Corn oil ^j	247 309	Henderson & Parkinson (1980)
Rat	M, F	Tac:N [SD]fBR	Oral	5% in corn oil ^e	334	Freeman (1987)
Rat	M	NS	Oral	Glycerol formal	200–400	Coombs et al. (1976)
Rat	F	NS	Oral	Glycerol formal	approximately 200	Coombs et al. (1976)
Rat	M	NS	Oral	Aqueous suspension	400–800	Coombs et al. (1976)
Rat	F	NS	Oral	Aqueous suspension	approximately 400	Coombs et al., 1976
Rat	F	NS	Oral	Aqueous suspension	4123 ^b	Jaggars (1979)

Rat	M	NS	Oral	Aqueous suspension	3000 ^c	Jaggers (1979)
Rat	M, F	Wistar	Oral	50% aqueous suspension ^c	4000	Rose (1982)
Rat	M, F	NS	Oral	DMSO	303	Coombs et al. (1976)
Rat	M, F	Wistar	Oral	40% in DMSO ^c	4000	Rose (1982)
Rat (3 weeks) ^d	M, F	NS	Oral	DMSO	163	Rose & Dewar (1978)
Rat (6 weeks) ^d	M, F	NS	Oral	DMSO	322	Rose & Dewar (1978)
Rat (12 weeks) ^d	M, F	NS	Oral	DMSO	526	Rose & Dewar (1978)
Rat	F	NS	I.p.	Aqueous suspension	> 500 ^b	Jaggers (1979)
Rat	M, F	NS	I.p.	Propylene glycol	1000–2000 ^b	Jaggers (1979)
Rat	F	NS	Dermal	Undiluted	> 4800 ^b	Jaggers (1979)
Rat	M, F	Alderley Park	Dermal	Undiluted	> 4920 ^j	Henderson & Parkinson (1980)
Rat	M, F	NS	Dermal	40% in xylene	> 1600	Coombs et al. (1976)
Rat	M, F	Alpk: APfSD	Inhalation (4 h exp.) ^h	MMAD 3.95–5.20 µm; 16.9–28.8% respirable	1260 ^f	Brammer (1989)
Rat	MF	NS	Inhalation (4 h exp.) ⁱ	MMAD 2.3–2.5 µm;	> 1320 2500	Mount (1992)
Syrian hamster	M, F	NS	Oral	Corn oil	> 400	Combs et al. (1976)
Chinese hamster	M, F	NS	Oral	5% in corn oil	203	Coombs et al. (1976)
Guinea-pig	M	NS	Oral	20% in corn oil	approximately 500	Coombs et al. (1976)
Guinea-pig	F	NS	Oral	Corn oil	> 1000	Coombs et al. (1976)
Guinea-pig	M	NS	Oral	Aqueous suspension	> 4000 ^b	Jaggers (1979)
Rabbit	F	NS	Oral	Undiluted	> 2400 ^b	Jaggers (1979)
Rabbit	F	NS	Dermal	Undiluted	> 2400 ^b	Jaggers (1979)
Rabbit	M, F	NZW	Dermal	Undiluted	> 2460 ^j	Henderson & Parkinson (1980)
Domestic fowl	M, F	NS	Oral	DMSO	> 2000	Coombs et al. (1976)
Partridge	M, F	NS	Oral	DMSO	> 3000	Coombs et al. (1976)

DMSO, dimethyl sulfoxide; F, female; M, male.

NZW, New Zealand White

^a Unless specified, all values refer to data generated using cypermethrin (*cis* : *trans* 50 : 50).

^b Data generated using cypermethrin (*cis* : *trans* 40 : 60).

^c Data generated using cypermethrin (*cis* : *trans* 53 : 46).

^d Refers to the age of the rats.

^e Purity, 98.1%; *cis* : *trans*-isomer ratio 51 : 49.

^f Technical material, purity, 72.9%; *cis* : *trans*-isomer ratio not stated.

^g Purity, 93.5%; *cis* : *trans*-isomer ratio not stated.

^h Nose-only exposure.

ⁱ Whole-body exposure; purity, 95.7%; *cis* : *trans*-isomer ratio not stated

^j Purity, 91.5%; *cis* : *trans*-isomer ratio 53 : 47.

Table 2. Effect of *cis* : *trans* ratio on acute toxicity of cypermethrin

Species	Sex	Strain	Route	Vehicle	<i>Cis</i> : <i>trans</i> ratio	LD ₅₀ (mg/kg bw)	Reference
Rat	M, F	?	Oral	DMSO	<i>Cis</i> only	160–300	Brown (1979a)
Rat	M, F	?	Oral	DMSO	<i>Trans</i> only	> 2000	Brown (1979b)
Rat	F	?	Oral	Corn oil	90 : 10	367	Jaggers (1979)
Rat	F	?	Oral	Corn oil	40 : 60	891	Jaggers (1979)

DMSO, dimethyl sulfoxide; F, female; M, male.

(b) *Dermal and ocular irritation*

Groups of four male and four female rabbits were given cypermethrin dermally in a 24-h skin test. A single application of cypermethrin was observed to be a moderate irritant to rabbit skin (Annex 1, reference 33; Coombs et al., 1976).

When 0.1 ml of cypermethrin (purity, 91.5%; *cis* : *trans* ratio, 53 : 47) was applied undiluted to the skin of five Alderley Park albino rats under occlusive dressings as a single application for 24 h, or as five consecutive 24-h applications, no reactions were reported other than transient desquamation in one rat, resolving by 24 h after removal of the dressings. When 0.5 ml of the same test material was applied to the intact or abraded skin of six New Zealand White rabbits for 24 h under occluded conditions, slight to mild erythema was reported for all animals, resolving in all but one animal by 72 h. Transient slight erythema was observed on the abraded skin of one rabbit. Cypermethrin was not an irritant to rat skin, but a slight irritant to rabbit skin (Henderson & Parkinson, 1980).

A single application of undiluted cypermethrin to rabbit eyes produced mild transient conjunctivitis lasting 2 days (Annex 1, reference 33; Coombs et al., 1976).

A single application of 0.1 ml of undiluted cypermethrin (purity, 91.5%; *cis* : *trans*, 53 : 47) into one eye of each of six New Zealand White rabbits produced slight conjunctival redness, slight chemosis and some discharge that resolved in four of the rabbits by day 7, the final observation day. In another three rabbits treated similarly, but in which the eyes were rinsed shortly after instillation, similar conjunctival effects resolved by day 7 (Henderson & Parkinson, 1980).

(c) *Dermal sensitization*

Groups of 10 male and 10 female guinea-pigs were used to assess the skin-sensitizing potential of cypermethrin. Two guinea-pigs out of the 20 exposed to cypermethrin showed a positive skin reaction, indicating that cypermethrin may have a weak skin sensitizing potential under the maximization procedure of Magnusson & Kligman (Annex 1, reference 33; Coombs et al., 1976).

Using the Buehler test, cypermethrin (purity, 91.5%; *cis* : *trans*, 53 : 47) in corn oil was not a sensitizer in guinea-pigs (Henderson & Parkinson, 1980).

2.2 *Short-term studies of toxicity*

Rats

Groups of rats (12 of each sex per group, 24 of each sex as controls) were fed diets containing cypermethrin at a concentration of 0, 25, 100, 400, or 1600 ppm for 13 weeks. After 2 weeks

exposure at 1600 ppm, both males and females exhibited hypersensitivity and varying signs of ataxia. Mortality was observed with male rats up to the fifth week of feeding after which the surviving animals improved clinically and appeared normal at the end of the study. Reductions in body weight, growth and food intake were also noted at 1600 ppm. At the conclusion of the study, small increases in plasma urea concentration were noted in both sexes. Males had a slight increase in plasma potassium concentration, while females had a slight increase in alkaline phosphatase activity and plasma protein concentrations at 1600 ppm. Haematological abnormalities noted at 1600 ppm after 13 weeks included a reduction in haemoglobin, erythrocyte volume fraction and erythrocyte count in females and a reduction in kaolin-cephalin clotting time in males. Gross and microscopic pathology performed at the conclusion of the study showed axonal breaks and vacuolation in the sciatic nerve of rats at 1600 ppm. This was especially noted with those animals that showed clinical signs of ataxia and died during the course of the study. At the conclusion of the 13-week trial, sciatic nerve lesions were not noted in any surviving animals. An increased kidney weight in males at 400 ppm was observed that was not associated with any clinical or pathological signs of abnormality. The no-observed-adverse-effect level (NOAEL) was 400 ppm, equal to 40 mg/kg bw per day, on the basis of deaths, clinical signs of neurotoxicity, reduced body-weight gain and food consumption, microscopic abnormalities of the sciatic nerve, and changes in a number of haematological and clinical chemistry parameters at 1600 ppm, equivalent to 160 mg/kg bw per day (Annex 1, reference 33; NOAEL based on the JMPR summary of Hend & Butterworth, 1976).

Groups of 15 male and 15 female SD albino rats were fed diets containing cypermethrin (FMC 45806; purity, 92.6%; *cis* : *trans*, 52 : 48) at a concentration of 0, 150, 500 or 1500 ppm for 90 days. The cypermethrin was dissolved in corn oil before incorporation into the diet. The animals were observed twice per day for mortality and daily for clinical signs. Palpation for internal masses and measurement of body weight and food consumption were performed weekly. All rats were given an ophthalmoscopic examination at the beginning and end of the study. Haematology and clinical chemistry evaluations were performed on 10 rats of each sex per dose at the conclusion of the study, but urine analysis was not conducted. Animals found dead, or killed at study termination were examined for gross pathological effects, selected organs were weighed, and histopathology performed on selected tissues. The mean daily intake by rats in the groups at 0, 150, 500 and 1500 ppm was, respectively, 0, 11.8, 37.2 and 116 mg/kg bw per day for males and 0, 13.5, 45.0 and 132 mg/kg bw per day for females. Additional groups of five rats of each sex per dose were killed after 90 days, livers were removed and hepatic microsomes prepared for the assay of aminopyrine *N*-demethylase (APDM) activity.

Two males and two females in the groups at 1500 ppm were found dead during the first 4 weeks of the study. Clinical signs of toxicological significance that were observed regularly in both sexes at 1500 ppm included staggered gait, splayed hind legs, tremors, shaking, loss of muscle coordination, hypersensitivity, unthriftiness, and yellow abdominal staining, with clonic convulsions reported in one female. These signs were not observed at the lower doses. At 1500 ppm, overall body-weight gain was reduced in males and females by approximately 20% and 12% respectively, relative to controls, and was associated with reduced food consumption. Ophthalmoscopic investigations detected no abnormalities.

Table 3. Significant haematological and clinical chemistry findings in a 90-day study in rats fed diets containing cypermethrin

Parameter	Sex	Dietary concentration (ppm)			
		0	150	500	1500
Erythrocytes (10 ⁶ /ml)	M	8.78	8.65	8.72	8.32*
	F	8.30	8.23	8.15	7.87*
Haemoglobin (g/dl)	M	17.59	17.43	17.40	17.20
	F	17.08	16.97	16.75	16.20*
Erythrocyte volume fraction (%)	M	46.08	45.71	45.56	44.91*
	F	46.43	45.80	44.77	44.12*
MCH (10 ⁻¹² g)	M	20.07	20.16	19.98	20.71*
	F	20.61	20.62	20.57	20.65
MCV (10 ⁻¹⁵ l)	M	52.2	53.0	52.3	54.2*
	F	55.9	55.6	54.9	56.1
ALT (U/l)	M	32.8	34.5	35.9	37.2
	F	21.9	25.2	22.8	31.9*
SGGT (U/l)	M	0.68	0.66	0.64	0.82*
	F	1.83	1.46	1.73	1.83
Blood urea nitrogen (mg/dl)	M	13.3	13.5	14.4	14.9
	F	13.7	16.7	15.8	20.1*
Albumin (g/dl)	M	3.84	3.82	3.81	3.89
	F	4.07	3.86	3.96	3.73*
Glucose (mg/dl)	M	127	124.6	121.6	110.5*
	F	100.3	107.5	93.5	90.1
Potassium	M	5.07	5.01	4.94	5.07
	F	4.73	4.81	4.89	5.19*
Hepatic APDM (nmol formaldehyde produced/mg protein per 15 min)	M	52.2	53.4	64.6*	66.8*
	F	14.6	20.0	17.2	23.4

From Norvell (1983)

ALT, alanine aminotransferase; APDM, aminopyrine *N*-demethylase; MCH, mean cell haemoglobin; MCV, mean cell volume; SGGT, serum gamma-glutamyl transferase.

* Significantly different from controls ($p < 0.05$).

Male and female rats at 1500 ppm showed slight, but statistically significant reductions in erythrocyte count, erythrocyte volume fraction and/or haemoglobin, accompanied by increases in mean corpuscular haemoglobin and mean corpuscular volume in males (Table 3). Increased alanine aminotransferase (ALT) activity and decreased albumin in females and increased serum gamma-glutamyl transferase (SGGT) activity in males at 1500 ppm were indicative of toxic effects on the liver. Elevated blood urea nitrogen (BUN) and potassium in females at 1500 ppm suggested mild renal toxicity. The findings in liver were supported by increased liver weight relative to body weight in females at 1500 ppm (3.42, 3.47, 3.62, 3.90 (%) at 0, 150, 500 and 1500 ppm, respectively) and in both sexes in the APDM group (10–16% greater than control weights), but macroscopic and microscopic examination revealed no abnormalities in the liver and kidney, or other organs. The small decrease in serum glucose concentrations in males at 1500 ppm was within normal limits for this strain of rat and was not considered to be biologically significant. Mean hepatic APDM activity was increased in males at 1500 and 500 ppm, but this was considered to be an adaptive response rather than a toxicological effect.

The NOAEL in rats was 1500 ppm, equal to 37 mg/kg bw per day in males and 45 mg/kg bw per day in females, on the basis of deaths, clinical signs, decreased body-weight gain and effects on haematological and clinical chemistry parameters at 1500 ppm (Norvell, 1983).

In a short-term study, groups of five male and five female Alpk:APfSD (Wistar-derived) rats were exposed (nose-only) to cypermethrin technical (purity 87.1%, *cis* : *trans* 50.1 : 49.9) at concentrations of 0, 10, 50 or 250 mg/m³ for 15 days by inhalation for 21 days. The mass median aerodynamic diameter (MMAD) of the aerosol particles in the chamber was 2.6–2.9 µm, with a geometric standard deviation (GSD) of 1.8–2.1 µm. Satellite groups of five males and five females from rats in the control groups and from those receiving the highest dose were retained for 14 days after the exposure period. Concentrations of cypermethrin were determined in the brains of additional control and highest-dose interim-sacrifice groups (five of each sex, killed on day 10) and an additional five of each sex for all doses, killed on day 22. Rats were monitored daily for clinical signs, and detailed clinical examinations and body-weight measurements were made on days 1, 2, 3, 8, 15 and 22, and weekly thereafter for the satellite groups. Food consumption was calculated on a weekly basis. At termination, haematology and clinical chemistry parameters were determined for all animals in the main study and satellite groups, a full postmortem was conducted, and selected organs weighed. Histopathology was restricted to the control group and group at 250 mg/m³ groups, plus lungs and abnormal tissues from the other groups.

There were no deaths. Immediately after exposure, salivation and lachrimation were observed in rats in the group at 250 mg/m³, together with decreased activity and tail erection in both sexes, and head/paw flicking, reduced stability and tiptoe gait in females. At 50 mg/m³, there were sporadic observations of salivation that were probably related to exposure to the test substance. As no other signs were present at this dose, the study author did not regard this as toxicologically relevant. However, given that the highest dose produced salivation and this was not noted in controls, the salivation findings at 50 mg/m³ should not be dismissed. On non-exposure days, piloerection or ungroomed appearance were noted for some animals exposed at 250 mg/m³. Slight body-weight loss (< 5%) was observed at 250 mg/m³ on day 2 in both sexes, and while female body weight recovered after cessation of treatment, male body weights remained below controls (6–8%) for the remainder of the treatment and recovery periods. Food consumption was reduced at 250 mg/m³ in the first week of treatment (12–15%), but was subsequently similar to controls. Relative to controls, slight (5–7%) but statistically significant reductions in haemoglobin, erythrocyte volume fraction and erythrocyte counts were seen in males and females at 250 mg/m³, and occasionally at lower doses, but as these changes were small and dose–response relationships were lacking, they were not attributed to treatment. Similarly, there were slight (5–6%) but statistically significant decreases in total protein in males at ≥ 50 mg/m³, and in females at 250 mg/m³, the latter accompanied by a decrease in albumin of a similar magnitude. However, a dose–response relationship was not present in males, and taking into account the small differences from control values, these findings were not considered toxicologically significant. Decreases in alanine aminotransferase activity in males at ≥ 50 mg/m³ (approximately 25%) also lacked a dose–response relationship and were not supported by changes in other liver enzymes or histopathology. Differences in organ weights between control and treated groups that attained statistical significance were generally small (< 10%), lacked dose–response relationships, or were not significant when expressed as a percentage of body weight, and therefore were not attributed to treatment. In addition, other than the observation of red lungs in one male exposed to cypermethrin at 250 mg/m³, and for which no histopathology was reported, there were no findings at macroscopic or microscopic examination that indicated treatment-related effects. Cypermethrin was detected in the brain of one treated animal killed at day 10 (65 ng/g tissue), but concentrations were below the limit of detection in all other animals. The no-observed-adverse-effect concentration (NOAEC) was 10 mg/m³ for males and females on the basis of clinical signs of salivation at 50 mg/m³ (0.05 mg/l) (Parr-Dobrzanski, 1994).

Rabbits

Occluded dermal applications of cypermethrin at a dose of 0, 2, 20 or 200 mg/kg bw in PEG 300 were made to abraded and intact skin of groups of 10 male and 10 female New Zealand White rabbits. The applications were made for 6 h/day, 5 days per week for 3 weeks. No effects were observed on haematology, clinical chemistry or at macroscopic or microscopic examination. Slight to severe skin irritation was observed in rabbits at 200 mg/kg bw and slight to moderate skin irritation was observed in rabbits at 2 or 20 mg/kg bw. Decreased food consumption and body-weight gain were observed in rabbits treated at 200 mg/kg bw. Absolute and relative gonad weights were reduced in male rabbits at 200 mg/kg bw. The NOAEL was 20 mg/kg bw per day on the basis of decreased body-weight gain, and a decrease in testicular weights at 200 mg/kg bw per day (JECFA, 1996; Henderson & Parkinson, 1981).

Dogs

Groups of four male and four female beagle dogs were fed diets containing cypermethrin (1 : 1 *cis* : *trans*-isomeric mixture) at a concentration of 0, 5, 50, 500 or 1500 ppm for 13 weeks. There was no mortality over the course of the study. However, there were significant signs of poisoning observed at 1500 ppm, including diarrhoea, anorexia and tremors as well as ataxia, incoordination and hyperesthesia. On account of these clinical signs, two male and two female dogs at the highest dose had to be sacrificed before the end of the experiment. Minor variations were observed in various haematological parameters, with the kaolin-cephalin clotting time observed to be consistently lower throughout the study in females at 500 ppm. However, because of the lack of a dose-response relationship, the variability of kaolin-cephalin clotting time throughout the study, and the fact that there were no changes in the prothrombin time, this finding was not considered to be relevant. There were no other significant differences with respect to standard haematological or clinical chemistry parameters. Gross examination of kidneys and organs showed no effect on organ weights attributable to the diet. Microscopic examination of tissues and organs revealed a non-specific focal bronchopneumonia in the lungs of the animals surviving at 1500 ppm. There were no compound-related changes and no histological abnormalities in other tissues examined with the exception of a variation in the intensity of the pink colour of the optic disc noted on ophthalmological examination at the conclusion of the study.

Because of the pink coloration observed in the optic disc, a further experiment was undertaken to determine its cause. Two groups of three male dogs were fed diets containing cypermethrin at a concentration of 0 or 500 ppm for 13 weeks. Specific ophthalmological examinations were made to evaluate the degree of coloration of the optic disc. After 13 weeks, there were no consistent differences between the colour of the optic discs of the treated dogs and controls. The NOAEL was 500 ppm, equivalent to 12.5 mg/kg bw per day, on the basis of clinical signs at 1500 ppm (equivalent to 37.5 mg/kg bw per day) (JECFA, 1996; Buckwell & Butterworth, 1977).

Groups of four male and four female beagle dogs received diets containing cypermethrin (FMC 30980 technical; purity, 95.7%) at a concentration of 0, 300, 600, 800 or 1100 ppm for 3 months. The animals were observed twice per day for clinical signs. Detailed physical examinations, and measurement of food consumption and body weight were performed before treatment and weekly thereafter. Haematology and serum chemistry parameters were evaluated before the study, and at 1.5 and 3 months, but urine analysis was not conducted. All animals were killed on days 92–94, selected organs were weighed, and tissues were examined at the macroscopic and microscopic level. The mean test substance consumption for dogs fed diets containing cypermethrin at 300, 600, 800 and 1100 ppm was, respectively, 10.4, 20.7, 24.6 and 37.0 mg/kg bw per day for males and 12.2, 25.4, 34.3 and 45.2 mg/kg bw per day for females.

