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7-11-83

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

003062

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: Thiodicarb--Union Carbide's Larvin. 264-GUE/ 264-GUR/ 3F2773/3H5372. Registration of Larvin Technical: Larvin 500 and Larvin 75WP; Tolerances on Field and Sweet Corn. Caswell 900 AA.

TO: Jay Ellenberger/ Beverly Comfort, PM-12
Registration Division (TS-767C)

THUR: Chistine Chaisson, Section Head
Toxicology Branch (TS-769C)

Christine T. Chaisson
7/7/83
WBS 7/11/83

Requests

In a letter dated October 13, 1982, J. Steve Lovell, Registration Manager for Union Carbide Agricultural Products Company, submitted a request for amended registrations for formulations, Larvin 500 and Larvin 75WP and a petition for pesticide tolerances of field corn grain (0.05 ppm), sweet corn kernals plus cobs (1.5 ppm) and feed additive tolerances for field corn forage and fodder (60 ppm) and sweet corn canner wastes (40 ppm). The tolerance requests were revised in a communication dated 12/16/82 to the following:

Commodity	Tolerance
Corn, forage	60 ppm
Corn, fodder	60 ppm
Corn, grain	0.05 ppm
Corn, fresh (including sweet K + CWHR)	1.5 ppm

The Company also submitted a number of additional acute toxicity studies involving technical larvin.

RECOMMENDATIONS

1) The registrations for Larvin Technical, Larvin 500 and Larvin 75WP can be approved with the following provisions:

a) The signal on the Larvin Technical will need to be changed from "Warning" to "Danger" with the skull and cross bones. The Company with this submission provided a number of acute

oral toxicity studies which were in Toxicity Catagory I. A rabbit eye irritation studies indicated that the treated eyes developed ulcerations (also Toxicity Catagory I). The company also submitted a monkey eye irritation study (Study No. 17) on Larvin Technical which did not indicate any damage to the eye. However, the study was judged Supplementary because a) the concentration of the agent used was not specified; examinations at 48 and 72 hours which are routine were not made and because a slit lamp examination which could examine possible damage deeper in the eye (especially the endothelium of the cornea which regenerates in the rabbit but not in the monkey (nor human). These findings necessitate changing the signal word Warning on the previous submitted label for Larvin Technical to Danger with the addition of the skull and cross bones marker.

An antidote statement is missing and note to the physician such as those provided by the Larvin 500 label should be added.

b) The labels for Larvin 500 and Larvin 75WP should have added the statement "Keep out of the reach of Children".

c) The labels for Larvin 500 and Larvin 75WP indicate that reentry may be made when the sprays have dried. Dislogeable residue data on treated crops seems to be lacking, however, such residues theoretically should not provide hazards to workers. The registration of these formulations can be provisionally approved, however, the Company should provide the dislogeable residue data as soon as possible.

2) The requested tolerances can be toxicologically supported.

Support for these recommendations is contained in the attached sections.

Stanley B. Gross 4/1/83

Stanley B. Gross, Toxicologist
Toxicology Branch (TS-769C)

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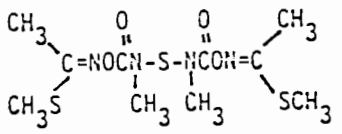
BACKGROUND INFORMATION

Larvin (thiodicarb) is a thiocarbamate-like insecticide which Union Carbide company proposes to use on for uses on cotton, soybean and corn. Since 1979, Union Carbide has submitted to the Agency a number of studies in support of the use of Larvin Technical and formulations of larvin (Larvin 500, Larvin 75WP, Larvin 3.2 and UCLF-2). Toxicology Branch approved the use of Larvin Technical for formulation purposes in Nov. 3, 1980 (memo by W. Dykstra) and more recently (memo by W. Dykstra, April 30, 1982) for the use of Larvin 500 and Larvin 75WP on cotton and soybeans. A final ADI for the larvin for use in the assessment of tolerance requests was made by Dykstra (Memo of May 13, 1982). TMRC's for larvin on soybeans, cotton and corn based on this ADI was approved by this Reviewer (memo of March 2, 1983).

The present summary draws together information from several previous reviews which provide support for the requested uses.

Composition of Formulations

Thiodicarb has the following structure:



Chemical names:

Dimethyl-N,N'[thiobis[(methylimino)carbonyloxy]]bis-[ethanimidothioate].
Ethanimicothioic acid, N,N'-(thiobis{(methylimino)-carbonyl}oxy)bis,-dimethyl ester.
CAS Registry No.: 59669-26-0

Technical Larvin in previous information provided by the Company (Dykstra, Nov.3, 1980) indicated the ingredients:

Ingredients	Percent Weight
Thiodicarb	96.0
[redacted]	

INERT INGREDIENT INFORMATION IS NOT INCLUDED

in which all of the ingredients other than thiodicarb were impurities remaining from the manufacturing process. The current application lists technical Larvin as containing:

Thiodicarb (technical)	93.0
[redacted]	

where all except thiodicarb and [redacted] are impurities. The [redacted] is an approved inert which is added during the manufacturing process as a [redacted] Larvin Technical varies from 92% to 98% AI as shown in the following table:

Composition Limits:	Minimum	Typical	Maximum
Thiodicarb (technical)	92.0	93.0	97.8
[redacted]			

These variations in composition of the technical product may help to explain differences in toxicological testing results, especially those seen amoung the numerous oral acute studies presented below. The Company did not usually list the specific compositions of the test agents used in the different experiments.

Larvin 500 is listed as typically containing 43% thiodicarb, however, the limits of composition indicated by the Company are as follows:

	Minimum	Typical	Maximum
Thiodicarb (93%)	80.2	80.8	81.6
[redacted]			

Larvin 75WP (75% AI) has compositon limits which range as follows:

	Minimum	Typical	Maximum
[redacted]			

A

Inerts. All of the inerts used in Larvin 500 and Larvin 75WP have been cleared under 180.1001 (Dykstra, 2/17/81).

