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OPP OFFICIAL RECORD
HEALTH EFFECTS DIVISION
SCIENTIFIC DATA REVIEWS
EPA SERIES 361

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: **THIODICARB**: Review of Acute Toxicity Data

FROM: Linda L. Taylor, Ph.D. 7/8/96
Toxicology Branch II, Section II,
Health Effects Division (7509C)

THRU: K. Clark Swentzel 7/9/96
Section II Head, Toxicology Branch II
Health Effects Division (7509C)

and

Stephanie R. Irene, Ph.D. 7/16/96
Acting Chief, Toxicology Branch II/HED (7509C)

TO: Bonnie Adler
PM Team Reviewer (52)
Reregistration Branch, SRRD (7508W)

Registrant:	Rhône-Poulenc Secteur Agro
Chemical:	Thiodicarb
Synonym:	Larvin
Submission No.:	S506723
DP Barcode:	D226938
Caswell No.:	900AA
Case:	816454
Identifying No.:	114501-000264
P.C.Code:	114501
MRID No.:	44025501, 44025502, 44025503

Action Requested: Please review the following acute toxicology data for the chemical thiodicarb: acute dermal toxicity, primary eye irritation, and primary dermal irritation. Please be advised that this chemical is in the que for a RED early next FY. Please cc: a copy to Tom Myers [RCAB Coordinator].

Comment: The Registrant has submitted three acute toxicity studies on Thiodicarb Technical. These have been reviewed, and the DERs are appended.

1) MRID 44025501 - In an acute dermal toxicity study, groups of young adult Hra:(NZW)SPF rabbits [5/sex] were exposed [dermally] to Thiodicarb [96.6% a.i.] for 24 hours (≈10% of body surface area) at the limit dose [2000 mg/kg]. The observation period was 14 days.

There were no deaths, treatment-related clinical signs, necropsy findings, or adverse effects on body weight in either sex.

Dermal LD_{50} [Males & Females] > 2000 mg/kg (limit dose). Thiodicarb is TOXICITY CATEGORY III.

This acute dermal study is classified Acceptable, and it satisfies the guideline requirement for an acute dermal study (81-2) in the rabbit.

2) MRID 44025502 - In a primary eye irritation study, 33 mg of Thiodicarb [96.6 % a.i.] was instilled into the everted lower lid of the right eye of each adult albino rabbit [Hra:(NZW)SPF (3/sex)], and the treated eyes were observed for ocular irritation at 1, 24, 48, 72, and 96 hours post treatment and at day 7 post treatment. Irritation was scored by the method of Draize.

In this study, Thiodicarb was an eye irritant, as evidenced by positive reactions observed in all 6 rabbits [iridal involvement including miosis at 1 hour and moderate to severe conjunctival irritation, which had cleared of positive reactions by 96 hours. All eyes returned to normal appearance by day 7. Thiodicarb is TOXICITY CATEGORY III for primary eye irritation.

This study is classified as Acceptable, and it satisfies the guideline requirement for a primary eye irritation study [§81-4] in] the rabbit.

3) MRID 44025503 - In a primary dermal irritation study, adult albino rabbits [Hra:(NZW)SPF (3/sex)] were dermally exposed to 0.5 g of Thiodicarb [96.6 % a.i.] for 4 hours to 6.25 cm^2 on their backs/flanks. The test sites were observed for dermal irritation at 30 minutes, 24-, 48-, and 72-hours post dose. Irritation was scored by the method of Draize.

In this study, Thiodicarb was not a dermal irritant, as evidenced by the zero scores in all 6 rabbits at each time point. Thiodicarb is TOXICITY CATEGORY IV for primary dermal irritation.

This study is classified Acceptable, and it satisfies the guideline requirement for a primary dermal irritation study [§81-5] in the rabbit.

CONCLUSION: These three acute studies are Acceptable, and they satisfy their respective guideline requirements for Thiodicarb. The Toxicity Category for acute dermal toxicity remains the same. The Toxicity Category for dermal irritation is IV, based on the new study; the previous Toxicity Category for primary dermal irritation was III. The Toxicity Category for primary eye irritation is III, based on the new study; the previous Toxicity Category was I/II.