No dogs died during the study. Slight tremors were observed in one male in each of the groups at 800 and 1100 ppm on days 66/67 and 71/86 respectively. Tremors were observed in another male at 1100 ppm on most days, commencing on day 60. These were described as slight, except for days 76/77 when they reached moderate intensity. Starting on day 49, slight tremors were reported in one female at 1100 ppm on most days for the remainder of the study. Moderate tremors were reported in this female during the detailed physical examinations at weeks 7, 9 and 12. There were no ophthalmic lesions indicative of toxicity attributable to cypermethrin. At 1100 ppm, overall body-weight gain was reduced in males (24% of control values) and females lost weight (−0.2 kg vs 1.3 kg overall weight gain in controls). Females at 800 ppm also showed a net body-weight loss in the first 5 weeks of the study (−0.4 kg vs 0.7 kg weight gain in controls). For the first 3–5 weeks of the study, food consumption was reduced in both sexes at 800 and 1100 ppm. From week 5, diets were supplemented with an additional 400 g of food for one female at 800 ppm and one male at 1100 ppm that had been losing weight. Thereafter, food consumption remained below control levels in males at 800 ppm only. At 1.5 months, erythrocyte volume fraction was decreased, and mean cell haemoglobin concentration (MCHC) increased to a statistically significant extent in 1100 ppm males, along with decreases in erythrocyte numbers and haemoglobin that did not attain statistical significance. Findings were similar at 3 months, but given that comparable differences existed before testing, they were not attributed to treatment. Slightly increased chloride concentrations were reported in females at 800 and 1100 ppm at 1.5 months (110, 111, 112, 113*, 112* mEq/l; * $p < 0.05$, parametric ANOVA) and in females at 1100 ppm at 3 months (115, 115, 117, 118, 119*; * $p < 0.05$). The lack of a dose–response relationship suggests that the findings at 1.5 months were not related to treatment and, given the lack of related findings, the increase at 3 months is unlikely to have biological significance. There was no treatment-related effect on organ weights, and no macroscopic or microscopic lesions were detected.

The NOAEL was 600 ppm, equal to 20.7 mg/kg bw per day in males and 25.4 mg/kg bw per day in females, on the basis of tremors in one male at 24.6 mg/kg bw per day and body-weight loss in females at 34.3 mg/kg bw per day (Daly, 1994).

Groups of four male and four female beagle dogs were fed diets containing cypermethrin (FMC 30980; purity, 95.7%) at a concentration of 0, 100, 200, 600 or 1100 ppm for 12 months. Cypermethrin was incorporated into the diet as a solution in corn oil. Animals were observed twice daily for clinical signs, and detailed physical examinations and measurement of body weight and food consumption were performed before testing and weekly thereafter. Ophthalmoscopic examinations took place at the beginning and end of the study. Haematology and urine analysis testing were performed before treatment and at 3, 6 and 12 months, and evaluation of clinical chemistry parameters before testing and at 6 and 12 months. All animals found dead or killed at the end of the study were subjected to macroscopic examination, and brain, kidneys, liver, testes/epididymides and thyroid/parathyroid were weighed and tissues taken for histopathology. The mean daily intake of cypermethrin in the groups at 100, 200, 600 and 1100 ppm was 2.9, 6.0, 20.4 and 33.9 mg/kg bw per day for males and 3.3, 5.7, 18.1 and 38.1 mg/kg bw per day for females. Two males at 1100 ppm were killed after being found in a moribund condition (days 276 and 324) and one male at 600 ppm was found dead (day 133). Clinical signs in these animals, along with the remaining males and two females at 1100 ppm, and another male at 600 ppm, included irregular gait and whole-body tremors, and/or excessive salivation, prostration, incoordination, decreased activity, clonic convulsions, unthrifty coat and moderate alopecia. There were no treatment-related ophthalmoscopic findings. At 600 ppm, body weights in males were 7–12% less than those of controls from week 19, and approximately 10% less than controls in the second half of the study in females. At 1100 ppm, body weights in males were 4–11% below control values for most of the study, and females weighed 11–24% less than did the controls from week 16. Only body-weight change in females at 1100 ppm reached statistical significance with respect to the controls, mainly in the latter half of the study. Food consumption was decreased by up to 20% in males at 1100 ppm in weeks 1 and 2, and in females at 800 ppm and

1100 ppm in weeks 1–6, with increased food consumption of up to 50% in females at 1100 ppm throughout the last 5 months of exposure. There were no effects on haematology, clinical chemistry and urine analysis parameters and organ weights, and no ophthalmic, gross or microscopic lesions indicative of cypermethrin toxicity.

The NOAEL was 200 ppm, equal to 6.0 mg/kg bw per day in males and 5.7 mg/kg bw per day in females, on the basis of mortality, clinical signs (particularly irregular gait and whole-body tremors), and decreased body weight at 600 ppm and greater (Daly, 1995).

A 2-year feeding study has been carried out in which groups of four male and four female beagle dogs were fed diets containing cypermethrin at 0, 3, 30, 300 and (initially) 1000 ppm. When severe signs of intoxication were observed in the groups at 1000 ppm, this highest dose was reduced to 750 ppm, and when signs of intoxication persisted it was further reduced to 600 ppm. Signs of intoxication consisted of licking and chewing of the paws, a stiff high-stepping gait, whole-body tremors, head shaking, incoordinate ataxia and, in some cases, convulsions. Some dietary inappetence was observed in males fed cypermethrin at 1000 ppm. These signs were observed in the group fed at 1000 ppm and 750 ppm, but not when the dietary concentration of cypermethrin was reduced to 600 ppm. No signs of intoxication were observed in groups of dogs at 3, 30 and 300 ppm. A reduction in body weight was observed in the group of males at the highest dose in the main feeding study. This was considered a consequence of the dietary inappetence observed early in the study when the dogs were fed cypermethrin at 1000 ppm. No effect on body weight (attributable to feeding of the compound) was observed in dogs at 3, 30 and 300 ppm. Significant but small differences between controls and treated dogs were observed randomly throughout the study. Sodium concentrations in the blood plasma of male dogs at 600 ppm showed a significant decrease in some weeks, but were always within the normal physiological range. Three dogs tended to have high alkaline phosphatase activity throughout most weeks of the study; this made values for males at 300 ppm significantly higher than those of the controls. This effect was not observed at 600 ppm. No similar effect was observed in female dogs. This observation was not therefore considered to be of toxicological significance. Overall, no significant differences were detected in clinical chemistry and haematological estimations that could be attributed to feeding with cypermethrin for 2 years. No compound-related pathological abnormalities were found. A small number of minor organ-weight changes were found in intermediate dose groups, but were not considered to be due to treatment.

The NOAEL was 300 ppm, equivalent to 7.5 mg/kg bw per day, on the basis of reduced body weight in males at 600 ppm, equivalent to 15 mg/kg bw per day (Annex 1, reference 37; Buckwell, 1981).

2.3 Long-term studies of toxicity and carcinogenicity

Mice

Groups of 70 male and 70 female SPF-Swiss-derived mice received diets containing cypermethrin (purity, 91.5%, *cis* : *trans* 53 : 47; or purity, 94.0–94.2%, *cis* : *trans* 54 : 46) at a concentration of 0 (two groups), 100, 400 or 1600 ppm for up to 101 weeks. Ten mice of each sex were killed after 52 weeks for interim necropsy. Observations included mortality, clinical signs, body-weight gain, food consumption, haematology, clinical chemistry, organ weights, and macroscopy and microscopy. Body-weight gain of both males and females at 1600 ppm was reduced when compared to that in the combined control groups. Several haematological changes, consistent with mild anaemia, were found in the group at 1600 ppm at the interim kill, but not at termination. At interim kill and at termination, an increase in thrombocytosis and absolute and relative liver weight was seen in males at 1600 ppm. An increase in the incidence of benign alveologenic tumours was observed in females at 1600 ppm, but was within the range of incidence for historical controls.

The NOAEL was 400 ppm, equivalent to 60 mg/kg bw per day, on the basis of reduced body-weight gain at 1600 ppm, equivalent to 240 mg/kg bw per day. The NOAEL for carcinogenicity was 1600 ppm, equivalent to 240 mg/kg bw per day, the highest dose tested (JECFA, 1996; Lindsay et al., 1982).

Rats

Groups of 48 male and 48 female rats (96 males and 96 females were used as controls) were maintained under specific pathogen-free (SPF) conditions and fed diets containing 1 : 1 *cis* : *trans* cypermethrin at a concentration of 0, 1, 10, 100 and 1000 ppm for 2 years. Chemical analyses were made confirming stability of cypermethrin in the diet over the test interval.

There was no mortality over the course of the study attributable to cypermethrin in the diet. General health and behaviour of the cypermethrin-fed animals was not different from that of the control animals. Body weight and food consumption data showed a reduction in dietary intake and growth in males and females in groups fed at a dietary concentration of 1000 ppm. Gross morphological changes were noted periodically over the course of the study. At 6 months, males at 1000 ppm had a slightly reduced testes weight, which was not seen thereafter. Slight changes in the gross kidney weight at periodic intervals in the study were not accompanied by notable changes in clinical measurements or microscopic findings. The changes in kidney weight were believed to be unrelated to the presence of cypermethrin in the diet. Liver weight increases were noted at 18 months, again in those animals maintained at the highest dose. The only clinical chemistry change noted over the course of the study was a slight decrease in alkaline phosphatase activity in males at 2 years. The decrease in alkaline phosphatase activity was not dose-related and was not noted in females. Minor fluctuations were seen in various haematological parameters over the course of the study but these, too, were not compound-related or statistically significant. These changes are not believed to be related to the presence of cypermethrin in the diet. Gross and microscopic examination of tissues and organs periodically over the course of the study did not suggest adverse somatic effects.

The kidneys of most animals after 12 months showed chronic nephrosis, histologically characterized as tubular dilatations, interstitial chronic inflammatory infiltration and glomerular scarring. In the liver, varying degrees of chronic inflammatory infiltration, hepatocyte vacuolation and bile-duct proliferation were observed. These changes were characteristic of ageing processes and were not attributable to cypermethrin. Dermal ulceration was present in a number of animals over the course of the study. A portion of the sciatic nerve from 12 animals fed cypermethrin at 1000 ppm for 1 year and 12 animals in the control group was histologically examined for signs of neurotoxicity. There were no differences in the incidence of abnormal fibres in the controls and animals fed cypermethrin for 12 months (Trigg et al., 1977). Microscopic examination of the sciatic nerve from animals sacrificed at the conclusion of the study showed a small number of nerve fibres exhibiting slight Wallerian degeneration changes. These degenerative changes increased with age, but did not appear to be dose-related with respect to severity. Thus, cypermethrin did not induce neuropathy clinically nor did it induce histological evidence of nerve degeneration. There did not appear to be a significant increase in the incidence of tumour formation in either males or females over the course of the study. A large number of pituitary adenomas were reported predominantly in females at all doses including controls. This occurrence did not appear to be dose-related as similar events were recorded at all doses.

The NOAEL for toxicity was 100 ppm, equivalent to 5 mg/kg bw per day, on the basis of reduced body weights in both sexes at 1000 ppm, equivalent to 50 mg/kg bw per day. The NOAEL for carcinogenicity was 1000 ppm, equivalent to 50 mg/kg bw per day, the highest concentration tested (Annex 1, reference 33; McAusland et al., 1978).

Wistar-derived (Alderley Park) rats were fed diets containing cypermethrin (*cis* : *trans* 54 : 46; purity, 88.9–93.1%) at a concentration of 0, 20, 150 or 1500 ppm. Groups of 52 rats of each sex per dose and 12 of each sex per dose (interim kill) were treated for 24 and 12 months respectively, with corresponding groups (two groups of 52 of each sex and two groups of 12 of each sex) receiving the control diet. The group at the highest dose received 1000 ppm for the first 3–6 weeks but as few signs of toxicity were seen, the dose was increased to 1500 ppm. Rats were observed at least daily for clinical signs, with more detailed examinations also performed on each day for the first few weeks, then weekly. Body weight was recorded weekly for 14 weeks, then fortnightly, and food consumption was measured weekly for 13 weeks, at week 16, then every fourth week. Haematology and clinical chemistry parameters (excluding electrolytes) were measured in different animals, comprising 12 rats of each sex per dose before treatment, weeks 4 and 13, then every 13 weeks, and in a further six of each sex per dose at the interim sacrifice. Prothrombin and kaolin-cephalin times were evaluated at 52 and 104 weeks. Urine analysis was performed on the same animals evaluated for clinical chemistry, and at the same times, except that there was no testing of urine between 52 and 104 weeks. Urine was also analysed for cypermethrin metabolites in two or three animals of each sex per dose before treatment, then at 13-week intervals for 52 weeks. Ophthalmological examinations were conducted for 20 rats of each sex at 0 and 1000 ppm at weeks 52 and 104, on the same animals if possible. All animals, including unscheduled deaths, were necropsied, selected organs were weighed (including pituitary gland, but not thyroid) and tissues were taken for pathology. Liver APDM activity was assayed in six males and six females per group at 52 and 104 weeks, and livers were examined by electron microscopy for the quantification of smooth endoplasmic reticulum (SER).

There were no significant differences in survival among the treated groups. At 1000 ppm, clinical signs of frequent face washing, lack of coordination in hind limbs and/or increased sensitivity to sound were observed up to day 6 of dosing. Clinical signs that occurred when this dose was increased to 1500 ppm were described as very mild signs of neurotoxicity, and typical of those associated with pyrethroid poisoning, but no details were provided. Overall body-weight gain was reduced in males and females at 1500 ppm by 12% and 18%, respectively, relative to controls, and was associated with decreased food consumption in males during the first half of the study. At 150 ppm, body-weight gain was less than that of the combined control groups to a statistically significant extent for the most part of weeks 24 to 64 in females, and in week 68 in males. However, these differences were generally too small (4–6%) to be considered biologically significant. There were no treatment-related ophthalmoscopic effects. At 1500 ppm, erythrocyte parameters differed from control values to a statistically significant extent starting at 6 months, but not at all sampling points. These differences were small (< 5%), and within normal limits, so they were not considered to be adverse findings. Leukocyte and platelet counts were unaffected. Relative to controls, prothrombin time was increased in males at 1500 ppm at 12 and 24 months (Table 4), but there was no effect on kaolin-cephalin clotting time. Changes in clinical chemistry parameters relative to controls were limited to the groups at 1500 ppm (Table 4). Urea was increased in the first half of the study, particularly in females. Cholesterol and triglycerides were decreased in males mainly early in the study, with similar effects apparent in females from 6 months. As the animals aged, plasma lipid concentrations became very variable, so that no clear effects were apparent at termination. Also at 1500 ppm, urine volume (18 h) was decreased in males relative to controls at 12 months, accompanied by a slight increase in specific gravity and a slight decrease in urinary protein. The cypermethrin metabolite 3-(4'-hydroxyphenoxy)-benzoic acid was present in the urine of all treated groups, the amount increasing with dose.

Table 4. Significant findings related to haematology and clinical chemistry ($n = 12$)^a in rats fed diets containing cypermethrin

Finding	Time-point (weeks)	Sex	Dietary concentration (ppm)				
			0	0	20	150	1500
Prothrombin time (s)	104	M	14.4 (6)	15.0 (6)	15.2 (5)	15.0 (1)	15.8* (6)
		F	14.8 (6)	14.6 (5)	14.4 (5)	14.8 (3)	15.2 (6)
Urea	26	M	43.1	41.2 (9)	44.7	43.1 (11)	49.9*
		F	59.3	51.3	50.4 (11)	56.3	64.9**
Cholesterol (mg/dl)	65	M	175	174 (10)	165 (10)	145 (10)	132*
		F	148 (11)	138 (11)	153	128	105*
Triglycerides (mg/dl)	26	M	149	126	152	146	82**
		F	126	106	110	108	79*

From Milburn et al. (1982a)

F, females; M, male.

* Significantly different from combined control groups, $p < 0.05$ (t-test, two-sided).

** Significantly different from combined control groups, $p < 0.01$ (t-test, two-sided).

^a The numbers in parentheses represent the number of animals tested when this varied from $n = 12$.

At 1500 ppm, the weights of several organs (adjusted for body weight) differed from controls by $> 10\%$ (Table 5). In females, liver and lung weights were increased at 12 months, but were similar to controls at the end of the study. Kidney weights were decreased in both sexes at 24 months, though kidney weight was increased in males at 12 months. Spleen weights were decreased in both sexes at 24 months. As the organ-weight changes at 1500 ppm were not consistent throughout the study, and did not coincide with changes in clinical chemistry parameters, they are not considered to be related to treatment. Also, no treatment-related histopathological findings were detected in these or other organs examined microscopically.

Table 5. Selected organ weights adjusted for body weight (g)^a in rats fed diets containing cypermethrin

Organ	Time-point (months)	Sex	Body weight (g)				
			Dietary concentration (ppm)				
			0	0	20	150	1500
Liver	12	M	19.7 (12)	19.5 (12)	18.7 (12)	19.9 (10)	20.8 (12)
		F	12.5 (12)	13.3 (12)	13.8 (12)	12.8 (12)	15.1** (12)
Kidney	12	M	3.43 (12)	3.50 (12)	3.45 (12)	3.45 (11)	3.78* (12)
		F	2.36 (10)	2.50 (12)	2.64* (12)	2.52 (11)	2.52 (12)
	24	M	5.14 (27)	4.68 (27)	4.76 (21)	4.89 (27)	4.39 (27)
		F	3.60 (24)	3.51 (22)	3.59 (23)	3.53 (24)	2.98** (27)
Spleen	24	M	1.77 (26)	1.80 (26)	1.79 (26)	1.73 (21)	1.58* (27)
		F	1.32 (24)	1.21 (22)	1.28 (23)	1.29 (23)	1.18 (27)
Lung	12	M	1.87 (12)	1.86 (12)	1.89 (12)	1.85 (10)	1.88 (12)
		F	1.56 (12)	1.52 (12)	1.49 (12)	1.41 (12)	1.36* (12)

From Milburn et al. (1982a)

* Significantly different from combined control groups, $p < 0.05$ (t-test, two-sided).

** Significantly different from combined control groups, $p < 0.01$ (t-test, two-sided).

^a The numbers in parentheses represent the number of animals tested.

At 1500 ppm, liver APDM activity was increased and hepatic SER was increased in both sexes at 12 and 24 months, and in females at 150 ppm at 24 months (Table 6). These changes were considered to be adaptations, and not of toxicological significance.

Table 6. Liver aminopyrine *N*-demethylase activity and smooth endoplasmic reticulum proliferation^a in rats fed diets containing cypermethrin for 2 years

Finding	Sex	Dietary concentration (ppm)				
		0	0	20	150	1500
Aminopyrine <i>N</i> -demethylase activity (μmol formaldehyde/h per g liver)	M	15.3	17.1	17.6 (8)	17.1 (4)	20.9 (7)
	F	9.8	11.0 (5)	11.4	10.9	16.1**
Smooth endoplasmic reticulum proliferation§	M	141 (7)	127 (7)	138 (7)	132	156*
	F	104 (7)	119 (5)	113 (5)	135**	137**

From Milburn et al. (1982a)

F, female; M, male.

^a Means based on six observations per group unless otherwise indicated by the number in parentheses.

^b Figures represent the number of analysis points in a 320-point analysis grid coinciding with smooth endoplasmic reticulum.

Benign neurinomas of the heart were identified in one, one, and two male rats at 20, 150 and 1500 ppm, respectively. This type of tumour is not normally reported for Wistar rats, but given the flat dose–response relationship over a wide range, it is unlikely that these tumours arose as a result of treatment. Overall, there were no treatment-related neoplastic changes.

The NOAEL was 150 ppm, equivalent to 7.5 mg/kg bw per day, on the basis of clinical signs and decreased body-weight gain at 1500 ppm, equivalent to 75 mg/kg bw per day (Milburn et al., 1982a).

2.4 Genotoxicity

A battery of tests was conducted to determine the genotoxic potential of cypermethrin in vitro and in vivo (Table 7). The weight of evidence of the results indicated that cypermethrin is not genotoxic.

Table 7. Results of studies of genotoxicity with cypermethrin

End-point	Test object	Concentration	Purity (%)	Results	Reference
<i>In vitro</i>					
Reverse mutation (Ames)	<i>S. typhimurium</i> TA1538; <i>E. coli</i> WP2 <i>uvrA</i>	0–500 $\mu\text{g}/\text{plate}^a$	NR ^c	Negative	Brooks (1976)
Reverse mutation (Ames)	<i>S. typhimurium</i> TA98, TA100, TA1535, TA1537, TA1538	0–1000 $\mu\text{g}/\text{plate}^b$	NR ^c	Negative	Suzuki (1977)
Mitotic gene conversion	<i>S. cerevisiae</i>	NR ^{ac}	NR ^c	Negative	Brooks (1976)
Comet assay	Human peripheral lymphocytes	10, 50, 100, 200 $\mu\text{g}/\text{ml}$ in DMSO	97.1	Positive ^f	Undeger & Basaran (2005)
<i>In vivo</i>					
Chromosomal aberration	Chinese hamster	0, 20, 40 mg/kg bw per day for 2 days orally in DMSO ^d	NR ^c	Negative	Dean (1977)
Host-mediated assay	Mouse/ <i>S. cerevisiae</i>	0, 25, 50 mg/kg bw single oral dose; killed 5 h after intraperitoneal injection of suspension of <i>S. cerevisiae</i>	NR ^c	Negative	Brooks (1976)

Alkaline Comet assay	<i>D. melanogaster</i> larvae (first instar); brain ganglia and anterior mid-gut	0.004–0.5 µg/ml; killed after 96 ± 2 h exposure in the food	98.5	Positive ^e	Mukhopadhyay et al. (2004)
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NR, not reported; DMSO, dimethyl sulfoxide.

