



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

CASWELL FILE

JUL - 6 1992

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JUL - 6 1992

OFFICE OF
PESTICIDES AND TOXIC
SUBSTANCES

MEMORANDUM

Subject: Triforine Technical Data Review.
Tox. Chem. No. 890 AA D174768
HED Project No. 2-1453

From: Dan W. Hanke, Ph. D. *Dan W Hanke 19 June 92*
Review Section III
Toxicology Branch II (HFASB)
Health Effects Division (H7509C)

To: Ms. Barbara Briscoe
Product Manager, Team 51
Reregistration Division

Thru: James N. Rowe, Ph. D. *James N. Rowe 6/22/92*
Lead, Review Section III
Toxicology Branch II (HFASB)
Health Effects Division (H7505C)

and

Marcia van Gemert, Ph. D. *Marcia van Gemert 6/24/92*
Chief, Toxicology Branch II (HFASB)
Health Effects Division (H7505C)

ACTION:

Shell International Chemical Co. has submitted three acute studies (§81) entitled: Acute Oral Toxicity Study with Triforine Technical in Rats; Acute Dermal Toxicity Study With Triforine Technical In Rats; 4-Hour Acute Inhalation Toxicity Study with Triforine Technical In Rats. The results of reviews of these studies are summarized below.

SUMMARY:

1. Acute Oral Toxicity Study with Triforine Technical in Rats (§81-1). MRID No. 421727-01. The acute (15 day) oral LD₅₀ for Triforine Technical, administered one time via gavage to five female and five male Wistar rats at 5g/kg (the limit dose), was > 5 gm/kg body weight. None of the rats died on study (DOS), and the clinical signs and necropsies were unremarkable.

Toxicity Category: IV

A signed quality assurance statement was present.

Core Classification: Acceptable

This study satisfies the guideline requirements (§81-1) for an Acute Oral Toxicity study.

2. Acute Dermal Toxicity Study With Triforine Technical In Rats (§81-2). MRID No. 421727-02. The acute dermal toxicity of Triforine was evaluated at a dose level of 2 g/kg in five rats of each sex. None of the rats died on study (DOS). Triforine had no significant effects on any parameter evaluated, i.e., clinical signs, body weights or pathology. Since the acute dermal toxicity of Triforine was tested at the guideline limit dose of 2000 mg/kg with no toxic effects noted, the LD₅₀ would have to be > 2000 mg/kg. The toxicity category can't be accurately determined based on this study. The results of the current study, however, were consistent with a previous study, which established the LD₅₀ for dermal toxicity to be greater than 10 g/kg (Tox. document No. 002366). An LD₅₀ of greater than 2 g/kg for this study, therefore, would place Triforine in Toxicity Category III.

Toxicity Category: III

A signed quality assurance statement was present.

Core Classification: Acceptable

This study does satisfy the guideline requirements (§81-2) for an Acute Dermal Toxicity study.

3. 4-Hour Acute Inhalation Toxicity Study with Triforine Technical In Rats (§81-3). MRID No. 421727-03. The acute 4-hour inhalation toxicity of a Triforine Technical dust aerosol was evaluated at a concentration of 5120 mg/cubic meter of air (5.120 mg/L) in five rats of each sex. None of the rats died on study (DOS). Triforine had no significant effects on any parameter evaluated, i.e., clinical signs, body weights or pathology. Since the acute inhalation toxicity of Triforine was tested above the guideline limit dose of 5 mg/L with no toxic effects noted, the LC₅₀ is > 5.12 mg/L.

This study is evaluated as acceptable and is placed in Toxicity Category IV, because the limit dose of 5 g/l was actually exceeded. However, it is important to point out the average particle size did not fall within the EPA SEP for inhalation studies requiring at least 25% of the particles to be one micron or less. Only one percent of the particles of Triforine averaged roughly one micron or less, and 98.1% of the particles averaged

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between 9 and 10 microns. Nevertheless, based on discussions with colleagues John Whalan and James Rowe, it was decided that testing above the limit dose, a sufficient amount of Triforine Technical dust aerosol would have been taken in by the rats to permit evaluation of toxic effects.

Toxicity Category: IV

A signed quality assurance statement was present.

Core Classification: Acceptable

This study does satisfy the guideline requirements (§81-3) for an Acute Inhalation Toxicity study.

