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UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

**DATE:** **December 10, 1997**

**MEMORANDUM**

**SUBJECT:** **IMIDACLOPRID - FQPA REQUIREMENT.**

**FROM:** Jess Rowland 12/10/97
Branch Senior Scientist.
Science Analysis Branch, Health Effects Division (7509C)

**THROUGH:** K. Clark Swentzel 12/11/97
Chairman, Hazard Identification Assessment Review Committee
Toxicology Branch II, Health Effects Division (7509C)

**TO:** Donna Davis
Chief, Registration Action Branch, Health Effects Division (7509C)

and

Elizabeth Haeberer
Product Manger
Registration Action Branch, Registration Division (7508W)

**PC Code: 129099**

On September 11, 1997, the Health Effects Division's Hazard Identification Review select toxicological endpoints and determined the Uncertainty Factors (UF's) for acute and chronic dietary risk assessments. However, the rationale used in determining the additional UFs to address enhanced sensitivity to infants and children as required by FQPA was not clear. Therefore, this Memorandum provides clarification on the UFs used for acute and chronic dietary risk assessments.

## I. BACKGROUND

On September 11, 1997, the Health Effects Division's Hazard Identification Review select toxicological endpoints and determined the Uncertainty Factors (UF's) for acute and chronic dietary risk assessments. The Committee's decisions were provided in the "Report of the Hazard Identification Assessment Committee" (Memorandum: J. Rowland, HED to E. Haeberer, RD, dated September 22, 1997). However, the rationale used in determining the additional uncertainty factors to address enhanced sensitivity to infants and children as required by FQPA was not clear. Therefore, this Memorandum provides clarification on the UFs used for acute and chronic dietary risk assessments as well as the rationale used in the Committee's conclusion on the need for a developmental toxicity study with Imidacloprid.

1. Acute Dietary Risk Assessment

The endpoint selected for acute dietary risk assessment is based on neurotoxicity characterized by decreases in motor or locomotor activity in female rats at 42 mg/kg/day (LOEL) in an acute neurotoxicity study. A NOEL was not established in this study.

For acute dietary risk assessment, the Committee determined that the 10 x factor to account for enhanced sensitivity of infants and children (as required by FQPA) should be reduced to 3 x for a total UF of 300 (10 x for inter-, 10 x for intra-species variations and 3 x for FQPA) and thus a MOE of 300 is required..

Although developmental toxicity studies showed no increases sensitivity in fetuses as compared to maternal animals following *in utero* exposures in rats and rabbits, no increased sensitivity in pups as compared to adults and offspring was seen in the two generation reproduction toxicity study in rats showed no increased sensitivity in pups as compared to adults and offspring and the toxicology data base is complete (i.e., no data gaps), the Committee determined that a MOE of 300 is required based on the following weight-of-the-evidence considerations:

(i) There is concern for structure activity relationship. Imidacloprid, a chloronicotinyl compound, is an analog to nicotine and studies in the published literature suggests that nicotine, when administered causes developmental toxicity, including functional deficits, in animals and/or humans that are exposed *in utero*.

(ii) There is evidence that Imidacloprid administration causes neurotoxicity following a single oral dose in the acute study and alterations in brain weight in rats in the 2-year carcinogenicity study.

(iii) The concern for structure activity relationship along with the evidence of neurotoxicity dictates the need of a developmental neurotoxicity study for assessment of potential alterations on functional development.

Conventionally, when a LOEL from the critical study is used for risk assessment, an additional UF will be applied. For acute risk assessment with Imidacloprid, however, the Committee determined that the 3 x factor (used for FQPA as indicated above) is adequate to cover the use of the LOEL as well because: 1) of the low confidence in the endpoint based on the minimal nature of the effect (decreased motor activity only in females); 2) this effect was seen in adult rats; and 3) the same effect was not seen in the subchronic toxicity study following repeated doses.

2. Chronic Dietary Risk Assessment

The endpoint selected for chronic risk assessment is decreased body weight gains in females and increased thyroid lesions observed at 7.6 mg/kg/day in male rats in a combined chronic toxicity/carcinogenicity study. The NOEL was 5.7 mg/kg/day. A UF of 100 was applied to account for inter (10)- and intra (10)-species variation.

For chronic dietary risk assessment, the Committee determined that the 10 x factor to account for enhanced sensitivity of infants and children (as required by FQPA) is reduced to a 3-fold for a total UF of 300 (10 for inter-species variation x 10 for intra-specie variation x 3 for FQPA). The UF of 300 is supported by the following factors:

Although developmental toxicity studies showed no increased sensitivity in fetuses as compared to maternal animals following *in utero* exposures in rats and rabbits, no increased sensitivity in pups as compared to adults was seen in the two generation reproduction toxicity study in rats, and the toxicology data base is complete (i.e., no data gaps), the Committee determined that a UF 300 is required based on the following weight-of-the-evidence considerations:

(i) There is concern for structure activity relationship. Imidacloprid, a chloronicotinyl compound, is an analog to nicotine and studies in the published literature suggests that nicotine, when administered causes developmental toxicity, including functional deficits, in animals and/or humans that are exposed *in utero.*

(ii) There is evidence that Imidacloprid administration causes neurotoxicity following a single oral dose in the acute study and alterations in brain weight in rats in the 2-year carcinogenicity study.

(iii) The concern for structure activity relationship along with the evidence of neurotoxicity dictates the need of a developmental neurotoxicity study for assessment of potential alterations on functional development.

3. Need for a Developmental Neurotoxicity Study

The Committee recommended that a developmental neurotoxicity study be required for Imidacloprid based on the following weight-of-evidence considerations.

- Imidacloprid is a neurotoxic chemical. There is evidence of functional neurotoxicity in the acute neurotoxicity study where a single oral dose caused a dose-related decrease in motor or locomotor activity in all treated females, including a 25% decrease at the lowest dose tested (42 mg/kg/day).

- There has been no assessment for delayed neurotoxicity study in the hen.

- Imidacloprid is a nicotine analog and is expected to act as a nicotinic agonist.

- With this class of chemical, there is no readily available biomarker (e.g.,Cholinesterase inhibition) for assessment of subtle neurotoxic effects.

- In the 2-year chronic study in rats, significant alterations to brain weight were noted in males and females at 900 ppm (51.3 and 73 mg/kg/day in males and females).

- A review of the literature suggests that nicotine causes developmental toxicity, including functional deficits, in animals and/or humans exposed *in utero*.