^a With and without metabolic activation (preparation from rats).

^b With and without mouse liver subcellular activation (preparation from six strains of PCB-treated mice)

^c Summarized from JMPR 1979 evaluation (Annex 1, reference 33); these details not provided therein.

^d Positive control, cyclophosphamide at 100 mg/kg bw; negative control, DMSO.

^e A dose-related increase relative to controls was seen in tail DNA, tail length and tail moment in the single-cell gel electrophoresis (Comet) assay for both tissues examined.

^f Increased tail length (50 and 200 µg/ml), increased tail intensity (10 and 200 µg/ml) and increased tail moment (200 µg/ml) were observed, but as dose–response relationships were lacking, only the results at 200 µg/ml were considered to significantly increase DNA damage in human lymphocytes in this test.

2.5 Reproductive toxicity

(a) Multigeneration studies

Rats

Groups of 30 male and 30 female Wistar rats received diets containing cypermethrin (purity, 98%) at a concentration of 0, 10, 100 or 500 ppm for 5 weeks before mating and then throughout pregnancy and lactation for three successive generations. Two litters were bred per generation. The first litters were discarded at weaning. Males and females from the second litter were randomly selected to breed the next generation. A significant reduction in body-weight gain was seen in the male and female parent rats receiving cypermethrin at 500 ppm in all three generations. This was correlated with a reduction in food consumption. Litter size was reduced at 500 ppm in the F_{1a} litter at birth and after 7 and 21 days. Litter weights were reduced at 500 ppm in the F_{1a} litters on days 7, 14 and 21 of lactation. No other effects on fertility or reproduction parameters were found and no compound-related gross or microscopic pathological findings were noted in any rats.

The NOAEL for parental toxicity was 100 ppm, equivalent to 7.5 mg/kg bw per day, on the basis of reduced body-weight gain and food consumption at 500 ppm, equivalent to 38 mg/kg bw per day. The NOAEL for reproductive toxicity was 100 ppm, equivalent to 7.5 mg/kg bw per day, on the basis of reduced litter size and litter weights at 500 ppm, equivalent to 38 mg/kg bw per day (JECFA, 1996; Hend et al., 1978; Fish, 1979; Thorpe, 1985).

Groups of 15 male and 30 female Wistar (Alderley Park) rats received diets containing cypermethrin (purity, 91.5%, *cis* : *trans* 55 : 45) at a concentration of 0, 50, 150 or 750 ppm for 11–12 weeks before mating, then throughout pregnancy and lactation for three successive generations. Rats in the F₀ group receiving the highest dose were initially treated at 1000 ppm, but due to clinical signs of neurotoxicity in most animals in the first 3 weeks of the study, this was reduced to 750 ppm after 12 weeks. Clinical observations were performed at least daily, and food consumption was recorded weekly. Body weights were recorded weekly in the period before mating and during pregnancy, then every 4 weeks until termination (but weekly during pregnancy). Pup body weights were recorded on postnatal days 0, 4, 10, 21 and 28. Two litters were bred per generation, with males and females from the second litter randomly selected to breed the following generation. Parental males were sacrificed after mating for the second litters of each generation, and parental females were killed after weaning (21 days postpartum, except for the F_{1a} litters that were separated from their mothers after 28 days). Gross necropsies were performed on all parental animals and 50% of each generation of offspring, the remainder being discarded. Selected organs were weighed and tissues taken for histopathology

for premature deaths, 10 male and 25 female F_1 parents, 5 pups of each sex per group in the F_{1b} and F_{2b} , and 10 pups of each sex per group in the F_{3b} .

Several parental deaths occurred in all groups, but aside from one male at 1000 ppm that was killed in extremis on day 9 after showing signs of severe neurological disturbance, they were not attributed to treatment. Clinical signs observed in most F_0 parental animals during the first 3 weeks of exposure at 1000 ppm were high-stepping gait, ataxia/uncoordinated movement, increased sensitivity to sound, piloerection, increased or decreased activity and unsteady gait, with a low incidence of trembling, weak, hunched, salivation, and increased sensitivity to touch. Toxicity in the F_0 and F_2 parental groups was indicated by significant reductions in body-weight gain in the periods before mating of 10–40% for both sexes at ≥ 750 ppm, and at 150 ppm for F_0 females and F_2 males and females (approximately 10%). Relative to controls, food consumption (g per rat) was reduced at 1000/750 ppm in parental males of all generations, in parental females in the F_0 and F_2 , and in 150 ppm F_0 females. During pregnancy, body-weight gain in F_{1b} and F_{2b} females at 750 ppm was 10% less than that of controls up to day 14 of gestation and weight gain in the F_{1b} , F_{2b} and F_{3b} litters at 750 ppm was also less, relative to that of controls (approximately 12%). There were no treatment-related effects on fertility, gestation length, live births, litter size or pup survival index. At 750 ppm, a mammary gland adenocarcinoma was observed in one F_1 parental female, but as this is a common neoplasm in this strain of rat, this isolated finding was not attributed to treatment. One abnormal pup was reportedly observed at 750 ppm in both the F_{2b} and F_{3a} , but no details were provided. Three weanlings died or were killed in extremis. The cause of death of a F_{2a} female pup at 750 ppm could not be determined due to cannibalization. One F_{3a} male pup at 750 ppm had severe internal hydrocephalies, but this abnormality was also seen in a control pup and a pup at 150 ppm in the F_{1b} , so was not attributed to treatment. Clinical signs of ataxia were noted for one male F_{1a} pup at 150 ppm, but histopathology indicated congenital lymphoid hypoplasia, and as there were no similar findings at the highest dose, this was not considered treatment-related. Microphthalmia was observed in three pups in the F_{1b} (0, 150, and 750 ppm), and was not seen in subsequent generations, so was not ascribed to treatment. Overall, there were no treatment-related macroscopic or microscopic findings in the parental animals or the F_{2b} pups.

The NOAEL for parental toxicity was 50 ppm, equal to 3.8 mg/kg bw per day, on the basis of reduced body-weight gain at the higher doses. The NOAEL for pup development was 150 ppm, equal to 11 mg/kg bw per day, due to reduced body-weight gain during lactation. There were no reproductive effects at the highest dose of 750 ppm, equal to 56 mg/kg bw per day (Milburn, 1982b).

(b) *Dominant lethal studies*

Mice

Groups of 12 male mice (36 mice were used as controls) were given cypermethrin (dissolved in dimethyl sulfoxide) as a single dose at 0, 6.25, 12.5 or 25 mg/kg bw or as five successive daily oral doses at 0, 2.5 and 5.0 mg/kg bw. After dosing, each male was caged with three virgin females for 7 days. The mating procedure was repeated weekly over an interval of 8 weeks in a standard dominant-lethal test. Females mated to males treated with five daily oral doses at 2.5 mg/kg bw and those mated to males receiving a single dose of 12.5 mg/kg bw showed a significant reduction in the incidence of pregnancy during the second and third week respectively of the onset of treatment. This did not occur with other groups receiving higher or lower doses or at other intervals. In females mated to males treated daily with doses of cypermethrin, a significant reduction in fetal implants was observed during the second week of mating. Early fetal deaths were increased in the second week at 5 mg/kg bw. No such increases occurred in any other weekly interval or any other dosed group. Thus, multiple administration of cypermethrin on five successive days induced a significant reduction in fetal implants during the second week of mating and a marginal increase in early fetal deaths at the same time interval.

To evaluate the potential (noted above) for a dominant lethal effect, a second experiment was performed. Groups of 12 male mice (the control group consisted of 36 mice) were given cypermethrin (dissolved in DMSO) as five daily oral doses at 0, 2.5, 5.0, 7.5 or 10 mg/kg bw. After dosing, each male was mated with three virgin females for 4 days and subsequently provided with virgin females every 4 days for 3 weeks. Female mice were examined for evidence of dominant lethality 13 days after mating. In addition, 40 males of proven fertility were treated for five successive days at the same doses, 0, 2.5, 5.0, 7.5 and 10 mg/kg bw. These animals were also mated with four virgin females on four successive days for 3 weeks. Four animals from each group were sacrificed for histological examination of the testes and epididymis on days 1 and 7 after last dose. In contrast to the previous trial, no reduction in fetal implants was noted in any of the animals mated with cypermethrin-treated males. The number of early fetal deaths was marginally increased at the highest dose in the 12–16 days after dosing and in the first 4 days after treatment with 7.5 mg/kg bw in males. In the groups of animals examined histologically, no abnormalities were detected in the testes and epididymis and there were no observable histological differences between any of the test groups and the controls (Annex 1, reference 33; Dean et al., 1977).

(c) *Developmental toxicity*

Rats

Groups of 25 pregnant female Sprague-Dawley rats were given cypermethrin at a dose of 0, 17.5, 35 or 70 mg/kg bw per day by gavage in corn oil during days 6 to 15 of gestation. The females were sacrificed on day 21 of gestation for examination of uterine contents, and fetuses were given a gross examination, including skeletal and somatic examinations. One female at 70 mg/kg bw per day was found dead and one female at 70 mg/kg bw per day was killed for ethical reasons following severe convulsions. Eleven out of 25 females in the group at 70 mg/kg bw per day showed neurological disturbances (ataxia, convulsions, hypersensitivity to noise). A dose-related reduction in maternal body-weight gain was observed in the groups at 35 and 70 mg/kg bw per day. There were no indications of any embryotoxic or teratogenic effects.

The NOAEL for maternal toxicity was 17.5 mg/kg bw per day on the basis of reduced body-weight gain at 35 mg/kg bw per day and higher. The NOAEL for developmental toxicity was 70 mg/kg bw per day on the basis of the absence of fetal effects at the highest dose tested (Annex 1, reference 33; Tesh et al., 1978).

Rabbits

Groups of 20 pregnant rabbits (30 rabbits were used as an additional control group) were given cypermethrin at an oral dose of 0, 3, 10 or 30 mg/kg bw dissolved in corn oil by gavage from day 6 to day 18 of gestation. On day 28 of gestation, the rabbits were sacrificed and examination made of live fetuses, dead fetuses, resorption sites and corpora lutea. Live fetuses were maintained for 24 h to assess viability. Fetuses were also examined for gross somatic and skeletal deformities. There was no significant mortality or differences in weight gain during gestation. There were no significant differences between control and test groups with respect to pregnancy, fetal death or survival. Although a wide range of skeletal and visceral abnormalities were found in the course of the study, there were no differences between control and test groups with respect to abnormalities.

The NOAEL for maternal and developmental toxicity was 30 mg/kg bw per day as there were no treatment-related effects at the highest dose tested (Annex 1, reference 33; Dix, 1978).

Groups of 20 mated New Zealand White rabbits were given cypermethrin technical (purity, 95.7%) at a daily dose of 0, 100, 450 or 700 mg/kg bw per day as a 50% concentration in corn oil

by gavage for days 7 to 19 of gestation. The dose was varied by adjusting the volume, the control group receiving the same volume of corn oil as the group at the highest dose. Animals were observed daily for clinical signs and body weight was recorded on day 0 of gestation, daily during days 7–19 of gestation, and on days 24 and 29. A set amount of food (approximately 150 g/dam per day) was provided, and usually consumed in its entirety. On day 29, the dams were killed and necropsied. Gravid uterine weights were recorded, uteri were examined, and the weight, sex, external, soft tissue, head and skeletal alterations of fetuses were recorded.

One dam at 700 mg/kg bw per day was killed on day 11 due to swelling, scabbing and severe ulceration of the vaginal area (red fluid-filled cyst-like swelling in the vaginal wall noted at necropsy), and one dam at 450 mg/kg bw per day was killed on day 26 after aborting. One dam in the control group and one dam at the lowest dose died due to dosing accidents. Otherwise, clinical signs likely to be treatment-related comprised ataxia, red staining of the cage pan liner, and decreased faeces in dams receiving 700 mg/kg bw per day, and pink or red staining of the cage pan liner at 450 mg/kg bw per day, although in the absence of other effects at this dose, this was not considered an adverse finding. Maternal body-weight gain at 700 mg/kg bw per day was less than that in the control group for days 7–19 (0.28, 0.27, 0.21, 0.18*g at 0, 100, 450 and 700 mg/kg bw per day respectively; * $p = 0.048$, Welch trend test). At 700 mg/kg bw per day, persistent truncus arteriosus and abnormal course of the aortic arch, along with additional lobulation of the left lung were observed in one fetus. Another fetus at this dose had misshapen thoracic centrum, lumbar centrum misshapen, absent thoracic transverse process and enlarged thoracic transverse process. As most of these malformations had been seen in historical controls, these single findings were not attributed to treatment. An increase in incompletely ossified hyoid bodies at 700 mg/kg bw per day (fetal incidence, 12.4 %; litter incidence, 44.4%) compared with the control group (4%/20%) was also dismissed, as this is a common skeletal variation in rabbits, and findings were within the range of incidence for historical controls (2.1–14.6%/15.8–66.7%). Overall, there was no evidence of fetal toxicity at any dose.

The NOAEL for maternal toxicity was 450 mg/kg bw per day on the basis of decreased body-weight gain and clinical signs at 700 mg/kg bw per day. The NOAEL for fetal toxicity was 700 mg/kg bw per day, the highest dose tested (Freeman, 1994).

2.6 *Special studies*

(a) *Neurotoxicity*

Rats

Groups of 6 or 12 male rats and 6 or 12 female rats were given cypermethrin (purity, 97%) as a single oral dose at 100, 200 or 400 mg/kg bw as a 5% dispersion in corn oil. The observation period was 9 days. The rats were then killed and examined histologically. All rats showed signs of intoxication. At 400 mg/kg bw, within 4 h after dosing, rats developed signs of intoxication, including coarse tremors, spasmodic movements of the body and tail and bleeding from the nose. Tip-toe walking was also seen in some rats. All animals, except one, were killed, owing to the severity of the signs. Histological examination revealed swelling of the myelin sheaths and breaks of some of the axons of the sciatic nerves. At 200 mg/kg bw, similar effects were observed; eight rats of each sex died or were killed within 48 h of dosing. The remaining four rats survived the observation period. At 100 mg/kg bw all animals survived the 9 days. One female out of 12 showed minimal lesions in the sciatic nerve in this group. A no-effect level (NOEL) could not be determined (Annex 1, reference 33; Carter & Butterworth, 1976).

The aim of the following study was to compare the effects of cypermethrin with permethrin, but only the aspects of the study relevant to cypermethrin are considered here. The neurobehavioural effects

of cypermethrin (purity, 97%; containing approximately equal proportions of *cis*- and *trans*-isomers), were studied in male and female adult Long Evans rats, employing a functional observational battery (FOB) and an automated measure of motor activity. Cypermethrin was administered as a single dose at 0, 20, 60 or 120 mg/kg bw by gavage to groups of eight males and eight females for the FOB, and groups of 12 males and 12 females for the tests for motor activity. For the tests for motor activity, the highest dose was reduced to 100 mg/kg bw owing to lethality in the FOB study. As preliminary studies indicated that different effects were evident at different times after dosing, FOB assessments were made at 1.5 h and 3 h after dosing, as well as immediately before dosing, with motor activity testing performed at 3, 24 and 48 h after treatment. One male and six female rats treated with cypermethrin at 120 mg/kg bw died on the day of dosing, as did two males at 100 mg/kg bw. Treatment with cypermethrin affected gait, muscle function, tone and equilibrium, and produced autonomic signs and burrowing behaviours, with female rats generally being the more sensitive sex. Animals were often observed lying flat in the home cage, with tremors; they displayed excessive lateral head movements on the open field; and profuse salivation was observed. At ≥ 60 mg/kg bw, salivation, choreoathetosis, altered righting reflex, splayed limbs and flattened posture were observed; urination, landing foot-splay and click response were increased; and arousal, grip strengths, touch response and tail-pinch response were decreased. Resistance to removal from the home cage, and gait abnormalities were increased, and total activity counts were decreased at 20 mg/kg bw and above. Effects were generally present in both sexes, and peaked within a few hours of dosing. Notably, salivation and increased removal reactivity (males) peaked at 1.5 h, subsiding by 3 h, at which point motor and sensory effects were the most evident, with motor effects persisting for 1 to 2 days after dosing, particularly in females. A NOEL could not be determined (McDaniel & Moser, 1993).

In a study on the effect of cypermethrin on spontaneous motor function, groups of 8–18 male Long Evans rats were given cypermethrin (49 : 51, *cis* : *trans*-isomer ratio) at a dose of 0.1 to 120 mg/kg bw by gavage. A marked decrease in spontaneous motor function was seen at 40 mg/kg bw. The dose producing the minimum reliably detectable (30%) decrease in activity was estimated to be 10 ± 1.3 mg/kg bw, and the highest no-effect level was 4.3 mg/kg bw (95% confidence limits, 2.0–6.5 mg/kg bw) (Wolansky et al., 2006).

In a paired feeding study to examine the neurotoxicological effects of high dietary concentrations of cypermethrin, groups of 10 male rats were fed diets containing cypermethrin (45 : 55, *cis* : *trans*-isomer ratio) at a concentration of 0, 1250, 2500, or 5000 ppm for 14 days. Growth was monitored and clinical evaluations for adverse behaviour were recorded during the course of the study. Gross pathology on tissues and organs and microscopic examination of the sciatic nerve were performed at the conclusion of the study. At 5000 ppm, mortality was observed with all rats either dying or being sacrificed in a moribund condition within the first week. At 2500 ppm, six out of 10 rats died before the conclusion of the study. There was no mortality in the group at the lowest dose. Clinical signs of neurotoxicity were characterized by an impaired ability to walk and splayed hind limbs. In extreme cases, clinical signs of ataxia and paralysis were reported. Other clinical signs included: hypersensitivity to external stimuli, gross disorientation and convulsions, the latter generally seen at high doses. The neurotoxic signs of poisoning observed in the group at 1250 ppm after day 3 were spontaneously reversed by day 9 when all surviving animals that were initially affected appeared to be normal. Remission of ataxia in the group at 2500 ppm was also noted within 11 days of treatment. Growth reduction was observed in all animals in the study. At the lowest dose, the rate of growth was delayed for the first few days after which time the rate was consistent with that of controls for the remainder of the study. The absolute body weight of the treated animals, however, was significantly lower than that of the controls at the conclusion of the 2-week study. Reduction in body weight was consistent with reduction in food consumption. Ultrastructural changes in the sciatic nerve were

observed at the intermediate and highest dose, although the number of animals examined was small. There was some evidence of axonal damage in the myelinated nerves primarily in the groups at the intermediate and highest dose. Changes in unmyelinated axons were not observed. In general, the histological and ultrastructural changes in the sciatic nerve, accompanied by clinical signs of poisoning, were not readily apparent at low doses. Thus, cypermethrin, at acutely toxic dietary concentrations, induces damage to sciatic nerves, the clinical signs of which may be reversible (Annex 1, reference 33; Glaister et al., 1977a).

Groups of six male and six female rats (14 males and 14 females in the control group) were fed diets containing cypermethrin *trans*-isomer at a concentration of 0, 30, 100, 300, 1000 or 3000 ppm for 5 weeks. No mortality was observed over the course of the study. Food intake and growth were reduced in the group at the highest dose. Alkaline phosphatase activity was increased at the two higher doses. Minimal changes were observed at the two higher doses, including several haematological parameters (erythrocyte count and haemoglobin concentration). Spleen weights were increased at 1000 ppm and higher and kidney and liver weights were increased at 3000 ppm. Gross and microscopic histopathological examination of several tissues and organs revealed no cypermethrin-related injuries. Special reference was given to the examination of the sciatic nerve, which showed no damage (Annex 1, reference 33; Hend & Butterworth, 1977a).

Groups of rats (six male and six female rats per group, 10 of each sex were used as controls) were fed diet containing *cis*-isomer at concentrations of 0, 30, 100, 300, 750 and 1500 ppm for 5 weeks following a protocol similar to that described above. Mortality was observed at 1500 ppm at intervals from 4 to 17 days after the start of the experiment, with all animals displaying signs of poisoning by neurotoxicity. At the next lower dose (750 ppm), almost all of the animals showed gross neurotoxic signs of poisoning, abnormal sensitivity to sound and touch and slight cases of ataxia. There was no compound-related mortality at doses of 750 ppm or less. Growth was reduced at 750 ppm over the course of the study. Significant reductions in food intake were also noted at concentrations of 300 ppm and higher at the initial phase of the study. Gross examination of tissues and organs again revealed a reduction in heart, liver, spleen and kidney weights. Adjustment of the data for terminal body weight revealed a statistically significant change in kidney weight at 300 ppm and higher, while liver weight was increased at 750 ppm. Plasma protein concentrations were decreased and urea and potassium concentrations were increased in male rats at 750 ppm. Gross and microscopic examinations of tissues and organs showed substantial degeneration in both the liver and sciatic nerve at 1500 ppm and higher. Liver lesions consisted of a coagulative necrosis of hepatocytes occurring in males and females. The sciatic nerve from both sexes showed swelling and breaks in axons with concomitant myelin degeneration and vacuolation. There were no lesions observed in the brain or the spinal cord (Annex 1, reference 33; Hend & Butterworth, 1977b).

