

8EHQ-0193-0594/s
CIBA-GEIGY

EPA OTS 000787312 AT

899310000375

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January 5, 1992

Document Processing Center (TS-790)
(Attention: Section 8(e) Coordinator)
Office of Pollution Prevention and Toxics
Environmental Protection Agency
401 M St., SW
Washington, DC 20460

COMPANY SANITIZED

SANITIZED COPY

93 JAN 11 AM 11:39

Dear Section 8(e) Coordinator:

Subject: 8EHQ-0386-0594: Octyltin Ester Mixture Supplemental Submission

Ciba-Geigy Corporation (Ciba) claims product trade name as Confidential Business Information. We enclose a sanitized copy of this letter and the toxicity study for the public file.

In accordance with EPA's March 16, 1978 policy statement on Section 8(e) reporting under the Toxic Substances Control Act, and EPA's June 1991 TSCA Section 8(e) Reporting Guide, Ciba wishes to bring to the attention of the Environmental Protection Agency potential neurotoxic effects seen in an acute oral toxicity study conducted in rats with []. [] is a liquid mixture of octyltin esters comprised predominately of approximately 70% dioctyltin bis(thioglycolic acid), 2-ethylhexyl ester (CAS No. 15571-58-1) and approximately 30% octyltin tris(thioglycolic acid), 2-ethylhexyl ester (CAS No. 27107-89-7).

Previous 8(e) notices were submitted for this chemical substance in 1986. As noted in these submissions, importation by Ciba and sampling to non-Ciba-Geigy companies were very limited. No material remains in inventory nor has any such importation or sampling been conducted since the 1986 submissions, nor is any planned in the future. Since Ciba no longer manufactures, imports processes or distributes the subject material, we are not required to submit this information (see June 1991 TSCA 8(e) Reporting Guide at page 3.) However, in the "spirit" of Section 8(e) reporting, and in accordance with good product stewardship practices, we are submitting the following study since, to our knowledge, other companies distribute this chemical substance in the U.S.

21 pgs.

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Section 8(e) Coordinator
page 2 of 2

The present submission is a study entitled "Acute Oral Toxicity in the Rat, Test No. 924128, TK 10315 [()] Report". The overall acute oral LD₅₀ in rats of both sexes was 2000 mg/kg. Signs and symptoms suggestive of neurotoxic effects included ataxia, which was observed in one male and all females of the high-dose (2000 mg/kg) group. One female was not moribund. In addition, reduced locomotor activity was observed in all animals. Based upon these observed signs and symptoms, it is felt that this study would meet the current EPA criteria for reporting under TSCA 8(e).

Please call the undersigned if you have any questions about this submittal.

Very truly yours,

CIBA-GEIGY Corporation

a. DiBattista

Anthony DiBattista
Manager
Regulatory Affairs and Toxic Substance Compliance
T.R.A.C.

Enclosures: Sanitized copies of this letter and the submitted study

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Confidential Information Bracketed [].

page 1

93 JAN 11 AM 11:40
ORIGINAL RECEIVED

Acute Oral Toxicity in the Rat

Test No. 924128

TK 10315 [

] **SANITIZED
COPY**

Report

Study director: Dr. phil. H.R. Hartmann
Testing facility: Short-term Toxicology
CIBA-GEIGY Limited
4332 Stein / Switzerland
Test Guideline: OECD 401
Study completed: November 2, 1992
Sponsor: CIBA-GEIGY Limited
Additives Division
4002 Basel / Switzerland

This report contains: 16 pages

0005

Acute Oral Toxicity in the Rat
Test No.: 924128
Test Article: TK 10315

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Proprietary information

Proprietary information of CIBA-GEIGY Limited.
Not to be disclosed to third parties without previous consent
of CIBA-GEIGY Limited.

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Acute Oral Toxicity in the Rat
Test No.: 924128
Test Article: TK 10315

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Certification of GLP and verification of the report

(Certification of Good Laboratory Practice and verification of a complete and unaltered copy of the report by the sponsor)

To the best of my knowledge and belief, the statement of compliance with Good Laboratory Practice found on page 4 of this report, and signed by the Study Director is truthful and accurate, and this report as provided by the testing facility is complete and unaltered.

