UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
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OFFICE OF
PREVENTION, PESTICIDES, AND
TOXIC SUBSTANCES

23-APR-1998

MEMORANDUM

SUBJECT: ***IMIDACLOPRID*** - Report of the FQPA Safety Factor Committee.

FROM: Brenda Tarplee, Executive Secretary
FQPA Safety Factor Committee
Health Effects Division (7509C)
and
Jess Rowland, Executive Secretary
Hazard Identification Assessment Review Committee
Health Effects Division (7509C)

THROUGH: Ed Zager, Chairman
FQPA Safety Factor Committee
Health Effects Division (7509C)

TO: Rick Loranger, Branch Senior Scientist
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PC Code: 129099

The Health Effects Division (HED) FQPA Safety Factor Committee met on April 13, 1998 to evaluate the hazard and exposure data for Imidacloprid and recommend application of the FQPA Safety Factor (as required by FQPA), to ensure the protection of infants and children from exposure to this chemical. The Committee recommended that the 10x Safety Factor for enhanced sensitivity to infants and children (as required by FQPA) should be reduced to 3x.

I. HAZARD ASSESSMENT

1. Determination of Susceptibility

The Hazard Identification Assessment Review Committee (HIARC) determined that the available studies demonstrated **no indication of increased sensitivity of rats or rabbits to *in utero* and/or postnatal exposure to Imidacloprid.** In the prenatal developmental toxicity studies in rats and rabbits and in the two-generation reproduction study in rats, developmental toxicity to the offspring occurred at equivalent or higher doses than maternal toxicity (*Memorandum:* J. Rowland to D. Davis, dated September 22, 1997).

2. Adequacy of Toxicity Database

There are **no data gaps** for the assessment of the effects of Imidacloprid following *in utero* and/or postnatal exposure. However, the HIARC determined that a postnatal developmental neurotoxicity study in rats is **required** for Imidacloprid based on the following weight-of-the-evidence considerations:

- Imidacloprid is a neurotoxic chemical. Evidence of functional neurotoxicity was seen in the acute neurotoxicity study where a single oral dose caused a dose-related decreased motor activity in all dosed females, including a 25% decrease at the lowest dose tested (42 mg/kg/day).

- Imidacloprid is a nicotine analog and is expected to act as a nicotinic agonist. A review of the literature suggests that nicotine causes developmental toxicity, including functional deficits, in animals and/or humans exposed *in utero*.

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

- In the 1993 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).

II. EXPOSURE ASSESSMENT

1. Dietary Exposure Considerations

Imidacloprid is a systemic insecticide. Its primary use is on various vegetable crops, cereal grains, and pome fruits. Established plant and animal commodity tolerances (40 CFR 180.472) range from 0.05 - 15 ppm. Per 40 CFR 180.472, the regulated residue in plant and animal commodities consists of the combined residues of parent Imidacloprid and its metabolites containing the 6-chloropyridinyl moiety, all expressed as parent Imidacloprid. Meat, milk, poultry, and egg tolerances are established.

Imidacloprid and its residues are systemic. Residues will translocate throughout the plant, regardless of the method of application: seed, soil, or foliar. Use is via seed treatment, banded soil application, and/or foliar spray. Use rates via soil application range from 0.2-0.4 lb ai/A/application, depending on the crop; and via foliar sprays range from 0.05-0.25 lb ai/A/application, depending on the crop and/or pest to be controlled. Regardless of formulation or type of application, no more than a TOTAL of 0.5 lb ai/A/year may be used (from any combination of seed + soil + foliar treatments).

The HED DRES system was used to assess the chronic and acute risk from dietary exposure to Imidacloprid in food. The chronic dietary risk assessment is partially refined to reflect a slightly less exaggerated level of exposure by using tolerance values for all crops and the available percent crop treated (% CT) information. The acute dietary risk assessment was not refined, it included the very conservative assumption that all commodities will contain residues of Imidacloprid at the level of the tolerance. This results in an overestimate of acute dietary exposure.

2. Drinking Water Exposure Considerations

EFED reports that the surface and groundwater drinking water assessments were not complete for Imidacloprid at the time of this meeting. No ground or surface water monitoring data are available for Imidacloprid. Therefore, for surface water, PRZM3.1/EXAMS modeling will be conducted to estimate representative concentrations.

3. Residential Exposure Considerations

Imidacloprid is registered for home lawn and garden use and for "localized" pet treatments products are applied either to back of the neck or onto the back of the animals). Chemical specific or site specific data were not provided to assess exposure associated with these uses, therefore, the DRAFT Standard Operating Procedures (SOPs) for Residential Exposure Assessments were utilized. The DRAFT SOPs normally rely on one or more upper-percentile assumptions and are intended to represent Tier 1 assessments.

Since the Draft SOPs do not specifically address "localized" per applications, a modified approach was developed to assess post application hand-to-mouth ingestion exposure for toddlers. The following assumptions were made: 1) 1% of the application rate is available on the pets as dislodgeable residue on the day of application. (SOP uses 10% for pet dips and 1% for flea collars); 2) there is a one-to-one relationship between the dislodgeable residue on the surface of the pet and on the surface area of the skin after contact; 3) postapplication activities are assessed on the day of application since toddlers could handle/touch pets immediately after application; and 4) toddlers (age 3 years) are used to represent the 1 to 6 year old age group and weigh 15 kg.

PHED Version 1.1 is also used for residential turf handler (mixer/loader/applicator) scenarios. The PHED scenarios reflect the actual use patterns and the data ranges from low to medium level quality. Mixer/loader/applicators are assumed to be wearing short pants, short sleeves, and no gloves.

III. RISK CHARACTERIZATION

1. Determination of the Factor

The Committee recommended that the **10x factor** for enhanced sensitivity to infants and children (as required by FQPA) should be **reduced to 3x.**

2. Rationale for Selection of the FQPA Factor

Although the available studies demonstrated no indication of increased sensitivity of rats or rabbits to *in utero* and/or postnatal exposure to Imidacloprid, the Committee determined that the 10x Safety Factor should be reduced to 3x 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) There is concern for accidental oral exposure (hand-to-mouth) for infants and children from the use pattern (pet and outdoor residential).

3. Identification of Population Subgroup

The Committee determined that the FQPA Safety Factor (3x) is applicable for the following subpopulations:

Acute Dietary: **General populations which include Infants and Children** because: 1) There is concern for structure activity relationship since 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*; 2) There is evidence that Imidacloprid administration causes neurotoxicity following a single oral exposure and was selected as the endpoint for this risk assessment; and 3) There is concern for accidental oral exposure (hand-to-mouth) for infants and children from the use pattern (pet and outdoor residential).

Chronic Dietary: **General populations which include Infants and Children** because: 1) There is concern for structure activity relationship since 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*; 2) There is evidence that Imidacloprid administration causes neurotoxicity following repeated exposure characterized as alterations in brain weight; 3) The endpoint used for this risk assessment is thyroid lesions; and 4) There is concern for accidental oral exposure (hand-to-mouth) for infants and children from the use pattern (pet and outdoor residential).

Residential: **General populations which include Infants and Children** because 1) There is concern for structure activity relationship since 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*; 2) 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; 3) the pet and outdoor residential uses of Imidacloprid are a potential source of exposure to infants and children.