Reviewed by: Dan W. Hanke, Ph. D.
Section III, Tox. Branch II(H7509C)
Secondary Reviewer: Whang Phang, Ph. D.
Section III, Tox. Branch II(H7509C)

Dan W. Hanke 12 June 82
James M. Rowe 6/16/92

DATA EVALUATION RECORD

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STUDY TYPE: Acute Oral Toxicity (§81-1)

TOX. CHEM. NO. (CASWELL NO.): 890 AA

MRID NO. (ACCESSION NO.): 421727-01

CAS REG. NO.: 26644-46-2

EPA PESTICIDE CHEMICAL CODE/ACTIVE INGREDIENT CODE (SHANGHNESSY NO.): 107901

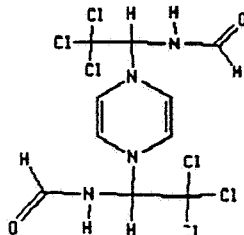
REREGISTRATION CASE NO.: 2720

FIFRA 88 LIST: B

PRODUCT MANAGER/NO.: Susan J. Lewis/21

HED PROJECT NO.: 2-1453

TEST MATERIAL: Triforine, Technical; systemic fungicide;
N,N'-(1,4-piperazinediylbis(2,2,2-trichloro-ethylidene))bis-
formamide



SYNONYMS: ANSI, Biformylchlorazin, Funginex, Cela W-524, CA 73021, Compound W, CA 70203, Cela 50, CME 74770, CW 524, Saprol, Denarin

STUDY NUMBER: 076151

SPONSOR: Shell International Chemical Co.
Celamerck GMBH & Co KG, Postfach, D-6507 Ingelheim am Rhein,
Federal Republic of Germany

SUBMITTER: Biologic, Inc., Research & Development, 11 Lake Ave.
Extension, Danbury, Connecticut 06811

TESTING FACILITY: Research & Consulting Company AG, CH 4452
Itingen, Switzerland

00958:

TITLE OF REPORT: Acute Oral Toxicity Study with Triforine Technical in Rats

AUTHOR(S): L. Ullman

STUDY COMPLETED: December 4, 1986

SUMMARY AND CONCLUSIONS:

The acute (15 day) oral LD₅₀ for Triforine Technical, administered one time via gavage to five female and five male Wistar rats at 5g/kg (the limit dose), was > 5 gm/kg body weight. None of the rats died on study (DOS), and the clinical signs and necropsies were unremarkable.

Toxicity Category: IV

A signed quality assurance statement was present.

Core Classification: Minimum

This study satisfies the guideline requirements (§81-1) for an Acute Oral Toxicity study.

MATERIALS:

1. Test Compound: Triforine Technical; N,N'-(1,4-piperazinediylbis(2,2,2-trichloro-ethylidene))bis-formamide. Description: white powder. Batch No./Lot # Charge 2764. Purity: 99.1 % (taken from the acute dermal toxicity study in rats MRID No. 421727.02). Stability: The test material was reported as stable for two years, however, the analytical method and results were not stated. The test material dosing solution was reported stable for at least two hours, however, no analytical data were provided.

2. Test animals: Species: Rat. Strain: KFM-Han. Wistar (outbred, SPF-Quality). Age: 9 to 11 weeks at start of dosing. Weight: at start of dosing the females were 180 g - 189 g, and the males were 215 g - 235 g. Source: Received from Kleintierfarm Madoerin AG, CH 4414 Fuellinsdorf/Switzerland.

METHODS & STATISTICS:

Rats were fasted 12-18 hrs prior to dosing, and water was available ad libitum. Test material was administered orally by gavage. Food was offered again one hour post dosing. Animals were observed four times during day one after dosing and once daily for a total of 15 days for signs of toxicity. The animals were observed four times on day one and daily on days 2-15 for mortality. Rats were weighed on days 0, 8, and 15. Necropsy was

performed on all animals that DOS and on all survivors, which were sacrificed on day 15.

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RESULTS & DISCUSSION:

Clinical Signs.

None of the rats DOS. Signs and symptoms were essentially unremarkable. There were slight signs of sedation and ruffled fur observed in both sexes over only the first 24 hrs post dosing.

Gross Signs and Macroscopic Findings at Necropsy.

The test animals gained weight during the study. Necropsy revealed no signs of pathology, and the observations were otherwise unremarkable.

