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

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OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

DATE: September 23, 1997

MEMORANDUM

SUBJECT: ***IMIDACLOPRID*** - Report of the Hazard Identification Assessment Review Committee.

FROM: Jess Rowland Jess Rowland 9/23/97
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THROUGH: K. Clark Swentzel K. Clark Swentzel 9/23/97
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)

On September 11, 1997, the Health Effects Division's Hazard Identification Review committee met to evaluate the toxicology data base of Imidacloprid to select toxicological endpoints for acute dietary as well as occupational and residential exposure risk assessments. The Committee also re-assessed the Reference Dose established for chronic dietary risk assessment and addressed the sensitivity of infants and children from exposure to Imidacloprid as required by the Food Quality Protection Act of 1996.

cc: S.Knizer

Committee Members in Attendance

Committee members in attendance: David Andersen, Karl Baetcke, Susan Makris, Nancy McCarroll, Kathleen Raffeale, John Redden and Jess Rowland. Members in absentia: William Buram and Melba Morrow. The data was presented by Dr Willimas- Foy, Registration Action Branch 2.

Data Presentation: S. A. Williams Foy
Dr. S. Williams-Foy

Report Preparation: Jess Rowland
Jess Rowland, M.S

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I. TOXICOLOGY PROFILE

A. Acute Toxicity

Guideline No.	Study Type	MRIDs #	Results	Toxicity Category
81-1	Acute Oral	42055331	LD_{50} = 424 mg/kg (M) > 450 mg/kg (F)	III
81-2	Acute Dermal	42055332	LD_{50} = >5000 mg/kg	IV
81-3	Acute Inhalation	42256317	LC_{50} = > 5.33 mg/L	IV
81-4	Primary Eye Irritation	4205534	Non irritant	IV
81-5	Primary Skin Irritation	42055335	Non-irritant	IV
81-6	Dermal Sensitization	42055336	Non-sensitzer	NA
81-8	Acute Neurotoxicity	4317301	NOEL = Not established LOEL = 42 mg/kg/day	NA

B. Subchronic Toxicity

In a dermal toxicity study, groups of 5 male and 5 female New Zealand White rabbits received repeated dermal applications of Imidacloprid (95%) at 1000 mg/kg/day (Limit Dose), 6 hours/day, 5 days/week for three weeks. No dermal or systemic toxicity was seen. For systemic and dermal toxicity, the NOEL was > 1000 mg/kg/day; a LOEL was not established (MRID No. 42256329).

In an oral toxicity study, groups of Fischer 344 rats (12/sex/dose) were fed diets containing Imidacloprid (98.8%) at 0, 150, 1000, or 3000 ppm (0, 9.3, 63.3, or 196 mg/kg/day in males and 0, 10.5, 69.3 or 213 mg/kg/day in females, respectively) for 90 days. No treatment-related effects were seen at 150 ppm. Treatment-related effects included decreases in body weight gain during the first four weeks of the study at 1000 ppm (22% in males and 18% in females) and 3000 ppm (50% in males and 25% in females) with an associated decrease in forelimb grip strength especially in males. The NOEL was 150 ppm (9.3 and 10.5 mg/kg/day in males and females, respectively) and the LOEL was 1000 ppm (63.3 and 69.3 mg/kg/day in males and females, respectively) (MRID No. 43286401).

C. Chronic Toxicity

In a chronic toxicity study, groups of beagle dogs (4/sex/dose) were fed diets containing Imidacloprid (94.9%) at 0, 200 or 1250/2500 ppm (0, 6.1, 15 or 41/72 mg/kg/day, respectively) for 52 weeks. The 1250 ppm was increased to 2500 ppm from week 17 onwards. The threshold NOEL was 1250 ppm (41 mg/kg/day). The LOEL was 2500 ppm (72 mg/kg/day) based on increased cytochrome-P-450 levels in both sexes and was considered to be a threshold dose (MRID No. 42273002).

D. Carcinogenicity

In a combined chronic toxicity/carcinogenicity study, groups of Bor WISW rats (50/sex/dose) received Imidacloprid (95.3%) at 0, 100, 300 or 900 ppm (0, 5.7, 16.9 or 51.3 mg/kg/day in males and 0, 7.6, 24.9, or 73 mg/kg/day in females, respectively) for 104 weeks. In another study, rats of the same strain (50/sex) received Imidacloprid at 0 or 1800 ppm (0, 102.6 and 143.7 mg/kg/day in males and females, respectively) for 104 weeks. For chronic toxicity, the NOEL was 100 ppm (5.7 mg/kg/day) and the LOEL was 300 ppm (16.9 mg/kg/day) based on decreased body weight gains in females and increased thyroid lesions in males. There was no evidence of carcinogenicity in either sex (MRID No. 42256331 and 42256332).

