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

FEB 22 1994

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: **Section 18: ID# 94OH0001.** Emergency Exemption for Use of ADMIRE 2 Flowable (Imidacloprid) on Potatoes in Ohio

Tox. Chem. No.: 497E
PC No.: 129099
Barcode No.: D199139
Submission No.: S457537

TO: Rebecca Cool, Manager, PM Team 41
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Registration Division (H7505C)

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THRU: Myron S. Ottley, Ph.D.
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I. CONCLUSIONS

The toxicology data requirements are complete for the issuance of a Section 18 emergency exemption by the State of Ohio for the temporary use of imidacloprid (ADMIRE 2 Flowable) to control pesticide-resistant Colorado potato beetles on potatoes. The margins of exposure (MOEs) for acute exposure are greater than 100. Imidacloprid is a "Group E" carcinogen, so there is no cancer risk associated with exposure to this chemical.

Toxicology Branch I has no objection to the issuance of this exemption.

II. ACTION REQUESTED

In a letter dated January 25, 1994, the Ohio Department of Agriculture requested an emergency exemption under Section 18 for the use of imidacloprid to control Colorado potato beetle (CPB, Leptinotarsa decemlineata Say) on potatoes. This is the first request made by Ohio for this use. Most of the CPB populations in 24 counties, scattered throughout the state, are resistant to all available synthetic insecticides. Alternative products for control of highly-resistant CPB include cryolite and BT products.

ADMIRE 2 Flowable (Miles, Inc.) is the formulation for the active ingredient. The pesticide will be used once per growing season, as an at-planting soil systemic treatment for CPB. The maximum estimated acreage to be treated in Ohio is 8,000. The rate of application will be 0.9-1.3 fl. oz. of ADMIRE 2 Flowable per 1000 feet of row in furrow. This is equivalent to 11.2 to 22.7 fl. oz. of formulated product per acre, depending on row spacing.

III. TOXICOLOGY BRANCH I COMMENTS

The toxicology data base for imidacloprid is sufficient to support the proposed Section 18 exemption.

IV. RISK/EXPOSURE ASSESSMENT

This action was submitted to OREB (Occupational and Residential Exposure Branch) for determination of exposure estimates (see attached memo from J. Tice to W. Dykstra, dated February 22, 1993, subordinate bean: D199381). Acute MOEs were based on the Michigan exposure estimates, since oral communication with M. Dow on 2/17/94 indicated that Ohio worker exposures would be less than in the Michigan Section 18 potato calculations due to the smaller potato farm sizes in Ohio. Therefore, the Michigan exposure estimates and the rabbit maternal and developmental NOEL of 24 mg/kg/d (see Toxicology Profile, below) were used to determine the Acute MOEs. Calculations were based on a dermal absorption of 100%, because no dermal absorption data is available for imidacloprid. Cancer risk is not quantitated, since imidacloprid is a group E carcinogen, and there is no Q_1* for this chemical.

Formula used in calculations:

Acute MOE = NOEL (24 mg/kg BW/d) ÷ Exposure (mg/kg BW/d)

OPERATION*	EXPOSURE (mg/kg/d)	ACUTE MOE
Mixer/Loaders, open pour	0.012	2,000
Applicator, open cab	0.011	2,182

* Minimum clothing requirements for Applicators are long pants, short-sleeved shirt, and no gloves; Mixer/Loader exposure is based on wearing long pants, long sleeves, and gloves (Worker Protection Standard for Agricultural Pesticides).

V. SPECIAL TOXICOLOGY ISSUES AND PROBLEMS

1. Labelling. The labelling precautionary statements for ADMIRE 2 Flowable are governed by toxicity studies on the active ingredient.

2. Carcinogenicity. There is no cancer risk associated with exposure to this chemical, because the HED RfD Review Committee has determined that the test compound is a "Group E" carcinogen.

3. RfD. The RfD/Quality Assurance Peer Review Committee met on April 22, 1993 to assess the reference dose for this chemical. The Committee recommended that an RfD of 0.057 mg/kg/day should be established, based upon a NOEL of 5.7 mg/kg/d in a chronic toxicity study in rats. An uncertainty factor of 100 was used to account for interspecies extrapolation and intraspecies variability.