Groups of 20 male and 20 female rats were fed diets containing cypermethrin (44 : 56 *cis* : *trans* ratio; purity, 92%) at a concentration of 0, 75, 150 or 1500 ppm for 90 days. Random samples were chemically analysed periodically during the course of the study. At the conclusion of the study, four rats of each sex were maintained on control diets for a 1-week recovery period. There was no mortality over the course of the study, although males and females at 1500 ppm had reduced body weight and food consumption in the first month. After the first month, the growth rate was similar to that of controls, although the rats never achieved the weight noted in the other groups. At the conclusion of the study, haematology, clinical chemistry, urine analysis and histopathology were performed on all rats. With the exception of a slight increase in myeloid/erythroid ratio in the bone marrow of female rats fed at a dietary concentration of 1500 ppm, there were no haematological or urine analysis effects. An increased microsomal (SER) oxidative activity was noted as an increased

hepatic APDM activity in males and females at 1500 ppm and in males at 150 ppm. These adaptive changes in the subcellular portions of the liver were substantially reversed within the 4-week recovery period. Increased liver weight was not noted on gross examination at the conclusion of the study. A slight reduction in pituitary weight of males, while statistically significant, was not dose-related. A slight decrease in female kidney weight was dose-dependent and significantly different from control values at the highest dose. The decrease in kidney weight in males was slight and not significantly different from controls in any of the dietary concentrations. Gross and microscopic (including electron microscopic) examinations of tissues and organs showed no significant differences from the observations noted in controls. Examination of the sciatic nerve from animals in the control group and in the group at 1500 ppm showed no changes that could be directly attributable to the presence of cypermethrin in the diet. Seven of the 16 males at 1500 ppm and 2 of 12 male controls showed slight changes in myelin that may or may not have been brought about by histological fixation of the material before examination. The condition of the sciatic nerve of females was similar to that noted in females in the control group. There were no effects noted in unmyelinated axons in males and females. Interim histological examination at 30 days, during which time clinical signs of poisoning were noted, was not performed in this study.

The NOAEL was 150 ppm, equivalent to 150 mg/kg bw per day, on the basis of clinical signs and reduced body-weight gain and food consumption at 1500 ppm, equivalent to 150 mg/kg bw per day (Annex 1, reference 33; NOAEL based on JMPR summary of Glaister et al., 1977b).

Hamsters

Groups of male and female Syrian hamsters were given cypermethrin at oral doses exceeding the median lethal dose (LD_{50}) in an attempt to define clinical signs of poisoning and to evaluate histological damage to the sciatic nerve. At doses of 794 mg/kg bw and higher, all animals showed clinical signs of poisoning including tremors, abnormal irregular movements, and an unusual gait. As noted with rats, axon and myelin degeneration was noted in all groups treated. The lesions included swelling and breaks in the axons and clumping of myelin (Annex 1, reference 33; Butterworth & Clark, 1977).

A series of experiments was performed to further evaluate the neurotoxic potential after short-term, oral administration of cypermethrin to Chinese hamsters. Clinical examination, functional testing and enzyme determinations using β -galactosidase and β -glucuronidase were performed. The functional test consists of measuring the mean slip angle where the animal is maintained on an inclined plane that steadily increases its angle until the animal can no longer maintain a stationary position. The average angle of five replicate trials constituted the mean slip angle test.

Groups of 20 male and 20 female Chinese hamsters were given cypermethrin at a oral dose of 40 mg/kg bw followed by a dose of 20 mg/kg bw per day for the following 4 days. Fifteen animals of each sex served as controls. There was extensive weight loss in all dosed groups and some mortality was observed, primarily as a result of the initial administration of 40 mg/kg bw. There was a loss of fur and a dermal ulceration was observed in the early parts of the study. This dermal occurrence was transient, disappearing rapidly after the treatments were concluded. There was significant weight loss in the initial phase of the study. However, after the last dose, the surviving animals rapidly gained weight at a rate consistent with the control animals. There were no effects noted on the mean slip angle experiment and a marginal increase in β -galactosidase activity was observed in peripheral nerve.

A further experiment with five male and five female Chinese hamsters given cypermethrin at a dose of 0, 5, 10 and 20 mg/kg bw per day for 5 days showed no mortality over the course of the study. There was a slower growth of the animals treated at 20 mg/kg bw, which was reversed by the conclusion of the treatment period. Hyperexcitability was noted in one female at the highest dose. There were no notable differences in behaviour in any other animals. There was a significant deficit in the mean slip angle test with females showing an earlier dose-related deficit than noted in males.

The females recovered from this deficit earlier than males, who showed an erratic pattern of recovery. β -Galactosidase activity was increased at all doses 3 weeks after the start of the experiment. This increase was statistically significant at the intermediate and highest doses. Dermal irritation and fur loss was not noted in this experiment.

Sixteen male and sixteen female Chinese hamsters were given cypermethrin as five daily doses at 30 mg/kg bw or a control of dimethyl sulfoxide only. An additional group of eight animals of each sex were given methylmercury at a dose of 7.5 mg/kg bw as five daily doses as a positive control. With cypermethrin, there was no mortality and the rate of weight gain was consistent with that of the controls. There was transient dermal irritation accompanied by skin ulceration in the majority of the animals. This condition disappeared at the conclusion of the treatment interval. One male administered cypermethrin had an unusual gait. There was a slight deficit in the inclined-plane test which was noted in the early parts of the experiment but was absent by the end of the third week. Increases in β -glucuronidase and β -galactosidase activity were evident in peripheral nerve tissue. The Meeting concluded that cypermethrin when administered at high 'subacute' doses, produced changes in the sciatic nerve consistent with Wallerian degeneration. Biochemical changes were evident as increases in β -glucuronidase and β -galactosidase activity and clinically functional deficits were noted (Annex 1, reference 33; Dewar & Moffett, 1978b).

Hens

In a study of delayed neurotoxicity, six adult domestic hens received cypermethrin at a dose of 1000 mg/kg bw per day in DMSO for 5 days. After 3 weeks, the dosing regime was repeated and a further 3 weeks later the birds were killed. Positive-control (tri-*ortho*-tolyl phosphate) and negative-control (not dosed) groups were used. None of the cypermethrin-treated hens developed any signs of intoxication. Histological examination of the nervous system revealed no lesions. All birds receiving the positive control developed clinical signs of neurological damage within 15 days and became progressively more unsteady and ataxic thereafter. Histological examination of these animals showed lesions in the cerebellum, sciatic nerve and spinal cord, including axonal and myelin degeneration (Annex 1, reference 33; Owen & Butterworth, 1977).

In a study to determine the LD₅₀ and the delayed neurotoxicity of cypermethrin (purity, 87.8%; *cis* : *trans* 53 : 47) in hens, cypermethrin (in corn oil) was given as single gavage doses at 0, 4096, 5120, 6400, 8000 or 10 000 mg/kg bw to groups of five hens in the LD₅₀ study and at 0, 500, 2500, 5000 or 10 000 mg/kg bw to groups of 10 hens in the study of neurotoxicity. Ten birds were dosed similarly with tri-*ortho*-cresyl phosphate (TOCP) as the positive control in the study of neurotoxicity. In the study of LD₅₀, hens were observed daily for clinical signs in the 2 weeks after treatment, and body weight was measured weekly (commencing 2 weeks before dosing). In the study of neurotoxicity, hens were assessed daily for ataxia, body weight was measured twice weekly for 3 weeks, all birds were examined post mortem, and the spinal cord and sciatic nerve were examined microscopically. In the study of LD₅₀, there were no mortalities and no treatment-related clinical signs for 14 days after dosing. In the study of neurotoxicity there were no deaths except for one positive control hen that was sacrificed on day 19 after exhibiting severe ataxia. Ataxia was observed in all hens in the positive-control group, but not in any birds treated with cypermethrin. Relative to negative controls, body weights in cypermethrin-treated hens were decreased in the study of LD₅₀ at ≥ 5120 mg/kg bw in the first week after dosing, and in all treated groups in the study of neurotoxicity for the first 3 days after dosing, which was associated with reduced food consumption. No abnormalities were observed at macroscopic examination. Microscopic examination revealed a slightly increased incidence of abnormalities of the spinal cord at 5000 and 10 000 mg/kg bw per day relative to controls, which were also slightly more severe in two of the hens at 10 000 mg/kg bw per day, but as no clinical signs of neurotoxicity were observed in the treated hens, it is unlikely that these represented effects

of treatment. Microscopic findings in most hens in the positive-control group were more severe than in the negative-control group. The LD₅₀ of cypermethrin in hens was therefore > 10 000 mg/kg bw. There was no evidence of delayed neurotoxicity in cypermethrin-treated hens (Roberts et al., 1981).

(b) *Biochemistry and electrophysiology*

Preliminary evidence suggested that an increase in the activity of certain lysosomal enzymes in peripheral nerves and deficits in tests of behavioural function could serve as indicators of peripheral nerve damage. During Wallerian degeneration, the activity of enzymes such as β -glucuronidase and β -galactosidase as well as other enzymes in nerve preparations were shown to be increased significantly (Annex 1, reference 33; Dewar, 1977a).

Groups of male and female rats were given cypermethrin (1 : 1 *cis* : *trans*) at doses ranging from 25 to 200 mg/kg bw day by oral intubation as a 10% w/v solution in DMSO for five consecutive days. A dose-related functional deficit was observed when the mean slip angle test and the landing foot spread test were applied to the animals. The deficit was maximal from 6 to 14 days after the beginning of treatment and complete functional recovery occurred within 4 weeks. Substantial variation in data from the landing foot-spread test was noted. Data were inconsistent over the course of the study. β -Glucuronidase activity was increased in a dose-dependent fashion in both males and females. The results suggest that cypermethrin produced a primary axonal degeneration, readily measurable 28 days after treatment as an increase in β -glucuronidase activity and in deficits in specific behavioural-function testing of rats (Annex 1, reference 33; Dewar, 1977b).

When further studies were performed on the biochemical indices of nerve degeneration to compare results with known degenerating compounds (methylmercury), it was observed that the changes in β -glucuronidase and β -galactosidase activity were considerably smaller and less reproducible than those obtained after methylmercury poisoning (7.5 mg/kg bw per day for 7 days). Compared with central versus (vs) peripheral nerve damage, there was no evidence that the trigeminal nerve was more sensitive to the effects of cypermethrin than the sciatic and posterior tibial nerves. At near-lethal doses of cypermethrin, biochemical changes in the trigeminal nerve were consistent with those of Wallerian degeneration. The changes were similar qualitatively to those seen with methylmercury, but were quantitatively much less intense (Annex 1, reference 33; Dewar & Moffett, 1978a).

Electrophysiological studies were performed to determine whether intoxication with cypermethrin given as single dose or over a short period of time produced changes in the conduction velocity of slower fibres in peripheral nerves or alterations in the maximal motor conduction velocity. There was no evidence to suggest that cypermethrin, at doses that induced severe clinical signs of intoxication, including ataxia, had any effect on maximal motor conduction velocity or conduction velocity of the slower motor fibres in peripheral nerves. Doses used in the study ranged from a single dose at 200 mg/kg to seven consecutive doses at 150 mg/kg followed by two doses at 400 mg/kg. At near-lethal doses there were no effects noted on conduction velocity in the slower motor fibres of the sciatic nerve and tail or on the maximal conduction velocity, even in the presence of clinical signs of acute intoxication and at doses at which previous studies had shown functional degeneration. These electrophysiological findings are reflective of motor function which would suggest that the physiological and functional deficits observed as a result of acute intoxication may be primarily sensory in nature (Annex 1, reference 33; Dewar & Deacon, 1977).

The following experiment in Wistar rats was performed in two phases. The first phase was conducted to determine the time-course for neurochemical changes occurring in the sciatic/posterior

tibial nerve (SPTN), trigeminal nerve and trigeminal ganglion after treatment with cypermethrin for 5 days per week for 4 weeks. Cypermethrin (purity, 98.2%) was given at a dose of 150 mg/kg bw per day in DMSO (reduced to 100 mg/kg bw per day in arachis oil, after 10 doses, because of mortality). Alpha-cypermethrin (purity, 96.6%) was given at a dose of 37.5 mg/kg bw per day in DMSO (also reduced after 10 days to 25 mg/kg bw per day in arachis oil). Five animals of each sex, treated with either cypermethrin or alpha-cypermethrin, were killed at 2, 3, 4, 5, 6, 8, 10 or 12 weeks and examined.

Dosing resulted in the death of 56% of the cypermethrin-treated animals and 21% of the alpha-cypermethrin-treated animals. The most frequent signs of intoxication included abnormal gait, ataxia, lethargy, chromodacryorrhoea, salivation and hypersensitivity to sensory stimuli. The β -glucuronidase and β -galactosidase activities in the SPTN were increased at 5, 6 and 8 weeks, when compared with controls. The increase was maximal after 5 weeks, and after 12 weeks was comparable to that in the controls. No significant enzyme changes were found in the trigeminal ganglia and trigeminal nerve of treated animals.

The second phase was conducted to establish a dose that did not cause peripheral nerve degeneration in the SPTN, trigeminal nerve and ganglia. Groups of 10 male and 10 female rats were given cypermethrin at a dose of 37.5, 75 or 150 mg/kg bw per day in DMSO or alpha-cypermethrin at a dose of 10, 20 or 40 mg/kg bw per day in DMSO, on 5 days per week for 4 weeks. A control group of 10 animals was used. Signs of intoxication similar to those reported in the first phase were seen at the highest dose. A large increase in β -glucuronidase and β -galactosidase activities in the SPTN was seen with cypermethrin at 150 mg/kg bw per day and with alpha-cypermethrin at 40 mg/kg bw per day. In the groups given cypermethrin at 75 mg/kg bw per day or alpha-cypermethrin at 20 mg/kg bw per day, a small increase in β -galactosidase activity was found in the distal and proximal sections of the SPTN. The magnitude of the enzyme changes was similar to those in the first phase. Significant enzyme changes were also found in the trigeminal ganglia and to a lesser extent in the trigeminal nerve of the groups given cypermethrin at 75 or 150 mg/kg bw per day and alpha-cypermethrin at 20 or 40 mg/kg bw per day. No peripheral nerve degeneration was observed with cypermethrin at 37.5 mg/kg bw or with alpha-cypermethrin at 10 mg/kg bw (JECFA, 1996; Rose, 1983).

Alpha-cypermethrin

3. Biochemical aspects: absorption, distribution, metabolism and excretion

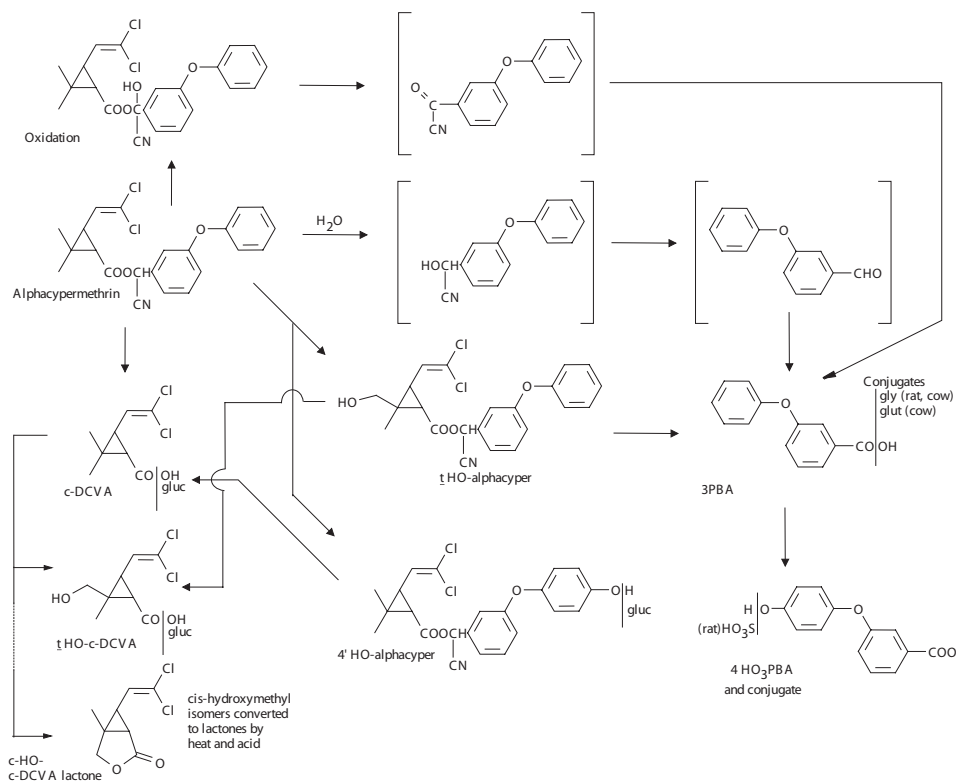
The elimination and retention of alpha-cypermethrin was investigated in male and female Wistar rats. Groups of five male and five female rats received [^{14}C -benzyl]alpha-cypermethrin (radiochemical purity, 99.6%) at a dose of 1.9 mg/kg bw in corn oil by gavage, and were sacrificed 96 h later. The distribution of radioactivity in the excreta was 51–54% in the urine and 38–43% in the faeces. Approximately 75% of the radioactivity in the faeces was unchanged alpha-cypermethrin, with no evidence of conversion from the *cis*-isomer to the *trans*-isomer. Other metabolites identified in faeces were WL 48801 (a dihydroxy metabolite, 4%), 3-(4-hydroxyphenoxy) benzoic acid (6%) and 3-phenoxybenzoic acid (less than 1%). The proposed metabolic pathway for alpha-cypermethrin is provided in [Figure 2](#). More than 75% of the administered radioactivity was excreted within 24 h of treatment. Low concentrations of radioactivity were found in the tissues (total, 1.5% of administered radioactivity). The highest concentration was in fat (0.42 and 0.22 $\mu\text{g/g}$ tissue for males and females, respectively), with the concentration of radioactivity in other tissues at least an order of magnitude less. There were no sex differences (Hutson, 1982).

The depletion of radiolabel from liver, kidney, skin and fat (parovarian, peri-renal and subcutaneous) was studied in 24 female Wistar rats given [^{14}C -benzyl]alpha-cypermethrin

(radiochemical purity, > 99%) as single oral doses at 2 mg/kg bw in corn oil. The concentrations of radioactivity were determined in these tissues at 1, 3, 8, 14, 16, 18, 22 and 42 days after dosing (three animals per time-point). The elimination half-lives in liver and kidney were 2.3 days and 2.0 days respectively. Depletion of radiolabel from fat and skin was biphasic. Elimination half-lives for the initial phase were 1.6–2.5 days, then 17–26 days for the second phase in fat, and 40 days in skin. An analysis of pyrethroids present in the peri-renal and parovarian fat indicated that the administered alpha-cypermethrin had undergone little or no isomerization (Logan, 1983).

In a study in humans, groups of two volunteers received capsules containing alpha-cypermethrin as a single oral doses at 0.25, 0.50 or 0.75 mg (purity, 99.8%) in corn oil. Three weeks later, a repeat-dose trial was performed wherein the same subjects received the same dose as in the first trial, but for five consecutive days. Urine (24 h) samples collected for 4 days after the single dose, and for 10 days after the first of the repeat doses, were analysed for *cis*-cyclopropanecarboxylic acid (free and conjugated). The amount of metabolite excreted varied considerably between individuals, and was related to dose. Excretion was rapid. When expressed as a percentage of the administered dose, the amount of metabolite recovered in the urine was similar for the 24 h period after a single oral dose (range, 35–57%; average, 43%) or any of the repeat doses (range, 30–75%; average 49%), and was fairly consistent over the 5-day dosing period for each individual. Little (1–8% of the administered dose per day) was excreted subsequent to 24 h after dosing. There was no evidence of bioaccumulation in this study (van Sittert et al., 1985).

Figure 2. Metabolic pathways of alpha-cypermethrin, partly gained from analogy with cypermethrin



4. Toxicological studies

4.1 Acute toxicity

The acute toxicity of alpha-cypermethrin is summarized in Table 8.

(a) Oral, dermal and inhalational toxicity

Clinical signs induced by alpha-cypermethrin, like those of cypermethrin, are typical of cyano-containing pyrethroid. The observed signs included ataxia, abasia, gait abnormalities, choreoathetosis, tip-toe walking, increased salivation, lacrimation, piloerection, diarrhoea, unkempt appearance, lethargy, tremor and clonic convulsions. Surviving animals recovered within 9 days (Rose, 1982; Gardner, 1993). Salivation, hypersensitivity to stimuli and hyperactivity were reported in the dermal study in rats (Gardner, 1993).

Table 8. Results of studies of acute toxicity with alpha-cypermethrin

Species	Sex	Strain	Route	Vehicle/comments	LD ₅₀ (mg/kg bw)/ LC ₅₀ (mg/m ³)	Reference
Mouse	M, F	CD	Oral	5% in corn oil ^a	35	Rose (1982)
Mouse	M, F	CD	Oral	40% in DMSO ^a	762	Rose (1982)
Mouse	M, F	CD	Oral	50% aqueous suspension ^a	798	Rose (1982)
Mouse	M, F	CD	Dermal	5% in corn oil ^a	> 100	Rose (1982)
Rat	M, F	Wistar	Oral	40% in DMSO ^a	4000	Rose (1982)
Rat	M, F	Wistar	Oral	50% aqueous suspension ^a	> 5000	Rose (1982)
Rat	M, F	CrI:CD BR	Oral	50% aqueous CMC ^b	64	Gardner (1993)
Rat	M, F	CrI:CD BR	Dermal	Undiluted technical ^b	> 2000	Gardner (1993)
Rat	M, F	SD	inhalation (4 h exp.) ^c	Powder, purity 95.6% MMAD 6.1–9 µm	1590	Jackson (1993)

CMC, carboxymethylcellulose; DMSO, dimethyl sulfoxide; MMAD, mass median aerodynamic diameter; SD, Sprague-Dawley.

