

US EPA ARCHIVE DOCUMENT

3/12/92

BACKGROUND

The Ecogen Co. submitted acute oral toxicity studies generated with Foil Bioinsecticide (EPA Reg. NO. 55638-10), in response to Phil Hutton's letter to Ecogen. Phil's letter specifically requested:

- a. an inhalation acute toxicity study conducted using animals exposed in an exposure chamber, and;
- b. a primary eye irritation study.

Both studies to evaluate Foil end use products.

Ecogen had been granted a conditional registration which included tentative acceptance of an intratracheal inhalation study, pending generation of an exposure chamber study.

RECOMMENDATION

The acute inhalation studies (both rats and mice were exposed) submitted by Ecogen are acceptable.

Current acute toxicity profile for Foil
Bioinsecticide EPA Reg. NO. 55638-10):

study Classification Tox. Category
 MRID 413086-01 (current), 409511-02 (original) no mortality.
Acute oral, rat. Foil OF 2.38×10^{10} CFU/ml B.t.k.
 strain EG 2424. Annual dose; 1ml of $1/30$ dil. of
 test mat. containing 7.93×10^8 CFU B.t.k. strain EG 2424.
Classification : Acceptable Toxicity Category IV

MRID 413086-06 rabbit

Acute Dermal and Dermal irritation. Foil product
 containing 2.38×10^{10} CFU - dose 1ml of $1/30$ dil of test
 material containing 7.9×10^8 CFU B.t.k. strain EG 2424.
 Moderate to severe erythema with mean combined
 max. P.T.S. of 3.8 at day 4 post-dosing. Signs of
 severe erythema observed in some animals at 11-12 days.
 24 hr exposure. Dosing; 2g/animal. No mortality.
Classification : Acceptable Toxicity Category 2,

acute dermal III

Toxicity Category, dermal
irritation: II

study Classification Tox. Category

MRID 413 086-04

Acute oral, mouse. Foil product containing 2.5×10^{10} C.F.U./g. Mouse dose of 5g/kg (3×10^9 CFU/mouse). No mortality.

Classification: Acceptable Toxicity Category IV

MRID 419537-01, reviewed by Woodrow 3-11-92

Acute inhalation studies, using both rats and mice (inhalation chamber studies).

Rat study - No mortality. animals dosed with Foil, Lot 04-10117 tan/yellow liquid. LC₅₀ value > 3.9 mg/L

Classification: Acceptable Toxicity Category III

MRID 419537-01, reviewed by Woodrow 3-11-92

Acute inhalation study - mice. All mice survived dosed with 6.4 mg/L, or 2.5 mg/L (inhalation chamber exposure). All mice died, exposed to 3.4 or 3.9 mg/mL. Mouse LC₅₀ > 2.5 mg/L, ≤ 3.4 mg/L.

Foil product, Lot 04-10117. tan/yellow liquid.

Classification: Acceptable Toxicity Category III

MRID 413086-05 Classification Tox. Category

Intratracheal pulmonary study - mice.

Fail OF not lethal at 0.005 - 0.05 mg/animal, lethal for all mice at 5 mg/animal, and at 0.5 mg/animal, 2/5 M and 1/5 F died.

Classification: Acceptable - did support conditional registration. Tox. Category II

MRID 413086-03 Classification Tox. Category

Intratracheal pulmonary study - mice.

Fail OF 1.5×10^6 CFU/animal - not lethal.

4.7×10^7 CFU/animal lethal for mice.

8.25×10^7 CFU/mouse (autoclaved) not toxic.

3/18 mice died when test material not autoclaved.

Classification - Acceptable Toxicity Category II

MRID 415400-01 Classification Tox. Category

Primary eye irritation, rabbit

Fail OF, 0.1 ml undiluted/treated eye (approximately 1.2×10^9 viable spores). No corneal opacity or irrit.

Conjunctival redness and chemosis through 10 days post-treatment.