Applications and Labeling.

Larvin 95% Technical is being registered for use only by formulators. The label for this formulation (Addendum #1) is acceptable except for the signal word. Because several of of the oral acute studies submitted with this request were in Toxicity Catagory I, the signal word Warning needs to be changed to "Danger" with skull and cross bones. Because the rabbit eye experienced ulceration, the eye test also placed the technical product in the Toxicity Catagory I. An antidote statement and note to physician should similar to the labeling for Larvin 500 and Larvin 75WP should also be added to this label.

Larvin 500 is an aqueous flowable formulation which is diluted with water to be applied by areal or ground spray equipment on corn at the rates of 0.5 to 1.0 pounds AI/acre. A sample label was not provided with the submission, however, the safety statements on the label for soybeans and cotton provided in Addendum #2 is adequate from the standpoint of safety, if the statement "Keep out of the reach of children" is added.

Larvin 75WP is a wettable powder concentrate formulation that is mixed with water to application as a spray using areal or ground equipment at rates of 0.5 to 1.0 pounds AI/ acre. The label (Addendum #3, designed for use on soybeans and cotton) is adequate from the standpoint of safety and can be used for corn with the addition "Keep out of the reach of children".

Rentry

The label for Larvin 500 and Larvin 75WP indicates that workers may reenter treated fields once the spray on the foliage dries. The Company also indicated (page G-9 of the submission) that the residues degrade rapidly and are below detectable levels except for one value of 0.09 ppm. Enviromental Fate Brach review (memo from Willa Garner, May 12, 1982) indicated that there were shortcomings in the field dissipation studies. It is not clear to this Reviewer whether this refers to dislodgeable residues which would relate to worker exposure upon reentry. Based on dermal animals studies indicating toxicity catagories of III-IV, dermal exposures should not provide significant hazard. Although the Company indicated that the particles as they occur in the formlulations are mostly non-respirable, they should determine demonstrate this by sampling the air while

workers work in fields that have been treated with the products. The acute inhalation toxicity studies in animals shows that under conditions of testing, technical Larvin and Larvin 75WP is quite toxic (Toxicity Catagory II).

Summary of Toxicity

An overview of the toxicity of larvin is provided here. A listing of the studies supporting the registration of Larvin Technical, Larvin 500 and Larvin 75WP is provided in a later section: Supporting Toxicity Studies.

Thiodicarb is a substituted carbamate-like choline esterase inhibitor producing in survivors of acute exposures, choline esterase inhibition including tremors, incoordination, prostration, exophthalmos, chromdacryorrhea, constricted pupils, etc. Acute oral toxicity of the technical formulation is in the Toxicity Catagories I and II, while the end-use formulations produced toxicity in the toxicity catagory II. By the dermal route, these formulations were of relatively low toxicity, greater than 2000 mg/kg (catagory III). Thiodicarb produced only slight dermal irritation, however, appreciable but reversible irritation was produced in the eye by the formulated products (catagory III). The technical product produced corrosion in the rabbit eye (catagory I) which was not seen upon superficial examination of the monkey eye. Animal and human testing produce evidence of hypersensitivity.

Acute delayed neurotoxicological effects in the hen at the LD50= 660 mg/kg were considered marginal. Atropine sulfate administration to rats administered thiodicarb at the LD50 dosage range was able to reduce toxic signs and delay time to death but was not able to prevent all of the deaths. Chronic and subchronic exposures in the rat, mouse and dog did not produce neurotoxicolgical signs or damage at the high dose levels although the animals did show depression of the blood choline esterase. NOEL's choline esterase depression was found to be 10 mg/kg/day in a 28 day rat feeding study; and 15 mg/kg/day in a 6 month dog feeding study;

Systemic NOEL's were 10 mg/kg/day for the rat in a 28 day feeding study; 3 mg/kg/day in a 2 year rat feeding study. No adverse effects on reproduction were seen at 10mg/kg/day in a three generation rat study. Technical Larvin produce no terata in the rat (HDT=30 mg/kg) or in the mouse (HDT=200 mg/kg) although maternal and fetotoxicity was seen at the higher exposure levels. Body weight reductions, hematological and/or biochemical changes were seen in LEL=45 mg/kg/day in a 6 month dog study and LEL=10 mg/kg/day in a two year rat study. There appears to be at least a 3 fold saftey margin, LEL/NOEL, in the dog and rat.

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Larvin was negative for mutagenicity in the dominant lethal, Ames and micronucleus tests, yeast reverse mutation and mitotic cross-over test but was positive in a yeast gene conversion test at 0.025 to 0.25 mg/ml. Larvin was negative in two cancer studies at levels of 10 mg/kg/day in the mouse and 10 mg/kg/day in the rat.

Key metabolites in plants are show in Figure 1 taken from RCB's review by Allen Smith (memo of Jan. 21, 1981) are primarily thiodicarb itself and methomyl. In animals (Figure 2), thiodicarb and methomyl are rapidly metabolized to carbon dioxide or ends up in the carbon pool of the body. Acetamide is one of the metabolites through which these chemicals go during metabolism. However, only small amounts of acetamide are found only with exaggerated dosage levels. A number of experimental studies from the literature indicate that acetamide when administered at high dosage rates, produced tumors in rats.

Using data from a 1969 literature report by Weisberger et al. (Toxicol. Appl Pharmacol. 14: 163-175 (1969)) Dykstra (memorandum to Ellenberger dated June 10, 1981) calculated a risk of 8.78×10^{-8}. In reviews by this Reviewer (memorandum to J. Ellenberger, Jan. 14, 1983; and, to O.E. Paynter, Jan. 27, 1983), it was pointed out that the tumor studies exposed animals at extremely high dosages leading to early deaths; that the acetamide was in animal tissues in small quantities only with administration of 300 to 1000 times the expected maximum exposure and that there were four approved negative cancer studies using thiodicarb and methomyl. Further as was pointed out by B. Litt (memorandum to Paynter, Feb. 8, 1983), one of the authors (Dr. Jackson) of the acetamide cancer reports, pointed to the fact that the rat tumors were seen only when the animals were maintained on Wayne Lab Blox but not when maintained on Purina Laboratory Chow. It was speculated that the Wayne chow may have been deficient in arginine, which was experimentally shown to prevent the tumors when added to the ration in the Weisberger paper.