^a Purity of test material, 96.6%.

^b Purity of test material, 95.6%.

^c Nose-only exposure.

(b) Dermal and ocular irritation

Six New Zealand White rabbits receiving a semi-occlusive topical application of 500 mg of alpha-cypermethrin technical developed very slight erythema that persisted in two animals up to 72 h after removal of the dressings. There were no other dermal reactions (Gardner, 1993).

Six New Zealand White rabbits receiving an instillation of 0.1 ml (equivalent to 45 mg) of alpha-cypermethrin technical showed slight conjunctival redness and ocular discharge at up to 72 h after treatment. No effects on the cornea or iris irritation were observed (Gardner, 1993).

(c) Dermal sensitization

No positive reactions were obtained in a Magnusson & Kligman test performed with guinea-pigs (Gardner, 1993).

4.2 *Short-term studies of toxicity*

Mice

Groups of eight male and eight female CD-1 mice received diets containing alpha-cypermethrin (purity, 95.4%) at a concentration of 0, 200, 400, 800, 1200 or 1600 mg per kg feed for 29 days, respectively equal to 0, 27, 56, 121, 166 and 241 mg/kg bw per day for males, and 0, 34, 73, 146, 212, and 294 mg/kg bw per day for females. One male at 1600 mg/kg and one female at 1200 mg/kg were killed in a moribund condition. These animals showed neurological disturbances. Mice at 1200 and 1600 mg/kg developed ungroomed coats, ataxia/abnormal gait, over-activity or hunched posture. At 800 mg/kg, some animals had ungroomed coats and abnormal gait. Body-weight gain was dose-relatedly decreased in mice at 1200 and 1600 mg/kg and in females at 800 mg/kg. A similar, but less marked effect was apparent in males receiving 800 mg/kg and females receiving 400 mg/kg. Food consumption was lowered in rats at 1200 and 1600 mg/kg during the first 2 weeks. A depression in lymphocyte numbers was noted in males at 1600 mg/kg. ALT and aspartate aminotransferase (AST) activities were increased in males at 1600 mg/kg. Urea concentrations were increased in all dosed males and females, without a clear dose-response relationship. Plasma albumin and albumin/globulin ratio were decreased in males at 1600 mg/kg. Relative kidney weight was increased in males at 800, 1200 and 1600 mg/kg. Relative lung weight was increased in males at 1600 mg/kg. No macroscopic or microscopic effects were seen. No effects were seen at 400 mg/kg feed, equal to 56 mg/kg bw per day (JECFA, 1996; Green, 1993).

Groups of 12 male and 12 female CD-1 mice received diets containing alpha-cypermethrin (purity, 95.4%) at a concentration of 0, 50, 250 or 1000 mg per kg feed for 13 weeks, equal to 0, 6.3, 33 and 170 mg/kg bw per day for males, and 0, 7.4, 36 and 185 mg/kg bw per day for females. Four males at 1000 mg/kg died during week 12, probably due to stress of treatment and refusal of food and water. The relative kidney weights of these animals appeared to be slightly increased. One mouse at 250 mg/kg died. Clinical signs included thin build, ungroomed coat, hair loss and encrustations of the dorsal body surface in animals receiving 1000 mg/kg, ungroomed haircoat in mice at 250 mg/kg, hair loss and encrustations in males at 250 mg/kg and hair loss in two males at 50 mg/kg, and three males in the control group. Body-weight gain was markedly lower in mice at 1000 mg/kg and lower in mice at 250 mg/kg. Food consumption was slightly higher in mice at 1000 mg/kg. Overall food conversion efficiency of animals at 1000 mg/kg (and to a lesser extent, at 250 mg/kg) was lower than that of controls. In males at 1000 mg/kg, erythrocyte volume fraction, haemoglobin, erythrocyte, total leukocyte and lymphocyte counts were decreased. AST activity was increased in a dose-dependent manner in males at 250 and 1000 mg/kg, and glucose was decreased in males at 1000 mg/kg. Serum alkaline phosphatase activity was increased in females at 1000 mg/kg. Urinary specific gravity was increased in mice at the highest dose. In males at 1000 mg/kg, relative brain, adrenal, heart, kidney, liver, spleen, lung and testes weights were increased. In females, relative liver weight was increased at 250 and 1000 mg/kg and relative brain and spleen weight at 1000 mg/kg. Two males and 11 females at 1000 mg/kg were considered to be emaciated at necropsy. No histological changes were observed.

The NOAEL was 50 mg/kg feed, equal to 6.3 mg/kg bw per day, on the basis of one death, clinical signs, reduced body-weight gain and decreased food conversion efficiency, and increased AST activity in males at 250 mg/kg feed, equal to 33 mg/kg bw per day (JECFA, 1996; modified with reference to the original report of Amyes et al., 1994).

Rats

Groups of 10 male and 10 female Wistar were fed diets containing alpha-cypermethrin (purity, 96.5%) at a concentration of 0 (20 rats of each sex), 20, 100, 200, 400 or 800 mg per kg feed

for 5 weeks. Observations included mortality, clinical signs, body weight and food consumption, haematology, clinical chemistry, urine analysis, organ weight, and macroscopic and microscopic lesions. One male at 800 mg/kg died as a result of factors unrelated to treatment and two males at 800 mg/kg were killed, owing to signs of severe neurological disturbance. Both sexes at 800 mg/kg showed an abnormal gait and increased sensitivity to noise. Abnormal gait was seen in one male at 400 mg/kg. The mean body weights and food intake of males and females at 400 or 800 mg/kg were significantly lower than those of controls. In males and females at 800 mg/kg and in males at 400 mg/kg, prothrombin time was increased. In males at 800 mg/kg, the kaolin-cephalin coagulation time was increased and the percentage of polymorphic neutrophils was increased at 800 mg/kg. In females, platelet count, total leukocyte count and absolute values of polymorphic neutrophils and lymphocytes were increased, but haemoglobin and erythrocyte volume fraction values were decreased. The MCV was decreased at 200, 400 and 800 mg/kg but not in a dose-related manner. Relative brain, liver and kidney weights were increased in males at 800 mg/kg and relative brain and liver weights were increased in males at 400 mg/kg. In females at 800 mg/kg relative brain, liver and kidney weights were increased. One male at 800 mg/kg that was removed from the study showed scanty axonal lesions of the sciatic nerves.

The NOAEL was 200 mg/kg feed, equivalent to 10 mg/kg bw per day (JECFA, 1996; Thorpe, 1982).

In a dose range-finding study, groups of five male and five female rats (CrI:CD BR) were fed diets containing alpha-cypermethrin (purity, 95.6%) at a concentration of 0, 50, 200, 800 or 1200 mg/kg feed, equivalent to 0, 5, 20, 80 and 120 mg/kg bw per day, for up to 6 weeks. No effects were found on food consumption, haematology, clinical chemistry and microscopy. All rats at 1200 mg/kg and all males at 800 mg/kg were killed during weeks 2 to 4 because of severe clinical signs. These signs included high stepping, splayed gait, abasia and hypersensitivity. Cachexia was seen in extreme cases. There were no significant changes in fore or hind-limb grip strength or hind-limb landing foot-splay. Female rats at 800 mg/kg had a lower mean body weight and food intake compared with controls. These females also had a lower leukocyte count. Microscopic examination revealed lymphocytolysis and lymphocyte depletion of the cortical region of the thymus in males at 800 mg/kg and males and females at 1200 mg/kg. No adverse effects were seen at 200 mg/kg feed, equivalent to 20 mg/kg bw per day. No adverse effects were seen at 200 ppm, equivalent to 20 mg/kg bw per day (JECFA, 1996; Fokkema, 1994a).

Groups of 30 male and 30 female Wistar rats received diets containing alpha-cypermethrin (purity, 94.9%) at a concentration of 0 (60 rats of each sex), 20, 60, 180 or 540 mg per kg feed for 90 days. After 6 weeks, 10 rats of each sex (controls, 20 of each sex) were sacrificed for interim examinations. Three males at 540 mg/kg developed an abnormal gait consisting of splayed hind limbs. Skin sores and fur loss were observed in all males with the highest incidence at 540 mg/kg and in females at 0 and 540 mg/kg. Two males, one from the control group and one at 540 mg/kg were removed because of severe skin lesions. Reduced body weight and reduced food consumption were seen in rats at 540 mg/kg. During the second part of the study, body-weight gain was also reduced in males at 60 and 180 mg/kg, but not in a clearly dose-related manner. Food consumption was lower at 60 mg/kg than at 180 mg/kg. At termination, the haemoglobin value was decreased in males and females at 540 mg/kg. MCV and MCHC were decreased in females at 540 mg/kg. Platelet counts were increased in males and females at 540 mg/kg. The number of lymphocytes was increased and the number of eosinophils was decreased in males at 540 mg/kg. Urea concentration was increased in females at 540 mg/kg. Alkaline phosphatase activity was decreased in females at 180 and 540 mg/kg. Urinary volume was decreased in females at 540 mg/kg and specific gravity was increased in males and females at 540 mg/kg. In females fed 540 mg/kg, relative spleen, heart and brain weights were

increased. In both sexes at 540 mg/kg, relative kidney weight was increased, and relative liver weight was increased in both sexes at 180 and 540 mg/kg. Relative testis weight was increased in males at 540 mg/kg. Histopathological investigations showed a solitary form of axonal degeneration, affecting the fibre only, in the sciatic nerve, in two males fed 540 mg/kg, but there were no clinical signs of toxicity.

The NOAEL was 180 mg/kg feed, equivalent to 18 mg/kg bw per day, on the basis of abnormal gait in males, decreased body-weight gain and food consumption, haematological changes, and axonal degeneration of the sciatic nerve at 540 mg/kg feed, equivalent to 54 mg/kg bw per day (JECFA, 1996; Clark, 1982).

Dogs

This study was conducted in two parts. In the first part, one male and one female beagle dog were fed diets containing alpha-cypermethrin at concentrations of 200 mg/kg feed for 7 days, 400 mg/kg feed for 2 days and 300 mg/kg feed for 7 days. Owing to severe intoxication of the animals at 400 mg/kg, dosing was discontinued after 2 days. The animals were fed the control diet and treatment was restarted at 300 mg/kg in week 3. After the third week, the dogs were killed. Clinical signs including ataxia, body tremors, subdued behaviour, head nodding, food regurgitation, diminished response to stimuli and inflammation of gums and tongue were obtained when dogs were dosed at 300 and 400 mg/kg. Body-weight loss was observed at 300 mg/kg. Examination of the cellular composition of blood and the chemical components of plasma showed no abnormalities, and no macroscopic changes were observed.

In the second part of the study, one male and one female beagle dog were fed diets containing alpha-cypermethrin at a concentration of 300 mg/kg food for 3 days (male dog) or 4 days (female dog), and then 250 mg/kg food for 7 days. At 300 mg/kg, the same effects were obtained as above. At 250 mg/kg, only the female dog developed the clinical signs shown by the dogs treated with 300 and 400 mg/kg (JECFA, 1996; Greenough & Goburdhun, 1984).

Groups of four male and four female beagle dogs received diets containing alpha-cypermethrin (purity, 95.8%) at a dose of 0, 30, 90 or 270 mg (six males and six females) per kg feed for 13 weeks. No effects on mortality, body weight, food consumption, ophthalmoscopy, haematology, clinical chemistry, macroscopy, organ weights or microscopy were seen. One female at 270 mg/kg was killed on day 5 of week 5 because of severe head and body tremors, ataxia, poor limb coordination, inflamed gums and elevated temperature; all dogs at 270 mg/kg developed clinical signs 3–6 h after dosing on days 2 or 3. The clinical signs observed were body tremors and variable incidences of head nodding, lip licking, subdued behaviour, ataxia, and agitation. During week 3, all dogs developed a high-stepping gait and the incidences of the other clinical signs increased as the study progressed. The duration of clinical signs observed early in the study usually resolved within hours after dosing but as the study progressed the duration increased such that they no longer resolved between dosing.

The NOAEL was 90 mg/kg feed, equivalent to 2.25 mg/kg bw per day, on the basis of clinical signs of neurotoxicity at 270 mg/kg feed, equivalent to 6.75 mg/kg bw per day (JECFA, 1996; modified with reference to the original report of Greenough et al., 1984).

Four groups of four male and four female beagle dogs received diets containing alpha-cypermethrin at a concentration of 0, 60, 120 or 240 ppm daily for 52 weeks. No effects were observed on body weight, food consumption, ophthalmoscopy, haematology, clinical chemistry, urine analysis or organ weights, and no changes were observed in macroscopic or microscopic examinations. Two males at 240 ppm developed skin reddening on the tail during week 2 of the study. The tail reddening

caused obvious irritation and resulted in ulceration and necrosis in one male leading to amputation of part of the tail. The tail reddening in the second male resolved after week 8. Abdominal skin reddening and alopecia were seen in a third male at 240 ppm and one female at 120 ppm between weeks 37 to 41.

The NOAEL was 60 ppm, equivalent to 1.5 mg/kg bw per day, on the basis of abdominal skin reddening and alopecia at 120 ppm, equivalent to 3 mg/kg bw per day (JECFA, 1996; modified with reference to the original report of Dean & Jackson, 1995).

4.3 *Long-term studies of toxicity and carcinogenicity*

Mice

Groups of CD-1 mice were fed diets containing alpha-cypermethrin (purity, 95.4%) at a concentration of 0, 30, 100 or 300 ppm for 12 months (20 of each sex) or 18 months (52 of each sex). Animals were observed at least twice daily for mortality and clinical signs. A more detailed examination that included palpation was performed weekly. Food consumption was recorded weekly and body weights were recorded weekly for 14 weeks, and fortnightly thereafter. The only haematological investigations performed were differential leukocyte counts at 50 and 77 weeks. Clinical chemistry and urine analysis were not carried out. Detailed necropsies were performed on all mice found dead or killed in extremis, as well as scheduled deaths at 12 and 18 months. Selected organs were weighed and tissues preserved for histopathology for the groups at 0 and 300 ppm as well as kidneys, liver, and lungs for all mice. The mean daily intake of alpha-cypermethrin in the groups at 30, 100 and 300 ppm was 3.0, 10.6 and 35.2 mg/kg bw per day for males and 3.5, 11.5 and 37.7 for females, respectively.

Survival was not affected by treatment. In males at 300 ppm, the incidences of various clinical signs (thin build, hunched posture, ungroomed coat, hair loss and skin encrustations) were increased, with an increased incidence of ungroomed coat and hair loss in males at 100 ppm also. Mean body-weight gain was significantly decreased by 26% and 24% respectively in males and females in the groups at 300 ppm, and by 13% in males at 100 ppm. Females in the groups at 30 and 100 ppm had mean body-weight gains of 8–11% less than controls, but as these findings did not show a dose–response relationship and lacked statistical significance, they were not considered to be treatment-related. Food consumption in treated and control groups was not significantly different. For the period for which food conversion efficiency was calculated (weeks 1–14), this parameter was reduced in both sexes at 300 ppm, and to a lesser extent in males at 100 ppm. No abnormalities were detected in blood smears, and organ weights were not affected by treatment. The incidence of glandular dysplasia of the stomach was increased to a statistically significant extent in females at 300 ppm (incidence in males/females, 17/6, 9/7, 9/6, 11/15* at 0, 30, 100 and 300 ppm respectively; * $p < 0.05$, Fisher exact test). There were no treatment-related neoplastic findings.

The NOAEL was 30 ppm, equal to 3.5 mg/kg bw per day for males and 3.0 mg/kg bw per day for females, on the basis of decreased body-weight gain at the higher doses (Green, 1996a, 1996b; Cooper, 1999).

4.4 *Genotoxicity*

The results of assays for genotoxicity with alpha-cypermethrin are summarized in [Table 9](#).

Table 9. Results of studies of genotoxicity with alpha-cypermethrin

End-point	Test object	Concentration	Purity (%)	Results	Reference
<i>In vitro</i>					
Forward and reverse gene mutation ^{b, g}	<i>S. cerevisiae</i> XV185-14C	31.25–4000 µg/ml in DMSO ^a	95.8	Negative	Brooks (1984)
Reverse mutation (Ames) ^f	<i>S. typhimurium</i> TA98, TA100, TA1535, TA1537, TA1538; <i>E. coli</i> WP2 uvrA	31.5–5000 µg/ml in acetone ^a	95.6	Negative ^c	Brooks & Wiggins (1993a)
Forward mutation ^f	L5178Y mouse lymphoma cells	3.3–50 µg/ml in DMSO ^a	95.4	Negative	Vanderwaart (1994)
Chromosomal aberration ^f	Human peripheral lymphocytes	–S9: 93.75–1000 µg/ml; + S9: 125–1000 µg/ml in acetone	95.6	Negative ^d	Brooks & Wiggins (1993b)
<i>In vivo</i>					
Chromosomal aberration ^g	Rat femoral bone marrow	2–8 mg/kg bw, single oral dose in corn oil ^e	95.8	Negative	Clare & Wiggins (1984)
Micronucleus formation ^h	Mouse	1–10 mg/kg bw single oral dose in corn oil	95.4	Negative	Vanderwaart (1995)
Alkaline elution analysis ^g	Rat liver	40 mg/kg single oral dose in 20% DMSO, 6 h exposure	96.5	Negative	Wooder (1981)

DMSO, dimethylsulfoxide; S9, 9000 × *g* supernatant from livers of male Sprague-Dawley rats.

^a With and without metabolic activation.

^b In log- and stationary-phase cultures; positive controls were cyclophosphamide (25 mg/ml in water) and 4-nitroquinoline-*N*-oxide (1 mg/ml in DMSO).

^c No cytotoxicity.

^d Precipitation was seen.

^e Initially doses of 10, 20 or 40 mg/kg were used, but the animals exhibited severe signs of toxicity and the experiment was terminated at these doses. Surviving females were evaluated for chromosomal damage and none was observed.

^f Two independent experiments performed; positive controls included; GLP and QA statements included.

^g Positive controls included; QA but no GLP statements included.

^h Positive controls included; GLP and QA statements included.

4.5 Reproductive toxicity

(a) Developmental toxicity

Rats

In a dose range-finding study, five pregnant female Sprague-Dawley rats received alpha-cypermethrin (purity, 95.6%) at a daily dose of 0, 3, 9, 15 or 18 mg/kg bw in corn oil by gavage during days 6–15 of gestation. Maternal body weights, food consumption and clinical observations were recorded. On day 20 of gestation the females were killed and the fetuses were weighed, sexed and externally examined. Four dams at 18 mg/kg bw per day and one dam at 15 mg/kg bw per day showed hindlimb splay and unsteady gait during dosing. Mean body-weight gain was reduced in a dose-related manner at 9, 15 and 18 mg/kg bw per day and food consumption was reduced in rats at 15 and 18 mg/kg bw per day. No other treatment-related abnormalities were observed (JECFA, 1996; Irvine & Twomey, 1994).

In the definitive study, groups of 24 pregnant female Sprague-Dawley rats received alpha-cypermethrin (purity, 95.6%) at a dose of 0, 3, 9 or 18 mg/kg bw per day in corn oil by gavage during

days 6–15 of gestation. After marked clinical signs of toxicity, the dose of 18 mg/kg bw per day was lowered to 15 mg/kg bw per day on day 10 of gestation. Clinical signs, body weights and food consumption were recorded. On day 20 of gestation the females were killed and necropsied. The fetuses were weighed, sexed and examined for external, visceral and skeletal abnormalities. Females at 18 mg/kg bw per day showed unsteady gait, piloerection, limb splay and hypersensitivity to sound. After reduction of the dose the signs were similar but less marked. After treatment at 18/15 mg/kg bw per day, reduced body-weight gain and food consumption was seen. At 9 mg/kg bw per day, slight body-weight reduction was seen. Mean fetal weights were slightly reduced at 18/15 mg/kg bw per day. There was no indication of teratogenicity.

The NOAEL for maternal and fetal toxicity was 9 mg/kg bw per day on the basis of decreased body-weight gain in the dams, and reduced fetal weights (JECFA, 1996; Irvine, 1994c).

Rabbits

In a dose range finding study, groups of five mated female New Zealand White rabbits received alpha-cypermethrin (purity, 95.6%) at a dose of 0, 5, 15, 25 or 30 mg/kg bw per day as solutions in corn oil by gavage during days 7–19 of gestation. On day 28 of pregnancy the females were killed and a necropsy was performed. The fetuses were weighed, sexed and externally examined. One female each at 15 and 25 mg/kg bw per day was killed prematurely. At 25 and 30 mg/kg bw per day, marked reductions in body weight and food consumption were seen. There was no indication of either embryotoxicity or teratogenicity (JECFA, 1996; Irvine, 1994a).

In the definitive study, groups of 16 pregnant New Zealand White rabbits received alpha-cypermethrin (purity, 95.6%) at a dose of 0, 3, 15 or 30 mg/kg bw per day in corn oil by gavage during days 7–19 of gestation. Maternal clinical signs, body weight and food consumption were recorded. The females were killed on day 28 of pregnancy. The uterus was weighed and the numbers of corpora lutea, implantations and live fetuses were counted. The fetuses were weighed, sexed and examined for external, visceral and skeletal abnormalities. Two control females, three at 15 mg/kg bw per day and two at 30 mg/kg bw per day were killed, because of severe weight loss and low food consumption. One female at 15 mg/kg bw aborted on day 28. In all groups, including controls, there was a similar mean body-weight loss after the onset of dosing, which continued until day 11. At 30 mg/kg bw per day, there was a further reduction in mean body-weight gain towards the end of the dosing period. Food consumption reflected the changes in mean body-weight gain.

