

9 pp.

March 21, 1986

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

Document Control Officer
Chemical Information Division
Office of Toxic Substances (WH-557)
Environmental Protection Agency
401 M Street, S.W.
Washington, D. C. 20460

SANITIZED COPY

8E HQ-0386-0594S
88-86000'69

Re: TSCA Section 8(e) Notice, Diocetyltn Developmental Product

Dear Madam/Sir:

[] requests that all information shown in brackets in this letter and the attached toxicity study be treated 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, [] wishes to bring to the attention of the Environmental Protection Agency certain results, consistent with diocetyltn immuno-suppression effects, that were observed in a 90-day dietary study in rats with the subject diocetyltn substance. The tested substance is a liquid mixture of octyltn esters comprised predominantly of [] diocetyltn bis (thioglycolic acid), 2-ethylhexyl ester (CAS No. 15571-56-1) and []

We imported [] of this substance in 1981 for potential sampling. However, only one sample of approximately [] was sent to one customer for development purposes. No further sales or distribution were made. [] have remained in warehouse inventory since 1981 and we expect that this material will ultimately be disposed of as waste, probably by incineration.

Our toxicologist recently reviewed the subject toxicology study in connection with [] OSHA hazard assessment review for inactive products currently in warehouse inventory. A copy of the study, entitled "90 Day Dietary Study in Rats with Compound []" is attached. The results are summarized as follows:

The test material was administered to rats at oral dose levels of approximately 0, 1.6, 3.3 or 6.6 mg/kg for 90 days. The test material did not produce any detrimental effects in the following parameters: body weight gain, food consumption, clinical chemistry, hematology values, urine analysis and necropsy findings.

Weights of the thymus gland (absolute and relative) showed a statistically significant dose-related reduction in the 3.3 and 6.6 mg/kg groups. In addition, 2 of 10 females in the 6.6 mg/kg group showed "very mild changes consisting of a reduction in cortical lymphocytes and a less clear distinction between the cortex and medulla in the thymus gland." In a post-dose recovery period lasting 15-30 days, the effects appeared reversible as no alterations were seen in the 6.6 mg/kg recovery group with 10 males and 10 females.

Although we are submitting this study under TSCA Section 8(e), [] does not believe this product, in fact, presents a substantial risk of injury to health or the environment for the following reasons:

1. Immuno-suppressive effects of dioctyltin compounds are generally well known and can be controlled by appropriate engineering controls and work practices.
2. An OSHA TLV of 0.1 mg/m^3 already exists for organotin compounds.
3. The development substance in question has not been broadly distributed in the U. S. by []. Only one customer was sampled a small amount of the substance.

Additionally, [] will do the following:

1. Discontinue any further development of this substance.
2. Notify our warehouse workers of these findings by means of a revised Material Safety Data Sheet and label.
3. Dispose of the remaining warehouse inventory in the near future.

Please contact the undersigned if you have any questions or need additional information.

Sincerely yours,

[]
[]
Enc.

SANITIZED COPY

71/74/S.I.

90 Day Dietary Study in Rats
with Compound

To:

From:

6th November, 1974.

ASSESSMENT

Compound when administered in the diet to rats at a rate of 100 p.p.m. for not less than 90 days caused a statistically significant weight reduction (both absolute and relative) in the thymus glands ($P < 0.05$). In two females, histopathological examination showed a reduction of cortical lymphocytes of the thymus gland in 2/40 animals (both females).

At 50 p.p.m. a statistically significant ($P < 0.05$) reduction in thymus weights (both absolute and relative) was recorded.

The "no effect" level is considered to be 25 p.p.m.

SUMMARY OF EXPERIMENTAL RESULTS

Compound was administered in the diet to rats at dose levels of 0, 25, 50 and 100 p.p.m. (equivalent to an approximate average daily intake of 0, 1.6, 3.3 and 6.6 mg/kg), for not less than 90 days.

No deaths occurred during the test and no clinical symptoms were recorded.

Body weight gains, food consumption and laboratory parameters (haematology, clinical chemistry and urine analysis) were within normal limits and treated groups were comparable to controls.

At autopsy no changes caused by treatment were seen.

Histopathological examination showed very mild changes consisting of a reduction in cortical lymphocytes and a less clear cut distinction between cortex and medulla in the thymus gland of two female rats in group 4 (6.6 mg/kg). Other changes were not related to treatment.

Weights of the thymus gland (absolute and relative) showed a statistically significant dose related reduction in group 3 (3.3 mg/kg) and 4 (6.6 mg/kg) ($P < 0.05$ in each case when examined by the Mann-Whitney U-test).

Ophthalmic examination did not reveal any abnormalities in treated groups.

RECOVERY EXPERIMENT

In each group, 20 rats (10 ♂ and 10 ♀) were retained without treatment, after the termination of the main study, as a recovery experiment. Five males and five females from each group were killed after 15 days of the recovery period and the remainder after 30 days.

One animal in group 2 (25 p.p.m.) was found dead on day 98. The cause of death was not ascertained.

Apart from some urea values outside normal limits in females of group 2 (25 p.p.m.), laboratory parameters were unremarkable.