For the Sponsor:

Signature:

Alchut Ben

Date:

November 9, 1996

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Acute Oral Toxicity in the Rat
Test No.: 924128
Test Article: TK 10315

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Statement of compliance with Good Laboratory Practice.

To the best of my knowledge and belief this study has been performed in compliance with Good Laboratory Practice (GLP) in Switzerland (Verfahren und Grundsätze der Guten Laborpraxis (GLP) in der Schweiz), Procedures and Principles, March 1986, issued by the Swiss Federal Department of the Interior and the Intercantonal Office for the Control of Medicaments. These procedures are in essence consistent with:

- OECD Principles of Good Laboratory Practice (Council Decision 81/30, adopted on May 12, 1981, and the OECD Recommendation 83/95 concerning the 'Mutual Recognition of Compliance with Good Laboratory Practice', adopted on July 26, 1983).
- United States Environmental Protection Agency, Title 40 Code of Federal Regulations Part 160 (FIFRA); Federal Register, August 17, 1989.
- United States Environmental Protection Agency, Title 40 Code of Federal Regulations Part 792 (TSCA); Federal Register, August 17, 1989.
- Japan Ministry of Agriculture, Forestry and Fisheries, NohSan, Notification No. 3850, Agricultural Production Bureau, August 10, 1984.

Study director: Dr. phil. H.R. Hartmann

Signature:

 Date: November 2, 1982

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Acute Oral Toxicity in the Rat
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Reserved page for flagging statements

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Acute Oral Toxicity in the Rat
Test No.: 924128
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Quality assurance statement

Test Article: TK 10315
Study Title: Acute Oral Toxicity in the Rat
Test Number: 924128
Study Director: Dr. phil. H.R. Hartmann

I hereby certify that the following Quality Assurance activities were performed:

| <u>QA-Activity</u> | <u>Date performed</u> | <u>Date reported</u> |
|---------------------|-----------------------|----------------------|
| Facility Inspection | 01.04.92 | 27.04.92 |
| Protccol Audit | 28.08.92 | 28.08.92 |
| Final Report Audit | 29.10.92 | 29.10.92 |

Quality Assurance
Inspector: H. Schneylin

Signature:

..... *H. Schneylin* Date: *02/14/1992*

Acute Oral toxicity in the rat
Test No.: 924128
Test Article: TK 10315

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2. INTRODUCTION

2.1. Purpose

At the request of the Additives Division of CIBA-GEIGY Limited, Test No. 924128, was conducted to determine the acute oral toxicity of TK 10315 in albino rats.

2.2. Basis

The study design followed the OECD Guideline 401, "Acute Oral Toxicity", adopted February 24, 1987 and the study protocol.

As requested by the sponsor, the whole study was subjected to quality assurance.

2.3. Testing facility

All the work was done in the testing facility:

CIBA-GEIGY Limited
Short-term Toxicology
4332 Stein / Switzerland

Technical assistant:

Mr. S. Winter

Archives are located at:

CIBA-GEIGY Limited
Werk Stein
4332 Stein / Switzerland
Raw data, protocol and report will be stored at this location.

The job descriptions and the summaries of training and professional experience for all personnel participating in this study are archived in the testing facility.

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Acute Oral Toxicity in the Rat
Test No.: 924128
Test Article: TK 10315

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2.4. Dates

Date of protocol: August 21, 1992
Date of administration: September 1, 1992
September 8, 1992
September 16, 1992
Date of completion: September 30, 1992

2.5. Distribution

Dr. H.J. Weideli (for the sponsor)
Archives

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3. MATERIALS AND METHODS

3.1. Test Article

| | |
|-------------------------|-----------------------|
| Test article: | TK 10315 |
| Trade name: | [] |
| Batch No.: | 08340205 |
| Purity: | Mixture |
| Physical properties: | liquid; colorless |
| Storage conditions: | room temperature |
| Validity: | July, 1996 |
| Safety precautions: | gloves and face masks |
| Test material received: | July 16, 1992 |

3.2. Animals

3.2.1. Choice of species

The rat has been selected for this test as being a standard species for the determination of the acute oral toxicity.