The NOAEL for maternal toxicity was 15 mg/kg bw per day on the basis of decreased body-weight gain at 30 mg/kg bw per day. The NOAEL for embryotoxicity was 30 mg/kg bw per day, the highest dose tested. There was no indication of teratogenicity (JECFA, 1996; modified with reference to the original report of Irvine, 1994b).

4.6 Special studies

(a) Neurotoxicity

Rats

The acute neurotoxicity of alpha-cypermethrin was studied in CrI:CD:BR rats in two separate studies, each using four groups of 10 males and 10 females or 5 males and 5 females (additional study). The groups received alpha-cypermethrin (purity, 95.6%) as a single dose at 0, 4, 20 or 40 mg/kg bw in corn oil. During the 14-day observation period, clinical signs and body weight were analysed. In the main study, a detailed clinical assessment for neurotoxicological effects was performed. This included a FOB and measurements of fore- and hindlimb grip strength, hindlimb landing foot-splay

and motor activity. In each study, five rats of each sex were killed on day 15 and brain, eyes, muscle, nerves, spinal cord and spinal ganglia were analysed.

One male rat in each of the groups at 20 and 40 mg/kg bw of the additional study was found dead on the day after dosing. Clinical signs were seen in male rats dosed at 20 and 40 mg/kg bw. The signs (similar in both studies) developed between 3 to 8 h after dosing and resolved by 3 days after dosing. The signs included abnormal/splayed gait, thrashing, prostration, vocalization, piloerection, hunched posture, unkempt appearance, soiled/stained body areas and diarrhoea. The signs in females were similar but lower in frequency. In addition to these signs there were also isolated cases of twitching, tremors, abasia, hypersensitivity, pale eyes, soft faeces and thinning of the fur. During the FOB conducted 5 h after dosing, gait abnormalities and clinical signs of increased reactivity were seen in most male rats at 20 and 40 mg/kg bw. In females the signs were less frequent. In the groups at 20 and 40 mg/kg bw there was an increase in very slight to slight sporadic fibre degeneration in the sciatic nerve. The changes were more frequent in the proximal than in the distal part of the nerve.

The NOAEL was 4 mg/kg bw on the basis of death, clinical signs, findings in the FOB and degenerative changes to the sciatic nerve at doses of 20 mg/kg bw and higher (JECFA, 1996; Fokkema, 1994b).

Zeta-cypermethrin

5. Toxicological studies

5.1 Acute toxicity

(a) Oral and dermal toxicity

The acute toxicity of zeta-cypermethrin is summarized in Table 10.

Clinical signs induced by zeta-cypermethrin were similar to those induced by cypermethrin, including tremors, staggered gait, writhing, abnormal posture, squinting eyes, walking on toes, splayed hindlimbs and clonic convulsions, mainly confined to the first 24 h after dosing (Freeman, 1999a; Freeman, 1999b)

Table 10. Studies of acute toxicity with zeta-cypermethrin

Species	Sex	Strain	Route	Vehicle	Purity (%)	LD ₅₀ (mg/kg bw)	Reference
Rat	M	SD	Oral	5% in corn oil	88.2	134	Freeman (1989)
	F					86	
Rat	M	SD	Oral	5% in corn oil	91.2	257	Freeman (1999a)
	F					367	
Rat	M	SD	Oral	5% in corn oil	86.0	269	Freeman (1999b)
	F					285	
Rabbit	M	NZW	Dermal	Undiluted	88.2	> 2000	Freeman (1990b)
	F						

F, female; M, male; NZW, New Zealand White.

(b) Dermal and ocular irritation

After the application of zeta-cypermethrin technical (0.5 ml; purity, 88.2%) to the intact skin of New Zealand White rabbits (three of each sex) for 4 h under semi-occlusive dressings, erythema

was observed in two males at 72 h (Draize score, 1–2), but not before, resolving by day 4 or 6. Zeta-cypermethrin was a slight irritant to rabbit skin in this test (Freeman, 1990d).

After instillation of 0.1 ml of zeta-cypermethrin (purity, 88.2%) into one eye of each of nine New Zealand White rabbits (eyes of three rabbits were washed out with water 20–30 s after treatment), conjunctival redness was present at 1 h, along with chemosis and discharge, persisting until 48 h, but resolving in all except one animal in the washed-out group by day 4. Otherwise, results for washed and unwashed eyes were similar. Corneal opacity and iritis were not observed (Freeman, 1990c).

(c) *Dermal sensitization*

Zeta-cypermethrin (purity, 88.2%) produced positive reactions in the Buehler test. Slight erythema (Draize score, 1) was observed at 24 h in 9 out of 10 guinea-pigs, and mild erythema (Draize score, 2) was seen in one animal, which also had a scab at the test site. Slight erythema persisted in five animals at 48 h (Freeman, 1990e).

5.2 *Short-term studies of toxicity*

Rats

In a dose range-finding study, groups of five male and female Fischer 344 rats received diets containing zeta-cypermethrin (purity, 88.2%) at a concentration of 0, 50, 300, 600, 900 or 1500 ppm for 28 days. Animals were observed twice daily for mortality, once daily for clinical signs, and body weight and food consumption were measured weekly. All animals were necropsied and brain, liver, kidney and testes were weighed. Histopathology was not performed. The mean test substance consumption for rats fed zeta-cypermethrin at 50, 100, 300, 600, 900 and 1500 ppm was, respectively, 4, 9, 26, 48, 69 and 105 mg/kg bw per day for males and 5, 10, 27, 52, 74 and 102 mg/kg bw per day for females. All rats at 1500 ppm died between days 7 and 9. Body-weight gain was reduced by 94% in males at 900 ppm and by 18% at 600 ppm. Females at 900 ppm lost weight (–1.8 g compared with a mean gain of 40.6 g in the controls). Food consumption at 900 ppm was reduced by 35% in males and by 28% in females. Treatment-related clinical signs were confined to the groups at 900 ppm, and comprised abdominal staining, ataxia, chromorhinorrhea, decreased faeces, dehydration, splayed hind limbs and unthriftiness. Tremors, convulsions and hypersensitivity to touch were observed in some rats at 1500 ppm before death. The absolute and relative weights of the selected organs were not affected in males, but in females absolute, but not relative, liver weight was reduced compared with controls. No treatment-related gross pathology was present at necropsy (Freeman, 1990a).

Groups of 10 male and 10 female Fischer 344 rats were given diets containing zeta-cypermethrin (purity, 88.2%) at a concentration of 0, 10, 50, 150, 250, 500 or 900 ppm for 90 days. Animals were observed twice per day for mortality, once per day for clinical signs, and body weight and food consumption were measured weekly. Ophthalmoscopic examinations were performed before the start of treatment and at its conclusion. Haematology and clinical chemistry parameters were determined at termination, after which all animals were given a macroscopic examination and selected organs were weighed. All tissues from rats in the control group and groups at 500 and 900 ppm were subjected to microscopic examination, along with lungs, liver, and kidneys from all groups. The mean test substance consumption for rats at 10, 50, 150, 250, 500, and 900 ppm was, respectively, 0.7, 3.3,

10, 17, 34 and 68 mg/kg bw per day for males and 0.8, 4, 12, 20, 38 and 80 mg/kg bw per day for females.

Mortality was limited to the group at 900 ppm, with all females and seven males dying at this dose. Relative to controls, body-weight gains were reduced in males at 500 ppm (15%) and 900 ppm (63%). In females, body-weight gains were reduced by 15% at 150 ppm, 10% at 250 ppm and 21% at 500 ppm. Food consumption followed a similar pattern to body weight in males, with reductions of 11% and 22% at 500 ppm and 900 ppm respectively, with food consumption in females at 500 ppm reduced by 12%. Observed clinical signs were restricted to the group at 900 ppm and comprised abdominal staining, ataxia, chromorhinorrhea, decreased faeces, dehydration, splayed hindlimbs, unthriftiness, clonic convulsions, and hypersensitivity to touch and sound. There were no toxicologically or statistically significant haematological findings in females at any dose. In males at 900 ppm, there were reductions in leukocytes ($5.5 \times 10^6/\text{mm}^3$ compared with the control value of $8.7 \times 10^6/\text{mm}^3$) and erythrocytes ($6.8 \times 10^6/\text{mm}^3$ compared with $8.0 \times 10^6/\text{mm}^3$ in the controls).

A number of significant differences occurred in various biochemical parameters in both sexes. Total protein was increased in males at 250 and 500 ppm (7.2 g/dl compared with 6.7 g/dl in rats in the control group), but did not differ from controls at 900 ppm. In females, total protein was decreased at all doses greater than 10 ppm (6.5–6.7 g/dl vs 7.5 g/dl in controls). In general, biochemical differences were not dose-related, were not consistent across both sexes, were small in magnitude (generally less than 10%), and in many cases were statistically significant owing predominantly to tight clustering of individual values at some doses, and unlikely to be toxicologically significant. In males, blood urea nitrogen values were substantially increased at 900 ppm (27 mg/dl vs 18 mg/dl in controls) and this was probably a treatment-related effect. In females, a 16% reduction in blood glucose concentrations at 500 ppm was observed, but was not seen in males at 500 or 900 ppm. In males at 900 ppm, absolute weights of heart, kidney and liver were less than controls by 23%, 21% and 37% respectively, and the relative weights of brain, adrenals, testes and heart were increased by 55%, 75%, 46% and 23%, respectively. In females at 500 ppm, the relative weights of brain, heart and kidneys were increased by 10%, 8% and 8% respectively. The differences in organ weights relative to corresponding control values were largely attributable to reduced body-weight gain. No treatment-related changes in gross pathology or histomorphology were observed at necropsy.

The NOAEL was 250 ppm, equal to 17 mg/kg bw per day for males and 20 mg/kg bw per day for females, on the basis of decreased body-weight gain at 500 ppm (34/38 mg/kg bw per day for males/females) (McCarty, 1990).

(a) *Dermal*

In a 21-day repeat-dose dermal study, zeta-cypermethrin (purity, 86%; total cypermethrin isomers, 95.7%) was applied undiluted to the clipped dorsal surface of Charles River Sprague-Dawley CD rats (10 of each sex per group) at a dose of 0, 100, 500 or 1000 mg/kg bw per day, occluded, for 6 h on consecutive days. At the end of each exposure period, the test sites were wiped with methanol, then rinsed with tap water and dried. Animals were observed for mortality twice per day and detailed physical examinations were performed daily. Food consumption and body weight were assessed weekly, as was irritation at the application site. Ophthalmological examinations were performed on all animals before testing and at the end of the study. On the day after the final dose, all animals underwent FOB and motor activity testing before necropsy. Haematology and clinical chemistry parameters were evaluated, selected organs were weighed (including thymus, but not thyroid) and tissues taken for histopathology (including treated and untreated skin).

No treatment-related clinical signs were observed, and body-weight gain and food consumption were similar in control and treated groups. Hindlimb grip strength in males at 1000 mg/kg bw per day was less than other groups, but this was mainly due to sporadic atypically high values in the

control and other treated groups (Table 11). Motor activity was decreased relative to controls in males at 500 and 1000 mg/kg bw per day. However, the difference at 500 mg/kg bw per day was largely due to a particularly low score in one animal, and at 1000 mg/kg bw per day, only two out of 10 session totals were below the range for controls. One female at the highest dose showed moderately impaired gait, uncoordinated landing (righting reflex), uncoordinated movement/ataxia, walking on toes, and mobile abnormal posture. As there were no other behavioural abnormalities in treated males or females the Meeting considered that none of these findings was due to exposure to zeta-cypermethrin.

Table 11. Statistically significant FOB and motor activity findings in rats receiving zeta-cypermethrin as a dermal application

Parameter	Sex	Dose (mg/kg bw per day)			
		0	100	500	1000
Hindlimb grip strength	M	0.413	0.387	0.400	0.324 [§]
	F	0.269	0.315	0.301	0.258
Motor activity (number of breaks/beam)	M	304	307	234**	270*
	F	339	290	315	314

From Freeman (1999c)

F, female; M, male.

[§] $p = 0.034$; * $p = 0.027$; ** $p = 0.005$; Welch trend test.

No treatment-related effects were detected at the ophthalmoscopic examinations. In males at 1000 mg/kg bw per day, haemoglobin and MCH were decreased to a statistically significant extent relative to controls ($p \leq 0.3$, Welch trend test), but as changes were small (2–3%) and results for individual rats at 1000 mg/kg bw per day were all within the range for concurrent controls, they were not considered to be biologically significant. Local irritation (erythema, eschar, desquamation and/or ulceration) was observed at the application sites in some treated animals, mainly at the 2- and 3-week examinations, at ≥ 100 mg/kg bw per day in females and ≥ 500 mg/kg bw per day in males. Macroscopic and microscopic examination of these sites indicated that many of these reactions were associated with trauma, were focal in nature, and possibly the result of self-excoriation or clipping. However, there were no similar findings in control animals, so it is possible that these findings were due to the test material. There were no other treatment-related histopathological findings. Statistically significant changes in clinical chemistry were limited to the groups at 1000 mg/kg bw per day and comprised decreased AST activity in both sexes, increased ALT activity in males, and increased chloride concentrations but decreased sorbitol dehydrogenase (SDH), sodium and blood urea nitrogen values in females (Table 12). The decreases in AST and SDH are not considered to be adverse effects, and considering that the increase in ALT in males occurred in the absence of a change in SDH, this is not considered to be a toxicologically significant finding. As sodium concentrations in females lacked a dose–response relationship, chloride was only increased by 3%, and blood urea nitrogen values were within the normal range for rats of this strain, none of these was considered to have toxicological relevance.

Table 12. Statistically significant clinical chemistry findings in rats receiving zeta-cypermethrin as a dermal application

Parameter	Sex	Dose (mg/kg bw per day)			
		0	100	500	1000
AST (U/l)	M	118	111	99	98*
	F	102	99	85	84**
ALT (U/l)	M	50	59	51	61 [§]
	F	47	49	45	48
SDH (U/l)	M	14	16	14	14
	F	16	11	11	12 [^]
Na	M	144	144	143	143
	F	143	141	141	142 [*]
Cl	M	103	103	103	103
	F	97	98	98	100 [□]
BUN	M	15	17	14	14
	F	15	15	14	13 [~]

From Freeman (1999c)

BUN, blood urea nitrogen; SDH, sorbitol dehydrogenase; ALT, alanine aminotransferase; AST, aspartate aminotransferase.

* $p = 0.015$; ** $p = 0.001$; [§] $p = 0.045$; [^] $p = 0.001$; [^] $p = 0.018$; [□] $p = 0.045$; [~] $p = 0.029$; Welch trend test

In females at 1000 mg/kg bw per day, kidney, adrenal and spleen weights were increased relative to controls to a statistically significant degree (Table 13). As the changes in kidney and liver weight lacked a dose–response, and the dose–response for relative spleen weights was flat across a 10-fold dose range, with no supporting microscopic findings, these were not considered to be adverse. The NOAEL was 1000 mg/kg bw per day, the maximum dose tested (Freeman, 1999c).

Table 13. Statistically significant organ weights relative to body weight (%) in rats receiving zeta-cypermethrin as a dermal application

Organ	Sex	Dose (mg/kg bw per day)			
		0	100	500	1000
Kidneys	M	0.795	0.808	0.766	0.813
	F	0.742	0.832	0.875	0.834 [*]
Adrenals	M	0.017	0.017	0.016	0.016
	F	0.027	0.032	0.032	0.033**
Spleen	M	0.202	0.196	0.209	0.208
	F	0.215	0.235	0.246	0.248 [§]

From Freeman (1999c)

F, female; M, male.

* $p = 0.004$; ** $p = 0.009$; [§] $p = 0.003$; Welch trend test

5.3 Genotoxicity

The results of assays for genotoxicity with zeta-cypermethrin are summarized in [Table 14](#).

Table 14. Results of studies of genotoxicity with zeta-cypermethrin

End-point	Test object	Concentration	Purity (%)	Results	Reference
<i>In vitro</i>					
Reverse mutation (Ames) ^a	<i>S. typhimurium</i> , TA98, TA100, TA1535, TA1537, TA1538	100–10000 µg/plate in DMSO	88.2	Negative –S9 Positive +S9 ^b	Batt (1990)
Gene mutation ^c	Chinese hamster ovary cells Hgp ^r t locus	1–1000 µg/ml (solvent not specified)	88.2	Negative	Sigler & Harbell (1990)
Chromosome aberration ^a	Chinese hamster ovary cells	255–1020 µg/ml in DMSO	88.1	Negative	Murli (1990)
Unscheduled DNA synthesis	Rat primary hepatocytes	14–4500 µg/ml in DMSO ^c	88.2	Negative	Curren (1989)
<i>In vivo</i>					
Chromosome aberration ^d	Rat bone marrow	31.25, 62.5, 125 mg/kg bw, single gavage dose in corn oil; killed 6, 18 or 30 h after dosing	82.6 (<i>s</i> -isomer) 91.9 (total isomers)	Negative	Murli (1993)

DMSO, dimethylsulfoxide; S9, 9000 × *g* supernatant from livers of male Sprague-Dawley rats.

^a Duplicate experiments, with and without metabolic activation. GLP and QA statements included.

^b Zeta-cypermethrin produced a small but reproducible and dose-dependent increase in the frequency of revertants in *S. typhimurium* TA100 in the absence of metabolic activation in two separate assays (mean revertants per plate: 128, 123, 123, 123, 195, 260 at concentrations of 0, 100, 333, 1000, 3333 and 10 000 µg/plate respectively in the first study, and 130, 133, 180, 196, 203 and 261 at 0, 333, 1000, 3333, 5000 and 10 000 µg/plate respectively in the replicate study. The test was negative in the presence of S9 mix, and in the other strains tested.

^c GLP and QA statements included. Small macroscopic droplets of the test material were observed in the culture medium at ≥ 150 µg/ml, and microscopically at all concentrations, even though the test material appeared completely soluble in the chosen solvent (DMSO).

^d GLP and QA statements included.

^e Positive controls included; QA but no GLP statements included.

5.4 Reproductive toxicity

(a) Multigeneration studies

Male and female Sprague-Dawley rats (CrI:CD(SD)BR) were given diets containing zeta-cypermethrin technical (purity, 89.6%) in the diet at concentrations of 0, 7.5, 25, 100, 375 or 750 ppm for two generations. The parental (F₀) generation (30 of each sex per dose) was pretreated for 12 weeks then paired for 21 days for mating, after which males were sacrificed. F₀ females that littered were sacrificed on day 28 of lactation. Females that failed to litter were sacrificed on the 25th day after mating. Where possible, at least one pup of each sex was selected from each litter to make up the 20 animals of each sex per group of the F₁ generation. Pups not selected for breeding the second generation were sacrificed and necropsied. Evidence of toxicity was assessed according to general physical condition, body-weight increases, food consumption, litter sizes and viability, fertility, duration of gestation, and gross pathology and histology at necropsy. At concentrations of 7.5, 25, 100, 375 and 750 ppm, average achieved doses in the F₀ in the period before mating were 0.4, 1.5, 6, 22 and 43 mg/kg bw per day, respectively, for males and 0.6, 1.9, 7, 28 and 53 mg/kg bw per day for females. Achieved doses were similar in females during lactation, and in the F₁ parental generation.

There were four deaths in the F₀, comprising one control male and three females (one at 100 ppm and two at 750 ppm), the female deaths occurred during days 18–28 of lactation, and were considered to be treatment-related at 750 ppm. In addition, four females were sacrificed in error on day 21 (two at 750 ppm and one each at 100 and 375 ppm). At 750 ppm, male body weight and food consumption

were reduced by 13% relative to controls, with food consumption reduced by 12% in 375 ppm males. Relative to the control group, maternal body-weight gain was reduced by 35% at 750 ppm, and marginally (10%) at 375 ppm during the period before mating. Body weight was not affected during gestation, but during lactation the group at 750 ppm lost weight for days 1–4 (–7.4 g vs +4.4 g in the control group), days 10–14 (–12.1 g vs +6.3 g in the control group), but weight gain was markedly increased in this group for days 21–28 of lactation (+13.6 g vs –4.4 g in the control group). In the group at 375 ppm, maternal body-weight gains were generally lower than those of the controls during lactation, although not to a statistically significant extent. Food consumption for F_0 females followed a similar pattern to body weight, being significantly reduced (17%) throughout the period before mating, marginally reduced (10%) during gestation, and significantly reduced (41%) during lactation. At 375 ppm, maternal food consumption during lactation was also significantly reduced (17%) relative to controls. At 750 ppm, a significant number of F_0 males had soft or liquid faeces, and in maternal animals emaciated appearance, ataxia, hypersensitivity to sound and clonic convulsions were observed during lactation, a period during which food consumption and achieved dose were the highest (0.9, 2.9, 12, 41 and 67 mg/kg bw per day at doses of 7.5, 25, 100, 375 and 750 ppm respectively). Treatment did not affect reproductive and developmental indices, and there was no evidence of teratogenicity or embryotoxicity in the F_1 pups. However, at 750 ppm, 12 out of 30 dams had total litter loss before postnatal day 28, compared with 0 of 30 in the control group. Of 331 pups born live at this dose, 150 died before day 28 (140 of 189 those remaining post-cull on day 4 post partem), compared to 2 of 285 in the control group (0 of 186 post-cull). Body weights were reduced by 10–14% in pups of the group at 375 ppm, and by more than 50% at 750 ppm at postnatal day 21 (21 g vs 47 g in the control group). Owing to the high mortality rate in pups of the group at 750 ppm, this group was discontinued at week 3 after weaning. No dose-related abnormalities were observed at necropsy.