SUMMARY OF ACUTE TOXICITY DATA ON THIODICARB [96.6%]

TEST	RESULTS	CATEGORY
Dermal LD50--rabbit	♂♂ & ♀♀ > 2000 mg/kg [limit dose]	III
Eye irritation--rabbit	eye irritant; positive reaction in all rabbits [iridal involvement including miosis at 1 hour and moderate to severe conjunctival irritation]; positive reactions cleared by 96 hours; all eyes returned to normal by day 7	III
Dermal irritation--rabbit	not a dermal irritant	IV

cc: Tom Myers [RCAB]
Teung Chin [RD]

[THIODICARB] Acute Dermal Study (81-2)

EPA Reviewer: Linda L. Taylor, Ph.D. 7/2/96
Review Section II, Toxicology Branch II (7509C)
EPA Secondary Reviewer: K. Clark Swentzel 7/8/96
Review Section II, Toxicology Branch II (7509C)

DATA EVALUATION RECORD

STUDY TYPE: Acute Dermal Toxicity - rabbit
OPPTS 870.1200 [§81-2]

DP BARCODE: D226938 SUBMISSION CODE: S506723
P.C. CODE: 114501 TOX. CHEM. NO.: 838B

TEST MATERIAL (PURITY): Thiodicarb Technical [96.6%]

SYNONYMS: Larvin® brand Technical

CITATION: Glaza, S.M. (1996) Acute Dermal Toxicity Study of Thiodicarb Technical in Rabbits. Corning Hazleton Inc., Madison, Wisconsin. Laboratory Project No. CHW 50702036, 8/10/95-2/8/96. MRID 44025501. Unpublished

SPONSOR: Rhone-Poulenc Ag Company

EXECUTIVE SUMMARY: In an acute dermal toxicity study [MRID 44025501], groups of young adult Hra:(NZW)SPF rabbits [5/sex] were exposed [dermally] to Thiodicarb [96.6% a.i.] for 24 hours (≈10% of body surface area) at the limit dose [2000 mg/kg]. The observation period was 14 days. There were no deaths, treatment-related clinical signs, necropsy findings, or adverse effects on body weight in either sex.

Dermal LD_{50} Males and Females > 2000 mg/kg (limit dose)

Thiodicarb is TOXICITY CATEGORY III.

This acute dermal study is classified as acceptable, and it satisfies the guideline requirement for an acute dermal study (81-2) in the rabbit.

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

I. MATERIALS AND METHODS

A. MATERIALS

1. Test Material: Thiodicarb Technical
   Description: off-white powder
   Batch #: 128
   Purity: 96.6% a.i.
   CAS #: 59669-26-0

2. Vehicle and/or positive control:

3. Test animals: Species: rabbit
   Strain: Hra:(NZW)SPF
   Age: adult
   Weight: 2352-2633 grams
   Source: HRP, Inc., Kalamazoo, Michigan
   Acclimation period: ≥ 7 days
   Diet: Laboratory Rabbit Diet HF #5326; measured amount
   Water: source not provided; ad libitum
   Housing: individual; standard laboratory conditions

B. STUDY DESIGN and METHODS

1. In life dates - start: August 10, 1995; end: February 8, 1996

2. Animal assignment and treatment - Five male and 5 female rabbits were administered the test material in a single dose at a dose level of 2000 mg/kg via the dermal route. One day prior to dosing, the back of each rabbit was clipped free of fur [≈20% of total body surface]. The amount of test material administered was based on each rabbit's body weight on the day of dosing to dosing. Each dose [4.7 to 5.3 grams] was moistened with ≈6 mL of distilled water prior to application. The test material was applied to the intact skin at a rate of ≈0.02 g/cm^2 in a thin and uniform layer, and the area of application was covered with a 9.5 cm x 21.0 cm 4-ply gauze patch secured by paper tape and overwrapped with Saran Wrap® and Elastoplast® tape to provide an occlusive dressing. Each rabbit was restrained with a collar during the 24-hour exposure period. After 24 hours, the collars and bandages were removed, and the test site was washed with tap water and dried. Clinical observations and mortality checks were performed at ≈ 1, 2.5, and 4 hours after application, and clinical observations and twice-a-day mortality checks were performed daily thereafter for 14 days. Body weights were recorded prior to dosing, on day 7, and at termination. Initial dermal irritation readings were performed ≈30 minutes [day 1 score] after removal of the test material according to the Draize technique, and subsequent readings were performed on days 3, 7, 10, and 14. Survivors were sacrificed and subjected to an abbreviated gross necropsy

examination.