Young adult albino rats of both sexes (Tif: RAI f (SPF), bred and raised on the premises, were used in the experiment.

| | |
|---------|---|
| Source: | CIBA-GEIGY Limited Animal Production 4332 Stein / Switzerland |
|---------|---|

| | |
|----------------------------|--------------|
| Initial body weight range: | 190 to 215 g |
|----------------------------|--------------|

3.2.2. Husbandry and Diet

The rats were kept in an animal room under conventional laboratory conditions, on a 12 hour/day light cycle. The air conditioning system (approximately 15 air changes per hour) maintained a temperature of 22 ± 2 °C and a relative humidity of 55 ± 10 %.

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Acute Oral Toxicity in the Rat
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The animals were housed in Macrolon cages type 4, with standardized soft wood bedding (Societe Parisienne des Sciures, Pantin, France). They were acclimatized at least for 5 days before administration. Rat diet (NAFAG 890 Fox, NAFAG, Gossau/SG, Switzerland) and water were provided ad libitum. Prior to dosing, the animals were fasted overnight.

3.2.3. Group size and identification

The animals, segregated by sex, were group-housed (5 animals per cage). Within the groups the animals were identified with numbers from 1 to 5 using picric acid stain on the fur. After dosing, the animals were placed in their cages, which were marked with a cage card containing the date of administration and the characteristics of the experiment and dose group.

3.3. Design and Procedure

| | |
|-------------------------------------|--|
| Administration of the test article: | one single oral dose, by gastric intubation (gavage) |
| Dose levels, sex group: | 1000 mg/kg, males 2000 mg/kg, males and females |
| Total number of animals: | 15 |
| Vehicle: | 0.5 % (w/v) carboxymethylcellulose in 0.1 % (w/v) aqueous polysorbate 80 |
| Volume applied: | 10 ml/kg body weight |
| Observation period: | 14 days |

3.4. Observations and records

| | |
|---------------------|---|
| Mortality: | daily; a.m. and p.m. on working days, a.m. on weekend days |
| Signs and symptoms: | daily for 14 days |
| Body weight: | immediately before administration, on days 7, 14, and at death |
| Necropsies: | Spontaneously dying animals were submitted to a gross necropsy as soon as possible; survivors at the end of the observation period. |

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Acute Oral Toxicity in the Rat
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3.5. Statistical Analysis

From the body weights, the group means and their standard deviations were calculated.

The ED50 value and the lower 95% confidence limit of both sexes were computed by the logit model (J. Berkson, J. Am. Stat. Ass. 39 (1944), 357-365).

4. RESULTS

4.1. In-life observations

In life observations are depicted in table 1.

Piloerection, hunched posture, and dyspnea were seen, being common symptoms in acute tests. Additionally, reduced locomotor activity was observed in all animals. Ataxia was noticed in one male and all females of the 2000 mg/kg dose group. In one male dosed with 2000 mg/kg cyanosis was observed.

The surviving animals recovered within 6 to 13 days.

4.2. Body weight changes

Individual body weight, their group means and standard deviations are shown in table 2.

4.3. Mortalities

See table 2.

4.4. Necropsies

At necropsy, no deviations from normal morphology were found.