Classification - Acceptable Toxicity Category II

(Reviewed by Roy Sjoberg March, 1990)

MRID 413086-02 Classification Tox. Category
 Acute intravenous administration of Fowl OF, Rat
 0.2ml of Fowl OF (3.9×10^8 CFU/ml - B.t. var
 Kurstaki, strain EG 2424) No mortality, no effect
 on body wt. Recovery from spiked lungs - average
 recovery approx. 124 %
 Classification: Acceptable Tox. Category IV

MRID 413086-07 Classification Tox. Cat.
 Acute intraperitoneal administration of Fowl - mice
 1.7×10^8 viable units (spores - autoclaved or not
 autoclaved) not lethal for mice.
 Classification: Acceptable Tox. Category IV

Summary - Acute Toxicity - Fowl OF Insecticide,
 EPA Regs. NO. 55638-10: (3-12-92)

Study	MRID NO.	Classification	Tox. Category
Acute oral, rat	413086-01	Acceptable	IV
Acute oral, mouse	413086-4	Acceptable	IV
Acute dermal, rabbit	413086-06	Acceptable	II
Acute irritation (dermal)	413086-06	Acceptable	II
Acute inhalation, Rat	419537-01	Acceptable	III
Acute inhalation, mouse	419537-01	Acceptable	III

Acute Tox. Summary (cont.)

<u>study</u>	<u>MRID</u>	<u>classification</u>	<u>Tox. Cat.</u>
<u>Intratracheal</u>	<u>413086-05</u>	<u>Acceptable</u>	<u>II</u>
<u>Pulmonary</u>	<u>(Interim Conditional Reg.) mouse</u>		
<u>Intratracheal</u>	<u>413086-03</u>	<u>Acceptable</u>	<u>II</u>
<u>Pulmonary</u>	<u>(Interim Cond. Registration)</u>		
<u>Eye irritation, rabbit</u>	<u>415400-01</u>	<u>Acceptable</u>	<u>II</u>
<u>Acute intravenous, Rat</u>	<u>413086-02</u>	<u>Acceptable</u>	<u>IV</u>
<u>Acute intraperitoneal, Mouse</u>	<u>413086-07</u>	<u>Acceptable</u>	<u>IV</u>

Note: Dermal sensitization studies for Microbial Pest Control Agents are not required, according to Subdivision M of the Pesticide Testing Guidelines, dated March, 1989. The only requirement for such pesticides - is reporting of hypersensitivity incidents.

Authority for current adequacy of acute toxicity testing for Fial OF, EPA Reg. NO. 55638-10:

Science assessment coordination Branch Conclusions:
"All submitted studies either were Acceptable or were adequate to upgrade existing studies."

(Continued)

An Acceptable and complete mammalian Toxicology data base exists for the TGI and for the Full OF end-use product." (Endorsed by Dr. Roy Sjoberg and Dr. Reta Engler). Quoted from Feb. 28, 1990 memo to Mike Mendelsohn from Roy Sjoberg.

LABELING

- 1) The WARNING signal word is appropriate.
- 2) Change the Precautionary Statements as follows:

"Causes substantial but temporary eye injury. Causes skin irritation. Harmful if inhaled. Harmful if ^{absorbed through skin.} ~~absorbed through skin.~~ Do not get in eyes, on skin or clothing. Wear (goggles, face shield, or safety glasses). Avoid breathing dust (vapor or spray mist). Wash thoroughly with soap and water after handling. Remove contaminated clothing and wash before reuse.

- 3) The Statements of Practical Treatment are acceptable.

RATS ONLY

DATA REVIEW FOR ACUTE INHALATION TOXICITY TESTING (§81-3)

Product Manager: (18) 7-23-91 Reviewer: W. Woodrow
MRID No.: 419537-01 Report Date: 3-10-92
Testing Laboratory: IIT Res. Institute Report No. L0X3086001
Author(s): V. G. Drummond
Species: Rat, CD
Sex: 10M x 10F Weight: M 209-288, F 209-227g.
Source: Charles River Breeding Labs., Portage, MI
Test Material: Foil, Lot 0Y-10117, tan/yellow liquid
Quality Assurance (40 CFR §160.12): yes (Q.A. & G.L.P.)