3. Statistics - No dermal LD_{50} was calculated since all rabbits survived until study termination. Statistical analyses were not performed.

II. **RESULTS AND DISCUSSION:**

A. Mortality: There were no deaths in either sex.

The dermal LD_{50} for males and females is greater than 2000 mg Thiodicarb/kg body weight [limit dose].

B. Clinical observations - There were no adverse effects observed. All rabbits appeared normal throughout the observation period. The only dermal irritation observed was a slight erythema, which was observed on day 1 in two female rabbits.

C. Body Weight - Each rabbit gained weight during the study.

D. Necropsy - No lesions were observed at necropsy in any of the rabbits.

E. Deficiencies - None that would affect interpretation.

EPA Reviewer: Linda L. Taylor, Ph.D. 7/8/96
Review Section II, Toxicology Branch II (7509C)
EPA Secondary Reviewer: K. Clark Swentzel 7/9/96
Review Section II, Toxicology Branch II (7509C)

DATA EVALUATION RECORD

STUDY TYPE: Primary Eye Irritation - Rabbit
OPPTS 870.2400 [§81-4]

DP BARCODE: D226938 SUBMISSION CODE: S506723
P.C. CODE: 114501 TOX. CHEM. NO.: 838B

TEST MATERIAL (PURITY): Thiodicarb Technical [96.6%]

SYNONYMS: Larvin® brand Technical

CITATION: Glaza, S.M. (1996) Primary Eye Irritation Study of Thiodicarb Technical in Rabbits. Corning Hazleton Inc., Madison, Wisconsin. Laboratory Project No. CHW 50702038, 8/10/95-2/8/96. MRID 44025502. Unpublished

SPONSOR: Rhône-Poulenc Ag Company

EXECUTIVE SUMMARY: In a primary eye irritation study [MRID 44025502], 33 mg of Thiodicarb [96.6 % a.i.] was instilled into the everted lower lid of the right eye of each adult albino rabbit [Hra:(NZW)SPF (3/sex)], and the treated eyes were observed for ocular irritation at 1, 24, 48, 72, and 96 hours post treatment and at day 7 post treatment. Irritation was scored by the method of Draize.

In this study, Thiodicarb was an eye irritant, as evidenced by positive reactions observed in all 6 rabbits [iridal involvement including miosis at 1 hour and moderate to severe conjunctival irritation, which had cleared of positive reactions by 96 hours. All eyes returned to normal appearance by day 7. Thiodicarb is TOXICITY CATEGORY III for primary eye irritation.

This study is classified as Acceptable, and it satisfies the guideline requirement for a primary eye irritation study [§81-4] in the rabbit.

COMPLIANCE: Signed and dated GLP, Quality Assurance, and Data Confidentiality statements were provided. No Flagging statement was included.

I. MATERIALS AND METHODS

A. MATERIALS

1. Test Material: Thiodicarb Technical
   Description: off-white powder
   Batch #: 128
   Purity: 96.6% a.i.
   CAS #: 59669-26-0

2. Vehicle and/or positive control: none

3. Test animals: Species: rabbit
   Strain: Hra:(NZW)SPF
   Age: adult
   Weight: 2379-2589 grams
   Source: HRP, Inc., Kalamazoo, Michigan
   Acclimation period: ≥ 7 days
   Diet: Laboratory Rabbit Diet HF #5326; measured amount
   Water: source not provided; ad libitum
   Housing: individual; standard laboratory conditions