TABLE 1

In-life observations

| Animal No. | Observations | Admin.day | | | Days after administration | | | | | | | |
|--------------------------|---------------|-----------|----|----|---------------------------|----|----|----|----|----|----|----|
| | | 1h | 3h | 5h | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 |
| 1000 mg/kg, males | | | | | | | | | | | | |
| 1 - 5 | piloerection | ++ | ++ | ++ | ++ | ++ | + | + | + | | | |
| 1 - 5 | hunched post | + | ++ | ++ | + | + | + | + | | | | |
| 1 - 5 | dyspnea | + | + | + | + | + | | | | | | |
| 1 - 5 | red.locom.act | | + | + | | | | | | | | |
| 2000 mg/kg, males | | | | | | | | | | | | |
| 1 | piloerection | + | + | + | + | + | + | ++ | ++ | ++ | ++ | # |
| 2 | piloerection | + | + | + | + | + | + | ++ | ++ | ++ | ++ | # |
| 3 | piloerection | + | + | + | + | + | + | ++ | ++ | ++ | ++ | + |
| 4 | piloerection | + | + | + | + | + | + | ++ | ++ | ++ | ++ | # |
| 5 | piloerection | + | + | + | + | + | + | ++ | ++ | ++ | ++ | # |
| 1 | hunched post | + | ++ | ++ | ++ | ++ | ++ | ++ | ++ | ++ | ++ | + |
| 2 | hunched post | + | ++ | ++ | ++ | ++ | ++ | ++ | ++ | ++ | ++ | + |
| 3 | hunched post | + | ++ | ++ | ++ | ++ | ++ | ++ | ++ | ++ | ++ | + |
| 4 | hunched post | + | ++ | ++ | ++ | ++ | ++ | ++ | ++ | ++ | ++ | + |
| 5 | hunched post | + | ++ | ++ | ++ | ++ | ++ | ++ | ++ | ++ | ++ | + |
| 1 | dyspnea | ++ | ++ | ++ | + | + | + | + | + | + | | |
| 2 | dyspnea | ++ | ++ | ++ | + | + | + | + | + | + | | |
| 3 | dyspnea | ++ | ++ | ++ | + | + | + | + | + | + | ++ | ++ |
| 4 | dyspnea | ++ | ++ | ++ | + | + | + | + | + | + | | |
| 5 | dyspnea | ++ | ++ | ++ | + | + | + | + | + | + | | |
| 1 | red.locom.act | + | + | + | + | + | + | | | | | |
| 2 | red.locom.act | + | + | + | + | + | + | | | | | |
| 3 | red.locom.act | + | + | + | + | + | + | + | + | + | + | + |
| 4 | red.locom.act | + | + | + | + | + | + | | | | | |
| 5 | red.locom.act | + | + | + | + | + | + | | | | | |
| 3 | ataxia | | | | | | | | | | | + |
| 3 | cyanosis | | | | | | | | | | | + |

hunched post - hunched posture
 red.locom.act - reduced locomotor activity
 + = slight, ++ = moderate, # = slight until day 9

In-life observations (continued)

| Animal No. | Observations | Admin. day | | | Days after administration | | | | | | | |
|----------------------------|---------------|------------|----|----|---------------------------|----|----|----|----|----|----|-----|
| | | 1h | 3h | 5h | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 |
| 2000 mg/kg, females | | | | | | | | | | | | |
| 1 | piloerection | + | + | + | ++ | ++ | ++ | ++ | ++ | ++ | ++ | * |
| 2 | piloerection | + | + | + | ++ | ++ | ++ | ++ | ++ | ++ | ++ | * |
| 3 | piloerection | + | + | + | ++ | ++ | ++ | ++ | ++ | ++ | ++ | ** |
| 4 | piloerection | + | + | + | ++ | ++ | ++ | ++ | ++ | ++ | ++ | ++ |
| 5 | piloerection | + | + | + | ++ | ++ | ++ | ++ | ++ | ++ | ++ | *** |
| 1 | hunched post | ++ | ++ | ++ | ++ | ++ | ++ | ++ | ++ | ++ | ++ | # |
| 2 | hunched post | ++ | ++ | ++ | ++ | ++ | ++ | ++ | ++ | ++ | ++ | # |
| 3 | hunched post | ++ | ++ | ++ | ++ | ++ | ++ | ++ | ++ | ++ | ++ | ## |
| 4 | hunched post | ++ | ++ | ++ | ++ | ++ | ++ | ++ | ++ | ++ | ++ | ## |
| 5 | hunched post | ++ | ++ | ++ | ++ | ++ | ++ | ++ | ++ | ++ | ++ | ## |
| 1 | dyspnea | + | + | + | + | + | + | + | + | + | + | ## |
| 2 | dyspnea | + | + | + | + | + | + | + | + | + | + | ## |
| 3 | dyspnea | + | + | + | + | + | + | + | + | + | + | ## |
| 4 | dyspnea | + | + | + | + | + | + | + | + | + | + | ## |
| 5 | dyspnea | + | + | + | + | + | + | + | + | + | + | ## |
| 1 | red.locom.act | | + | + | + | | | | | | | ### |
| 2 | red.locom.act | | + | + | + | | | | | | | ## |
| 3 | red.locom.act | | + | + | + | | | | | | | ## |
| 4 | red.locom.act | | + | + | + | | | | | | | ## |
| 5 | red.locom.act | | + | + | + | | | | | | | ## |
| 1 | ataxia | | | | | | | | | + | + | + |
| 2 | ataxia | | | | | | | | | + | + | + |
| 3 | ataxia | | | | | | | | | + | + | + |
| 4 | ataxia | | | | | | | | | + | + | + |
| 5 | ataxia | | | | | | | | | + | + | + |

hunched post = hunched posture
 red.locom.act = reduced locomotor activity
 + = slight, ++ = moderate
 * = moderate until day 12, ** = until day 9, *** = until day 11
 # = slight until day 12, ## = until day 9, ### = until day 11