No changes referable to treatment were seen at autopsy. Histopathological examination of thymus in group 3 (3.3 mg/kg) and 4 (6.6 mg/kg) did not show any abnormalities.

EXPERIMENTAL PROCEDURE

Animals

Healthy Sprague Dawley derived rats bred on the premises having individual mean body weights of 142 g. (♂) and 120 g. (♀) at the start of the trial.

Dose/Groups

160 rats were allocated to 4 groups of 40 animals each (20 ♂ and 20 ♀).

Group	Dose level	Rat Numbers
1 Control	Nil	♂ 101, 103, 105, 107, 109, 111, 113, 115, 117, 119 121, 123, 125, 127, 129, 131, 133, 135, 137, 139 ♀ 102, 104, 106, 108, 110, 112, 114, 116, 118, 120 122, 124, 126, 128, 130, 132, 134, 136, 138, 140
2	25 p.p.m.	♂ 201, 203, 205, 207, 209, 211, 213, 215, 217, 219 221, 223, 225, 227, 229, 231, 233, 235, 237, 239 ♀ 202, 204, 206, 208, 210, 212, 214, 216, 218, 220 222, 224, 226, 228, 230, 232, 234, 236, 238, 240
3	50 p.p.m.	♂ 301, 303, 305, 307, 309, 311, 313, 315, 317, 319 321, 323, 325, 327, 329, 331, 333, 335, 339, 339 ♀ 302, 304, 306, 308, 310, 312, 314, 316, 318, 320 322, 324, 326, 328, 330, 332, 334, 336, 338, 340
4	100 p.p.m.	♂ 401, 403, 405, 407, 409, 411, 413, 415, 417, 419 421, 423, 425, 427, 429, 431, 433, 435, 437, 439 ♀ 402, 404, 406, 408, 410, 412, 414, 416, 418, 420 422, 424, 426, 428, 430, 432, 434, 436, 438, 440

20 rats (10 ♂ and 10 ♀) in each group were retained after 91 days as a recovery experiment. 5 ♂ and 5 ♀ in each group were autopsied after 15 days recovery and the remaining 5 ♂ and 5 ♀ after 30 days. All animals were kept under experimental conditions but without treatment for these respective periods.

Husbandry

Rats were caged in groups of 5 and maintained at a temperature of 21°C. ($\pm 2^\circ$) with a relative humidity of 50% ($\pm 10\%$). A commercial diet (Oakes Special Diet with added Vitamin E) to which the compound was added was fed ad lib. Water was available at all times.

Test Material

A light brown coloured liquid labelled

Laboratory Studies

Blood and urine samples for haematology and biochemistry were taken from all rats during weeks 5, 9 and 13.

The recovery animals were sampled - for to autopsy during weeks 15 and 17.

Observations

Records of various parameters were kept as follows:-

Clinical symptoms	-	daily
Body weights	-	weekly
Food consumption	-	weekly

An ophthalmic examination was carried out on all rats pre test and on 10 ♂ and 10 ♀ from groups 1 and 4 during weeks 5, 9 and 13. The recovery animals were examined prior to autopsy during weeks 15 and 17.

Terminal Studies

An autopsy examination was carried out where possible on animals which died or were killed during the course of the study and on all animals which survived until the end of the test.

The following organs were weighed:-

Adrenals	Brains	Heart	Thymus
Kidneys	Livers	Gonads	

Percentage organ weights were calculated with reference to brain weight.

The following organs and tissues were preserved for histopathological examination.

Adrenals	Aorta	Bone marrow
Brain	Colon	Eye (+ optic nerve)
Gonads	Gross lesions	Heart
Kidneys	Liver	Lungs
Lymph nodes (axillary & mesenteric)	Pancreas	Mammary gland
Muscle	Prostate (or uterus)	Peripheral nerve (sciatic)
Pituitary	Spinal cord	Small intestine
Spleen	Thyroids	Stomach
Thymus		Urinary bladder

Preparation of Medicated Diet

Powdered diet was mixed with dry extract of malt (Diamalt T) in the ratio of 85% food to 15% malt extract by weight. The compound was dissolved in ethanol (0.3 ml/kg. diet) mixed with water (15% of diet) and then added to the dry food in a mechanical mixer. The mixture was then passed through a mincer and the pellets so produced were dried for approximately 12 hours at a temperature not exceeding 45°C.

Administration of Compound

Medicated diet was freshly prepared each week and fed on an ad lib. basis.

Control animals received diet prepared in the same manner with ethanol, but without the addition of the test compound.

Tissues were fixed in the following solutions:-

CNS and peripheral nerve	-	10% buffered formalin
Bone marrow	-	Zenker formal
Other organs and tissues	-	Bouins fluid
Thin liver slices	-	Ice cold Rossmans fluid

Sections were cut at 5 - 7 μ and stained with haematoxylin and eosin. Liver sections fixed in Rossmans fluid were stained by the PAS technique to show glycogen. Frozen sections from liver and kidney were stained with Sudan IV in propylene glycol for fat.