In a carcinogenicity study groups of B6C3F1 mice (50/sex/dose) were fed diets containing Imidacloprid (95%) at 0, 100, 330 or 1000 ppm (0, 20, 66 or 208 mg/kg/day in males and 0, 30, 104 or 274 mg/kg/day in females, respectively) for 2 years. In a supplementary study conducted to evaluate the adequacy of the high dose tested in the main study, the same strain of mice (50/sex) received 0 or 2000 ppm (414 and 424 mg/kg/day in males and females, respectively) for the same time period. For chronic toxicity, the NOEL was 1000 ppm (208 mg/kg/day). The LOEL was 2000 ppm (414 mg/kg/day) based on decreased bodyweight gain, food consumption and water consumption. There was no evidence of carcinogenicity in either sex (MRID No. 42256335 and 42256336).

E. Developmental Toxicity

In a developmental toxicity with Sprague-Dawley rats, groups of pregnant animals (25/group) received oral administration of Imidacloprid (94.2%) at 0, 10, 30, or 100 mg/kg/day during gestation days 6 through 16. Maternal toxicity was manifested as decreased body weight gain at all dose levels and reduced food consumption at 100 mg/kg/day. No treatment-related effects were seen in any of the reproductive parameters (i.e., cesarian section evaluation). At 100 mg/kg/day, developmental toxicity manifested as characterized as wavy ribs (fetus =7/149 in treated vs. 2/158 in controls and litters, 4/25 vs. 1/25). For maternal toxicity, the LOEL was 10 mg/kg/day)LDT) based on decreased body weight gain; a NOEL was not established. For developmental toxicity, the NOEL was 30 mg/kg/day and the LOEL was 100 mg/kg/day based on increased wavy ribs (MRID No. 42256338).

In a developmental toxicity with Chinchilla rabbits, groups of 16 pregnant does were given oral doses of Imidacloprid (94.2%) at 0, 8, 24 or 72 mg/kg/day during gestation days 6 through 18. For maternal toxicity, the NOEL was 24 mg/kg/day and the LOEL was 72 mg/kg/day based on mortality, decreased body weight gain, increased resorption, and increased abortion. For developmental toxicity, the NOEL was 24 mg/kg/day and the LOEL was 72 mg/kg/day based on decreased fetal body weight, increased resorptions, and and increased skeletal abnormalities (MRID No. 42256339).

F. Reproductive Toxicity

In a two-generation reproduction study, 95.3% Imidacloprid was administered to Wistar/Han rats at dietary levels of 100, 250, or 700 ppm (7.3, 18.3, or 52.0 mg/kg/day for males and 8.0, 20.5, or 57.4 mg/kg/day for females) (MRID 42256340, Doc. No. 010537). The study DER indicated that the parental NOEL was 700 ppm (55 mg/kg/day) and the parental LOEL was not determined. The DER also stated that the reproductive NOEL was 100 ppm (8 mg/kg/day) and the reproductive LOEL was 250 ppm (19 mg/kg/day), based upon decreased pup body weight in both generations. The Committee reviewed the adult and pup body weight data and provided the following comments: 1) Based upon body weight data in parental animals, significant decreases in premating, gestation, and lactation body weight were observed in males and/or females of both generations at 700 ppm. 2) Overall body weight gains during premating were reduced although they did not appear to be significantly affected. The assertion by the study reviewer, that decreased palatability was the primary cause for the body weight decrements was not supported by the body weight data from the first week of dosing (during which no body weight decreases occurred).

Therefore, the Committee agreed that the parental systemic LOEL should be 700 ppm, based upon decreased mean body weight in males and females of both generations, and the parental systemic NOEL, 250 ppm. The Committee also reviewed the body weight data for the four sets of litters produced during this study. Although the study reviewer determined that the reproductive toxicity LOEL was 250 ppm, based upon decreased pup body weight, the Committee found that effects at that dietary level were inconsistent between and within generations. The significant differences noted for the F1a and F1b litters were actually increases in body weight; then in the second generation, significant decreases were only observed on day 7 for the F2a pups and on day 21 for the F2b pups, although a dose response was suggested. The Committee concluded that the evidence for a treatment-related effect on pup body weight at 250 ppm was equivocal. For parental/systemic/reproductive toxicity, the NOEL was 250 ppm (18.3 mg/kg/day) and the LOEL was 750 ppm (52 mg/kg/day), based on decreases in body weight in both sexes in both generations. Based on these factors, **the Committee recommended that the Data Evaluation Record should be revised to indicate the parental/systemic/ reproductive NOEL and LOEL to be 250 and 700 ppm, respectively, based upon the body weight decrements observed in both sexes in both generations.**