After weaning, 27 of 30 of the male and 24 of 27 of the female F_1 pups from the group at 750 ppm that survived to day 1 after weaning died. Animals in this group were generally small, ataxic, and had whole body tremors. Some were hypersensitive to sound or very weak, and a few of the females had clonic convulsions. At necropsy, some of the 750 ppm animals had dried red substance around the mouth, urine stained abdominal fur, small testes (expected in small male rats), gaseous distention of the stomach, and evidence of gastric erosions. At 375 ppm, one rat of each sex displayed hypersensitivity to sound. A significantly increased incidence of alopecia was observed at 375 ppm in males (14 out of 40 vs 2 out of 40 in the control group) and females (9 out of 23 vs 0 out of 24 in the control group) during the period before mating. The significant reductions in body weights observed in F_1 pups at 375 and 750 ppm before weaning continued after weaning, with the body weights of males at 375 ppm remaining approximately 10% below that of controls. However, body-weight change was equivalent in all groups of males from day 29 after weaning onwards. In F_1 females, body-weight gain was largely unaffected by treatment, and although the weights of the group at 375 ppm remained consistently below those of the controls, after weaning the difference rapidly became marginal (5–10%). Organ weights (absolute and relative to body weight) in the F_1 were largely unaffected by treatment. Relative brain weights were increased at 375 ppm by about 10% in both sexes, considered an effect of reduced body weight. Reproductive and developmental indices were unaffected in the F_1 parents and F_2 pups. Pup body weights in the F_2 at birth and through to day 7 were not affected by treatment, but were significantly reduced at 375 ppm at postnatal days 14 and 21. There were no gross or microscopic findings in the F_1 adults or F_2 pups that were attributable to treatment. Overall, there were no effects on reproductive performance at the doses tested (750 ppm maximum in the first generation and 375 ppm in the second).

The NOAEL for pup development was 100 ppm, equal to 6 mg/kg bw per day, on the basis of decreased pup weight gain and clinical signs at 375 ppm, equal to 22 mg/kg bw per day. The NOAEL for adults was 100 ppm, equal to 6 mg/kg bw per day, on the basis of decreased body-weight gain and reduced food consumption during the periods before mating and lactation in the F_0 , and clinical signs in some F_1 adults at 375 ppm, equal to 22 mg/kg bw per day (Hoberman, 1991).

(b) *Developmental toxicity*

Rats

Groups of 25 female Sprague Dawley rats (CrI:CD(SD)BR) were given zeta-cypermethrin (purity, 89.6%) at a dose of 0, 5, 12.5, 25 or 35 mg/kg bw per day in corn oil by gavage from day 6 to day 15 post coitum. Clinical observations and measurement of body weight and food consumption were performed daily. Pathological investigations were conducted at the end of the study period (day 20 of presumed gestation). The ovaries and uteri of each animal were removed and examined for the number of corpora lutea, and the number and position of implantations, including the numbers of live fetuses, early and late resorptions, and dead fetuses. The sex and weight of each fetus was determined, and all fetuses were examined for external malformations. Approximately half the fetuses were examined for skeletal malformations and the remainder for visceral abnormalities. No animals died before sacrifice. Clinical observations related to toxicity were limited to the groups at 25 and 35 mg/kg bw per day and primarily comprised ataxia, hypersensitivity, urine-stained abdominal fur, emaciated appearance and soft faeces. Tremors and convulsions were seen only in one animal at 35 mg/kg bw per day. Maternal necropsy findings were minimal and not dose-related, with a single animal at 35 mg/kg bw per day having white cloudy fluid in the thorax and pericardium adhering to the diaphragm, and two animals in the group at 5 mg/kg bw per day having a mammary mass or a lesion on the back and base of the tail. Relative to the control group, maternal body-weight gains were significantly reduced by 23% and 51% at 25 and 35 mg/kg bw per day, respectively, during the dosing period, with an associated reduction in food consumption of 10% and 24%, respectively. Treatment did not affect the average number of resorptions or fetuses, nor did it affect the number of dams with viable fetuses. No treatment-dependent differences in average fetal body weights, sex ratios, percentage dead or resorbed conceptuses were observed. The numbers of fetuses with alterations (gross external, visceral and skeletal combined) were increased slightly at higher doses (7 out of 390, 9 out of 377, 8 out of 321, 11 out of 384, and 12 out of 347 in increasing order of dose, not statistically significant), but were not considered to be an effect of treatment, as all abnormalities considered individually were reported as common in this strain of rat, occurred at fetal or litter incidences that were not dose-dependent and/or statistically significantly increased relative to controls, and were within the ranges for their respective historical controls.

The NOAEL for maternal toxicity was 12.5 mg/kg bw per day on the basis of clinical signs of toxicity and reduced weight gain at 25 mg/kg bw per day and higher. As there was no evidence of treatment-related effects on fetal developmental or survival in this study, the NOAEL for developmental toxicity was 35 mg/kg bw per day, the highest dose tested (Hoberman, 1990).

5.5 *Special studies*

(a) *Neurotoxicity*

In a study of acute neurotoxicity, groups of 10 male and 10 female Long Evans rats (Charles River Laboratories) were given zeta-cypermethrin (FMC 56701; purity, 84.4%) undiluted as a single dose at 0 (tap water only), 10, 50 or 250 mg/kg bw by gavage on day 0. The animals were observed twice per day for mortality, a detailed physical exam was performed daily, and body weight was measured weekly. FOB and testing for motor activity were conducted for two of each sex per group before treatment and on days 0, 7 and 14. After testing on day 14, five of each sex in the control group and in the group at 250 mg/kg bw were anaesthetized, perfused in situ with fixative, and given a gross necropsy. Tissue samples from the nervous system (brain, spinal cord, sciatic, tibial and sural nerves, Gasserian ganglion, cervical and lumbar dorsal root fibres and ganglia, cervical and lumbar ventral root fibres), and gastrocnemius muscle were taken for histopathological examination. One female at 250 mg/kg bw died on day 0 after displaying treatment-related clinical signs. At 250 mg/kg bw,

splayed hindlimbs, staggered gait, convulsions, ataxia, loss of muscle control, oral discharge, abdominal staining, abdominal gripping, lacrimation, vocalization and decreased locomotion were observed, with splayed hind limbs, staggered gait and tremors also apparent in males at 50 mg/kg bw. All clinical signs resolved within 48 h of dosing. Additional findings at 250 mg/kg bw in the FOB on the day of dosing were impaired or absence of righting reflex, increased latency to tail flick, and tenseness/rigidity or limpness/lack of resistance during handling. There were no treatment-related findings in motor activity testing. Body weight was not affected by treatment, nor were there any treatment-related gross lesions or neuropathological findings at microscopic examination.

The NOAEL for acute neurotoxicity was 10 mg/kg bw on the basis of clinical signs and FOB findings at 50 mg/kg bw (Watt, 1998).

In a 90-day study of neurotoxicity, groups of 10 male and 10 female Charles River Long Evans rats were given diets containing zeta-cypermethrin (FMC 56701; purity, 86.0%) at a concentration of 0, 75, 400 or 750 ppm. The animals were observed twice per day for mortality and daily for clinical signs, and body weights and food consumption were measured weekly. Motor activity and FOB assessments were conducted on all rats before treatment and after 4, 8 and 13 weeks of treatment. At study termination, five rats of each sex per group were anaesthetized and perfused with fixative *in situ*. Tissue samples from the nervous system (brain, spinal cord, sciatic, tibial and sural nerves, Gasserian ganglion, cervical and lumbar dorsal root fibres and ganglia, cervical and lumbar ventral root fibres), and gastrocnemius muscle were taken for histopathological examination. The mean daily intake of zeta-cypermethrin at 75, 400 and 750 ppm was 5.0/5.9, 26.3/31.5 and 47.2/55.6 for males/females, respectively. There were no treatment-related deaths or clinical signs, nor were there any gross pathology or neuropathology findings that could be attributed to treatment. Overall body-weight gain was reduced by 28% and 31% in males and females respectively at 750 ppm, and by 15% in males at 400 ppm. At 750 ppm, this was associated with a reduction in food consumption of 13% and 11% respectively in males and females. In males at 400 and 750 ppm, relative to control animals, landing foot-splay was reduced in week 13, and motor activity was decreased at weeks 8 and 13. Tail-flick latency was decreased in these groups at week 8 only, but as this was not present at the later time-point, was not attributed to treatment.

The NOAELs for neurotoxicity were 75 ppm for male rats (5.0 mg/kg bw per day), on the basis of increased landing foot-splay and decreased motor activity at 400 ppm (26 mg/kg bw per day), and 750 ppm (56 mg/kg bw per day) for female rats, the highest dose tested. The NOAELs for systemic toxicity were 75 ppm for male rats (5.0 mg/kg bw per day) and 400 ppm (31.5 mg/kg bw per day) for female rats, on the basis of decreased body-weight gain and food consumption at 400 ppm (47 mg/kg bw per day) and 750 ppm (56 mg/kg bw per day), respectively (Freeman, 1999d).

6. Observations in humans exposed to cypermethrins

6.1 *Medical surveillance of manufacturing plant personnel*

Zeta-cypermethrin technical, along with other synthetic pyrethroids, has been produced on a batch basis at a manufacturing plant in Baltimore, Maryland, USA, since 1993. It was estimated that employees worked with zeta-cypermethrin about 15% of their time at work. Twenty-five employees had worked at the facility for 10 years. All employees participated in the Medical Surveillance Program at the plant, which included pre-employment baseline and annual measurements, comprising spirometry, audiometric testing, electrocardiogram (ECG), chest X-ray, vision screening, hands-on examination by a physician, blood chemistry, haematology and complete urine analysis. There were no unexplained or significant changes from baseline, or variations from reference ranges for employees working with synthetic pyrethroids. The only health effect associated with zeta-cypermethrin was

mild and temporary paraesthesia resulting from skin contact. A review of medical records of affected employees still employed at the manufacturing plant did not identify any subsequent health problems (Sheffield & Kerschner, 2003).

Similar findings were reported for a manufacturing plant in Jacksonville, Florida, at which a product containing zeta-cypermethrin has been formulated and packaged, and a related product also packaged, since 1993. In this case, employees, 100 of whom had been employed at the plant for a significant period of time during the 10-year period covered by this report, were working with products containing zeta-cypermethrin about 20% of their time at work (Chlada, 2003).

6.2 *Exposure of the general population*

A group of nine workers were exposed to cypermethrin after accidental contamination of an air-conditioning duct during slab injection with a diluted termiticide product containing 0.25% cypermethrin. The product also contained aromatic petroleum solvents (including xylene), plus trimethylbenzene and paraffinic oils. The employees entered the building on several occasions 2 days after it was treated, and again at 13 days after treatment, at which time the airborne concentrations of cypermethrin were below the limit of detection (0.02 ppm). Six weeks after treatment, though air-sampling tests were negative, wipe tests demonstrated cypermethrin in the carpet, with the highest concentration between two applicator holes. Symptoms common to five employees were shortness of breath, cough, congestion, burning of the eyes, and itching of the skin at the time of exposure. Dizziness, headaches, nausea and vertigo were also reported. The symptoms occurred each time the workers entered the building, worsened when the air conditioning was activated, and appeared to be exaggerated in smokers, though one non-smoker developed significant pulmonary dysfunction. The five workers reporting symptoms also experienced extreme anxiety. A further three workers reported no symptoms, and the remaining worker was unavailable for examination. The paper stressed the importance of full decontamination before re-entry and rapid referral of exposed individuals to a specialist in toxicological exposures (Lessenger, 1992).

A prospective epidemiological study was conducted from 1996 to 1999 to determine the systemic exposure of 40 male and 21 female volunteers exposed to pyrethroids after the indoor application of pyrethroid-containing products by professional pest control operators. Forty subjects were exposed to cyfluthrin, nine to permethrin, seven to cypermethrin and five to deltamethrin. Persons with various chronic medical conditions or a history of use of a pest-control operator in the 6 months before the study were excluded. They were admitted to treated premises at 8 h after treatment, following a 4-h period during which the premises were ventilated. Biological monitoring was performed before pesticide treatment and at 1 day, 4–6 months and 10–12 months after treatment. The study included general medical and neurological examination of the volunteers, a question-based interview, and blood and urine sampling to determine general clinical and immunological parameters, as well as biological monitoring. The concentration of the appropriate pyrethroid was determined in the plasma, and metabolites were determined in the urine. The ratio of *trans*-DCCA (3-(2,2-dichlorovinyl)-2,2-dimethylcyclo-propane carboxylic acid) to *cis*-DCCA was calculated to investigate whether the major route of uptake was via the dermal (ratio ≤ 1) or the inhalation/oral routes (ratio > 1). In all cases, the plasma concentration of pyrethroid was below the limit of detection ($< 5 \mu\text{g/l}$). A significant increase in the concentration of pyrethroid metabolites was found in the urine for days 1–3 after application of pyrethroid, but thereafter did not exceed published background levels. The route of exposure was ascribed to the inhalation/oral route for thirteen subjects and to the dermal route for five subjects (Leng et al., 2003).

During 1989–2003, 60 poisoning incidents with pesticides containing cypermethrin were recorded in the mandatory German reporting scheme, accessible through the INTOX database. Of these, 29

related directly to symptoms in humans, comprising two unsuccessful suicide attempts, four accidental child exposures without any serious effects, and 23 cases of either household exposure or professional use. All recorded cases included mild symptoms of vertigo, nystagmus (eye), drowsiness, emesis, hypertonia, nausea, headache, lassitude, anorexia, redness in the face, pyrexia, swelling of the lymph nodes, slight conjunctivitis, cauterization of the eyes, slight effects on the skin and ears and laboured breathing. There were no deaths, and no incidents were considered to be serious (Ullrich, 2003).

6.3 Occupational exposure

Urine obtained from operators spraying cypermethrin in experimental trials was analysed for the presence of the chlorinated cyclopropanecarboxylic acid metabolite. Using standard gas-liquid chromatography, the carboxylic acid metabolite was observed in urine of exposed workers at concentrations up to 0.4 µg/ml (the limit of detection was estimated to be 0.05 µg/ml) (Annex 1, reference 33; Baldwin, 1978).

Studies were carried out in the Ivory Coast, Africa where operators sprayed with a hand-held ultra-low volume (ULV) apparatus either cypermethrin or a control UW formulation. The cypermethrin sprayers were found to have residues on the exposed parts of their bodies. Medical and electrophysiological examinations showed no adverse effects from the exposure. The rate of dermal exposure of the operators during spraying ranged from 1.5 to 46.1 mg/h. There was a reasonable relationship between the total cypermethrin deposited dermally and the excretion in urine. The concentrations of the cyclopropanecarboxylic acid metabolite in the urine at 24 h were between <0.05 and 0.32 mg. This, together with the finding of 0.6 mg of this metabolite in 72 h urine from one man led to the estimation that approximately 3% of the total dermal dose was absorbed and rapidly excreted by the operators (Annex 1, reference 33; Prinsen & van Sittert, 1978).

A study was carried out in humans at the Institut de Recherches du Coton et des Textiles Exotiques (IRCT), Bouake, Ivory Coast, after hand-held ULV application to cotton of the cypermethrin ('Ripcord') during one season of spraying. The operators were seven indigenous Africans. Six of them had no previous pesticide application history; one had very limited experience. They sprayed the formulation EF 4922 (25 g Ripcord/l in a 50/50 (v/v) hexylene glycol and Shellsol AB mixture) on an area of 1 ha (10 000 m²) at the rate of 2 l/10 000 m² in six spray sessions at fortnightly intervals under the supervision of IRCT staff. In a seventh spray session, the same amount was sprayed under the supervision of the Exposure Monitoring Group. The operators wore their normal clothes and no special protective devices were used.

Exposure to Ripcord was monitored by collecting the total amount of urine passed during the first 24 h after each spray session and the determination of the excretion levels of the urinary metabolite *trans* WL 44776 3-(2,2-dichlorovinyl-2,2-dimethyl-cyclopropane-1-carboxylic acid). In many samples the excretion was below the limit of detection, indicating a low level of absorption. Skin contamination and inhalational exposure were monitored only in the seventh spray session. Skin and inhalational measurements did not correlate well with the urinary excretion. Inhalational exposure was about 1% of skin exposure. Skin exposure, as measured with aluminium foil, reflected the working procedures. It was concluded that exposures were low, in particular when the spraying recommendations were observed. The absorption was calculated to be substantially less than the equivalent of an oral dose of 1 mg of Ripcord per spray session. General medical and extensive clinical and neurological examinations, blood biochemistry and peripheral nerve function tests (including the trigeminal nerve) did not show abnormalities either before or after the series of six spray sessions nor after the seventh spray session. In some electroneurophysiological tests (motor conduction velocity, slow fibre conduction velocity and cornea reflex) a statistically significant change within the normal

range appeared to exist for the group of sprayers between the before and after exposure measurements. There was no evidence that these changes were compound-related; they probably reflected seasonal variations. The general conclusion is that under the conditions of this study the application of Ripcord caused no detectable adverse health effects (Annex 1, reference 33; Prinsen & Van Sittert, 1979).

Transient facial sensory symptoms after exposure to synthetic pyrethroids (e.g. cypermethrin, permethrin, fenvalerate and fenpropathin) in some workers have been reported. Among 23 workers exposed to synthetic pyrethroids, 19 had experienced one or more episodes of abnormal facial sensation that developed between 30 min and 3 h after exposure and persisted for 30 min to 8 h. There were no abnormal neurological signs and electrophysiological studies were normal in the arms and legs. It was concluded that the symptoms are most likely to be due to transient lowering of the threshold of sensory nerve fibres or sensory nerve endings after exposure of the facial skin to pyrethroids, similar to the phenomena that have been described in Wouters & van den Bercken (1978), after exposure of animal nerves to pyrethroids (Annex 1, reference 37; Le Quesne et al., 1981).

Skin sensations experienced by those handling cypermethrin or other pyrethroids are believed to arise by repetitive firing of sensory nerve terminals in the skin. It is said to be a strictly local effect, which may occur as soon as the concentration of pyrethroid on or in the skin reaches a certain level and is not considered as a sign of general intoxication (provided the pyrethroid does not reach the blood in any significant concentration). A possibility exists, however, that repeated occurrence of intense repetitive firing can perhaps eventually lead to dysfunction of sensory nerve terminals and sense organs and finally to degeneration of sensory nerve fibres (Annex 1, reference 33; van den Bercken, 1980).

A monitoring study was undertaken to determine the dermal exposure of two pilots and two mixer-loaders, and the systemic absorption by five mixer-loaders during operations for the aerial application to cotton of a ULV formulation of cypermethrin in oil. Cypermethrin absorption was measured in three mixer-loaders by assessing the concentrations of the cypermethrin metabolites 3-(2,2-dichloroethenyl)-2,2-dimethylcyclopropanecarboxylic acid (DCEA, *cis* and *trans*), 3-phenoxybenzoic acid (3PBA) and 4'-hydroxy-3-phenoxybenzoic acid (4OHPBA) on the day of application and for 6 days thereafter. The formulation used (Cymbush 3E) contained 360 g/kg cypermethrin which was diluted in fully refined soya bean oil to a spray concentration of 2.9% w/v cypermethrin. Each replicate application used 15 l of Cymbush. All mixer-loaders wore protective equipment. Dermal exposure to cypermethrin was 0.67 mg/8 h for pilots, and 2.4 mg/8 h for mixer-loaders. For pilots, most exposure was to the hands, while exposure was more uniform for mixer-loaders, principally involving the arms, trunk and hands, reflecting a high degree of protection afforded by gloves. The metabolites 4OHPBA and 3PBA were detected in the urine of all three subjects, and *trans*-DCEA (but not *cis*-DCEA) was detected in two subjects. The most persistent urinary metabolite was 4OHPBA, which was not detected on day 4 in two subjects, and was just detectable in the third subject on days 5 and 6. It was concluded that as the major metabolites in the urine were 3PBA and 4OHPBA, metabolism and excretion in humans resembled that in rats more closely than that in mice. Calculations of cypermethrin excreted indicated that systemic absorption (46–78 µg of cypermethrin) represented a small proportion of actual dermal exposure (approximately 0.63–3.6 mg of cypermethrin) (Chester et al., 1987).

A review of 573 cases of acute pyrethroid poisoning reported in the Chinese medical literature during 1983–1988 showed that 45 cases were involved cypermethrin. Of these, six were due to occupational exposure and 39 were accidental. In most cases of occupational pyrethroid poisoning, effects were reversible, so the prognosis was generally good. Details specific to the cypermethrin cases were not provided. After occupational exposure, symptoms of burning or itching sensations

of the face which usually developed at 4–6 h after exposure were consistent with the paraesthesia reported elsewhere for cypermethrin, and were transient in nature (He et al., 1989).

