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 product.

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 Biomisecticide 1 EPA Reg. NO. 55638-10):

study Classification Tox. Category

MRID 413086-01 (current), 40961102 (original) no mortality. Acute oral, rat. Foil OF (2.38 x 10^{10} CFU/ml B.t.k. strain EG 2424) Annual dose; 1ml of 1/30 dil. of test mat. containing 7.93 x 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 x 10^{10} CFU - dose 1ml of 1/30 dil of test material containing 7.9 x 10^{8} CFU B.t.k. strain EG 2424. Moderate to severe erythema with mean combined max. P.I.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 acute dermal III
Toxicity Category, dermal irritation II

Study Classification Tox. Category

MRID 413086-04

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

Classification: Acceptable Tox. 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 OY-1017 tan/yellow liquid. LC_{50} 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 1.4 mg/L, or 2.5 mg/L (inhalation chamber exposure). All mice died, exposed to 3.4 or 3.9 mg/ml. Mouse LC_{50} > 2.5 mg/L, < 3.4 mg/L. Foil product, Lot OY-1017 tan/yellow liquid.

Classification: Acceptable Toxicity Category III

MRID 413086-05 Classification Tox. Category

Intratracheal pulmonary study - mice.

Fail OE not lethal at 0.005 - 0.05 mg/animal, lethal for all mice at 5 mg/animal, and at 0.5mg/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 OE 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.

Classificatin - Acceptable Toxicity Category II

MRID 415400-01 Classification Tox. Category

Primary eye irritation, rabbit

Fail OE, 0.1ml undiluted / treated eye (approximately 1.2×10^9 viable spores). No corneal opacity or iritis. Conjunctival redness and chemosis through 10 days post-treatment.

Classification: Acceptable Toxicity Category II

(Reviewed by Roy Syblad March, 1990)

MRID 413086-02 Classification Tox. Category

Acute intravenous administration of Foil OF, Rat 0.2ml of Foil 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 Foil - mice. 1.7×10^8 viable units (spores - autoclaved or not autoclaved) not lethal for mice.

Classification: Acceptable Tox. Category IV

Summary - Acute Toxicity - Foil OF Insecticide, EPA Reg. 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	III
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.)

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

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 Fail OF, EPA Reg. NO. 55638-10:

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

(Continued)

An Acceptable and complete Mammalian Toxicology data base exists for the TGAI and for the Fail OF end-use product." (Endorsed by Dr. Roy Sjoblad and Dr. Reto Engler). Quoted from Feb. 28, 1990 memo to Mike Mendelsohn from Roy Sjoblad.

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. 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. LOX3086.001
Author(s): J. G. Drummond
Species: Rat, CD
Sex: 10M+10F Weight: M 209-288, F 209-227 g.
Source: Charles River Breeding Labs., Portage, Mi
Test Material: Foil, Lot OY-10117, tan/yellow liquid
Quality Assurance (40 CFR §160.12): yes (Q.A. + G.L.P.)

Summary: RATS

1. LC_{50} (mg/kg): Males = _____; Females = _____; Combined = _____
2. The estimated LC_{50} is > 3.9 mg/L
3. Mean Concentration: _____
4. Tox. Category: III. Classification: Guideline

Procedure (~~Deviations from §81-2~~): Animals quarantined 8 days prior to test. Two groups of 6M+6F rats each exposed to different dose levels of Foil test material, for 4 hours (exposure). Exposed animals

Results: RATS

Reported Mortality

Exposure Concentration (mg/L)	(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, or 7, and day 14 before necropsy. All test animals found dead were subjected to gross necropsy, all survivors were also subjected to gross necropsy.

Animals exposed in a 500 L Rochester-type SS 4 g Cass 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 (Spraying Systems Co. Fluid Cap and No. 120432 air cap + Spraying Systems Co. Test-mat reservoir, peristaltic pump transports liquid to atomizer - T. mat. constantly stirred w magnetic bar @ 60 psig. Atomizer output diverted at a covered 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 pre-weighed 25 mm open face filter. Filter wt. increase ÷ L air samples = mg/L air.