G. Mutagenicity

As shown below, mutagenicity studies have demonstrated that Imidacloprid is non-mutagenic both *in vivo* and *in vitro*

Assay	MRIDs #	Results
Ames-Salmonella	42256363	Negative
Recombination assay - yeast	42256353	Negative
Chromosomal aberration - *in vivo*	42256344	Negative
Chromosomal aberration - *in vitro*	42256345	Negative
Sister Chromatid assay - *in vivo*	42256346	Negative
Cytogenetics -CHO cells - *in vitro*	42256342	Negative
Micronucleus - mouse	42256366	Negative
DNA repair test	42256353	Negative
HGPRT assay - CHO	42256365	Negative

H. Dermal Absorption

No dermal absorption studies are available. The Committee noted the lack of dermal toxicity via this route with the dermal LD50 of >5000 mg/kg in rabbits as well as lack of dermal or systemic toxicity at 1000 mg/kg/day (Limit-Dose) in the 21-day dermal toxicity study in rabbits.

I. Recommendation for a Developmental Neurotoxicity Study

The Committee recommended that a developmental neurotoxicity study be required for Imidacloprid. The following information was considered in the weight-of-evidence evaluation.

1) Evidence that support requiring a developmental neurotoxicity study:

- 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.

- 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).

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

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

2) Evidence that do not support asking for a developmental neurotoxicity study:

- No effects on histopathology of the brain were observed in any of the guideline studies in which these parameters were measured including the acute and subchronic neurotoxicity studies in rats.

- No evidence of developmental anomalies of the fetal nervous system were observed in the prenatal developmental toxicity studies in either rats, or rabbits, at maternally toxic oral doses up to 100 and 72 mg/kg/day, respectively.

II. FQPA CONSIDERATIONS

The prenatal developmental toxicity data demonstrated no indication of increased sensitivity of rats or rabbits to *in utero* exposure to Imidacloprid. In addition, the multi-generation reproduction study data did not identify any increased sensitivity of rats to *in utero* or postnatal exposure. Maternal and parental NOELs were lower or equivalent to developmental or offspring NOELs.

III. HAZARD IDENTIFICATION

A. Acute Dietary (one-day)

Study Selected: Acute Neurotoxicity - Rat §81-8

MRID No 41370301 & 43285801

EXECUTIVE SUMMARY: In an acute neurotoxicity study, groups of Sprague-Dawley rats (18/sex/dose) were given a single oral administration of Imidacloprid (97.6%) in 0.5% methylcellulose with 0.4% Tween 80 in deionized water at 0, 42, 151 or 307 mg/kg. Parameters evaluated included: clinical pathology (6/sex/dose); Functional Observation Battery (FOB) measurements (12/sex/dose); and neuropathology (6/sex/dose). FOB measurements were made approximately 90 minutes post dosing, and on days 7 and 14. Motor activity measurements were made at approximately 2.5 hours post dosing.

At 307 mg/kg/day, 4/18 males and 10/18 females died and both sexes of rats at this dose exhibited decreased number of rears, grip strength (forelimb and hindlimb) and response to stimuli (auditory, touch, or tail pinch) as well as increased gait abnormalities and righting reflex impairments and body temperatures. These symptoms regressed by day 5. At 151 mg/kg/day, cage side FOB assessments revealed tremors in one male and one female and and red nasal staining in one male. On the day of dosing, a dose-related decrease in total session motor activity was observed in males at 151 mg/kg/day (25% decrease) and 307 mg/kg/day (73%) and in females at all dose levels with the decreases (25, 48, and 81%, respectively at 42, 151 and 307 mg/kg/day) reaching statistical significance ($p < 0.05$) at 151 and 307 mg/kg/day dose levels. Decreases in motor activity was seen at all time intervals. Total session locomotor activity was also decreased to about the same percentage difference but statistical significance were not reported. On days 7 and 14, decreases (not statistically significant) were still observed in motor and locomotor activity in surviving high-dose males. The LOEL was 42 mg/kg based on the decrease in motor and locomotor activities observed in females; a NOEL was not established (MRID No. 4137031 and 43285801).

Dose/Endpoint for Risk Assessment: LOEL=42 mg/kg/day based on the dose-related decreases in motor activity in females. A NOEL was not established.

Comments about Study/Endpoint: An Uncertainty Factor of 3 was assessed to this dose (LOEL) to account for the lack of a NOEL. A Margin of Exposure of 300 is required.