Reviewed by: Dan W. Hanke, Ph. D.
Section III, Tox. Branch II (H7509C)
Secondary Reviewer: Whang Phang, Ph. D.
Section III, Tox. Branch II (H7509C)

Dan W. Hanke 15 June 92
James W. Rowe 6/16/92

DATA EVALUATION RECORD

009581

STUDY TYPE: Acute Dermal Toxicity (S81-2)

TOX. CHEM. NO. (CASWELL NO.): 890 AA

MRID NO. (ACCESSION NO.): 421727-02

CAS REG. NO.: 26644-46-2

EPA PESTICIDE CHEMICAL CODE/ACTIVE INGREDIENT CODE (SHANGHNESSY NO.): 107901

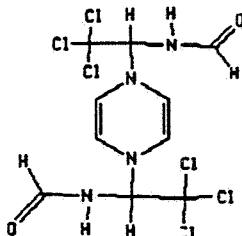
REREGISTRATION CASE NO.: 2720

FIFRA 88 LIST: B

PRODUCT MANAGER/NO.: Susan J. Lewis/21

HED PROJECT NO.: 2-1453

TEST MATERIAL: Triforine, Technical; systemic fungicide;
N,N'-(1,4-piperazinediylbis(2,2,2-trichloro-ethylidene))bis-
formamide



SYNONYMS: ANSI, Biformylchlorazin, Funginex, Cela W-524, CA 73021, Compound W, CA 70203, Cela 50, CME 74770, CW 524, SaproI, Denarin

STUDY NUMBER: 278774

SPONSOR: Shell International Chemical Co.
Celamerck GMBH & Co KG, Postfach, D-6507 Ingelheim am Rhein,
Federal Republic of Germany

SUBMITTER: Biologic, Inc., Research & Development, 11 Lake Ave.
Extension, Danbury, Connecticut 06811

TESTING FACILITY: Research & Consulting Company AG, CH 4452
Itingen, Switzerland

TITLE OF REPORT: Acute Dermal Toxicity Study With Triforine Technical In Rats

AUTHOR(S): L. Ullman, P. Althaus, TH. Janiak, and O. Vogel

STUDY COMPLETED: August 27, 1990

SUMMARY AND CONCLUSIONS:

The acute dermal toxicity of Triforine was evaluated at a dose level of 2 g/kg in five rats of each sex. None of the rats died on study (DOS). Triforine had no significant effects on any parameter evaluated, i.e., clinical signs, body weights or pathology. Since the acute dermal toxicity of Triforine was tested at the guideline limit dose of 2000 mg/kg with no toxic effects noted, the LD₅₀ would have to be \geq 2000 mg/kg. The toxicity category can't be accurately determined based on this study. The results of the current study, however, were consistent with a previous study, which established the LD₅₀ for dermal toxicity to be greater than 10 g/kg (Tox. document No. 002366). An LD₅₀ of greater than 2 g/kg for this study, therefore, would place Triforine in Toxicity Category III.

Toxicity Category: III

A signed quality assurance statement was present.

Core Classification: Minimum

This study does satisfy the guideline requirements (§81-2) for an Acute Dermal Toxicity study.

MATERIALS:

1. **Test Compound:** Triforine Technical (SAG 102); N,N'-(1,4-piperazinediylbis(2,2,2-trichloro-ethylidene))bis-formamide. Description: white powder. Batch No./Lot # Charge 2764. Purity: 99.1 %. Stability: The test material dosing solution was reported stable for at least two hours, however, no analytical data were provided.

2. **Test animals:** Species: Rat. Strain: HanIbm. Wistar (outbred, SPF-Quality). Age: males were 9 weeks old, and the females were 11 weeks old at start of dosing. Weight: at start of dosing the females were 176 g - 189 g, and the males were 224 g - 232 g. Source: Received from BRL, Biological Research Laboratories Ltd. Woelferstrasse 4, CH-4414 Fuellinsdorf.