Summary: RATS

- LC₅₀ (mg/kg): Males = _____; Females = _____; Combined = _____
- The estimated LC₅₀ is 3.9 mg/L
- Mean Concentration: _____
- Tox. Category: III. Classification: Guideline

Procedure (~~Deviations from §81-27~~): Animals quarantined 8 days prior to test. Two groups of 5M x 5F rats each exposed to different dose levels of Foil test material, for 4 hours (exposure). Exposed animals

Results: RATS

Exposure Concentration (mg/L)	Reported Mortality (NUMBER KILLED/NUMBER TESTED)		
	Males	Females	Combined
1.4 mg/L	0/5	0/5	0/10
3.9 mg/L	0/5	0/5	0/10

Symptomology & Gross Necropsy Findings:

were observed for clinical signs and mortality on day of exposure and at least once daily to 14 days. Animals were weighed before exposure, day 8, on 7, and day 14 before necropsy. All test animals found dead were subjected to gross necropsy, all survivors were also subjected to gross necropsy.

Aerosols diffused in a 500L Rochester-type SS glass chamber. Air supply conditioned room air passed through coarse and fine filters, as was chamber exhaust air. Chamber temperature and R.H. monitored continuously, as was chamber flow rate.

Aerosol generation - air atomizing nozzle (Spray set-up NO. FLC - NO. 35100 fluid cap and NO. 120432 air cap - Spraying Systems Co. Test-mat. reservoir, peristaltic pump through lines to atomizer - T. mat. constantly stirred & magnetic bar @ 60 psi. Atomizer output directed at a curved SS impaction plate to remove coarse particles to minimize particle size - material removed not recycled.

Exposure chamber concentration determined gravimetrically at 30 min intervals - Samples drawn through glass - weighed 25mm open face filter. Filter int. inches $\div$ L air sampled = mg/L air.

Particle size distribution determined at least once during each exposure using a Mercer Cascade Impactor.

Results: RATS

1) Chamber Concentration (Mice as well as rats were exposed, however, only the rats are of concern at present). (Gravimetric)

Quoted from the testator's report:

<u>Aerosol Mass</u>		<u>Particle Size</u>	
<u>Concentration, mg/L</u>		<u>MMAD(μ)</u>	<u>GSD</u>
<u>mean</u>	<u>$\pm$SD</u>	<u>mean $\pm$ SD</u>	<u>mean $\pm$ SD</u>
1.4 mg/L	0.12	1.9 μ 0.16	1.84 0.04
2.5 mg/L	0.20	2.3 μ 0.16	1.93 0.08
3.4 mg/L	0.28	1.9 μ -	1.84 -
3.9 mg/L	0.41	2.4 μ 0.51	2.11 0.09

Unquote

Clinical observations: (RATS)

1.4 mg/L: Few covered in test material. 3.9 mg/L

Few covered in test mat., alopecia, dyspnea, redness around eyes (mice), females only, desiccation around mouth tips active.

Body weights - most rats gained weight; 3 females lost wt. at 3.9 mg/L, 1 female lost wt. at 1.4 mg/L

Necropsy: No gross lesions.

—MICE ONLY—
DATA REVIEW FOR ACUTE INHALATION TOXICITY TESTING (S81-3)

Product Manager: (118) 7-23-91 Reviewer: W. Woodrow
MRID No.: 419537-01 Report Date: 3-10-92
Testing Laboratory: ITT Research Institute Report No. LO8308L001
Author(s): J. G. Drummond
Species: Mice
Sex: Male & Female Weight: 22.1 (F), m 29.6 g.
Source: Charles River Breeding Labs., ME.
Test Material: FOIL Lot OY-10117 tan/yellow liquid
Quality Assurance (40 CFR §160.12): yes (Q.A. & G.L.P.)