4. Non-carcinogenic risk assessment. In a chronic/oncogenicity study, male rats exhibited increased thyroid lesions at 16.9 mg/kg/day and above, and females at 73 mg/kg/day (see attached Toxicology Profile, study # 100652/101931). In a developmental study in rabbits, 72 mg/kg/d of technical imidacloprid (administered on days 6-19 of gestation) increased the number of resorptions and abortions in the dams, and increased skeletal abnormalities and decreased body weight in the pups.

5. Mutagenicity/genetic toxicity comments. Most of the genotoxicity studies for imidacloprid were negative, although an in vitro chromosome aberration study (human lymphocytes) was positive at cytotoxic concentrations (Tox. Doc. #099262), and an in vitro sister chromatid exchange mutagenicity study (CHO cells) was positive at cytotoxic doses (Tox. Doc. 102655).

6. Dermal Penetration. There are no available dermal penetration data for imidacloprid.

TOXICOLOGY PROFILE

Technical NTN 33893

Guideline	Study; Company; Date; MRID #; Category; Classification	Study Results
81-1	Acute oral LD50 Species: rat Bayer AG Institt. Fur Tox. Germ Study#: T 2033060 MRID: 420553-31 Date: 12/15/89 CORE - ACCEPTABLE DOC#s: 009375	Male Sprague-Dawley rats dosed at: 0, 50, 100, 250, 315, 400, 450, 1800 mg/kg. Females dosed: 0, 100, 250, 315, 400, 475, 500, and 18(mg/kg. LD50 (M) = 424 mg/kg (calculated). F > 450, < 475 mg/kg (estimatec Toxicity category II
81-2	Acute Dermal LD50 Species: rat Mobey Chem. Study#: T 5033063 MRID: 420553-32 Date: 11/15/89 CORE - ACCEPTABLE DOC#s: 009375	Sprague-Dawley rats dosed at 0 and 5000 mg/kg.n LD50 > 5000 mg/kg (limit test). Necropsy Observations: None Toxicity category IV
81-3	Acute inhalation LC50 Species: rat Bayer AG Institt. Fur Tox. Germ Study#: 16777 MRID: 420553-33 42289-01 Date: 06/06/88 CORE - ACCEPTABLE DOC#s: 009375 New Document DER Attached	Wistar rats dosed at 69 mg/m3 aerosol, 1220, 2577, and 5323 dust. C received conditioned air or 20,000 uL Lutrol vehicle. LC50 > 5323 mg/m3 (Tentative). upgraded Toxicity category IV
81-4	Primary eye irritation Species: rabbit Bayer AG Institt. Fur Tox. Germ Study#: T 8025515 MRID: 420553-34 Date: 02/25/89 CORE - ACCEPTABLE DOC#s: 009375	NZW rabbits given 0.1 mL of test substance in one eye. TIS: Primary Irrit. Index = 0. Non-irritating. Minimal redness (1 a & swelling (1 animal) observed 1 hr. post-dosing; was completely gon at 24 hrs. Toxicity category IV
81-5	Primary dermal irritation Species: rabbit Bayer AG Institt. Fur Tox. Germ Study#: T 8025515 MRID: 420553-35 Date: 02/25/88 CORE - ACCEPTABLE DOC#s: 009375	4 hr dermal exposure to NZWrabbits at 500 mg/kg. PIS = 0.0 (non-irritating). Toxicity category IV

