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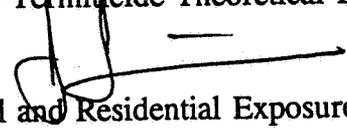
UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF
PREVENTION, PESTICIDES
AND TOXIC SUBSTANCES

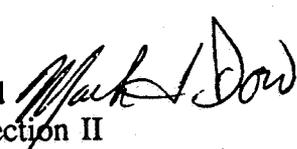
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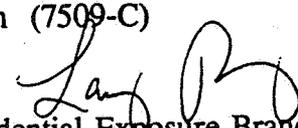
MEMORANDUM

SUBJECT: Imidacloprid Termiticide Theoretical Exposure Calculation

FROM: John Tice 
Occupational and Residential Exposure Branch
Health Effects Division (7509-C)

TO: Dennis Edwards, Jr. PM-19
Insecticide, Rodenticide Branch
Registration Division (7505-C)

THRU: Mark I. Dow, Ph.D., Section Head 
Special Review and Registration Section II
Occupational and Residential Exposure Branch
Health Effects Division (7509-C)

Larry Dorsey, Chief 
Occupational and Residential Exposure Branch
Health Effects Division (7509-C)

Please find below, the OREB review of:

DP Barcode: D-197419

Pesticide Chemical Code: 129099 Imidacloprid

EPA Reg. No.: Premise 2 Insecticide, 3125-EUP-204

EPA MRID No.: N/A

PHED: NOT USED

CCB should be consulted for a confirmation of the MOS.

I. INTRODUCTION:

In March, 1993 OREB evaluated a Section 5 (Experimental Use Permit) for a new Miles Termiticide. In that review, surrogate data were used (Termiticide treatment exposure studies) to estimate the exposures expected from the new imidacloprid product. OREB concurred with the use of the surrogate data and the estimates of exposure. It was suggested that limited confirmatory data be collected from the houses treated under the permit. These data could be used to check the accuracy of the surrogate data.

Miles Ag. Division, subsequently determined that because of the low vapor pressure of the product, there are numerous analytical problems with monitoring air to determine exposures in treated homes. It was suggested that a calculation of maximum theoretical concentration (Ideal Gas Law Calculation) may be sufficient. This review evaluates the submission of the concentration calculation.

II. DETAILED CONSIDERATIONS:

A. Use

Pryfon 6 TC is a termiticide product containing imidacloprid as the active ingredient. This submission evaluates the Ideal Gas Law Calculation which identifies the theoretical maximum concentration that could be in a closed space assuming maximum potential for volatilization. This calculation represents a conservative estimate of the maximum air concentrations to which humans and pets could be exposed.

B. Toxicology concerns

Currently, Toxicology has not identified specific toxicological end points of concern. Currently, the technical material is listed as Tox Category IV for both inhalation and dermal effects.

C. Detailed exposure calculations

The registrant has estimated the potential respiratory exposure of residents whose homes are treated with imidacloprid for subterranean termites. Their calculations are based on the Ideal Gas Law and required the following assumptions and parameters.

- the vapor pressure of imidacloprid is 1.5×10^{-9} mm Hg (registrant provided),

- the molecular weight of imidacloprid is 255.7 (registrant provided),
- the respiratory volume for a 70 kg adult performing light tasks is 1.7 M³ per hour,
- the respiratory volume for a 7.5 kg infant (6-9 months-old) was considered to be 0.5 m³ per hour.
- residents were assumed to be exposed continuously for 24 hours per day.

It must be realized that ALL of the above assumptions are very conservative and that saturation of indoor air with vapor would not occur under normal conditions. Residents are also unlikely to be performing light tasks for 24 hours per day. Vapor concentrations can be described by the following equation:

$$[\text{Imidacloprid}]_{\text{sat}} = \frac{VP \times (1.0 \times 10^6)}{P_{\text{atm}}}$$

$$[\text{Imidacloprid}]_{\text{sat}} = \frac{(1.5 \times 10^{-9} \text{ mmHg}) \times (1.0 \times 10^6)}{760 \text{ mmHg}}$$

$$[\text{Imidacloprid}]_{\text{sat}} = 1.973 \times 10^{-6} \text{ ppm}$$

Where: $[\text{Imidacloprid}]_{\text{sat}}$ = saturation vapor concentration of imidacloprid in ppm;
VP = vapor pressure of imidacloprid in mm Hg;
 P_{atm} = standard atmospheric pressure in mm Hg.
 1.0×10^6 converts micro-liters to liters which is \cong ppm.

To convert ppm to mg/m³:

$$\text{mg/m}^3 = \frac{\text{ppm} \times \text{molecular weight}}{24.45}$$

$$\text{mg/m}^3 = \frac{(1.973 \times 10^{-6}) (255.7)}{24.45}$$

$$= 2.06 \times 10^{-5} \text{ mg/m}^3$$

Where:

MW = molecular weight of imidacloprid; 24.45 = volume of air (L) per mole at 25°C and 760 mm Hg.

