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of 6

DATA EVALUATION RECORD

AMITRAZ/106201
NONGUIDELINE

STUDY TYPE: HUMAN TOLERANCE - DERMAL
MRID: 44639401

Prepared for

Health Effects Division
Office of Pesticide Programs
U.S. Environmental Protection Agency
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Arlington, VA 22202

Prepared by

Toxicology and Hazard Assessment Group
Life Sciences Division
Oak Ridge National Laboratory
Oak Ridge, TN 37831
Task Order No. 61-2004

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Disclaimer

This review may have been altered subsequent to the contractor's signatures above.

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NonguidelineEPA Reviewer: Pamela M. Hurley, Ph.D.Signature: Pamela M. Hurley

Reregistration Action Branch 3, Health Effects Division (7509C)

Date 1/27/00EPA Work Assignment Manager: Ghazi Dannan, Ph.D.Signature: Ghazi Dannan

Registration Action Branch 3, Health Effects Division (7509C)

Date 1/25/05

TXR#: 0052737

Supplemental

DATA EVALUATION RECORD

Root TXR: 0013255

STUDY TYPE: Double Blind Tolerance Study in Humans-Dermal.
Non-Guideline.**PC CODE:** 106201**DP BARCODE:** N/A
SUBMISSION NO.: N/A**TEST MATERIAL (PURITY):** Amitraz technical (100% a.i.)**SYNONYMS:** 1,5-Di(2,4-dimethylphenyl)-3-methyl-1,3,5-triazapenta-1,4-diene; Baam;
Formamidine, N-methyl-N'-2,4-xylyl-N-(N-2,4-xylylformimidoyl)-; Methyl-bis(2,4-xylyliminomethyl)amine; Mitac; Ovasyn; Taktic; Triazid**CITATION:** Langford, H. (1998). Amitraz (Code AE B049974): Human volunteer double-blind tolerance study. Simbec Research Ltd., Merthyr Tydfil, CF48 4DR United Kingdom. Study No. TOX 97228. July 28, 1998. MRID 44639401. Unpublished.**SPONSOR:** AgrEvo USA Company, 2711 Centerville Road, Wilmington, DE 19808.**EXECUTIVE SUMMARY:** In a double-blind sequential dosing study with a randomized crossover and placebo group, eight healthy male volunteers 32.0 ± 6.8 years and 76.6 ± 9.3 kg were given a total dose of either 0, 8, 16 or 24 mg/kg Amitraz (Lot No. B570R, Batch No. 459732, purity = 100%) applied dermally as four equal doses of 0, 2, 4 or 6 mg/kg in an aqueous 1:1 slurry every 2.5 hours over 10 hours according to a random schedule. Starch, 1:1 in water, was used as a placebo. The purpose of the study was to find a no effect level for acute pharmacological effects following administration by repeated dermal doses of Amitraz. The volunteers were evaluated for vital signs, ECG, and psychomotor measurements (pupil critical flicker threshold and reaction time in a choice scenario), hematology, clinical chemistry and urinalysis before and after dosing. The parameters were selected on the basis of the test material's pharmacological activity (sedation, hypotension and effects on body temperature in humans following oral dosing).

Vital signs and ECG parameters were normal for all subjects. No clinically significant changes were seen in pupil response. Psychomotor performance results such as choice reaction time and critical flicker fusion demonstrated no significant differences. None of the out-of-range ECG events were considered clinically significant by the investigating physician. Random out of normal range values for clinical chemistry were without biological significance. No treatment-related effects were found in hematological or urinalysis results.

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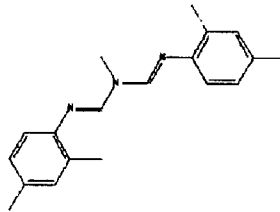
This dermal toxicity study in humans is **Acceptable/Nonguideline** and satisfies the intent of the study.

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

I. MATERIALS AND METHODS:

A. MATERIALS:

1. **Test material:** Amitraz
Description: off-white powder
Lot/Batch #: Lot No. B570R, Batch No. 459732
Purity: 100%
Compound Stability: not reported
CAS No. of TGAI: 33089-61-1
Structure:



2. **Vehicle and/or positive control:** water

3. **Subjects:**

Age:	32.0 ± 6.8 years
Sex:	male
Weight:	76.6 ± 9.3 kg
Height:	1.75 ± 0.05 m

B. STUDY DESIGN:

1. **In life dates:** Start: January 27, 1998; End: February 17, 1998
2. **Dose selection rationale:** Previous studies had demonstrated no effect at 0.03 mg/kg and sedation at 0.25 mg/kg amitraz. It was estimated that the maximum NOAEL was between 0.06 and 0.25 mg/kg in humans. Before the start of the study, the study protocol was reviewed and approved by an Ethics Committee. The study was done according to the Helsinki (South Africa 1996), ABPI Guidelines for Medical Experiments in Non-Patient Volunteers, 1998, amended 1990 and the ICH Harmonized Tripartite Guidelines for Good Clinical Practice.
3. **Dosing:** Each of the four study phases was 2 days duration with at least 7 days between phases (Table 1). For each phase of the study, one fourth of the total dose was administered at 2.5 hour intervals to individual 20 cm² sites on the forearm of the individual. A placebo of

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aqueous 1:1 corn starch was also used. The application sites were protected by semi-occlusive surgical gauze and left in place up to 10 hours. Each study individual was admitted to the Clinical Unit for 36 hours during test material application.