NTN 33893 Technical

Guideline	Study Identification	Study Results
82-2	21-day Repeated Dose Dermal Species: Rabbit Bayer AG Dept. of Toxicology Study #: T 7029592 MRID: 422563-29 Date: June 11, 1990 Core: Minimum DOC#s: DER Attached	NTN 33893 Technical was administered at 1000 mg/kg to shorn backs of 5 male and 5 female New Zealand White rabbits for 6 hours/day, 5 days/week for 3 weeks. NOEL Systemic: 1000 mg/kg/day Dermal: 1000 mg/kg/day LOEL Systemic: >1000 mg/kg/day Dermal: >1000 mg/kg/day
83-1b	Chrogic Species: Dog RCC, Research & Consulting Co. Study #: 100015 MRID: 422730-02 Date: Oct. 19,1989 Core: Minimum DOC #s: DER Attached	NTN 33893 Technical was administered in the diet to 4 male and 4 female Beagle dogs per group at 0, 200, and 1250 (increased to 2500 from week 17 onwards) ppm for 52 weeks. NOEL: 1250 ppm (41 mg/kg/d) LOEL: 2500 (72 mg/kg/d) Increased Cytochrome P-450 levels in males and females. Considered a threshold dose. 5000 ppm caused 50% mortality in rangefinding study.
83-1a, 83-2a	Chronic/Onco Species: Rat Bayer AG Study #: 100652 101931 MRIDs: 422563-31 422563-32 Dates: July 14, 1989, Aug 19, 1991 Core: Minimum DOC #s: DER Attached	NTN 33893 Technical was administered in the diet to 50 male and 50 female Bor WISW (SPF Cpb) rats per group at 0, 100, 300, 900 and 1800 ppm for 104 weeks. The 1800 ppm dose group tested in a separate study with its own concurrent controls. NOEL: Chronic Effects: 100 ppm (5.7 mg/kg/d in males, 7.6 mg/kg/d in females) LOEL: Chronic Effects: 300 ppm Increased thyroid lesions in males at 300 ppm (16.9 mg/kg/d) and above and in females at 900 ppm (73 mg/kg/d) and above; Decr. body wt. gain in females at 300 ppm (24.9 mg/kg/d) and above; weight changes in liver, kidney, lung, heart, spleen, adrenals, brain and gonads in males and/or females at 900 ppm (51.3 mg/kg/d in males, 73.0 mg/kg/d in females) or 1800 ppm. Oncogenicity: No apparent treatment-related effect at any dose.
83-3	Developmental Toxicity Species: Rabbit RCC, Research & Consulting Co. Study #: 083518 MRID: 422563-38 Date: Jan. 8, 1992 Core: Minimum DOC #s: DER Attached	NTN 33893 Technical was administered to 16 pregnant Chinchilla rabbits per group at 0, 8, 24, and 72 mg/kg/d during gestation days 6 through 19. Maternal NOEL 24 mg/kg/d LOEL 72 mg/kg/d. Decreased food consumption; at 72 mg/kg/d: decreased body weight, increased resorption, increased abortion, and death. Developmental NOEL 24 mg/kg/d LOEL 72 mg/kg/d. Decrease body weight, increased skeletal abnormalities.

NTN 33893 75% Formulation

Guideline	Study Identification	Study Results
83-1	Acute Oral LD50 Species: Rat Mobay Corp. Study #: 91-012-JJ MRID: 422563-12 Date: August 27, 1991 Core: Minimum DOC #: DER to be submitted with subsequent action	NTN 33893 75% Formulation was administered once by gavage to Sprague-Dawley rats (5/sex/dose) at 0, 1063, 2180, and 3170 mg/kg for males, and 0, 1063, 2180, 2750, and 3170 mg/kg for females. Animals were observed for 14 days. LD50 Male 2591 mg/kg (calculated) Female 1858 mg/kg (calculated Toxicity Category: III
81-2	Acute Dermal LD50 Species: Rat Mobay Corp. Study #: 91-022-JH MRID: 422563-14 Date: August 21, 1991 Core: Minimum DOC #: DER to be submitted with subsequent action	NTN 33893 75% Formulation was administered once dermally for 24 hr to Sprague-Dawley rats (5/sex/dose) at 0 and 2000 mg/kg. Animals were observed for 14 days. LD50 >2000 mg/kg Toxicity Category: III
81-3	Acute Inhalation Species: Rat Mobay Corp. Study #: 91-042-JZ MRID: 422563-16 Date: September 25, 1991 Core: Minimum DOC #: DER to be submitted with subsequent action	NTN 33893 75% Formulation was administered as a liquid aerosol by inhalation once for 4 hr to Sprague-Dawley rats (5/sex/dose) at 0, 2110, 2810, and 2990 mg/m3. Animals were observed for 14 days. LC50 Male: 2650 mg/m3 (calculated) Female: 2750 mg/m3 (calculated) NOEL <2110 mg/m3 LOEL 2110 mg/m3 Toxicity Category: III
81-4	Eye Irritation Species: Rabbit Mobay Corp. Study #: 91-335-JK MRID: 422563-18 Date: June 25, 1992 Core: Minimum DOC #: DER to be submitted with subsequent action	NTN 33893 75% Formulation was introduced into the conjunctival sac of the left eye of 6 male New Zealand White rabbits at 0.1 ml (44-46 mg). The right eye of each animal served as control. Animals were observed for 14 days. TIS: TIME 1hr 24hr 48hr 72hr 7d 14d IRRIT. SCORE 2.5 1.1 1 0.1 0 0 Toxicity Category: III
81-5	Primary Dermal Irritation Species: Rabbit Mobay Corp. Study #: 91-335-JG MRID: 422563-20 Date: August 15, 1991 Core: Minimum DOC #: DER to be submitted with subsequent action	NTN 33893 75% Formulation was administered for 4 hr once dermally to shaved backs of six male New Zealand White rabbits at 500 mg/animal, and observed for 7 days. PIS: 1.08 Mild irritation at 72 hr. Toxicity Category: IV
81-6	Dermal Sensitization Species: guinea pig Mobay Corp. Study #: 91-324-JC MRID: 422563-22 Date: August 23, 1991 Core: Minimum DOC #: DER to be submitted with subsequent action	NTN 33893 75% Formulation was administered, in 3 6-hr topical induction applications followed by one 24-hr topical challenge 14 days later, to shaved backs of 15 Hartley albino guinea pigs. Conclusion: Not a Sensitizer