Continued on page 7b

Tolerance Considerations.

Dykstra in his May 13, 1982 memo, set the final ADI =0.03 mg/kg/day based on the NOEL = 3.0 mg/kg/day in a 2 year rat feeding study. The MPI for a 60 kg person therefore is set at 1.8 mg/day. Based on the requested tolerances on soybeans, cotton, and field and sweet corn todate (Gross' memo of 2/17/83 and the attatched computer printout) the TMRC = 0.0352 mg/day for 1.5 kg diet which is equal to 1.96% of the ADI. Thus the tolerance requests can be approved.

(5/24/83 addendum to Summary of Toxicity) 003062

Union Carbide submitted to the Agency a risk assessment based on the studies mentioned above. Fred Betz, Science Integration Staff, in his memo to Jay Ellenberger (March 15, 1983) evaluated the Union Carbide assessment and concluded the following:

"Union Carbide's conclusions are presented on pages 39-42 of their report.

"HED accepts Union Carbide's carcinogenic risk estimate of one in 380 million for acetamide as resulting from the use of TDC [Thiodicarb] on cotton and soybeans. We also accept Union Carbide's eight assumptions as outlined on pages 40-41.

"HED has no comment as to how FDA would review a cancer risk of one in 380 million and we have no coment as to how FDA might handle an analogous situation.

"Finally, HED agrees with Union Carbide's conclusion 'that EPA could permit registration of TDC, without requiring an analytical method for monitoring acetamide [and] without creating [an unacceptable] human health risk...'".

An additional oncogenicity study on acetamide--"Carcinogenesis Bioassay of Acetamide, Hexanamide, Adipamide, Urea and P-Tolylurea in Mice and Rats" by V.R. Fleishlman, et al., J. Env. Path. & Tox. 3:149-170, 1980) was also found. However, this study was considered poorly designed and marred by gross misuse of statistics and distorted interpretation of the findings by Burt Litt (personal communication and draft Memo to Jay Ellenberger, dated May 20, 1983).

The above additional considerations do not change or conflict with this reviewers conclusions.

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Figure 1.

Metabolic pathways of UC 51762 in plants

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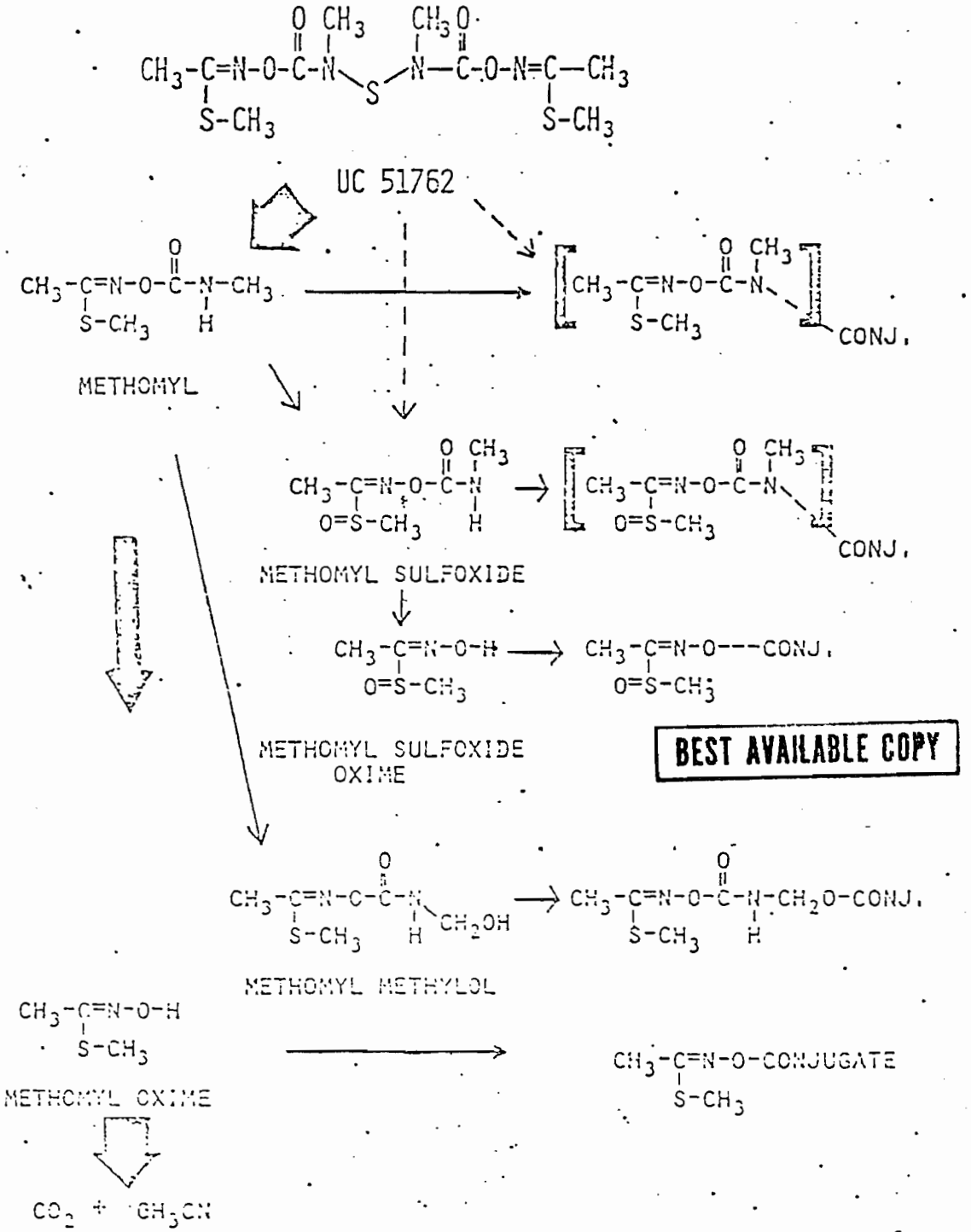