METHODS & STATISTICS:

Pelleted standard Kliba 343 from batches 71/90 and 73/90 of standard rat chow and water were available ad libitum. About 24 hrs prior to dosing, approximately 10 % of the body surface area was shaved from the backs of the rats. On the first test-day the Triforine was applied to the shaved skin in a four ml volume at 2000 mg/kg and covered with a semi-occlusive dressing. Twentyfour hrs later the dressing was removed, the treated skin was blotted, rinsed, and dried, and the affected areas were evaluated according to the method of Noakes and Sanderson [Noakes, D.N. and Sanderson, D.M. (1969). A method for determining the dermal toxicity of pesticides. Brit. J. Industr. Med. 26, 59-64.]. The rats were observed for mortality four times during the day of application of the test article and then daily over days 2-15. Body weights were taken on day one prior to administration of the test article and then on days eight and 15. The rats were observed for clinical signs four times on the day the test article was applied, then daily over days 2-15. All rats were killed via intraperitoneal injection of sodium pentobarbitone, and necropsies were performed. No statistical algorithm was applied to the data.

RESULTS & DISCUSSION:**Clinical Signs and Pathology.**

None of the rats died on study (DOS). Triforine had no significant effects on any parameter evaluated, i.e., clinical signs, body weights or pathology. Since the acute dermal toxicity of Triforine was tested at the guideline limit dose of 2000 mg/kg with no toxic effects noted, the LD₅₀ would have to be > 2000 mg/kg. The toxicity category can't be accurately determined based on this study. The results of the current study, however, were consistent with a previous study, which established the LD₅₀ for dermal toxicity to be greater than 10 g/kg (Tox. document No. 002366). An LD₅₀ of greater than 2 g/kg for this study, therefore, would place Triforine in Toxicity Category III.

Reviewed by: Dan W. Hanke, Ph. D.
Section III, Tox. Branch II(H7509C)
Secondary Reviewer: Whang Phang, Ph. D.
Section III, Tox. Branch II(H7509C)

Dan W Hanke 16 June 92
James N. Rowe 6/16/92

DATA EVALUATION RECORD

STUDY TYPE: Acute Inhalation Toxicity Study (\$81-3)

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TOX. CHEM. NO. (CASWELL NO.): 890 AA

MRID NO. (ACCESSION NO.): 421727-03

CAS REG. NO.: 26644-46-2

EPA PESTICIDE CHEMICAL CODE/ACTIVE INGREDIENT CODE (SHANGHNESSY NO.): 107901

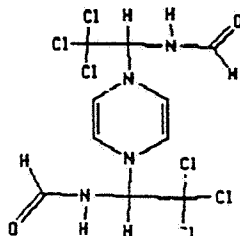
REREGISTRATION CASE NO.: 2720

FIFRA 88 LIST: B

PRODUCT MANAGER/NO.: Susan J. Lewis/21

HED PROJECT NO.: 2-1453

TEST MATERIAL: Triforine, Technical; systemic fungicide;
N,N'-(1,4-piperazinediylbis(2,2,2-trichloro-ethylidene))bis-
formamide



SYNONYMS: ANSI, Biformylchlorazin, Funginex, Cela W-524, CA 73021, Compound W, CA 70203, Cela 50, CME 74770, CW 524, SaproI, Denarin

STUDY NUMBER: 076162

SPONSOR: Shell International Chemical Co.
Celamerck GMBH & Co KG, Postfach, D-6507 Ingelheim am Rhein,
Federal Republic of Germany

SUBMITTER: Biologic, Inc., Research & Development, 11 Lake Ave.
Extension, Danbury, Connecticut 06811

TESTING FACILITY: Research & Consulting Company AG, CH 4452
Itingen, Switzerland

TITLE OF REPORT: 4-Hour Acute Inhalation Toxicity Study With Triforine Technical In Rats

AUTHOR(S): L. Ullman

REPORT ISSUED: December 12, 1986

SUMMARY AND CONCLUSIONS:

The acute 4-hour inhalation toxicity of a Triforine Technical dust aerosol was evaluated at a concentration of 5120 mg/cubic meter of air (5.120 mg/L) in five rats of each sex. None of the rats died on study (DOS). Triforine had no significant effects on any parameter evaluated, i.e., clinical signs, body weights or pathology. Since the acute inhalation toxicity of Triforine was tested above the guideline limit dose of 5 mg/L with no toxic effects noted, the LC_{50} is > 5.12 mg/L.