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

Results: RATS

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

Quoted from the tester's report:

Aerosol Mass Concentration, mg/L mean ± SD		Particle Size MMAD(μ) mean ± SD		GSD mean ± SD	
1.4 mg/L	0.12	1.9μ	0.16	1.84	0.04
2.5 mg/L	0.20	2.3μ	0.16	1.93	0.08
3.4 mg/L	0.28	1.9μ	—	1.84	—
3.9 mg/L	0.41	2.4μ	0.51	2.11	0.09

Ungroate

Clinical observations: (RATS)

1.4 mg/L: Few coated c. test material. 3.9 mg/L Few coated c. test mat., alopecia, dyspnea, redness around eyes (rats), Female only, Decoloration around mouth Lupo 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 (§81-3)

Product Manager: (18) 7-23-91 Reviewer: W. Woodrow
MRID No.: 419537-01 Report Date: 3-10-92
Testing Laboratory: IIT Research Institute Report No. L08308L001
Author(s): J. G. Drummond
Species: Mice
Sex: Male & Female Weight: 22.1(F), M29.6 g.
Source: Charles River Breeding Labs., MI.
Test Material: Eoil, Lot OY-1017 tan/yellow liquid
Quality Assurance (40 CFR §160.12): yes (Q.A. & G.L.P.)

Summary: MICE

1. LC_{50} (mg/kg): Males = ; Females = ; Combined =
2. The estimated LC_{50} is > 2.5 mg/L, < 3.4 mg/L
3. Mean Concentration:
4. Tox. Category: III. Classification: Guideline

Procedure (~~Deviations From §81-2~~): 4 groups of 5M+5F mice each were exposed for 4 hours to different dose levels of Eoil test material. The 500 L Rochester Type chamber was used. Following

Results: MICE

MICE

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

Symptomology & Gross Necropsy Findings:

~~exposure~~, animals were observed for clinical signs day of exposure and at least once per day (also mortality) to 14 days. Animal 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 unguinal fur. All dose levels showed fur crusted with test material. M+F at the low dose level displayed alopecia

Necropsy:

High dose level mice (3.9 mg/L) M/F showed dark, mottled red lungs, same for 3.4 mg/L mice. Least mos. of mice

Tox Chem. No. 066 Bacillus t. var. kurstaki

File Last Updated

Current date 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	7.93×10^8 spores no mortality	IV	Acceptable
acute oral, mouse	"	413086 -04	5g/kg (3×10^9 CFU (viable spores) no mortality	IV	Acceptable
acute inhalation, rat	"	419537 -01	$LC_{50} > 3.9$ mg/L	III	acceptable
acute inhalation, mouse	"	419537 -01	$LC_{50} > 2.5$ mg/L, < 3.4 mg/L	III	acceptable
Intratracheal, mouse (conditional reg. only)	"	413086 -05	0.05mg - 0.005mg /animal not lethal. 5mg/animal lethal	II	acceptable
Intratracheal, mouse (conditional reg. only)	"	413086 -03	1.5×10^6 Foil not lethal 4.7×10^7 CFU lethal	II	acceptable

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Tox Chem. No. 066 B.T.k.

File Last Updated

Current 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 iritis - Conj. redness - chemosis thru 10 days	II	Acceptable.
acute dermal, rabbit	"	413086 -06	1ml - 7.9×10^3 CFU not fatal	III	Acceptable
skin irritation, rabbit	"	413086 -06	severe erythema/ at 11-12 days post-dosing 2 g dose/animal	II	Acceptable
acute intravenous, Rat	"	413086 -02	0.2ml Foil of at 3.9×10^8 CFU/ml No mortality	IV	acceptable
acute intraperitoneal, mouse	"	413086 -07	1.7×10^8 Foil viable units - Autoclaved or not autoclaved	IV	acceptable

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