# REGULATORY TOXICOLOGY
# POSITION PAPER

**Subject :**

**Cyfluthrin technical**

CONTENTS :

Expert statement on findings in offspring during lactation and relevance for classification and labelling

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## 1. Introduction

Within the framework of the Biocide Products Directive review of cyfluthrin active substance, in the Draft Final CAR for the active substance, January 2015, prepared by the evaluating Competent Authority (eCA) (Germany), the following classification is proposed:

R64 – May cause harm to breastfed babies (Directive 67/548/EEC (incl. 31st ATP))

Lact., H362 – May cause harm to breastfed children (Regulation (EC) No. 1272/2008)

Bayer S.A.S., Environmental Science (business unit of Bayer CropScience), presents argumentation in this Position Paper for the rebutting of this classification.

## 2. Background

In a Two-Generation Reproduction Study in Rats ([redacted] 1996), technical grade cyfluthrin was administered via the diet at nominal dose levels of 0, 50, 125 and 400 ppm. The study was compliant with OECD Testing Guideline 416 (May 1983). The F0 and F1 adults were comprised of 30 rats/sex/group. The test material intake in F0/F1 parental animals is given in Table 1 below:

**Table 1. Achieved Intake of Cyfluthrin in F0/F1 Parental Animals**

| Nominal dietary level ppm | Dose in mg/kg bw/d | | |
|---|---|---|---|
| | Premating Males/Females | Gestation | Lactation (weeks 1 & 2) |
| 0 | 0/0 | 0 | 0 |
| 50 | 3/4 | 4 | 7 |
| 125 | 9/10 | 10 | 19 |
| 400 | 29/33 | 33 | 59 |

The mg/kg bw/d intake of cyfluthrin during the lactation phase was approximately double that of the premating/gestation phase, due to the high consumption of treated feed during lactation.

**Principal findings on the study were as follows:**

P/F1 Parental Toxicity

Reduced body weight gain in F0 and F1 high dose males and F1 males at the mid-dose. Reduced body weight gain during gestation in F0 females and during lactation in both F0 and F1 females, at the high dose. Splaying of the hind limbs was observed during lactation for both F0 and F1 females at the high dose. Splaying of the hind limbs (or hind limb abduction) is a classic transient neurotoxic sign associated with Type II pyrethroids (Soderlund et al., 2000).

Reproductive Toxicity

The only reproductive parameter affected was a slight reduction in the mean number of implantation sites in both the F0 and F1 females at the high dose.

FI/F2 Offspring Toxicity

Reduced birth weights of F1 and F2 offspring at the high dose, together with reduced body weight gain of the F1 and F2 offspring at both the mid and high dose. Coarse tremors were observed in the FI and F2 offspring at both the mid and high dose. Tremors were first observed on day 5 of lactation and had disappeared by day 18 of lactation. Coarse tremor is a classic transient neurotoxic sign associated with Type II pyrethroids (Soderlund et al., 2002).

**Table 2. Litter Incidence of Coarse Tremors**

| Clinical Observations | 0 ppm | 50 ppm (7 mg/kg bw/d)* | 125 ppm (19 mg/kg bw/d)* | 400 ppm (19 mg/kg bw/d)* |
|---|---|---|---|---|
| F1 pups | 0/30 | 0/27 | 4/25<br><br>Onset PND 7<br>Last seen PND 14 | 15/28<br><br>Onset PND 5<br>Last seen PND 17 |
| F2 pups | 0/25 | 0/26 | 19/26<br><br>Onset PND 7<br>Last seen PND 16 | 9/25<br><br>Onset PND 7<br>Last seen PND 13 |

- *Test substance intake in Dams during weeks 1 & 2 of lactation
- PND = post-natal day

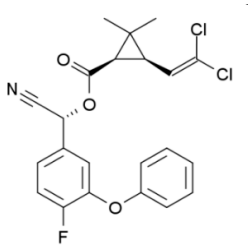
The excretion of cyfluthrin in rat milk has not been determined, but it is reasonable to assume that the offspring are exposed to cyfluthrin via the milk of the lactating dam, since pups only start to eat the diet from approximately the end of the second week of lactation. Therefore, the tremors seen in the early phase of lactation can be attributed to exposure of the pups to cyfluthrin, via the milk of the lactating parent females.

Test substance intake by the dams via the diet during lactation is approximately double the intake during the premating and gestation phases. In addition, as the pups are rapidly growing during lactation, the test substance intake/kg bw/d via the milk of the neonates in the treated groups will be disproportionately high during this phase, and will include exposure via consuming the treated diet during week 3 of lactation.

The coarse tremors seen in the neonates during lactation are transient, and characteristic of acute neurotoxicity associated with Type II pyrethroids, with no evidence of an adverse impact on long term development or reproductive capacity of the affected pups.