This study is evaluated as acceptable and is placed in Toxicity Category IV, because the limit dose of 5 g/l was actually exceeded. However, it is important to point out the average particle size did not fall within the EPA SEP for inhalation studies requiring at least 25% of the particles to be one micron or less. Only one percent of the particles of Triforine averaged roughly one micron or less, and 98.1% of the particles averaged between 9 and 10 microns. Nevertheless, based on discussions with colleagues John Whalan and James Rowe, it was decided that testing above the limit dose, a sufficient amount of Triforine Technical dust aerosol would have been taken in by the rats to permit evaluation of toxic effects.

Toxicity Category: IV

A signed quality assurance statement was present.

Core Classification: acceptable

This study does satisfy the guideline requirements (§81-3) for an Acute Inhalation Toxicity study.

MATERIALS:

1. **Test Compound:** Triforine Technical (SAG 102); N,N'-(1,4-piperazinediylbis(2,2,2-trichloro-ethylidene))bis-formamide. Description: white powder. Batch No./Lot # Charge 2764. Purity: 99.1 % (taken from same batch number from companion study MRID No. 421727-02). Stability: The test material was reported stable for at least two years, however, no analytical data were provided.

2. Test animals: Species: Rat. Strain: KFM-HAN. Wistar (outbred, SPF-Quality). Age: 11-13 weeks old at start of exposure. Weight: at start of exposure the females were 200 g - 219 g, and the males were 262 g - 299 g. Source: Received from Kleintierfarm Madoerin AG CH 4414 Fuellinsdorf/Switzerland.

METHODS & STATISTICS:

Pelleted standard Kliba 343 from batch 51/86 of standard rat chow and water were available ad libitum. A dust aerosol was administered to the rats via nose only. The aerosol was generated by the injection of Triforine Technical powder through a nozzle into a high velocity air stream (1000 L/hr at three atmospheres) into the air of the chamber. The nominal concentration was 549 g/4 hrs or 137 g/cubic meter of air (cbm). Exposure concentration was determined gravimetrically on selectron filters with pore size 0.2 micrometers and 50 mm in diameter, where the air flow was 10 L/min. The dust aerosol particle size was determined gravimetrically using an 8-stage Andersen Ambient Particle Sizing Sampler with selectron filters having a pore size of 0.2 micrometers and 76 mm in diameter, where the air flow was 28.3 L/min. The particle size distribution data show what percent each portion of particle sediment is of the total weight. Air temperature, humidity, and oxygen content were measured. The rats were observed for mortality four times during the day of application of the test article and then daily over days 2-15. Body weights were taken on day one prior to administration of the test article and then on days eight and 15. The rats were observed for clinical signs four times on the day of exposure, then daily over days 2-15. All rats were killed via intraperitoneal injection of sodium pentobarbitone, and necropsies were performed. No statistical algorithm was applied to the data.

RESULTS & DISCUSSION:

Clinical Signs and Pathology.

None of the rats died on study (DOS). Triforine had no significant effects on any parameter evaluated, i.e., clinical signs, body weights or pathology.

This study is evaluated as acceptable and is placed in Toxicity Category IV, because the limit dose of 5 g/l was actually exceeded. However, it is important to point out the average particle size did not fall within the EPA SEP for inhalation studies requiring at least 25% of the particles to be one micron or less. Only one percent of the particles of Triforine averaged roughly one micron or less, and 98.1% of the particles averaged between 9 and 10 microns.

Nevertheless, based on discussions with colleagues John Whalan and James Rowe, it was decided that testing above the limit dose, a sufficient amount of the Triforine Technical dust aerosol would have been taken in by the rats to permit evaluation of toxic effects. The particle size data as well as the temperature, relative humidity, and oxygen concentration are in Appendix 1 of this DER taken from p 29 of the study report.

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Appendix 1
MRID No. 421727-03

EXPOSURE CONDITIONS
GROUP 1 (1)

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EXPOSURE DATE : 02-OCT-86

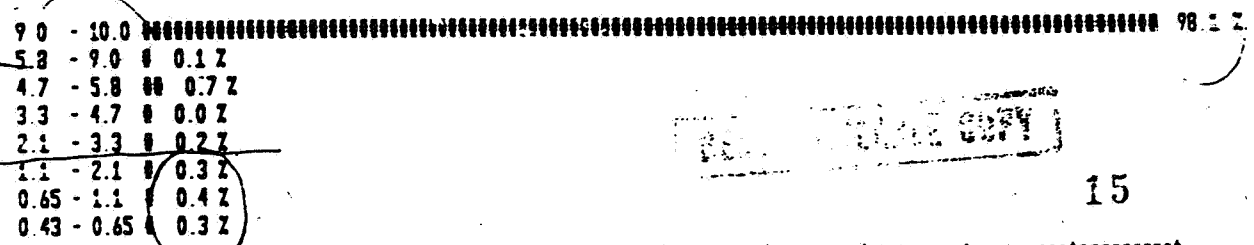
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Appendix No. 1
MRID No. 421727-03