B. STUDY DESIGN and METHODS

1. In life dates - start: August 16, 1995; end: August 23, 1995

2. Animal assignment and treatment - Three male and 3 female rabbits [random selection] were administered the test material in a single dose of 33 mg [0.1 mL weight equivalent], which was placed into the everted lower lid of the right eye. The left eye served as the untreated control. The upper and lower lids were held together gently for one second to prevent loss to test material. The eyes were not washed following exposure. One day prior to dosing, the eyes were examined using sodium fluorescein dye procedures, and only those rabbits without signs of ocular injury or irritation were used. The treated rabbits were observed for ocular irritation at 1, 24, 48, 72, and 96 hours and on day 7 after exposure. Body weights were recorded prior to dosing and on day 7. Irritation was graded and scored according to the Draize technique using a penlight as the source of illumination. Sodium fluorescein examinations were used to aid in revealing possible corneal injury at the 24- and 72-hour time points. At study termination, the rabbits were sacrificed and discarded.

II. RESULTS AND DISCUSSION

A. All rabbits displayed positive ocular reactions to Thiodicarb. Administration of Thiodicarb to the eye produced iridal involvement, including miosis at the 1-hour observation time and moderate to severe conjunctival irritation. All treated eyes had cleared by 96 hours and all were normal by day 7 post

dose. There was no corneal opacity observed at any time point. Iritis was observed in all rabbits at 1 hour post dose only. Conjunctival redness was observed in all rabbits at 1 hour, in 4 at 24 hours, and in one rabbit at 48 and 72 hours. Chemosis was observed in 5 of the 6 rabbits at 1 hour only. The average Primary Eye Irritation Scores are listed in Table 1. All rabbits gained weight during the study, and the sodium fluorescein examinations were negative at all time points.

Table 1. Average Primary Irritation Scores

Observation Period	Average Score♦
1 hour	14.3
24 hours	5.3
48 hours	4.7
72 hours	1.0
96 hours	0.3
day 1	0.0

♦ average score = total eye irritation score for all rabbits ÷ # rabbits at time point

B. Deficiencies - None that would impact negatively on the interpretation of the results.

SCALE FOR SCORING OCULAR LESIONS♪
[DRAIZE TECHNIQUE]

(1) Cornea

(A) Opacity - Degree of density (area most dense for reading)

No opacity	0
Scattered or diffuse area, details of iris clearly visible	1*
Easily discernible translucent areas, details of iris slightly obscured	2*
Opalescent areas, no details of iris visible, size of pupil barely discernible	3*
Opaque, iris invisible	4*

(B) Area of Cornea Involved

One-quarter or less, but not zero	1
Greater than one-quarter, but less than half	2
Greater than half, but less than three-quarters	3
Greater than three-quarters up to whole area	4

A x B x 5 Total Maximum = 80

(2) Iris

(A) Values

Normal	0
Folds above normal, congestion, swelling, circumcorneal injection (any or all of these or combination of any thereof) iris is still reacting to light (sluggish reaction is positive)	1*
No reaction to light, hemorrhage, gross destruction (any or all of these)	2*

A x 5 Total Maximum = 10

(3) Conjunctivae

(A) Redness (refers to palpebral and bulbar conjunctivae excluding cornea and iris)

Vessels normal	0
Vessels definitively injected above normal	1
More diffuse, deeper crimson red, individual vessels not easily discernible	2*
Diffuse beefy red	3*

(B) Chemosis

No swelling	0
Any swelling above normal (includes nictitating membrane)	1
Obvious swelling with partial eversion of the lids	2*
Swelling with lids about half closed	3*
Swelling with lids half closed to completely closed	4*

(C) Discharge

No discharge	0
Any amount different from normal(does not include small amounts observed in inner canthus of normal animals)	1
Discharge with moistening of the lids and hairs just adjacent to the lids	2
Discharge with moistening of the lids and hairs, and considerable area around the eye	3

Score (A + B + C) x 2 Total Maximum = 20

The total score for the eye is the sum of all scores obtained for the cornea, iris, and conjunctivae.

♪ copied from Attachment 1, page 27 of the report; * indicates a positive effect [FHSA interpretation]

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ONE-LINER

Study Type: Guideline: OPPTS 870.2400 (§81-4)
Study type: primary eye irritation
Species: rabbit

Test Material: Thiodicarb

Chemical: dimethyl N,N'-[thiobis[(methyliminocarbonyl)oxy]bis] ethanimidothioate;3,7,9,13-tetramethyl-5,11-dioxa-2,8,14-trithia-4,7,9,12-tetraazapentadeca-3,12-diene-6,10-dione

EPA MRID No.: MRID 44025502

Testing Facility: Corning Hazleton Inc.