## 3. Discussion

The coarse tremor that was seen in neonatal rats in the two-generation reproduction study with cyfluthrin is a classic transient sign of acute neurotoxicity associated with Type II pyrethroids, when threshold concentrations of the parent compound reach the brain Soderlund et al., 2002). This is a transient effect on neuronal sodium ion channels in the brain, which recovers following metabolism and clearance. The occurrence of this finding in the neonate at the mid and high dose, and evidence of splayed hind limbs only at the high dose in the adult, indicates the neonatal rat is more sensitive than the adult; **however, this age-dependent sensitivity in young rats is consistent with a mode of action that is not relevant to man**.




Age-dependent sensitivity has been shown in rats with oral administration of deltamethrin and cypermethrin, with the available evidence indicating this is due to the limited capacity of preweanling rats to metabolize Type II pyrethroids (Sheets et al., 1994; Sheets, 2000). For example, the acute oral (gavage) LD50 of deltamethrin is 81 mg/kg in adult rats, 11 mg/kg at PND 21 and 5 mg/kg at PND 10 (Sheets et al., 1994). Similarly, the acute oral LD50 for cypermethrin is 18 mg/kg in PND 10 rats and 439 mg/kg in adult rats (Sheets, 2000). By comparison, neonatal rats are not more sensitive to low doses of deltamethrin or cypermethrin, due to clearance of low doses, and they are not more sensitive to either permethrin or cismethrin (Type I pyrethroids) at low or lethal doses, because it appears that neonatal rats are able to metabolize Type I pyrethroids as efficiently as adults (Sheets, 2000). Differences in metabolism are associated with the α-cyano moiety that is present only in Type II pyrethroids.

**Therefore, the available evidence indicates age-related sensitivity to Type II pyrethroids in rats is a high-dose phenomenon associated with the limited metabolic capacity of neonatal rats.** The registrants of pyrethrins and pyrethroids are involved in ongoing research to more thoroughly investigate this issue, in response to a directive from the US-EPA. A number of laboratories are involved in this industry-sponsored program to examine pyrethroids for evidence of pharmacokinetic and pharmacodynamic sensitivity, using a variety of test systems and PBPK modeling. The results from this program and published studies show pyrethroids are metabolized primarily by cytochrome P450 enzymes in rats and carboxylesterase enzymes in humans and the human child has a greater capacity to metabolize pyrethroids than neonatal rats. **Therefore, the phenomenon of age-dependent differences in sensitivity associated with metabolism in the rat is not relevant to infants and children.** The research to date with liver samples from children show they are capable of metabolizing Type I and Type II pyrethroids and nerve tissues in children are not more sensitive than in the adult. The results with deltamethrin as a model Type II pyrethroid are being used to develop PBPK models for the immature and adult rat, as well as for children and adult humans.

It is also important to note that the biocidal products containing cyfluthrin as the active ingredient; 'Solfac EW 050' (5% w/w cyfluthrin, diluted to 0.08% for use) and Raid® Cyfluthrin foam (0.04% cyfluthrin for use) will be used in animal housing units and in domestic premises, respectively. Therefore, potential exposure of humans, including lactating females, to cyfluthrin via the dietary route would be minimal. The risk to human infants via breast milk to adverse neurotoxicological effects of cyfluthrin at the potential exposure levels are negligible and breast fed infants should not be regarded as a susceptible sub-population. Therefore, the following proposed classification in the Draft Final CAR for the active substance cyfluthrin, is neither warranted nor justified.

R64 – May cause harm to breastfed babies (Directive 67/548/EEC (incl. 31st ATP))

Lact., H362 – May cause harm to breastfed children (Regulation (EC) No. 1272/2008)

## 4. Conclusion

The coarse tremor that was seen in neonatal rats and splayed hind limbs in adults in the two-generation reproduction study with cyfluthrin are classic transient signs of acute neurotoxicity associated with a Type II pyrethroid, when threshold concentrations of the parent compound reach the brain. These are transient effects on neuronal sodium ion channels in the brain, which recovers following metabolism and clearance of the pyrethroid. The occurrence of an acute neurotoxic sign in the neonate at the mid and high dose and in the adult only at the high dose indicates the neonatal rat is more sensitive than the adult. The available evidence indicates age-related sensitivity to pyrethroids in rats is a high-dose phenomenon associated with the limited metabolic capacity of neonatal rats. However, this expression of age-dependent sensitivity at high doses is consistent with a mode of action that is not relevant to man. In addition, the potential exposure of humans to cyfluthrin via the dietary route would be negligible.

Therefore, the following proposed classification in the Draft Final CAR for the active substance cyfluthrin, is neither warranted nor justified.

R64 – May cause harm to breastfed babies (Directive 67/548/EEC (incl. 31st ATP))

Lact., H362 – May cause harm to breastfed children (Regulation (EC) No. 1272/2008)

## 5. References

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