SAMPLING TIME (hh:mm)	GRAVIMETRIC CONCENTRATION (MG/M3)	TEMPERATURE (DEGR. C)	RELATIVE HUMIDITY (ZRH)	OXYGEN CONTENTS (VOL%)
8.00	5260	22	44	20
8.30	5120	22	46	20
9.00	---	23	44	20
9.30	4980	23	48	20
10.00	---	23	48	20
10.30	5030	23	52	20
11.00	---	23	44	20
11.20	5210	23	48	20
MEAN	5120	23	47	20
ST. DEV.	118	0	3	0

SAMPLING TIME (hh:mm)	PARTICLE SIZE DISTRIBUTION IN Z (MICROMETER)							
	9.0-10.0	5.8-9.0	4.7-5.8	3.3-4.7	2.1-3.3	1.1-2.1	0.65-1.1	0.43-0.65
8.15	99.6	0.0	0.0	0.0	0.1	0.1	0.0	0.1
9.30	98.1	0.3	0.0	0.0	0.3	0.0	0.0	0.6
10.45	96.5	0.0	2.1	0.0	0.3	0.0	1.1	0.0

MEAN PARTICLE SIZE DISTRIBUTION IN Z (MICROMETER)



REPRODUCTION COPY

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is 1% is ... which ...
... the SEP ...
... (see p. 15 of the SEP) ... 00025
The study is unacceptable by these criteria

Tox. Chem. No. 890AA File Last Updated N/A Current Date 06 May 92 Document # _____

Study/Lab/Study #/Date	Material	EPA MRID No.	Results: LD50, LC50, PIS, NOEL, LEL	Tox Cat	Core-Grade
acute oral toxicity 81-1/ Research & Consulting Co. AG CH 4452 ttingen, Switzerland/ 76151/ 04 Dec 1986	Triforine Technical, systemic fungicide, N,N'-(1,4-piperazinediyl)bis (2,2,2-trichloro-ethylidene) bis-formamide; white powder	421727-01	LD50 > 5 g/kg Dose = 5 g/kg (limit dose) All observations and effects were unremarkable. None of the rats DOS.	IV	Minimum

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ox. Chem. No. 890AA File Last Updated N/A Current Date 16 Jun 92 Document # _____

Study/Lab/Study #/Date	Material	EPA MRID No.	Results: LD50, LC50, PIS, NOEL, LEL	Tox Cat	Core-Grade
<p>acute inhalation toxicity 81-2/ Research & Consulting Co. AG CH 4452 tingen, Switzerland/ ██████ / 27 Dec 1986 76/62</p>	<p>Triforine Technical, systemic fungicide, N,N'-(1,4-piperazinediyl)bis(2,2,2-trichloro-ethylidene) bis-formamide; white powder</p>	<p>421727-03</p>	<p>All observations and effects were unremarkable. None of the rats DOS. LC50 > 5 g/L The only dose tested was 5.120 mg/L, which exceeds the limit dose of 5 mg/L.</p>	<p>IV</p>	<p>Acceptable</p>

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Tox. Chem. No. 890AA File Last Updated N/A Current Date 15 June 92 Document #

Study/Lab/Study #/Date	Material	EPA MRID No.	Results: LD50, LC50, PIS, NOEL, LEL	Tox Cat	Core-Grade Minimum
acute dermal toxicity 81-2/ Research & Consulting Co. AG CH 4452 ttingen, Switzerland/ / 27 Aug 1990 8774	Triforine Technical, systemic fungicide, N,N'-(1,4-piperazinediyl)bis (2,2,2-trichloro-ethylidene) bis-formamide; white powder	421727-02	All observations and effects were unremarkable. None of the rats DOS. LD50 > 2 g/kg The only dose tested was the limit dose at 2 g/kg.	III	

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