The estimated adult exposure for 24 hrs of exposure doing moderate work is expressed with the following equations:

$$\text{Exposure dose}_{\text{adult}} = \frac{2.06 \times 10^{-5} \text{ mg/m}^3 \times 1.7 \text{ m}^3/\text{hr} \times 24 \text{ hr/day}}{70 \text{ kg}}$$

$$\text{Exposure dose}_{\text{adult}} = 1.24 \times 10^{-5} \text{ mg/kg/day}$$

where 1.7 is the adult respiratory volume/minute (moderate activity), and 70 kg = median adult body weight.

D. MARGIN OF SAFETY (MOS) CALCULATION

In consultation with Toxicology Branch I (Personal communication on 3/7/94) with Myron Ottley and Marion Copley), the appropriate sub-acute inhalation study was obtained for an MOS calculation. The study used for the calculation was a 28 day inhalation study in which Wistar rats were exposed for 6 hrs/day, 5 days /week for 4 weeks. No toxicological effects were observed. Based on these results, the NOEL of 0.191 mg/l will be used for the

MOS calculation. Using John Redden's conversion from mg/l to mg/kg/day (attached Table 1) the NOEL (average of male and female) is 43.08 mg/kg/day. Using this NOEL and the exposure calculated above the resulting daily dose of adults and infants are presented below.

$$MOS_{adult} = \frac{NOEL}{Exposure}$$

$$MOS_{adult} = \frac{43.08 \text{ mg/kg/day}}{1.24 \times 10^{-5} \text{ mg/kg/day}}$$

$$MOS_{adult} = 3.4 \times 10^6$$

Infant Exposure:

$$Exposure \text{ dose}_{infant} = \frac{2.06 \times 10^{-5} \text{ mg/m}^3 \times 0.5 \text{ m}^3/\text{hr} \times 24 \text{ hr/day}}{7.5 \text{ kg}}$$

$$Exposure \text{ dose}_{infant} = 3.30 \times 10^{-5} \text{ mg/kg/day}$$

$$MOS_{infant} = \frac{NOEL}{Exposure}$$

$$MOS_{infant} = \frac{43.08 \text{ mg/kg/day}}{3.30 \times 10^{-5} \text{ mg/kg/day}}$$

$$MOS_{infant} = 1.3 \times 10^6$$

III. CONCLUSIONS:

Using very conservative exposure assumptions (i.e., complete saturation of the air, 24 hrs/day exposure doing moderate work) the Margins of Safety are several orders of magnitude larger than required.

NOTE that the MOS calculations were provided in the interest of saving time. The Chemical Coordination Branch should be contacted for confirmation and interpretation of the MOS.

cc: Albin Kocialski (CCB)
Nan Gray (CCB)
Marion Copley (TB-I)
Correspondence File
Imidacloprid (129099)

Table 1 - assumptions used in mg/l to Mg/kg/day conversions²

Species - Strain	Respiratory Vol/24 hr (m ³ /24hr)		Body Weight (Kg)	
	♂	♀	♂	♀
Rat-Fisher	0.37	0.26	0.4	0.25
Sprague Dawley	0.50	0.34	0.6	0.35
Homo Sapiens	21.024	12.0	70.0	68.5
Rabbit-NZW	1.49		4.1	

²Values taken from EPA RfC workshop committee, RTP, phone conversation between Annie Jarabek's office and Henry Spencer, 3/30/92.

Respiratory Rate Vol/24 hr for SD ♀ rats = 0.34 m³ = 340 liters
 Volume for 6 hr = 0.085m³ = 85 liters

NOEL = 0.191 mg/l

Female Rat: mg/kg/day = 0.191 mg/l X $\frac{85 \text{ l}}{0.35 \text{ kg}}$ = 46.38

Male Rat: mg/kg/day = 0.191 mg/l X $\frac{125 \text{ l}}{0.6 \text{ kg}}$ = 39.79

MOE = $\frac{\text{NOEL mg/kg/day}}{\text{Exposure (mg/kg/day)}}$

Agriculture Division

November 19, 1993

Miles Inc.
8400 Hawthorn Road
P.O. Box 4913
Kansas City, MO 64120-0013
Phone: 816 242-2000Mr. Dennis H. Edwards, Jr.
Product Manager (19)
Registration Division (H7505C)
U.S. Environmental Protection Agency
401 M Street, SW
Washington, D.C. 20460-0001SUBJECT: PREMISE 2 Insecticide
EPA File Symbol 3125-EUP-204

Dear Mr. Edwards:

In EPA's acceptance of Miles' Experimental Use Permit for PREMISE 2 Insecticide, the Agency conditionally accepted the surrogate data which measured indoor air concentrations in houses treated with another Miles' insecticide (PRYFON 6). Contained in the Agency's acceptance was a request from the Occupational and Residential Exposure Branch (OREB) to conduct a limited air sampling study to confirm this surrogate data, prior to a Section 3 registration. The Agency also stated that a meeting could be held to discuss this data request.