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Figure 2

Metabolic pathway of UC 51762 in animals

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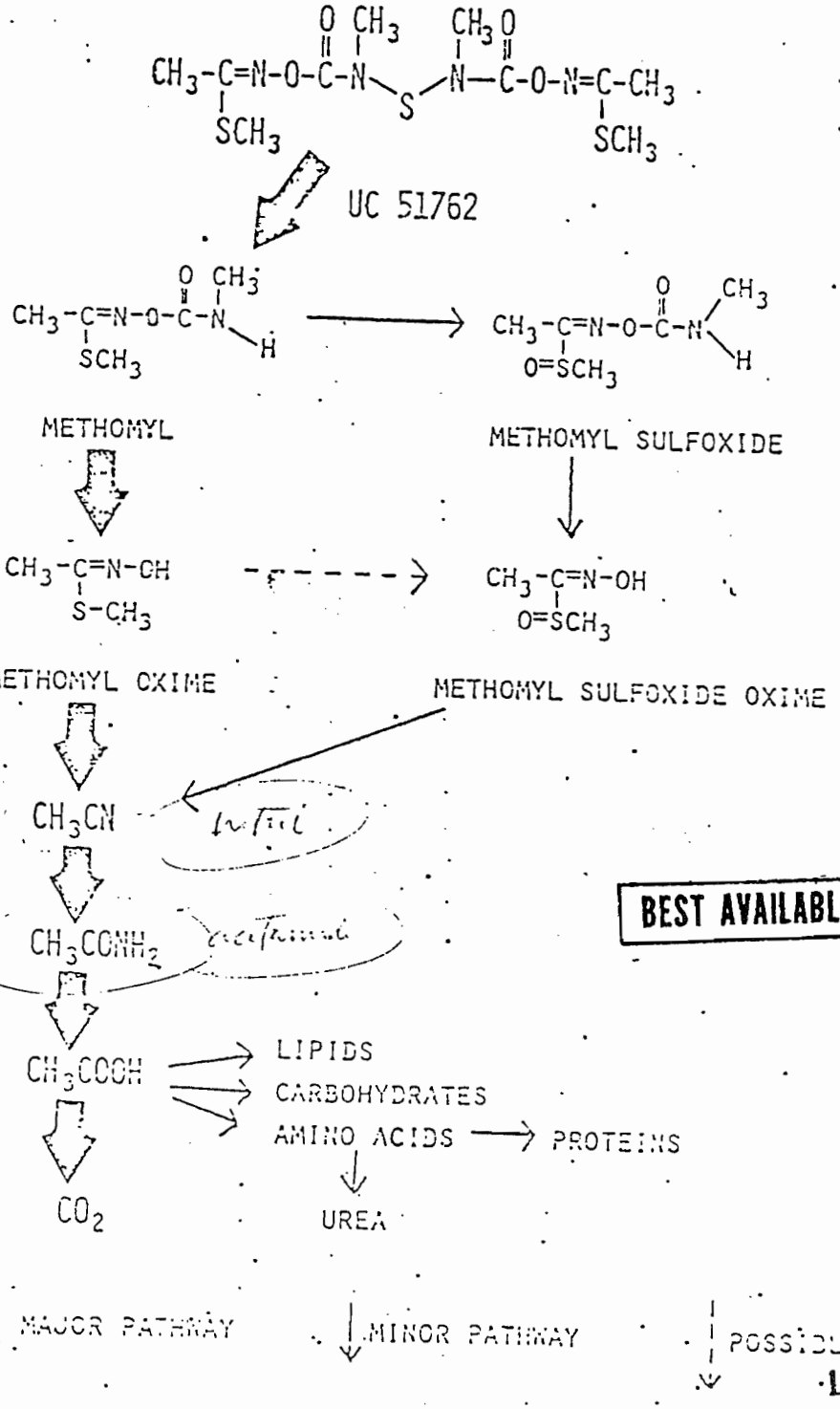

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Supporting Toxicity Studies

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Most of the reviews for the individual studies are contained the following memos: W. Dykstra and L. Anderson (May 23, 1979); W. Dykstra (Feb. 21, 1980); W. Dykstra (Nov. 3, 1980) and W. Dykstra (Feb. 17, 1981). The reviews of the studies submitted with this request are contained in the section, The "Review of Submitted Studies (Accession No. 071181)" below.

A. Technical Larvin

1A) Acute Oral Studies in rats*	LD50's (mg/kg)	Tox. Cat.
Hazleton Labs, 400-613	325(M,F)	II
Pharmakon Res. Intl.		
PH-402-UC-005-82	93(M,F)	II
-007-82	64.5(M,F)	II
	50.8 (F)	
-006-82	162 (M,F)	II
-010-82	156 (M,F)	II
-011-82	97 (M,F)	II
Union Carbide (Bushy Run labs)		
45-40	84.1 (M,F)	I
	50.0 (F)	
-141 A	75.0 (M,F)	II
-141 B	48.8 (M,F)	I
-151 A	74.6 (M,F)	II
-151 B	49.5 (M,F)	I
-152 A	87.1 (M,F)	II
-152 B	49.7 (M,F)	I

*Note: The highest LD50 (325) used water as the suspending medium. Other studies using methylcellose tended to be somewhat (not consistantly) more toxic than when corn oil was used as the suspending agent. Technical larvin tended to be (but not consistantly) somewhat more toxic to females rats.

1B) Acute oral toxicity in hens (for neurotoxicity studies).

FDRL #6064	LD50= 582 mg/kg	

2) Acute dermal toxicity, rabbits.