Study Number: Laboratory Project ID CHW 50702038

Report Issued: February 8, 1996

EXECUTIVE SUMMARY: In a primary eye irritation study [MRID 44025502], 33 mg of Thiodicarb [96.6 % a.i.] was instilled into the everted lower lid of the right eye of each adult albino rabbit [Hra:(NZW)SPF (3/sex)], and the treated eyes were observed for ocular irritation at 1, 24, 48, 72, and 96 hours post treatment and at day 7 post treatment. Irritation was scored by the method of Draize.

In this study, Thiodicarb was an eye irritant, as evidenced by positive reactions observed in all 6 rabbits [iridal involvement including miosis at 1 hour and moderate to severe conjunctival irritation, which had cleared of positive reactions by 96 hours. All eyes returned to normal appearance by day 7. Thiodicarb is TOXICITY CATEGORY III for primary eye irritation.

This study is classified as Acceptable, and it satisfies the guideline requirement for a primary eye irritation study [§81-4] in the rabbit.

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[THIODICARB TECHNICAL] Primary Dermal Irritation Study [§81-5]

EPA Reviewer: Linda L. Taylor, Ph.D. 7/8/96
Review Section II, Toxicology Branch II (7509C)
EPA Secondary Reviewer: K. Clark Swentzel 7/9/96
Review Section II, Toxicology Branch II (7509C)

DATA EVALUATION RECORD

STUDY TYPE: Primary Dermal Irritation - Rabbit
OPPTS 870.2500 [§81-5]

DP BARCODE: D226938
P.C. CODE: 114501
SUBMISSION CODE: S506723
TOX. CHEM. NO.: 838B

TEST MATERIAL (PURITY): Thiodicarb Technical [96.6%]

SYNONYMS: Larvin® brand Technical

CITATION: Glaza, S.M. (1996) Primary Dermal Irritation Study of Thiodicarb Technical in Rabbits. Corning Hazleton Inc., Madison, Wisconsin. Laboratory Project No. CHW 50702037, 8/10/95-2/8/96. MRID 44025503. Unpublished

SPONSOR: Rhône-Poulenc Ag Company

EXECUTIVE SUMMARY: In a primary dermal irritation study [MRID 44025503], adult albino rabbits [Hra:(NZW)SPF (3/sex)] were dermally exposed to 0.5 g of Thiodicarb [96.6 % a.i.] for 4 hours to 6.25 cm^2 on their backs/flanks. The test sites were observed for dermal irritation at 30 minutes, 24-, 48-, and 72-hours post dose. Irritation was scored by the method of Draize.

In this study, Thiodicarb was not a dermal irritant, as evidenced by the zero scores in all 6 rabbits at each time point. Thiodicarb is TOXICITY CATEGORY IV for primary dermal irritation.

This study is classified Acceptable, and it satisfies the guideline requirement for a primary dermal irritation study [§81-5] in the rabbit.

COMPLIANCE: Signed and dated GLP, Quality Assurance, and Data Confidentiality statements were provided. No Flagging statement was submitted.

[THIODICARB TECHNICAL] Primary Dermal Irritation Study [§81-5]

I. MATERIALS AND METHODS

A. MATERIALS

1. Test Material: Thiodicarb Technical
   Description: off-white powder
   Batch #: 128
   Purity: 96.6% a.i.
   CAS #: 59669-26-0

2. Vehicle and/or positive control: none

3. Test animals: Species: rabbit
   Strain: Hra:(NZW)SPF
   Age: adult
   Weight: 2253-2629 grams
   Source: HRP, Inc., Kalamazoo, Michigan
   Acclimation period: ≥ 7 days
   Diet: Laboratory Rabbit Diet HF #5326; measured amount
   Water: source not provided; ad libitum
   Housing: individual; standard laboratory conditions