NTN 33893 2.5% Granular

Guideline	Study Identification	Study Results
81-1	Acute oral LD50 Species: rat Mobay Chem. Study#: 89-012-DY MRID: 420553-24 Date: 02/26/90 CORE - ACCEPTABLE DOC#s: 009375	LD50 > 4820 mg/kg (5000 mg/kg nominal, limit test) Necropsy Observations: None. Toxicity category IV
81-2	Acute Dermal LD50 Species: rabbit Mobay Chem. Study#: 89-025-DS MRID: 420553-25 Date: 01/15/90 CORE - ACCEPTABLE DOC#s: 009375	NZW rabbits dose at 0 and 2000 mg/kg. LD50 > 2000 mg/kg. Necropsy: None Toxicity category III
81-3	Acute inhalation LC50 Species: rat Mobay Chem. Study#: 89-042-DX MRID: 420553-26 Date: 02/26/90 CORE - ACCEPTABLE DOC#s: 009375 9ER attached	Sprague-Dawley rats dosed at 0 and 5092 mg/m3. LC50 > 5092 mg/m3 (95% C.L. intervals) Tentative. Necropsy: None Data submission is incomplete. Verification of particle size & distribution in exposure chamber not possible. See deficiencies secti upgraded. Toxicity category IV
81-4	Primary eye irritation Species: rabbit Mobay Chem. Study#: 89-333-DT MRID: 420553-27 Date: 01/15/90 CORE - ACCEPTABLE DOC#s: 009375	NZW rabbits received 0.1 mL of pulverized test substance/animal. Reversible irritation by 14 days. TIS Time 1 hr 24 hr 48 hr 72 hr 7 d 14 d Iris Irrit Score 2.3 1.2 1.0 0.5 0.2 0.0 Toxicity Category II
81-5	Primary dermal irritation Species: rabbit Mobay Chem. Study#: 89-325-ED MRID: 420553-28 Date: 12/11/90 CORE - ACCEPTABLE DOC#s: 009375	4 hr dermal exposure to NZW rabbits at 50 mg/animal & observed for 72 hrs. PIS = 0.0. Nonirritating. Toxicity Category IV

NTN 33893 0.62% Granular

Guideline	Study Identification	Study Results
81-1	Acute oral LD50 Species: rat Mobay Chem. MRID#: 420553-23 Date: 09/30/91 DOC#s: 009375	Study waived. Use data from study #89-012-0Y (MRID 420553-24). Toxicity Category IV
81-2	Acute Dermal LD50 Species: Mobay Chem. MRID#: 420553-23 Date: 09/30/91 DOC#s: 009375	Study waived. Use data from study #89-025-0S (MRID 420553-25). Toxicity Category III
81-4	Primary eye irritation Species: rabbit Mobay Chem. MRID#: 420553-23 Date: 09/30/91 DOC#s: 009375	Study waived. Use data from study #89-335-0T (MRID 420553-27) Toxicity Category II
81-5	Primary dermal irritation Species: Mobay Chem. MRID#: 420553-23 Date: 09/30/91 DOC#s: 009375	Study waived. Use data from study #89-325-ED (MRID 420553-28) Toxicity Category II
81-6	Dermal sensitization Species: Mobay Chem. MRID#: 420553-23 Date: 09/30/91 DOC#s: 009375	Study waived. Use data from study #89-324-0N (MRID 420553-29) Not a sensitizer.