Table 1. Human volunteer dosing regimen				
Individual	Dermal dose of amitraz (mg/kg)			
	Phase I	Phase II	Phase III	Phase IV
1	P*	8	16	24
2	8	P	16	24
3	8	16	P	24
4	8	16	24	P
5	P	8	24	24
6	8	16	24	P
7	8	P	16	24
8	8	16	P	24

*P = Placebo (aqueous 1:1 starch)

1. **Examinations:** Before the start of the study and after study completion, the following examinations were given.

Pre-study examinations:

Medical history
Physical exam
Height
Weight
Frame size
Body Mass Index
Blood Pressure
Pulse
Respiration rate
12-lead ECG
Laboratory safety screen (biochemistry, hematology, urinalysis, and drugs of abuse)
Compliance with inclusion/exclusion criteria

Post-study examinations:

Physical exam
Weight
Blood Pressure
Pulse
Respiration rate
12-lead ECG
Laboratory safety screen (biochemistry, hematology, urinalysis, drugs of abuse)
Follow-up of unresolved adverse events.

2. **Observations:** During each phase of the study, all adverse reactions, whether minor or serious and whether considered related to treatment or not, were recorded. The following were recorded during each treatment phase:

Sitting blood pressure and pulse were recorded pre-dose at -1, -0.5, and 1, 3, 6, 12, 24, and 36 hours after treatment.

ECGs were done pre-dose at -1 hour and 3, 6, 12, 24, and 36 hours following treatment.

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Psychomotor performance (times to critical eyelid flicker fusion and reaction time in a choice scenario at 0.5 hours before first dose and at 5 and 10 hours afterwards.

3. **Hematology and clinical chemistry:** Blood was collected pre-study, and at 36 hours after each phase of the study. The CHECKED (X) parameters were examined.

a. **Hematology:**

X	Hematocrit (HCT)	X	Leukocyte Differential Count
X	Hemoglobin (HGB)	X	Mean corpuscular HGB (MCH)
X	Leukocyte count (WBC)	X	Mean corpusc. HGB conc.(MCHC)
X	Erythrocyte count (RBC)	X	Mean corpusc. volume (MCV)
X	Platelet count		

b. **Clinical chemistry:**

X	Potassium	X	Creatinine
X	Sodium	X	Urea nitrogen
X	Alanine aminotransferase (also SGPT)	X	Glucose
X	Aspartate aminotransferase (also SGOT)	X	Total bilirubin
X	Gamma glutamyl transferase (GGT)	X	Total protein (TP)

7. **Urinalysis:** Urine was collected pre-dose and 0-24, and 24-36 hours for the first phase. The CHECKED (X) parameters were examined.

X	Specific gravity/osmolality	X	Glucose
X	pH	X	Ketones
X	Protein	X	Bilirubin
		X	Blood/blood cells
		X	Urobilinogen

8. **Statistics:** Analysis of variance was used for vital signs and psychomotor measurements. Pairwise comparisons for each subject at each time-point were made by Dunnet's test.

III. **RESULTS**

1. **Adverse Events and Clinical Signs:** There were two adverse events reported by Subject 04. These were bruising on both upper arms after application of the placebo and unrelated to Amitraz treatment.
2. **Physiological Measurements:** Vital signs and ECG parameters were normal for all subjects. No clinically significant changes were seen in pupil response. Psychomotor performance results such as choice reaction time and critical flicker fusion demonstrated no significant differences. None of the out of range ECG events were considered clinically significant by the investigating physician.

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3. **Hematology and Biochemistry:** Random out of normal range values were found to be without clinical significance. No clinically significant effects related to treatment were found.
4. **Urinalysis:** Two abnormalities were detected which included bilirubin and blood traces. These were considered not clinically significant by the investigating physician.
5. **Drugs of Abuse:** No drugs of abuse were detected in any subject.

III. DISCUSSION AND CONCLUSIONS:

A. INVESTIGATORS' CONCLUSIONS:

The investigators concluded that dermal doses of Amitraz (8mg/kg, 16mg/kg and 24mg/kg) were tolerated in 8 healthy male volunteers, with no adverse effects. A NOAEL of 24 mg/kg was suggested by the authors.

B. REVIEWER COMMENTS:

This report has complete individual tables for all endpoints evaluated with statistics. No discrepancies in investigators' conclusions were found. The highest dose (24mg/kg) may be considered a NOAEL based on the parameters investigated. Reported clinical signs after human exposure to Amitraz in previous studies include drowsiness, loss of consciousness, confused mental state, or agitation which were observed following a single oral dose of 0.25 mg/kg (Ellenhorn, M.J. et al 1997). This study at 100 times that dose applied dermally indicates that dermal absorption is low. Depending on field dermal exposure and study results, a dermal absorption study with human skin may be advised.

A. STUDY DEFICIENCIES:

There are no EPA standards for human dermal studies. In this study of Amitraz, most of the known human effects were covered by the investigations and the doses were carefully chosen. More discussion of known human effects, rationale for choosing parameters for evaluation and any known additivity of doses and serious effects at higher doses or longer exposure would be helpful.

Protocol Deviations: Subject 5 received 24 mg/kg Amitraz in error during Periods 3 and 4.

References:

Ellenhorn, M. S. Schonwald, G. Ordog, J. Wasserberger. Ellenhorn's Medical Toxicology: Diagnosis and Treatment of Human Poisoning. 2nd ed. Baltimore, MD: Williams and Wilkins, 1997. pg. 1730 as Cited in HSDB 2004.