B. STUDY DESIGN and METHODS

1. In life dates - start: August 15, 1995; end: August 18, 1995

2. Animal assignment and treatment - Three male and 3 female rabbits [random selection] were administered the test material via the skin as follows: one day prior to exposure, the back and/or flanks of each rabbit were clipped free of fur. The test material was applied to the intact skin site on each rabbit [exposed area ≈6.25 cm^2] in the amount of 0.5 grams, which was moistened with ≈0.5 mL of distilled water before application. The application site was covered with a 2.5-cm x 2.5-cm gauze patch secured with paper tape to provide a semiocclusive dressing. After a 4-hour exposure period, the patches were removed, and the test sites were washed with tap water and dried with paper towels to remove as much of the test material as possible without irritating the skin. The degree of erythema and edema were read according to the Draize technique approximately 30 minutes after removal of the test material [4-hour score] and at 24, 48, and 72 hours post dose. The untreated skin of each rabbit served as a control. Each rabbit was weighed prior to exposure. At study termination, each rabbit was sacrificed and discarded.

II. **RESULTS AND DISCUSSION:**

A. Thiodicarb was not a dermal irritant; all individual dermal irritation scores were 0 at all time points.

B. Deficiencies - None that would affect study interpretation.

ONE-LINER

Study Type: Guideline: OPPTS 870.2500 (§81-5)
Study type: primary dermal irritation
Species: rabbit

Test Material: Thiodicarb

Chemical: dimethyl N,N′-[thiobis[(methyliminocarbonyl)oxy]bis] ethanimidothioate;3,7,9,13-tetramethyl-5,11-dioxa-2,8,14-trithia-4,7,9,12-tetraazapentadeca-3,12-diene-6,10-dione

EPA MRID No.: MRID 44025503

Testing Facility: Corning Hazleton Inc.

Study Number: Laboratory Project ID CHW 50702037

Report Issued: February 8, 1996

EXECUTIVE SUMMARY: In a primary dermal irritation study [MRID 44025503], adult albino rabbits [Hra:(NZW)SPF (3/sex)] were dermally exposed to 0.5 g of Thiodicarb [96.6 % a.i.] for 4 hours to 6.25 cm^2 on their backs/flanks. The test sites were observed for dermal irritation at 30 minutes, 24-, 48-, and 72-hours post dose. Irritation was scored by the method of Draize.

In this study, Thiodicarb was not a dermal irritant, as evidenced by the zero scores in all 6 rabbits at each time point. Thiodicarb is TOXICITY CATEGORY IV for primary dermal irritation.

This study is classified Acceptable, and it satisfies the guideline requirement for a primary dermal irritation study [§81-5] in the rabbit.

ONE-LINER

Study Type: Guideline: OPPTS 870.1200 (§81-2)
Study type: acute dermal toxicity
Species: rabbit

Test Material: Thiodicarb

Chemical: dimethyl N,N'-[thiobis[(methyliminocarbonyl)oxy]bis] ethanimidothioate;3,7,9,13-tetramethyl-5,11-dioxa-2,8,14-trithia-4,7,9,12-tetraazapentadeca-3,12-diene-6,10-dione

EPA MRID No.: MRID 44025501

Testing Facility: Corning Hazleton Inc.

Study Number: Laboratory Project ID CHW 50702036

Report Issued: February 8, 1996

EXECUTIVE SUMMARY: In an acute dermal toxicity study [MRID 44025501], groups of young adult Hra:(NZW)SPF rabbits [5/sex] were exposed [dermally] to Thiodicarb for 24 hours (≈10% of body surface area) at the limit dose [2000 mg/kg]. The observation period was 14 days. There were no deaths, treatment-related clinical signs, necropsy findings, or adverse effects on body weight in either sex.

Dermal LD_{50} Males and Females > 2000 mg/kg (limit dose)

Thiodicarb is TOXICITY CATEGORY III.

This acute dermal study is classified as acceptable, and it satisfies the guideline requirement for an acute dermal study (81-2) in the rabbit.

13544

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Chemical:	**Thiodicarb (ANSI)**
PC Code:	**114501**
HED File Code	**13000 Tox Reviews**
Memo Date:	**07/19/1996**
File ID:	**TX011986**
Accession Number:	**412-01-0082**

HED Records Reference Center
01/11/2001