TABLE 2

Body weight and necropsy findings

| Animal Number | Body Weights (g) | | | * | Gross Necropsy Findings |
|--------------------------------------|------------------|------|------|-----|-------------------------|
| | d 0 | d 7 | d 14 | | |
| Males dosed with 1000 mg/kg | | | | | |
| 1 | 204 | 246 | 289 | TS | NOA |
| 2 | 215 | 261 | 302 | TS | NOA |
| 3 | 203 | 248 | 291 | TS | NOA |
| 4 | 205 | 239 | 281 | TS | NOA |
| 5 | 195 | 245 | 279 | TS | NOA |
| mean | 204 | 248 | 288 | | |
| SD | 7.1 | 8.1 | 9.2 | | |
| Males dosed with 2000 mg/kg | | | | | |
| 1 | 207 | 231 | 262 | TS | NOA |
| 2 | 198 | 202 | 271 | TS | NOA |
| 3 | 197 | 168 | | d 9 | NOA |
| 4 | 195 | 218 | 283 | TS | NOA |
| 5 | 190 | 167 | 240 | TS | NOA |
| mean | 197 | 197 | 264 | | |
| SD | 6.2 | 29.0 | 18.2 | | |
| Females dosed with 2000 mg/kg | | | | | |
| 1 | 207 | 203 | 226 | TS | NOA |
| 2 | 200 | 167 | | d13 | NOA |
| 3 | 205 | 157 | | d10 | NOA |
| 4 | 210 | 169 | | d 9 | NOA |
| 5 | 196 | 160 | | d12 | NOA |
| mean | 204 | 171 | | | |
| SD | 5.6 | 18.4 | | | |

* TS terminal sacrifice
 * d<> found dead on day < > after application
 NOA no observable abnormalities

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Acute Oral Toxicity in the Rat
Test No.: 924128
Test Article: TK 10315

SUMMARY NOTIFICATION DOSSIER FOR SUBSTANCES NOTIFIED IN
CONFORMITY WITH ARTICLE 6.1 OF DIRECTIVE 79/831/EEC ON THE
CLASSIFICATION, PACKAGING AND LABELLING OF DANGEROUS SUBSTANCES

A4 Toxicological Studies

4.1 Acute toxicity

4.1.1 Administered orally

On the basis of the test results given below and in conformity with the criteria given in annex VI of the Directive, the substance should be:

Limit test: yes

LD50: 2000 (lower limit 1265) mg/kg

Species / strain: rat Tif:RAI f1

Vehicle: 0.5 % (w/v) carboxymethylcellulose in
0.1 % (w/v) aqueous polysorbate 80

Results:

| | dose mg/kg | number of animals | number of deaths |
|---------|---------------|----------------------|---------------------|
| Males | 1000 | 5 | 0 |
| | 2000 | 5 | 1 |
| Females | 2000 | 5 | 4 |

Acute Oral Toxicity in the Rat
Test No.: 924128
Test Article: TK 10315

4.1.1 Administered orally (continued)

Signs of toxicity

Piloerection, hunched posture, and dyspnea were seen, being common symptoms in acute tests. Additionally, reduced locomotor activity was observed in all animals. Ataxia was noticed in one male and all females of the 2000 mg/kg dose group. In one male dosed with 2000 mg/kg cyanosis was observed.

The surviving animals recovered within 6 to 13 days.

Effects in organs

At autopsy, no deviations from normal morphology were found in all animals.

Method:

Prior to dosing by gastric intubation, the animals were fasted overnight. After administration, the animals were observed daily for clinical signs and mortality. Body weight was recorded immediately before administration, on day 7 and day 14. All animals dying spontaneously or being sacrificed (either for humane reasons or at termination of the study) were subjected to a complete necropsy.

Body responsible for test:

CIBA-GEIGY Limited
Short-term Toxicology
4332 Stein / Switzerland

Comments: