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

OFFICE OF
PREVENTION, PESTICIDES
AND
TOXIC SUBSTANCES

13/APR/2004

MEMORANDUM

Subject:	Name of Pesticide Product:	Amitraz Solid
	EPA Reg. No. /File Symbol:	80490-R
	DP Barcode:	D300993
	Decision No:	341573
	PC Code:	106201
From:	Eugenia McAndrew, Biologist Technical Review Branch Registration Division (7505C)	
To:	Akiva Abramovitch, PM Team 07 Insecticide-Rodenticide Branch Registration Division (7505C)	
Applicant:	Fort Dodge Animal Health P.O. Box 5366 Princeton, NJ 08543-5366	

FORMULATION FROM LABEL:

	Active Ingredient(s):	% by wt.
106201	Amitraz	98.00
	Inert Ingredient(s):	2.00
	Total:	100.00%

ACTION REQUESTED: PM requests review of acute toxicity data for Amitraz Solid, EPA File Symbol 80490-R.

BACKGROUND: Fort Dodge Animal Health has submitted a six pack of acute toxicity studies in support of registration of a new manufacturing use product, Amitraz Solid, EPA File Symbol 80490-R. The studies were conducted at MB Research Laboratories, Spinnerstown, PA, with assigned MRID numbers 462102-04 to -09.

RECOMMENDATIONS: The six studies have been reviewed and are classified as acceptable.

The acute toxicity profile for Amitraz Solid, EPA File Symbol 80490-R, is as follows:

acute oral toxicity	III	Acceptable	MRID 46210204[a]
acute dermal toxicity	IV	Acceptable	MRID 46210205
acute inhalation toxicity	IV	Acceptable	MRID 46210206
primary eye irritation	IV	Acceptable	MRID 46210207
primary skin irritation	IV	Acceptable	MRID 46210208
dermal sensitization	Negative	Acceptable	MRID 46210209

[a] The incorrect protocol (OECD 401: Acute Oral LD50) was used for this test. Although, we accepted the study, in this case, our guidance is that OECD 401 is an unacceptable protocol. Please inform the Registrant that the preferred protocol is OECD 425: Acute Oral Toxicity-Up-and-Down Procedure.

LABELING: Based on the toxicity profile above, the following are the precautionary and first aid statements for this product as obtained from the Label Review System.

PRODUCT ID #: 080490-00001

PRODUCT NAME: Amitraz Solid

PRECAUTIONARY STATEMENTS

Hazards to Humans and Domestic Animals:

SIGNAL WORD: CAUTION

Harmful if swallowed. Wash thoroughly with soap and water after handling and before eating, drinking, chewing gum, or using tobacco.

First Aid:

If swallowed:
-Call a poison control center or doctor immediately for treatment advice.
-Have person sip a glass of water if able to swallow.
-Do not induce vomiting unless told to by a poison control center or doctor.
-Do not give anything to an unconscious person.

Have the product container or label with you when calling a poison control center or doctor or going for treatment. You may also contact 1-800-xxx-xxxx for emergency medical treatment information.

Reviewer: Eugenia McAndrew April 13 , 2004
Product Manager (EPA): 07

STUDY TYPE: Acute Oral Toxicity - S-D Rat; OPPTS 870.1100; OECD 401

TEST MATERIAL: Amitraz-technical (Lot/batch # 030603/030604; 98% amitraz; yellow crystalline powder)

CITATION: Cerven, D. Amitraz-technical. Acute Oral Toxicity/LD_{50} in Rats. MB Research Laboratories, Princeton, New Jersey. Laboratory Report Number MB 03-11647.01. February 18, 2004. MRID 46210204. Unpublished.

SPONSOR: Fort Dodge Animal Health, P.O. Box 5366, Princeton, NJ 08543-5366

EXECUTIVE SUMMARY: In an acute oral toxicity study (MRID 46210204), five/sex Wistar young adult albino rats (Source: Ace Animals, Inc., Boyertown, PA; 217-231 g males and 203-219 g females) were given a single oral dose of Amitraz-technical (Lot/batch # 030603/030604; 98% amitraz; yellow crystalline powder) at 500 mg/kg. The test article was mixed with distilled water to make dosing by gavage possible. Animals were then observed for 14 days.

Oral LD_{50} Males = > 500 mg/kg
Oral LD_{50} Females = > 500 mg/kg
Oral LD_{50} Combined = > 500 mg/kg

All animals survived. Clinical signs noted included chromorhinorrhea, few feces, chromodacryorrhea and red staining of body areas. The animals recovered from these symptoms by day 8. Three animals did not gain weight during days 0 and 7 but all animals gained weight by day 14. Necropsy results were normal.

Toxicity based on the lack of death at the limit dose. EPA Toxicity Category III.

This acute oral study is classified as acceptable. It does satisfy the guideline requirement for an acute oral study (OPPTS 870.1100; OECD 425) in the rat.

COMPLIANCE: Signed and dated GLP, Quality Assurance, and Data Confidentiality statements were provided.

RESULTS and DISCUSSION:

Dose (mg/kg bw)	Mortality/Number Tested		
	Males	Females	Combined
500	0/5	0/5	0/10

A. **Mortality** - as noted in table.

B. **Clinical observations** - Clinical signs noted included chromorhinorrhea, few feces, chromodacryorrhea and red staining of body areas. The animals recovered from these symptoms by day 8. Three animals did not gain weight during days 0 and 7 but all animals gained weight by day 14.

C. **Gross Necropsy** - Necropsy results were normal

D. **Reviewer's Conclusions**: Agree with the study author

Reviewer: Eugenia McAndrew April 13, 2004
Product Manager (EPA): 07

STUDY TYPE: Acute Dermal Toxicity - S-D Rabbit; OPPTS 870.1200; OECD 402

TEST MATERIAL: Amitraz-technical (Lot/batch # 030603/030604; 98% amitraz; yellow crystalline powder)

CITATION: Cerven, D. Amitraz-technical. Acute Dermal Toxicity/LD_{50} in Rabbits. MB Research Laboratories, Princeton, New Jersey. Laboratory Report Number MB 03-11647.02. February 18, 2004. MRID 46210205. Unpublished.

SPONSOR: Fort Dodge Animal Health, P.O. Box 5366, Princeton, NJ 08543-5366

EXECUTIVE SUMMARY: In an acute dermal toxicity study (MRID 46210205), five/sex of young adult New Zealand White rabbits (Source: Millbrook Breeding Labs, Amherst, MA; 2.3-2.8 kg males and 2.3-2.6 kg females) were dermally exposed to Amitraz-technical (Lot/batch # 030603/030604; 98% amitraz; yellow crystalline powder) applied to approximately 10% of body surface area at a dose of 5000 mg/kg. The test substance was moistened with 9.0 to 11 mL of distilled water to form a paste. Test sites were covered with a gauze patch and wrapped with plastic sheeting in a semi-occlusive manner and secured with tape for a 24 hours period. Animals were then observed for 14 days.

Dermal LD_{50} Males = > 5000 mg/kg
Dermal LD_{50} Females = > 5000 mg/kg
Dermal LD_{50} Combined = > 5000 mg/kg

All animals survived and gained weight. Clinical signs noted during the first week included lethargy, ataxia, sagging eyelids and few feces. Very slight erythema was noted at one site until day 7. All animals appeared normal between days 8 to 14. Necropsy results were normal.

Toxicity based on the lack of deaths at the limit dose. EPA Toxicity Category IV.

This acute dermal study is classified acceptable. It does satisfy the guideline requirement for an acute dermal study (OPPTS 870.1200; OECD 402) in the rabbit.

COMPLIANCE: Signed and dated GLP, Quality Assurance, and Data Confidentiality statements were provided.

RESULTS and DISCUSSION:

Dose (mg/kg bw)	Mortality/Number Tested		
	Males	Females	Combined
5000	0/5	0/5	0/10

A. Mortality - as noted in table.

B. Clinical observations - Clinical signs noted during the first week included lethargy, ataxia, sagging eyelids and few feces. Very slight erythema was noted at one site until day 7. All animals appeared normal between days 8 to 14.

C. Gross Necropsy - Necropsy results were normal.

D. Reviewer's Conclusions: Agree with the study author

Reviewer: Eugenia McAndrew April 13, 2004
Product Manager (EPA): 07

STUDY TYPE: Acute Inhalation Toxicity -S-D rat; OPPTS 870.1300; OECD 403

TEST MATERIAL: Amitraz-technical (Lot/batch # 030603/030604; 98% amitraz; yellow crystalline powder)

CITATION: Cerven, D. Amitraz-technical. Acute Inhalation Toxicity/LD_{50} in Rats. MB Research Laboratories. Princeton, New Jersey. Laboratory Report Number MB 03-11647.05. February 18, 2004. MRID 46210206. Unpublished.

SPONSOR: Fort Dodge Animal Health, P.O. Box 5366, Princeton, NJ 08543-5366

EXECUTIVE SUMMARY: In an acute inhalation toxicity study (MRID 46210206), five/sex of young adult Wistar albino rats (Source: Ace Animals, Inc., Boyertown, PA; 296-345 g males and 240-293 g females) were exposed nose only via the inhalation route to Amitraz-technical (Lot/batch # 030603/030604; 98% amitraz; yellow crystalline powder) for 4 hours at a concentration of 2.10 mg/L. Animals were then observed for 28 days.

LC_{50} Males = 2.10 mg/L
LC_{50} Females = 2.10 mg/L
LC_{50} Combined = 2.10 mg/L

All animals survived. Clinical signs noted during the exposure included sagging eyelids, tachypnea, closed eyelids, coating of the fur with test article and hunched posture. Lethargy, sagging eyelids, few feces, chromorhinorrhea, soiling of the anogenital area, chromodacryorrhea, wetness of the anogenital area, wetness of the nose/mouth area, red staining of the abdomen, emaciation, dyspnea, piloerection, tremors, tachypnea, red staining of the nose/mouth area, ocular discharge and crusting, hunched posture, brown staining of the nose/mouth area, vocalization when handled, red areas and eschar on the tail, red staining of the front paws, localized alopecia and malocclusion of the incisors were noted during the extended 28 day observation period. Some animals lost weight during the first 14 days but all animals gained weight by day 28. Necropsy results were normal in 7/10 animals. Localized alopecia was noted in two animals. One animal exhibited eschar at the base of the tail. Red areas on the thymus were noted in one animal. The gravimetric concentration was 2.10 mg/L. The mass median aerodynamic diameter was 3.25 µ with a geometric standard deviation of 2.18.

Toxicity based lack of deaths at the limit dose. EPA Toxicity Category IV.

This acute inhalation study is classified as acceptable. It does satisfy the guideline requirement for an acute inhalation study (OPPTS 870.1300; OECD 403) in the rat.

COMPLIANCE: Signed and dated GLP, Quality Assurance, and Data Confidentiality statements were provided.

RESULTS and DISCUSSION:

Nominal Concentration (mg/L)	Gravimetric Concentration (mg/L)	MMAD µm	GSD µm	Mortality/Number Tested		
				Males	Females	Combined
not reported	2.10	3.25	2.18	0/5	0/5	0/10

Test Atmosphere / Chamber Description:

Chamber Volume:	**57 L**
Airflow:	**18 LPM**
Temperature:	**22-26°C**
Relative Humidity:	**19%**
Time to Equilibrium:	**not reported**

A. Mortality - as noted in table.

B. Clinical observations - Clinical signs noted during the exposure included sagging eyelids, tachypnea, closed eyelids, coating of the fur with test article and hunched posture. Lethargy, sagging eyelids, few feces, chr0morhinorrhea, soiling of the anogenital area, chromodacryorrhea, wetness of the anogenital area, wetness of the nose/mouth area, red staining of the abdomen, emaciation, dyspnea, pilocrection, tremors, tachypnea, red staining of the nose/mouth area, ocular discharge and crusting, hunched posture, brown staining of the nose/mouth area, vocalization when handled, red areas and eschar on the tail, red staining of the front paws, localized alopecia and malocclusion of the incisors were noted during the extended 28 day observation period. Some animals lost weight during the first 14 days but all animals gained weight by day 28.

C. Gross Necropsy - Necropsy results were normal in 7/10 animals. Localized alopecia was noted in two animals. One animal exhibited eschar at the base of the tail. Red areas on the thymus were noted in one animal.

D. Reviewer's Conclusions: Agree with the study author

Reviewer: Eugenia McAndrew April 13, 2004
Product Manager (EPA): 07

STUDY TYPE: Primary Eye Irritation - NW Rabbit; OPPTS 870.2400; OECD 405

TEST MATERIAL: Amitraz-technical (Lot/batch # 030603/030604; 98% amitraz; yellow crystalline powder)

CITATION: Cerven, D. Amitraz-technical. Acute Eye Irritation in Rabbits. MB Research Laboratories, Princeton, New Jersey. Laboratory Report Number MB 03-11647.04. February 18, 2004. MRID 46210207. Unpublished.

SPONSOR: Fort Dodge Animal Health, P.O. Box 5366, Princeton, NJ 08543-5366

EXECUTIVE SUMMARY: In a primary eye irritation study (MRID 46210207), 0.1 mL (44 mg) of Amitraz-technical (Lot/batch # 030603/030604; 98% amitraz; yellow crystalline powder) was instilled into the conjunctival sac of the right eye of three young adult male New Zealand albino rabbits (Source: Millbrook Breeding Labs, Amherst, MA). Animals were then observed at 1, 24, 48, and 72 hours post-instillation. Irritation was scored by the method of Draize.

In this study, formulation is not irritating to the eye. EPA Toxicity Category IV.

No positive results were noted during the ocular observations.

This study is classified as acceptable. It does satisfy the guideline requirement for a primary eye irritation study (OPPTS 870.2400; OECD 405) in the rabbit.

COMPLIANCE: Signed and dated GLP, Quality Assurance, and Data Confidentiality statements were provided.

RESULTS AND DISCUSSION:

Observations	Number "positive"/number tested			
	Hours			
	1	24	48	72
Corneal Opacity	0/3	0/3	0/3	0/3
Iritis	0/3	0/3	0/3	0/3
Conjunctivae:				
Redness*	0/3	0/3	0/3	0/3
Chemosis*	0/3	0/3	0/3	0/3
Discharge*	0/3	0/3	0/3	0/3

*Score of 2 or more required to be considered "positive."

A. **Observations** - No positive results were noted during the ocular observations.

B. **Reviewer's Conclusions:** Agree with study author

Reviewer: Eugenia McAndrew April 13, 2004
Product Manager (EPA): 07

STUDY TYPE: Primary Dermal Irritation - NW Rabbit; OPPTS 870.2500; OECD 404

TEST MATERIAL: Amitraz-technical (Lot/batch # 030603/030604; 98% amitraz; yellow crystalline powder)

CITATION: Hoff, T. Amitraz-technical. Acute Dermal Irritation in Rabbits. MB Research Laboratories, Princeton, New Jersey. Laboratory Report Number MB 03-11647.03. February 18, 2004. MRID 46210208. Unpublished.

SPONSOR: Fort Dodge Animal Health, P.O. Box 5366, Princeton, NJ 08543-5366

EXECUTIVE SUMMARY: In a primary dermal irritation study (MRID 46210208), three young adult New Zealand White rabbits (2 male and 1 female; Source: Millbrook Breeding Labs, Amherst, MA) were dermally exposed to 0.5 mL of Amitraz-technical (Lot/batch # 030603/030604; 98% amitraz; yellow crystalline powder). The test substance was moistened with 0.3 mL of distilled water to form a paste and then applied to one 6 cm^2 dose site on the dorsal area of each animal. Test sites were covered with a gauze patch, secured with tape and wrapped with plastic in a semi-occlusive manner for a 4 hour period. Animals were then observed at 1, 24, 48 and 72 hours after patch removal. Irritation was scored by the method of Draize.

In this study, the formulation is not an irritant. EPA Toxicity Category IV.

Primary Dermal Irritation Index (PDII) - 0.00 "There was no erythema or edema noted at any observation period."

This study is classified as acceptable. It does satisfy the guideline requirement for a primary dermal irritation study (OPPTS 870.2500; OECD 404) in the rabbit.

COMPLIANCE: Signed and dated GLP, Quality Assurance, and Data Confidentiality statements were provided.

RESULTS and DISCUSSION:

A. Observations - "There was no erythema or edema noted at any observation period."

B. Results - PDII - 0.00

C. Reviewer's Conclusions - Agree with study author

Reviewer: Eugenia McAndrew
Product Manager (EPA): 07 April 13, 2004

STUDY TYPE: Dermal Sensitization - Guinea Pig; OPPTS 870.2600; OECD 406, 429

TEST MATERIAL: Amitraz-technical (Lot/batch # 030603/030604; 98% amitraz; yellow crystalline powder)

CITATION: Hall, D. Amitraz-technical. Delayed Contact Dermal Sensitization Test - Buehler Method. MB Research Laboratories, Princeton, New Jersey. Laboratory Report Number MB 03-11647.06. February 18, 2004. MRID 46210209. Unpublished.