Summary: MICE

1. LC₅₀ (mg/kg): Males = _____; Females = _____; Combined = _____
2. The estimated LC₅₀ is > 2.5 mg/L, < 3.4 mg/L
3. Mean Concentration: _____
4. Tox. Category: III. Classification: Guideline

Procedure (~~Deviations From S81-2~~): 4 groups of 5 m & 5 f mice each were exposed for 4 hours to different dose levels of FOIL test material. The 500 L Rochester Type Chamber was used. Following

Results: MICE

		Reported Mortality		
MICE {	Exposure Concentration (mg/L)	(NUMBER KILLED/NUMBER TESTED)		
		Males	Females	Combined
	<u>1.4 mg/L</u>	<u>0/5</u>	<u>0/5</u>	<u>0/10</u>
	<u>2.5 mg/L</u>	<u>0/5</u>	<u>0/5</u>	<u>0/10</u>
	<u>3.4 mg/L</u>	<u>5/5</u>	<u>5/5</u>	<u>10/10</u>
	<u>3.9 mg/L</u>	<u>5/5</u>	<u>5/5</u>	<u>10/10</u>

Symptomology & Gross Necropsy Findings:

exposure, animals were observed for clinical signs day of exposure and at least once per day (also mortality) for 14 days. A normal body weights recorded approximately day of exposure, days 7 or 8 and day 14 before necropsy.

All animals found dead, as well as all surviving mice subjected to gross necropsy.

The chamber concentration, particle size distribution, aerosol generation values are identical to those reported for the rat study reported above (same report).

Clinical: Most clinical observations occurred at the two highest dose levels (3.4 & 3.9 mg/L): dyspnea, wet coughed foam. All dose levels showed fur covered with test material. M & F at the low dose level displayed alopecia.

Necropsy:

High dose level mice (3.9 mg/L) 4/5 M & F showed dark, mottled, red lungs, same for 3.4 mg/L mice. Lowest no. of mice.

1 of 2

Tox Chem. No.File Last UpdatedCurrent date066 *Bacillus t. vars. kurstaki*

3-12-92

Study/Species/Lab/Study# Date	Material	MRID No.	Results	Tox. Cat.	Core Grade
acute oral, rat	Foil of B.t. kurstaki strain EG 2424	413086 -01	7.93×10^3 spores no mortality	IV	accept- able
acute oral, mouse	"	413086 -04	5g/kg (3×10^9 CFU (viable spores) no mortality	IV	accept- able
acute inhalation, rat	"	419537 -01	LC ₅₀ > 3.9 mg/L	III	accept- able
acute inhalation, mouse	"	419537 -01	LC ₅₀ > 2.5 mg/L, < 3.4 mg/L	III	accept- able
Intratracheal, mouse (conditional reg. only)	"	413086 -05	0.06 mg - 0.005 mg / animal not lethal. 5 mg / animal lethal	II	accept- able
Intratracheal, mouse (conditional reg. only)	"	413086 -03	1.5×10^6 FOI not lethal 4.7×10^7 CFU lethal	II	accept- able

Tox Chem. No.

066 B.T.k.

File Last UpdatedCurrent date

3-11-92

Study/Species/Lab/Study# Date	Material	MRID No.	Results	Tox. Cat.	Core Grade
eye irritation, rabbit	Foil B.T.k. strain EG 2424	415400 -01	No corneal opacity or irritis - Conj. redness - chemosis thru 10 days	II	Accept- able
acute dermal, rabbit	"	413086 -06	iml - 7.2×10^8 CFU not fatal	III	Accept- able
skin irritation, rabbit	"	413086 -06	severe erythema/ at 11-12 days post- dosing 2 g dose/animal	II	Accept- able
acute intravenous, Rat	"	413086 -02	0.2 ml foil of at 3.9×10^8 CFU/ml No mortality	IV	accept- able
acute intraperitoneal, mouse	"	413086 -07	1.7×10^8 Foil viable units - Autoclaved or not autoclaved	IV	accept- able