Hazleton Labs 400-614	LD50 > 6.31 mg/kg	III
Pharmakon Res Intl		
PH 422-UC-005-82	LD50 > 2000 mg/kg	III

3) Acute Inhalation, rats

Carnegie-Mellon/UC	LC50= 0.126 mg/L(M)	II
	= 0.115 mg/L(F)	
Hazleton Labs 400-615	LC50> 0.32 mg/L	II

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4) Skin Irritation.
Pharmakon Res. Intl., Rabbit
PH-420-UC-022-32 Slight Irrit. P.I.S=0.03 III
Note: Posative irritation in human volunteers with repeat exposure (see clincal patch test below).

5) Eye Irritation.

Hazleton Lab 400-617 Rabbit	Corneal opacity and irritation cleared by day 7	II
Pharmakon Res Intl PH-421-UC-004-82 Rabbit	Ulcerations, PIS=17 on day 14	I
Union Carbide 400-648 Monkey	Non irritant	Suppl.

6) Skin sensitization, GP
CUC-UC-004-79 Negative
See human patch testing, below-- Pos. sensitizer.

7) Acute Delayed Neurotox., Hen. PDRL #6065 — Produced marginial delayed neurotoxic signs at LD50= 660 mg/kg.

8) 28 day cholinesterase, rat. Bushy Run/UC #4-19 — Neg at 10mg/kg/day(HDT) ChE NOEL =10 mg/kg/day LEL = 30 mg/kg

9) 6 Month Feeding, Dog
Hazleton Labs. 400-626 — ChE Noel = 15 mg/kg/day Plasma and RCB ChE inhibition LEL = 45 mg/kg/day (HDT); systemic NOEL = 15 mg/kg/day; Systemic LEL =45 mg/kg/day (HDT). (Significant changes in hematological and clinical chem.)

10) Oncogenic,Mouse
Carnegie-Mellon #43-10 (Dykstra-- — Oncogenic potential negative at 10 mg/kg/day (HDT)

11) Chronic Oncogenic, Rat.
Carnegie-Mellon #43-18 (Dykstra-- — NOEL =3 mg/kg/day LEL =10 mg/kg/day decreased body weight in both sexes (HDT). ChE = 10 mg/kg/day.

12) 3-Generation Reproduction, Rat, Carnegie-Mellon 42-64. — NOEL = 10 mg/kg/day (HDT)

13) Teratology, Rat
toxicity exhibited at #369-029 — Maternal and fetal toxicity noted at all levels (10,20, and 30 mg/kg/day). Neg. teratogen at levels tested.

Mouse.
#369-031 — Teratogeinc and fetotoxic NOEL = 200 mg/kg/day (HDT) Levels-- 50, 100,200 mg/kg

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14) 16 Day Dermal, Rabbit
Carnegie-Mellon 42-52.
1 and 4 gm/kg/day produced diarrhea, reduced RBC's and Hb and BW. Applied 6 hours/day, 5 days/week, for 3 weeks.

21 Day Dermal, Rabbits
Snell #02413-090
Dose dependent macrocytic anemia at 1,2,& 4 gm/kg/day, 6 hours/day, 5 days/wk for 3 weeks.

15) Mutagenicity Studies.

Dominant Lethal	Negative
Ames Salmonella/ Microsome LBI #20838.	Negative
Micronucleus Test Pharmakon, PH-309-UC-001-79	Negative
Reverse mutation in S. cerevisiae Pharmakon PH-303-UC-001-79	Negative
Mitotic crossing ove in S. cerevisiae Pharmakon PH-302-UC-001-79	Negative
Mitotic gene conversion in S. cerevisiae Pharmakon PH-304-UC-001-79	Positive at 0.025 to 0.25 mg/ml concns.
Primary DNA Damage Pharmakon PH-305-AM-002-79	Negative.

16) Clinical patch testing
FDRL OE #2177
Posative sensitization in human volunteers, 10 occlussive applicatic over three week period. Irritation 2+ (erythema and mild edema) seen in a number of subjects during induction phaze.

17) Antidote study using atropine sulfate, rats.
Carnegie-mellon 41-59
Atropine injections 10mg/kg lessened signs of toxicty and prolonged life of anima (not at 100% survival) when dosed at 2 and 2.5 times LD (=149 mg/kg)

B. Larvin 500 formulation

		Tox.Ca
1) Acute oral, rat Hazleton Labs 400-613	LD50= 192 mg/kg (M,F)	II
2) Acute dermal, rabbit Hazleton Labs 400-614	LD50 > 2.04 gm/kg	III

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3) Acute inhalation, rat

Hazleton Lab 400-618 Further testing waived--liquid suspension of large particle sizes.	LC50 > 0.084 mg/L	II (Suppl)

4) Eye irritation, rabbit Hazleton	No corneal opacity in washed and unwashed eyes. Irritation cleared by day 7.	III
5) Skin Irritation, Rabbit Hazleton Labs 400-617	PIS=0.0	IV
6) Skin Sensitization, GP #CDC-UC-004-79	Neg. sensitizer	
Carnegie-Mellon, #42-26	Mild to mod. sensitizer	
7) Clinical patch testing in humans FDRL OE #2177	Posative sensitization in human volunteers. 10 occlusive applications over three week period. Irritation 2+ (erythema and mild edema) seen in a number of subjects during induction phase.	

C. Larvin 75WP

1) Acute Oral, Rats Hazleton Labs 400-619	LD50 = 140	II
2) Acute Dermal, Rabbits Hazleton Lab 400-620	LD50 >2000	III
3) Acute Inhalation, Rats Hazleton Labs 400-623	LC50 =0.776-1.14 mg/L	III
4) Skin Irritation, Rabbit Hazleton 400-622	PIS = 0.45 Slight irritation.	
5) Eye Irritation, Rabbit Hazleton Labs 400-621	Slight irritation at 24 hours cleared by 48 hours.	III
6) Skin Sensitization, GP CDC-UC-002-79	Negative.	