On 9/1/93, while meeting to review another Miles' product, our Dr. Monty Eberhart discussed this requirement with Mr. David Jaquith and Mr. John Tice of OREB. Following the discussion, it was agreed that the surrogate exposure estimates would be sufficient to support a Section 3 registration for PREMISE and that an indoor air monitoring study would not be required.

The following information is provided to document the 9/1/93 meeting with the Agency representatives:

Dr. Eberhart summarized our procedures for developing the surrogate estimates on imidacloprid and explained the extremely large safety factors that were obtained when estimated continuous exposures for adults and infant children were compared to the inhalation NOEL for imidacloprid (2.4×10^8 and 8.0×10^7 respectively). Even if the indoor air concentration of imidacloprid could reach the saturation vapor concentration of 2.1×10^{-5} mg/m³, safety factors of 1.9×10^5 and 7.3×10^4 would be achieved for continuously exposed adults and infant children, respectively.

The following sequence of calculations is provided to illustrate the procedure used to derive minimum margins of safety for adults and infant children assuming imidacloprid could reach the saturation vapor concentration:

The saturation vapor concentration of imidacloprid can be calculated using the following equation:

$$[\text{Imidacloprid}]_{\text{sat}} = \frac{VP \times 10^6}{P_{\text{atm}}}$$

$$[\text{Imidacloprid}]_{\text{sat}} = \frac{1.5 \times 10^{-9} \text{ mmHg} \times 10^6}{760 \text{ mmHg}}$$

$$[\text{Imidacloprid}]_{\text{sat}} = 1.974 \times 10^{-6} \text{ ppm}$$

where:

$[\text{Imidacloprid}]_{\text{sat}}$ = saturation vapor concentration of imidacloprid in ppm;

VP = vapor pressure of imidacloprid in mmHg;

P_{atm} = standard atmospheric pressure in mmHg.

Converting $[\text{Imidacloprid}]_{\text{sat}}$ to mg/m^3 :

$$[\text{mg}/\text{m}^3] = \frac{[\text{ppm}] \times MW}{24.45}$$

$$[\text{mg}/\text{m}^3] = \frac{(1.974 \times 10^{-6}) (255.7)}{24.45}$$

$$[\text{mg}/\text{m}^3] = 2.06 \times 10^{-5} \text{ mg}/\text{m}^3$$

where MW = molecular weight of imidacloprid; 24.45 = volume of air (L) per mole at 25°C and 760 mmHg.

Estimated continuous adult inhalation exposure dose:

$$\text{Exposure dose}_{\text{adult}} = \frac{2.06 \times 10^{-5} \text{ mg/m}^3 \times 1.75 \text{ m}^3/\text{hr} \times 24 \text{ hr/day}}{70 \text{ kg}}$$

$$\text{Exposure dose}_{\text{adult}} = 1.24 \times 10^{-5} \text{ mg/kg/day}$$

where 1.75 m³/hr = adult minute respiratory volume (moderate activity);
70 kg = median adult body weight.

Estimated adult inhalation margin of safety (MOS) for continuous exposure:

$$\text{MOS}_{\text{adult}} = \frac{\text{NOEL}}{\text{Exposure}}$$

$$\text{MOS}_{\text{adult}} = \frac{2.4 \text{ mg/kg/day}}{1.24 \times 10^{-5} \text{ mg/kg/day}}$$

$$\text{MOS}_{\text{adult}} = 193,548$$

0.191 mg/l

where NOEL = the imidacloprid no observable effect level from a subacute (20-day, 6 hr/day) inhalation study in rats.

Estimated continuous infant inhalation exposure dose:

$$\text{Exposure dose}_{\text{infant}} = \frac{2.06 \times 10^{-5} \text{ mg/m}^3 \times 0.5 \text{ m}^3/\text{hr} \times 24 \text{ hr/day}}{7.5 \text{ kg}}$$

$$\text{Exposure dose}_{\text{infant}} = 3.30 \times 10^{-5} \text{ mg/kg/day}$$

where 0.5 m³/hr = infant minute respiratory volume and 7.5 kg = median infant (6-9 month-old) body weight.

Estimated infant inhalation MOS for continuous exposure:

$$MOS_{infant} = \frac{NOEL}{Exposure}$$

$$MOS_{infant} = \frac{2.4 \text{ mg/kg/day}}{3.30 \times 10^{-5} \text{ mg/kg/day}}$$

$$MOS_{infant} = 72,727$$

These calculations should be provided to OREB for their documentation regarding Miles' PREMISE 2 Insecticide. As previously discussed in the 9/1/93 meeting, this information should be sufficient to enable the Agency to adequately determine the appropriate margins of safety with respect to PREMISE and therefore, an indoor air monitoring study should not be required.

If you have any questions regarding this submission, please contact Ms. Karen Cain at (816) 242-2838.

Yours very truly,

MILES INC.
AGRICULTURE DIVISION

John A Thornton

John S. Thornton
Manager, Registrations
Research and Development

JST:KSC:brh