An epidemiological survey of the prevalence of pyrethroid poisoning in cotton growers in Gaocheng County, China, was conducted in 1987/1988. A total of 3113 pyrethroid sprayers (2230 men, 883 women) were interviewed after spraying, and followed up over a 72-h period. Deltamethrin and fenvalerate were the main pyrethroids used, with only 12 subjects exposed to cypermethrin. About 25% of subjects were exposed to a pyrethroid/organophosphate mixture. A total of 834 subjects were clinically affected, reporting mainly abnormal facial sensations (burning and tingling) within 4 h after spraying commenced, and resolving within 24 h. Systemic symptoms of dizziness, headache, fatigue, nausea, and loss of appetite were also seen, but were described as minimal.

Ten subjects who developed significant systemic symptoms and showed listlessness or muscular fasciculation were diagnosed as having mild acute pyrethroid poisoning; all recovered in 3–4 days. A comparison of measured concentrations of pyrethroid in the breathing zone, on detection pads on the clothes/skin and in urine samples indicated that the predominant route of exposure was dermal. Causal factors for pyrethroid poisoning that emerged from the survey were lack of awareness of the toxicity of pyrethroids, unsatisfactory personal protection and unsafe work practices (Chen et al., 1991).

Comments

Biochemical aspects

The fate of orally administered cypermethrin was studied in mice, rats, dogs, and humans and alpha-cypermethrin was investigated in rats and humans. When administered orally to rats, cypermethrin and alpha-cypermethrin were partially absorbed, distributed widely in the tissues, and excreted rapidly. After a low single oral dose (2 mg/kg bw) of ^{14}C -labelled cypermethrin or alpha-cypermethrin, approximately 50–75% of the radioactivity was excreted in the urine, with little in the expired air, and the remainder in the faeces. As most of the radiolabelled material in the faeces comprised the unmetabolized parent molecule, the role of biliary excretion appears to be minor, although this was not measured directly, and the amount in the urine represents approximately the amount absorbed. Maximum concentrations in the blood were reached at 3–4 h after dosing at 2 mg/kg bw.

In rats given a single oral dose of ^{14}C -labelled cypermethrin or alpha-cypermethrin at 2 mg/kg bw, the highest tissue concentrations of radioactivity were found in the fat (< 1% of the administered dose), followed by the skin. In rats and mice, radioactivity in the fat was identified as unchanged cypermethrin, present mainly as the *cis*-isomer. Elimination of radiolabel from most tissues was rapid, but the elimination half-life of cypermethrin and alpha-cypermethrin in rodent adipose tissue and skin was prolonged (10–40 days). Repeat-dose studies in rats confirmed that cypermethrin accumulates in fat and skin, reaching a plateau after dosing for 4 weeks at 2 mg/kg bw per day. Concomitant increases in radioactivity also occurred in the plasma, liver and kidney, but concentrations were an order of magnitude lower than in fat.

In laboratory animals, cypermethrin was readily hydrolysed at the ester bond, followed by hydroxylation and conjugation of the cyclopropyl and phenoxybenzyl moieties of the molecule. Urinary metabolites consistent with a similar metabolic pathway in humans were recovered from orally dosed volunteers. The animal data indicated that there is little isomeric interconversion during metabolism of cypermethrin or alpha-cypermethrin.

Toxicological data

Cypermethrin has low to moderate acute oral toxicity in rats (LD_{50} , 163 to > 3000 mg/kg bw). This variability was only partly explicable by the vehicle used. The acute oral LD_{50} of *cis*-cypermethrin in rats was 160–300 mg/kg bw, indicating that it is considerably more toxic than *trans*-cypermethrin,

for which the LD_{50} was > 2000 mg/kg bw under the same conditions. From these results, it would be predicted that alpha-cypermethrin is approximately twice as acutely toxic as cypermethrin. A wide range of acute oral LD_{50} values in rats was also reported for alpha-cypermethrin (LD_{50} , 64 to > 5000 mg/kg bw). Similar studies with zeta-cypermethrin gave fairly consistent results (LD_{50} , 86–367 mg/kg bw). The dermal toxicity of cypermethrin and alpha-cypermethrin was low in rats (LD_{50} , > 1600 mg/kg bw and > 2000 mg/kg bw per day, respectively), as was the dermal toxicity of zeta-cypermethrin in rabbits (LD_{50} , > 2000 mg/kg bw), and inhalation toxicity was moderate for cypermethrin (LC_{50} , 1.260 mg/l) and alpha-cypermethrin (LC_{50} , 1.590 mg/l). Overall, the three isomeric mixtures displayed qualitatively similar profiles for acute toxicity in rats.

In rabbits, cypermethrin, alpha-cypermethrin and zeta-cypermethrin were slight eye irritants and slight skin irritants. Cypermethrin showed potential for skin sensitization in the maximization test in guinea-pigs, but was not a sensitizer according to the Buehler method, while alpha-cypermethrin was not a sensitizer in the maximization test, but zeta-cypermethrin was a skin sensitizer in the Buehler test. Cypermethrins also produce local paraesthesia (a tingling or burning sensation of the skin not associated with tissue damage) as an acute action that is distinct from irritancy.

Cypermethrin, alpha-cypermethrin and zeta-cypermethrin cause neurotoxicity in mammals and insects by causing a long-lasting prolongation of the normally transient increase in sodium permeability of nerve membrane channels during excitation. Salivation, and tremors that progress to clonic-tonic convulsions (choreoathetosis and salivation syndrome), along with gait abnormalities and ataxia are induced in rodents at high doses (> 100 mg/kg bw) but in dogs at lower doses (> 25 mg/kg bw), as seen in studies of acute toxicity and short-term studies of toxicity.

The main toxicological findings in repeat-dose studies in rodents were reduced weight gain, reduced food consumption, and at higher doses, signs of neurotoxicity (convulsions, tremors, hypersensitivity to touch and sound). Reduced weight gain and food consumption in rodents was observed with cypermethrin at dietary concentrations of 1000 ppm, equivalent to 50 mg/kg bw per day, and above. For alpha-cypermethrin these effects occurred at 100 ppm, equal to 11 mg/kg bw per day, in mice, while for zeta-cypermethrin the same effects were observed at 400 ppm, equal to 26 mg/kg bw per day, in rats. Dogs appeared to be the most sensitive species, with clinical signs of neurotoxicity being observed in the absence of body-weight loss at dietary concentrations of 600 ppm, equivalent to 15 mg/kg bw per day, and 120 ppm, equivalent to 3 mg/kg bw per day, for cypermethrin and alpha-cypermethrin respectively. Dogs dosed with alpha-cypermethrin for 3 months showed the usual clinical signs of pyrethroid toxicity, namely body tremors and variable incidences of head nodding, lip-licking, subduedness, ataxia, and agitation. The NOAEL for clinical signs in the 3-month study was 90 ppm, equivalent to 2.2 mg/kg bw per day. However, dogs dosed for 12 months showed no systemic toxicity. There was, however, abdominal skin reddening, skin reddening of the tail, including ulceration and necrosis of the tail in one male. The NOAEL for this effect was 60 ppm, equivalent to 1.5 mg/kg bw per day. There were no apparent methodological reasons for the disparity in clinical signs observed in the 3-month study in dogs, but not in the 12-month study in dogs. Similarly, the local skin irritation effects, possibly secondary to paraesthesia, observed after 3 weeks at 120 ppm, equivalent to 3 mg/kg bw per day, in the 12-month study were not found at higher doses (270 ppm, equivalent to 6.7 mg/kg bw per day) in the 3-month study. It was not possible to discount the possibility that this may have been caused by accidental contact with food containing alpha-cypermethrin. For zeta-cypermethrin, there were no studies in dogs. However, repeat-dose studies of neurotoxicity involving functional observational battery tests in rats given diets containing zeta-cypermethrin indicated reduced landing foot-splay and motor activity at 400 ppm, equal to 26 mg/kg bw per day.

There was no evidence of carcinogenicity with cypermethrin at dietary concentrations of up to 1600 ppm, equivalent to 240 mg/kg bw per day, in mice and at up to 1500 ppm, equivalent to 75 mg/kg bw per day, in rats. This was also the case in mice given diets containing alpha-cypermethrin at concentrations of up to 300 ppm, equal to 35 mg/kg bw per day, the highest dose tested.

Cypermethrin, alpha-cypermethrin and zeta-cypermethrin gave negative results in an adequate battery of studies of genotoxicity in vitro and in vivo.

In the absence of any carcinogenic potential in rodents and the lack of genotoxic potential in vitro and in vivo, the Meeting concluded that the cypermethrins are unlikely to pose a carcinogenic risk to humans.

In a three-generation study of reproductive toxicity in rats, adults receiving cypermethrin at a dietary concentration of 150 ppm, equal to 11 mg/kg bw per day, showed reduced body-weight gain and food consumption, and pups had lower body-weight gain during lactation at the higher dose of 750 ppm, equal to 56 mg/kg bw per day. Consistent with this, adult rats at 500 ppm, equivalent to 38 mg/kg bw per day, in a two-generation study of reproductive toxicity, also showed reduced body-weight gain and food consumption, but in this case litter size and litter weight were decreased at the same dose. In a two-generation study of reproductive toxicity with zeta-cypermethrin, decreased maternal body-weight gain and food consumption occurred at 375 ppm, equal to 22 mg/kg bw per day, along with decreased pup body weight. In contrast to the studies of reproductive toxicity with cypermethrin, clinical signs were observed in the dams and pups treated with zeta-cypermethrin at 22 mg/kg bw per day and higher, although similar NOAELs were obtained (6 mg/kg bw per day). No effects on reproductive performance were observed with either cypermethrin or zeta-cypermethrin.

In studies of developmental toxicity with cypermethrin and alpha-cypermethrin in rats and rabbits, and with zeta-cypermethrin in rats, teratogenicity was not observed. The only developmental effect noted in any of these studies was a slight but statistically significant reduction in fetal weight in rats treated with alpha-cypermethrin when clinical signs of neurotoxicity, and decreased body-weight gain and food consumption were seen in the dams. The NOAEL for these effects was 9 mg/kg bw per day. There were no developmental effects in rabbits given alpha-cypermethrin at up to 30 mg/kg bw per day or cypermethrin at 700 mg/kg bw per day, the highest doses tested, but alpha-cypermethrin was relatively more maternally toxic than cypermethrin in rabbits, causing a decrease in body-weight gain at 30 mg/kg bw per day, while the dose of cypermethrin at which similar effects were seen was 700 mg/kg bw per day.

Studies of acute neurotoxicity in rats were performed with cypermethrin, alpha-cypermethrin and zeta-cypermethrin. With cypermethrin, reduced activity and gait abnormalities were observed at a dose of 20 mg/kg bw; the NOAEL was 4 mg/kg bw. At doses of 60 mg/kg bw and above, salivation, choreoathetosis, altered righting reflex, splayed limbs and flattened posture were observed; urination, landing foot-splay and click response were increased; and arousal, grip strengths, touch response and tail-pinch response were decreased. Alpha-cypermethrin induced death, clinical signs, gait abnormalities, abnormal reactivity in the FOB, and slight to very slight degeneration of sciatic nerve fibres at doses of 20 mg/kg bw and above, with males being more severely affected than females. The NOAEL was 4 mg/kg bw. With zeta-cypermethrin at a dose of 50 mg/kg bw, clinical signs were observed, with additional findings of FOB abnormalities and one female death at 250 mg/kg bw. The NOAEL was 10 mg/kg bw.

Overall, the limited database for zeta-cypermethrin indicated that its toxicity profile was similar to that for cypermethrin and alpha-cypermethrin.

The Meeting concluded that the existing database was adequate to characterize the potential hazard of cypermethrins to fetuses, infants and children.

Toxicological evaluation

The Meeting acknowledged that since racemic cypermethrin already includes a substantial proportion of alpha- and zeta-cypermethrin, and that all three cypermethrins are qualitatively similar in their toxicity and metabolism, an ADI established for alpha-cypermethrin could apply for all three

substances. Since conventional testing of cypermethrin residues in treated commodities is unable to distinguish between the isomers, a group ADI is appropriate.

The Meeting established a group ADI of 0–0.02 mg/kg bw per day based on a NOAEL of 2.2 mg/kg bw per day for severe clinical signs of neurotoxicity in a 3-month dietary study in dogs treated with alpha-cypermethrin, and using a 100-fold safety factor. This NOAEL is supported by a similar NOAEL of 1.5 mg/kg bw per day for abdominal skin reddening and alopecia in a 12-month dietary study in dogs.

The Meeting established a group ARfD of 0.04 mg/kg bw based on the NOAEL of 4 mg/kg bw, and using a 100-fold safety factor. The NOAEL observed in a study of acute neurotoxicity was on the basis of death, clinical signs, changes in FOB tests and degenerative changes to the sciatic nerve at higher doses. Although the database indicated that dogs were more sensitive than rats to neurotoxic effects, the delayed onset of clinical signs (2 days) after dosing at 6.75 mg/kg bw per day in the 3-month study in dogs suggests that the NOAEL in the study of acute toxicity in rats would also be adequate for the most sensitive species.

Levels relevant to risk assessment

(a) Cypermethrin

Species	Study	Effect	NOAEL	LOAEL
Mouse	Two-year study of toxicity and carcinogenicity ^a	Toxicity	400 ppm, equivalent to 60 mg/kg bw per day	1600 ppm, equivalent to 240 mg/kg bw per day
		Carcinogenicity	1600 ppm, equivalent to 240 mg/kg bw per day ^d	—
Rat	Three-month studies of toxicity ^{a,b}	Toxicity	400 ppm, equivalent to 40 mg/kg bw per day	1500 ppm, equal to 116 mg/kg bw per day
	Two-year studies of toxicity and carcinogenicity ^{a,b}	Toxicity	150 ppm, equivalent to 7.5 mg/kg bw per day	1000 ppm, equivalent to 50 mg/kg bw per day
		Carcinogenicity	1500 ppm, equivalent to 75 mg/kg bw per day ^d	—
	Multigeneration reproductive toxicity ^{a,b}	Parental toxicity	50 ppm, equal to 3.8 mg/kg bw per day	150 ppm, equal to 11 mg/kg bw per day
		Offspring toxicity	100 ppm, equivalent to 7.5 mg/kg bw per day	500 ppm, equivalent to 38 mg/kg bw per day
	Developmental toxicity ^c	Maternal toxicity	17.5 mg/kg bw per day	35 mg/kg bw per day
		Embryo/fetotoxicity	70 mg/kg bw per day ^d	—
	Acute neurotoxicity ^c	Neurotoxicity	4 mg/kg bw	20 mg/kg bw
Rabbit	Developmental toxicity ^{b,c}	Maternal toxicity	450 mg/kg bw per day	700 mg/kg bw per day
		Embryo/fetotoxicity	700 mg/kg bw per day ^d	—
Dog	Three-month studies of toxicity ^{a,b}	Toxicity	500 ppm, equivalent to 12.5 mg/kg bw per day	800 ppm, equal to 25 mg/kg bw per day
	One-year study of toxicity ^a	Toxicity	200 ppm, equal to 5.7 mg/kg bw per day	600 ppm, equal to 18 mg/kg bw per day
	Two-year study of toxicity ^a	Toxicity	300 ppm, equivalent to 7.5 mg/kg bw per day	600 ppm, equivalent to 15 mg/kg bw per day

^a Dietary administration.

^b Two or more studies combined.

^c Gavage administration.

^d Highest dose tested.

(b) Alpha-Cypermethrin

Species	Study	Effect	NOAEL	LOAEL
Mouse	Three-month study of toxicity ^a	Toxicity	50 ppm, equal to 6.3 mg/kg bw per day	250 ppm, equal to 33 mg/kg bw per day
	Eighteen-month study of toxicity and carcinogenicity ^a	Toxicity	30 ppm, equal to 3 mg/kg bw per day	100 ppm, equal to 10.6 mg/kg bw per day
		Carcinogenicity	300 ppm, equal to 35 mg/kg bw per day ^d	—
Rat	Three-month study of toxicity ^a	Toxicity	180 ppm, equivalent to 18 mg/kg bw per day	540 ppm, equivalent to 54 mg/kg bw per day
	Developmental toxicity ^c	Maternal toxicity	9 mg/kg bw per day	18 mg/kg bw per day
		Embryo/fetotoxicity	9 mg/kg bw per day	18 mg/kg bw per day
	Acute neurotoxicity ^c	Neurotoxicity	4 mg/kg bw	20 mg/kg bw
Rabbit	Developmental toxicity ^c	Maternal toxicity	15 mg/kg bw per day	30 mg/kg bw per day
		Embryo/fetotoxicity	30 mg/kg bw per day ^d	—
Dog	Three-month study of toxicity ^a	Toxicity	90 ppm, equivalent to 2.2 mg/kg bw per day	270 ppm, equivalent to 6.7 mg/kg bw per day
	One-year study of toxicity ^a	Toxicity	60 ppm, equivalent to 1.5 mg/kg bw per day	120 ppm, equivalent to 3 mg/kg bw per day

^a Dietary administration.^b Two or more studies combined.^c Gavage administration.^d Highest dose tested.**(c) Zeta-Cypermethrin**

Species	Study	Effect	NOAEL	LOAEL
Rat	Three-month study of toxicity ^a	Toxicity	250 ppm, equal to 17 mg/kg bw per day	500 ppm, equal to 34 mg/kg bw per day
	Multigeneration reproductive toxicity ^a	Parental and offspring toxicity	100 ppm, equal to 6 mg/kg bw per day	375 ppm, equal to 22 mg/kg bw per day
	Developmental toxicity ^c	Maternal toxicity	12.5 mg/kg bw per day	25 mg/kg bw per day
		Embryo/fetotoxicity	35 mg/kg bw per day ^d	—
	Acute neurotoxicity ^c	Neurotoxicity	10 mg/kg bw	50 mg/kg bw
	Three-month study of neurotoxicity ^a	Neurotoxicity	75 ppm, equal to 5 mg/kg bw per day	400 ppm, equal to 26 mg/kg bw per day

^a Dietary administration.^b Two or more studies combined.^c Gavage administration.^d Highest dose tested.*Estimate of acceptable daily intake for humans*

0–0.02 mg/kg bw

Estimate of acute reference dose

0.04 mg/kg bw

Information that would be useful for continued evaluation of the compound

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

Critical end-points relevant for setting guidance values for exposure to cypermethrins

<i>Absorption, distribution, excretion and metabolism in mammals</i>	
Rate and extent of oral absorption	T _{max} , approximately 3 h; approximately 50–70% absorbed
Dermal absorption	Approximately 1% in humans
Distribution	Throughout the body; highest levels in fat, present mainly as <i>cis</i> -isomers
Potential for accumulation	The elimination half-life in fat was 10–25 days after a single oral dose; radioactivity accumulated in fat and skin after repeated oral dosing
Rate and extent of excretion	Rapid; > 95% excreted in 48 h
Metabolism in animals	Extensive, no unchanged cypermethrin excreted in the urine
Toxicologically significant compounds (animals, plants, environment)	Parent
<i>Acute toxicity (cypermethrin)</i>	
Rat, LD ₅₀ , oral	200 to > 3000 mg/kg bw
Rat, LD ₅₀ , dermal	> 1600 mg/kg bw (xylene vehicle); > 4800 mg/kg bw undiluted
Rat, LC ₅₀ , inhalation	1.260 mg/l air
Guinea-pigs, skin sensitization (test method used)	Sensitizer (maximization); non-sensitizer (Buehler)
<i>Acute toxicity (alpha-cypermethrin)</i>	
Rat, LD ₅₀ , oral	64 to > 5000 mg/kg bw, depending on vehicle
Rat, LC ₅₀ , inhalation	1.590 mg/l air
<i>Acute toxicity (zeta-cypermethrin)</i>	
Rat, LD ₅₀ , oral	86–367 mg/kg bw (corn oil vehicle)
<i>Short-term studies of toxicity</i>	
Target/critical effect	Clinical signs of neurotoxicity
Lowest relevant oral NOAEL	2.2 mg/kg bw per day (90-day study in dogs)
Lowest relevant dermal NOAEL	20 mg/kg bw per day (21-day study in rabbits)
Lowest relevant inhalation NOAEL	0.050 mg/l (21-day study in rats)
<i>Genotoxicity</i>	
	No genotoxic potential
<i>Long-term studies of toxicity and carcinogenicity</i>	
Target/critical effect	Reduced body-weight gain and food consumption
Lowest relevant NOAEL	7.5 mg/kg bw per day (2-year dietary study in rats)
Carcinogenicity	Not carcinogenic in rats and mice
<i>Reproductive toxicity</i>	
Reproduction target/critical effect	No reproductive effects; decreased pup body weight
Lowest relevant reproductive NOAEL	6 mg/kg bw per day (rats)
Developmental target/critical effect	Decreased fetal weights (rats)
Lowest relevant developmental NOAEL	9 mg/kg bw per day
<i>Neurotoxicity</i>	
Target/critical effect	Clinical signs, changes in FOB tests and degenerative changes to the sciatic nerve
Lowest relevant NOAEL	4 mg/kg bw per day (single-dose study in rats)
<i>Delayed neurotoxicity</i>	
Target/critical effect	No delayed effect
Lowest relevant NOAEL	> 1000 mg/kg bw per day (hens)
<i>Medical data</i>	
	Paraesthesia after dermal exposure

Summary for cypermethrins, including alpha-cypermethrin and zeta-cypermethrin

	Value	Study	Safety factor
Group ADI	0–0.02 mg/kg bw per day	Dog, 3-month dietary study with alpha-cypermethrin	100
Group ARfD	0.04 mg/kg bw	Rat, study of acute neurotoxicity with alpha-cypermethrin	100

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