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REVIEW OF SUBMITTED STUDIES (ACCESSION NO. 071181)

1. Acute Oral Toxicity Study in Rats (14 day). Larvin Technical. Carried out by Pharmakon Research International for Union Carbide Company, report no. PH 402-UC005-82, March 23, 1982.

Sprague Dawley rats (5/sex/level) were gavaged with technical larvin (purity unspecified) suspended in 0.25% methylcellulose/ Tween 80 and observed for 14 days post-treatment:

Dosage	Mortality	
	Males	Females
25 mg/kg	0/5	0/5
50 "	0/5	2/5
75 "	1/5	1/5
100 "	3/5	4/5
150 "	3/5	5/5

The animals experienced signs typical of carbamate choline esterase poisoning including tremors, abnormal gait, stance, flaccidity, prostration, exophthalmos, chromodacryorrhea, stained eye, genital and anal areas, etc.

The overall LD50 = 93 (72.7 to 119) mg/kg. Core guideline. Toxicity catagory II.

2. Larvin Technical Acute Peroral Toxicity Study. Carried out by Union Carbide Bushy Run Research Center report 45-40, April 21, 1982.

Male and female Hilltop-Wistar albino rats (10/sex/level) were gavaged with larvin technical (95% AI) suspended in 1% corn oil and were observed for 14 days:

Dosage	Mortality	
	Males	Females
200 mg/kg	9/10	10/10
100 "	7/10	3/10
50 "	1/10	-
25	-	2/10

The animals experienced signs of choline esterase inhibition as in the above study.

LD50 for males = 84.1 (61.5 to 115) mg/kg
LD50 for females = 50.0 (34.9 to 71.7) mg/kg
Toxicity catagory II, Core Guidelines

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3. Acute Oral Toxicity Study in Rats (14 Day). Larvin Technical Pilot Plant (Batch 34). Carried out by Pharmakon Research International for Union Carbide Company, Report no. PH-402-UC-007-82, July 12, 1982.

Sprague-Dawley rats (5/sex/level) were gavaged with technical larvin (%AI unspecified) suspended in 0.25% methylcellulose/Tween 80 and observed for 14 days:

Dosage	Mortality	
	Males	Females
30 mg/kg	0/5	0/5
45 "	0/5	2/5
68 "	1/5	4/5
101 "	4/5	5/5
152 "	5/5	5/5

The rats experienced signs of choline esterase poisoning as described under experiment no. 1 above.

LD50 for females = 50.8 (39.3 to 65.7) mg/kg
LD50 for males = 82.7 (65.7 to 104) mg/kg
Combined LD50 = 64. 5 (52.4 to 79.5) mg/kg
Core guideline, Toxicity Catagory II.

4. Acute Oral Toxicity Study in Rats (14 Day). Larvin Technical Pilot Plant (Batch 34). Study carried out by Pharmakon Research International for Union Carbide, report no. PH 402-UC-006-82, July 20, 1982.

Sprague Dawley rats 5/sex/level were gavaged with technical larvin (%AI unspecified) suspended in corn oil/Tween 80 and observed for 14 days:

Dosage	Mortality	
	Males	Females
30 mg/kg	0/5	0/5
45 "	0/5	0/5
68 "	0/5	0/5
101 "	0/5	1/5
152 "	0/5	3/5
228 "	4/5	5/5

The animals showed signs of choline esterase inhibition as seen in experiment no. 1 above.

Litchfield Wilcoxin method combined LD50 = 162 (122.7 to 213.8)mg/kg; LD50 for females = 136 (55.8 to 193.1) mg/kg. Core guideline, Toxicity catagory II.

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5. Larvin Technical-Pilot Plant (Batch 34) Acute Peroral Toxicity Study. Study carried out by Union Carbide's Bushy Run Research Center, Report no. 45-141, August 30, 1982.

Male and female Hilltop-Wistar albino rats (5/sex/level) were gavaged with larvin technical suspended in 0.25% methylcellulose/Tween 80 or suspended in corn oil/Tween 80 and observed for 14 days post-treatment with the following results:

A Corn oil suspension

Dosage	Mortality	
	Males	Females
228 mg/kg	5/5	-
152 "	3/5	-
101 "	2/5	5/5
68 "	1/5	2/5
45 "	1/5	1/5
30 "	1/5	1/5
20 "	0/5	0/5

Probit LD50 for males = 96.1 (59.9 to 154) mg/kg
LD50 for females = 57.4 (39.8 to 82.8) mg/kg
Combined LD50 = 75.0 (57.9 to 97.0) mg/kg
Core Guideline, Toxicity Catagory II.

B Methylcellulose as Vehicle

Dosage	Mortality	
	Males	Females
152 mg/kg	-	5/5
101	5/5	5/5
68	4/5	5/5
55	4/4	1/5
30	-	4/5
20	-	0/5

Probit LD50 for males = 51.6 (46.3 to 57.5) mg/kg
LD50 for females = 36.7 (28.6 to 47.2) mg/kg
Combined LD50 = 48.8 (40.2 to 59.3) mg/kg
Core Guideline, Toxicity catagory I

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6. Acute Oral Toxicity Study in Rats (14 Day). Larvin Technical Lab Preparation. Carried out by Pharmakon Research International for Union Carbide, Report no. PH 402-UC-008-82, July 20, 1982.

Sprague Dawley rats, 5/sex/level were gavaged with larvin technical (% purity unspecified) suspended in corn oil/Tween 80 and observed for 14 days:

Dosage	Mortality	
	Males	Females
30 mg/kg	0/5	0/5
45 "	0/5	0/5
68 "	0/5	0/5
101 "	0/5	0/5
152 "	0/5	3/5
228 "	2/5	3/5
342 "	5/5	5/5

The animals experienced toxic signs of choline esterase inhibition similar to those described in experiment no. 1 above.

Probit LD50 for males and females = 215 (172 to 268.8) mg/kg. Core guideline, Toxicity catagory II.