SPONSOR: Fort Dodge Animal Health, P.O. Box 5366, Princeton, NJ 08543-5366

EXECUTIVE SUMMARY: In a dermal sensitization study (MRID 46210209) with Amitraz-technical (Lot/batch # 030603/030604; 98% amitraz; yellow crystalline powder), 30 young adult Hartley albino guinea pigs (Source: Elm Hill Breeding Labs, Chelmsford, MA; 312-352 g males and 300-359 g females) were tested using the Buehler method. The procedures were validated using dinitrochlorobenzene (DNCB) as the positive control substance.

Once each week for three weeks, 0.4 mL of undiluted test substance was applied to the left side of each animal for a 6-hour exposure period for a total of three exposures. The animals rested for two weeks. Fourteen days after the last induction, 0.4 mL of undiluted test substance (the highest non-irritating concentration) was applied to a naive site on each test animal for a 6-hour challenge exposure. Ten naive control guinea pigs were treated with the undiluted test substance at challenge only. Readings were made 24 and 48 hours after each induction application and after the challenge application.

In this study, the formulation is not a dermal sensitizer.

No dermal irritation was noted at the test animal sites during the induction phase. Following the challenge, no dermal irritation was noted in either the test animal group or the naive control group. The results of the DNCB positive control study were appropriate to validate test procedures.

This study is classified as acceptable. It does satisfy the guideline requirement for a dermal sensitization study (OPPTS 870.2600; OECD 406, 429) in the Guinea pig .

COMPLIANCE: Signed and dated GLP, Quality Assurance, and Data Confidentiality statements were provided.

I. PROCEDURE

A. Induction - Once each week for three weeks, 0.4 mL of the undiluted test substance was applied to the left side of each animal for a 6-hour exposure period for a total of three exposures. The animals rested for two weeks. Readings were made 24 and 48 hours after each induction application.

B. Challenge - Fourteen days after the last induction, 0.4 mL of undiluted test substance (the highest non-irritating concentration) was applied to a naive site on each test animal for a 6-hour challenge exposure. Readings were made 24 and 48 hours after the challenge application.

C. Naive Controls - Ten naive control guinea pigs were treated with the undiluted test substance at challenge only.

II. RESULTS and DISCUSSION:

A. Reactions and duration - No dermal irritation was noted at the test animal sites during the induction phase. Following the challenge, no dermal irritation was noted in either the test animal group or the naive control group.

B. Positive control - The results of the DNCB positive control study were appropriate to validate test procedures.

C. Reviewer's Conclusions: Agree with study author

ACUTE TOX ONE-LINERS

1. **DP BARCODE:** D300393
2. **PC CODES:** 106201
3. **CURRENT DATE:** 13/APR/2004
4. **TEST MATERIAL:** Amitraz-technical (Lot/batch # 030603/030604; 98% amitraz; yellow crystalline powder)

Study/Species/Lab Study # /Date	MRID	Results	Tox. Cat.	Core Grade
Acute oral toxicity/rat MB Research Laboratories MB 03-11647.01/2-18-04	46210204	LD_{50} > 500 (males, females combined)	III	A
Acute dermal toxicity/rabbit MB Research Laboratories MB 03-11647.02/2-18-04	46210205	LD_{50} > 5000 mg/kg (males, females combined)	IV	A
Acute inhalation toxicity/rat MB Research Laboratories MB 03-11647.05/2-18-04	46210206	LC_{50} > 2.10 mg/L (males, females combined)	IV	A
Primary eye irritation/rabbit MB Research Laboratories MB 03-11647.04/2-18-04	46210207	Non-irritating	IV	A
Primary dermal irritation/rabbit MB Research Laboratories MB 03-11647.03/2-18-04	46210208	PDII = 0.00 Non-irritating	IV	A
Dermal sensitization/guinea pig MB Research Laboratories MB 03-11647.06/2-18-04	46210209	Not a sensitizer	-	A

Core Grade Key: **A =Acceptable, S = Supplementary, U = Unacceptable, W = Waived**