The Committee recommended that the DER should be revised to reflect a LOEL of 42 mg/kg/day based on the dose-related decreases in motor activity in female rats. This effect was seen in this sex at all dose levels at all time intervals.

B. Chronic Dietary [Reference Dose (RfD)]

Study Selected: Chronic toxicity/Carcinogenicity - Rat (§83- 5)

MRID No. 42256335 & 42256336

Executive Summary: In a combined chronic toxicity/carcinogenicity study, groups of Bor WISW rats (50/sex/dose) received Imidacloprid (95.3%) at 0, 100, 300 or 900 ppm (0, 5.7, 16.9 or 51.3 mg/kg/day in males and 0, 7.6, 24.9, or 73 mg/kg/day in females, respectively) for 104 weeks. For chronic toxicity, the NOEL was 100 ppm (5.7 mg/kg/day in males and 7.6 mg/kg/day in females) and the LOEL was 300 ppm (16.9 mg/kg/day in males and 24.9 mg/kg/day in females) based decreased body weight gains in females and increased thyroid lesions in males. Organ weight changes were observed in both sexes of rats at doses above 900 ppm. There was no evidence of carcinogenicity in either sex (MRID No. 42256331 and 42256332).

Dose/Endpoint for establishing the RfD: NOEL= 5.7 mg/kg/day based on increased thyroid lesions in males at 16.9 mg/kg/day (LOEL).

Uncertainty Factor (UF): An UF of 100 was applied to account for both inter-and intra-species variations.

Derivation of RfD: $\frac{\text{5.7 mg/kg/day (NOEL}}{\text{100 (UF)}} =$ **0.057 mg/kg/day**

C. Occupational/Residential Exposure

1. Short-Term Dermal (1-7 days)

Study Selected: None

Dose/Endpoint for Risk Assessment: Not applicable

Comments about Study/Endpoint: No dermal or systemic toxicity was seen in a 21-day dermal toxicity study in rabbits following repeated dermal applications of Imidacloprid at 1000 mg/kg/day (Limit-Dose) for 3 weeks. Therefore, this risk assessment is not required.

2. Intermediate-Term Dermal (7 days to several months)

Study Selected: None

Dose/Endpoint for Risk Assessment: Not applicable

Comments about Study/Endpoint: No dermal or systemic toxicity was seen in a 21-day dermal toxicity study in rabbits following repeated dermal applications of Imidacloprid at 1000 mg/kg/day (Limit-Dose) for 3 weeks. Therefore, this risk assessment is not required.

3. Long-Term Dermal (Several months to Life-time)

Study Selected: None

Dose/Endpoint for Risk Assessment: Not applicable

Comments about Study/Endpoint: No dermal or systemic toxicity was seen in a 21-day dermal toxicity study in rabbits following repeated dermal applications of Imidacloprid at 1000 mg/kg/day (Limit-Dose) for 3 weeks. Therefore, this risk assessment is not required.

4. Inhalation Exposure (Any-Time period)

Based on the LC_{50} of >5.33 mg/L (Limit-Dose), Imidacloprid is placed in Toxicity Category IV. Therefore, a separate risk assessment via this route is not required.

IV UNCERTAINTY FACTORS FOR DIETARY RISK ASSESSMENT

A. 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. An additional UF of 3 is applied due to the use of the LOEL for risk assessment.

Therefore, for acute dietary risk assessment, the Committee determined that **the additional UF of 10** to account for enhanced sensitivity of infants and children (as required by FQPA) **is reduced to 3 - fold** for a total UF of 300 (10 x each for inter-and intra-species variation and 3 for FQPA). Thus, **a MOE of 300 is adequate** to ensure protection of this population from exposure to Imidacloprid. **A MOE of 300 is supported by the following factors:**

(i) No maternal or developmental toxicity attributable to an acute (single dose) *in utero* exposure of Imidacloprid was seen in developmental toxicity studies.

(ii) The endpoint identified is neurotoxicity in adult rats.

(iii) Lack of a NOEL in the study used for selecting the dose and endpoint for this risk assessment.

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. An UF of 100 was applied to account for inter (10)- and intra (10)-species variation.

For chronic dietary risk assessment, the Committee determined that an **additional UF of 10** to account for enhanced sensitivity of infants and children (as required by FQPA) **be 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**:

(i) 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) Imidacloprid administration resulted in evidence of functional neurotoxicity in the acute toxicity study in rats. Dose-related decreases in motor activity was seen in females given a single oral dose. Significant alterations to brain weight were noted in the 2-year carcinogenicity study in rats.

(iii) Need of a developmental neurotoxicity study for assessment of potential alterations on functional development (i.e., data gap).