7. Acute Oral Toxicity Study in Rats (14 Day). Larvin Technical Lab Preparation. Carried out by Pharmakon Research International for Union Carbide. Report PH 402-UC-009-82. July 8, 1982.

Sprague Dawley rats (5/sex/level) were gavaged with techical larvin (%AI unspecified) suspended in 0.25% methyl cellulose/Tween 80 and observed for 14 days:

Dosage	Mortality	
	Males	Females
30 mg/kg	0/5	1/5
45 "	1/5	0/5
68 "	2/5	3/5
101 "	5/5	5/5
152 "	5/5	4/5

The animals experienced signs of choline esterase poisoning similar to those seen in experiment no. 1 above.

Probit LD50 for males and females 65 (52.4 to 80.6) mg/kg
LD50 for males = 71 (47.3 to 106.5) mg/kg
Core guideline, Toxicity Catagory II.

8. Larvin Technical-Lab Preparation. Acute Peroral Toxicity Study. Study carried out by Union Carbide's Bushy Run Research Center, report no. 45-151, August 30, 1982.

Hilltop-Wistar albino rats, 5/sex/level, were administered by gavage technical larvin (93.5% AI) suspended in 0.25% methyl cellulose/Tween 80 or corn oil/Tween 80 and observed for 14 days:

A Corn oil Vehicle

Dosage	Mortality	
	Males	Females
228	-	5/5
152	3/5	4/4
68	2/5	3/5
45	1/5	1/5
30	0/5	0/5

Probit LD50 for males = 74.8 (52.9 to 106) mg/kg
LD50 for females = 72.0 (49.2 to 105) mg/kg
Combined LD50 = 74.6 (59.6 to 93.4) mg/kg
Core guideline, Toxicity Catagory II.

B Methyl-cellulose Vehicle

Dosage		Mortality	
		Male	Female
101	mg/kg	5/5	5/5
68	"	4/5	5/5
61	"	4/5	-
55	"	-	4/5
50	"	-	4/5
45	"	2/5	0/5
30	"	-	1/5
20	"	-	0/5

The affected animals showed signs similar to choline esterase inhibition as described in experiment 1 above.

Probit LD50 for male = 46.5 (33.4 to 64.7) mg/kg
LD50 for females = 50.9 (46.1 to 56.2) mg/kg
Combined LD50 = 49.5 (41 to 59.8) mg/kg
Core guideline, Toxicity catagory I

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9. Acute Oral Toxicity Study in Rats (14 Day). Larvin Analytic1 Standard. Study carried out by Pharmakon Research International for Union Carbide, Report PH 402-UC-010-82, July 20, 1982.

Sprague Dawley rats, 5/sex/level, were gavaged with purified larvin (purity unspecified) suspended in corn oil/ Tween 80 and observed for 14 days post-treatment:

Dosages	Mortality	
	Males	Females
30 mg/kg	0/5	0/5
45 "	0/5	0/5
68 "	0/5	1/5
101 "	0/5	2/5
152 "	1/5	4/5
228 "	1/5	5/5

The affected animals showed signs of choline esterase inhibition toxicity as seen in experiment no. 1.

Probit LD50 combined for males and females was 156 (107.6 to 226.2) mg/kg. Core guideline, Toxicity Catagory II.

10. Acute Oral Toxicity Study in Rats (14 Day). Larvin Analytical Standard. Study carried out by Pharmakon Research International for Union Carbide, report no. PH 402-UC-011-82, July 7, 1982.

Sprague Dawley rats, 5/sex/level, were gavaged with purified larvin (purity unspecified) suspended in 0.25% methyl cellulose/Tween 80 and observed for 14 days for toxici y:

Dosage	Mortality	
	Males	Females
30 mg/kg	0/5	0/5
45 "	0/5	1/5
68 "	0/5	4/5
101 "	0/5	5/5
152 "	3/5	5/5

The affected animals experienced signs of choline esterase inhibition as described in experiment no. 1.

Probit LD50 for combined male and female 97 (66 to 138.2) mg/kg. Core guideline, Toxicity Catagory II.

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11. Larvin Analytical Standard. Acute Peroral Toxicity Study. Study carried out by Union Carbide's Bushy Run Research Center, report no. 45-152, August 30, 1982.

Hilltop-Wistar albino rats, 5/sex/level, were gavaged with purified larvin (purity unspecified) suspended in 0.25% methyl cellulose or corn oil and observed for toxicity for 14 days:

Suspended in Corn Oil

Dosage	Mortality	
	Males	Females
228	5/5	-
152	2/5	5/5
101	1/5	4/5
68	1/5	3/5
45	0/5	1/5
30	-	1/5
20	-	0/5

The affected animals experience signs of choline esterase inhibition similar to those in experiment no. 1.

Probit LD50 for males = 129 (89.6 to 186) mg/kg
LD50 for females = 59.1 (40.7 to 86.0) mg/kg
LD50 combined = 87.1 (67.4 to 113) mg/kg
Core guideline, Toxicity Catagory II.

Methyl Cellulose as Vehicle.

Dosage	Mortality	
	Males	Females
101	5/5	5/5
83	2/5	5/5
68	3/5	5/5
55	2/5	-
45	0/5	1/5
30	0/5	1/5
20	0/5	0/5

The affected animals experienced signs of choline esterase inhibition similar to that seen in experiment no. 1.

Probit LD50 for males = 68.9 (56.6 to 83.8) mg/kg
LD50 for females = 39.1 (29.4 to 52.1) mg/kg
LD50 combined for males and females = 49.7 (40.9 to 60.2) mg/kg.
Core guideline, Toxicity Catagory I.

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12. Larvin 75WP. Acute Peroral and Percutaneous Studies. Study carried out a Union Carbide's Bushy Run Research Center, Report no. 45-43 REVISED, August 6, 1982.

A. Peroral Study

Hilltop-Wistar albino rats, 10/sex/level, were gavaged with larvin 75WP (%AI not specified) dilluted with water to make a 0.5% suspension and were observed for 14 days for toxicity:

Dosage	Mortality	
	Males	Females
100 mg/kg	10/10	9/10
50 "	3/10	1/10
25 "	0/10	0/10

Affected animals showed signs of choline esterase inhibition (tremors, lacrimation, salivation).

Thompson's moving average LD50 for males = 56.1 (43.6 to 72.3) mg Larvin 75WP per kg B.W.: LD50 for females 70.7 (56.2 to 88.9). Core guideline, Toxicity Catagory II.

B. Percutaneous Study.

New Zealand White rabbits were used. Saline moistened formulation was applied to intact and abraided skins of 4 male rabbits for various dosage levels and to the abraided skin of 5 females at the 2000 mg/kg level. The agent was held on the skin for 24 hours, secured with the use of polyethylene and adhesive tape.

Dosage	Mortality	
	Males	Females
Intact Skins		
4000	0/4	-
2000	1/4	-
1000	0/4	-
Abraided skins		
4000	2/4	-
2000	2/4	1/5
1000	0/4	-

Affected animals experienced signs of choline esterase inhibition (primarily incoordinaton).

LD50 for males, intact skin greater than 4000 mg/kg
LD50 for males, abraided skin, 2830 (708 to 11300) mg/kg
LD50 for females with abraided skin, greater than 2000 mg/kg.
Core guideline, Toxicty Catagory III.

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13. Acute Oral Toxicity in Male and Female Rats. Larvin Insecticide Technical (UC 51762). Study carried out by Hazleton Laboratories for Union Carbide, Report no. 400-613, December 13, 1980 (Reviewed previous by Dykstra)

Sprague Dawley rats, 10/sex/level, were gavaged with technical agent (purity unspecified) suspended in distilled water and observed for 14 days post-treatment:

Dosage	Mortality	
	Males	Females
50 mg/kg	0/10	0/10
88.92 mg/kg	0/10	2/10
158.17 "	2/10	7/10
281.17	3/10	2/10
500	6/10	8/10

Affected animals experienced signs typical of choline esterase inhibition.

Probit LD50 for males = 398 (256 to 620) mg/kg
LD50 for females = 248 (120 to 511) mg/kg
Combined LD50 = 325 (204 to 516) mg/kg
Core guideline, Toxicity Catagory II.

14. Primary Dermal Irritation Study in Rabbits. Larvin Technical. Study carried out by Pharmakon Research International for Union Carbide, Report no. PH 420-UC-002-82, March 19, 1982.

Technical larvin (purity unspecified) was applied to intact and abraided skins of New Zealand albino rabbits, 3 animals/sex. The material was held against the skin for 24 hours with a rubber dam and Ace bandage and scored for irritation using the Draize method at 24 and 72 hours.

The results only included slight irritation was seen at 24 hours, PIS= 0.08, which was completely gone by 72 hours.

Core Guideline, Non-irritant for skin.

15. Acute Dermal Toxicity in Rabbits. Larvin Technical. Study carried out by Pharmakon Research International for Union Carbide, Report no. PH 422-UC-005-82, April, 26, 1982.

Technical larvin (purity not given) was moisten with physiological saline and applied at the rate of 2000 mg/kg to the abraided skins of 5 male and 5 female New Zealand rabbits for 24 hours. The agent was maintaned in contact with the skin by means of a rubber dam and Ace bandage. The animals were observed daily for toxicity or skin irritation.

There was no mortality, and no visible signs of damage to the skin. Core guideline. Toxicity Catagory III.

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16. Primary Eye Irritation Test in Rabbits. Larvin Technical. Study carried out by Pharmakon Research International for Union Carbide, Report no. PH 421-UC-004-82, April 20, 1982.

One hundred mg of larvin technical (purity unspecified) was applied to the eyes of 9 New Zealand albino rabbits. Three of the eyes were washed for one minute with warm water immediately after the agent was placed in the eye while the other 6 eyes remained unwashed. The treated eyes were scored according to the method of Draize at 24, 48 and 7? hours and on days 4, 7, 10 and 13.

The results are presented in Table II taken from the the report. For the unrinsed eyes, the PIS's were 15 at 24 hours, dropped to 7.by day 4, peaked at 24 on day 7 and remained high on the last day (PIS = 17) which would indicate that the compound produced mild irritation. However, the text of the report indicates that the corneas showed ulceration but does not say how many animals were involved or when the ulceration was seen. The washsed eyes had a PIS = 12 which decreased steadily to 0.0 by day 10.

Core Minimum Data-- inadequate documentation of the ulceration noted. Toxicity Catagory I based on reported ulceration.

17. Fourteen-Day Eye Irritation Study in Monkeys. Larvin Tech. Study carried out by Hazleton Laboratories America for Union Carbide, Report no. 400-648, August 18, 1982.

One hundred mg of the technical powder larvin was placed in the eyes of 4 mature cynomolgus monkeys and scored by the method of Draize at 24 hours, and days 4, 7 and 14. Two of the eyes were flushed with warm distilled water for thirty seconds after instillation of the agent. The corneas were treated with fluorescein prior to treatment and at the times of the Draize scorsing. The purity of the agent was not given however the fact that it was a white powder suggested that it may have been purified laboratory technical grade.

All of the eyes responded with pupil constriction seen at 5 minutes after treatment. Two of the unwashed eyes were slight conjunctival redness at 24 hours which was gone by day 4. Non adverse reactions were seen in the washed eyes. No eye examinations were made at 48 or 72 hours which is usually part of the Draize procedure.

SUPPLEMENTARY DATA:

1) Concentration of the agent unspecified.
2) Examinations at 48 and 72 hours not made.
3) Because of the ulcerations and irritation which occured when technical larvin was placed in rabbit eyes, it is suggested that a slit lamp examination be used for possible endothelial damage and that the number of unwashed eyes used in an eye irritation study be increased.

Thiodicarb

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