Quality Control

Quality control systems used in haematology and clinical chemistry were as follows:-

Hyland Q Pack control blood
Chemonitor I (Dade)
Chemonitor II (Dade)
Enzotrol (Dade)
Horse serum (B.W. & Co.)
Quantipiat (Diamed)



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

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMO TO THE RECORD:

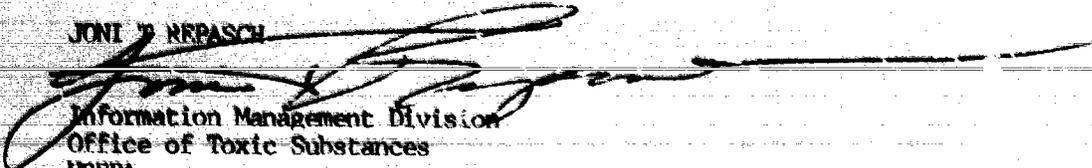
SUBJECT: REFQ 0594S

DATE: March 10, 1987

In its letter of July 23, 1986, CIBA-GEIGY relinquished certain TSCA CBI claims for its initial submission dated March 21, 1986, (REFQ 0386-0594S), follow up, dated April 29, 1986 (REFQ-0586-0594s) and follow up, dated May 21, 1986 (REFQ-0586-0594S) including its company name. See also letter of September 3, 1986 and all attachments. Therefore, company name may be indexed into TSCATS as "CIBA-GEIGY" for all three submissions.

This memo per Dave Williams documentation.

JONI M REPASCH


Information Management Division
Office of Toxic Substances
USEPA

attach (1)
CIBA-GEIGY

CIBA-GEIGY Corporation
Ardsley, New York 10602-2000
Telephone 914 478 3131

March 21, 1986

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

Document Control Officer
Chemical Information Division
Office of Toxic Substances (WH-557)
Environmental Protection Agency
401 M Street, S.W.
Washington, D. C. 20460

SANITIZED COPY

Re: TSCA Section 8(e) Notice, Dioctyltin Developmental Product

Dear Madam/Sir:

CIBA-GEIGY Corporation requests that all information shown in brackets in this letter and the attached toxicity study be treated 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, CIBA-GEIGY Corporation wishes to bring to the attention of the Environmental Protection Agency certain results, consistent with dioctyltin immunosuppression effects, that were observed in a 90-day dietary study in rats with the subject dioctyltin substance. The tested substance is a liquid mixture of octyltin esters comprised predominantly of [] dioctyltin bis (thioglycolic acid), 2-ethylhexyl ester (CAS No. 15571-58-1) and [] octyltin tris(thioglycolic acid), 2-ethylhexyl ester (CAS No. 27107-89-7).

We imported 220 lbs. of this substance in 1981 for potential sampling. However, only one sample of approximately 5 lbs. was sent to one customer for development purposes. No further sales or distribution were made. 215 lbs. have remained in warehouse inventory since 1981 and we expect that this material will ultimately be disposed of as waste, probably by incineration.

Our toxicologist recently reviewed the subject toxicology study in connection with CIBA-GEIGY Corporation's OSHA hazard assessment review for inactive products currently in warehouse inventory. A copy of the study, entitled "90 Day Dietary Study in Rats with Compound TK 10 317" is attached. The results are summarized as follows:

The test material was administered to rats at oral dose levels of approximately 0, 1.6, 3.3 or 6.6 mg/kg for 90 days. The test material did not produce any detrimental effects in the following parameters: body weight gain, food consumption, clinical chemistry/hematology values, urine analysis and necropsy findings.

Weights of the thymus gland (absolute and relative) showed a statistically significant dose-related reduction in the 3.3 and 6.6 mg/kg groups. In addition, 2 of 10 females in the 6.6 mg/kg group showed "very mild changes consisting of a reduction in cortical lymphocytes and a less clear distinction between the cortex and medulla in the thymus gland." In a post-dose recovery period lasting 15-30 days, the effects appeared reversible as no alterations were seen in the 6.6 mg/kg recovery group with 10 males and 10 females.

Although we are submitting this study under TSCA Section 8(e), CIBA-GEIGY does not believe this product, in fact, presents a substantial risk of injury to health or the environment for the following reasons:

1. Immuno-suppressive effects of dioctyltin compounds are generally well known and can be controlled by appropriate engineering controls and work practices.
2. An OSHA TLV of 0.1 mg/m^3 already exists for organotin compounds.
3. The development substance in question has not been broadly distributed in the U. S. by CIBA-GEIGY Corporation. Only one customer was sampled a small amount of the substance.

Additionally, CIBA-GEIGY will do the following:

1. Discontinue any further development of this substance.
2. Notify our warehouse workers of these findings by means of a revised Material Safety Data Sheet and label.
3. Dispose of the remaining warehouse inventory in the near future.

Please contact the undersigned if you have any questions or need additional information.

Sincerely yours,

A. Di Battista

Anthony Di Battista
Manager, Toxic Substances Compliance
Safety, Health & Ecology

ADB17:gg:38
Enc.

CIBA-GEIGY Corporation
Ardsley, New York 10502-2899
Telephone 914 478 3131

attach (2)
CIBA-GEIGY

April 29, 1986

Document Control Officer
Chemical Information Division
Office of Toxic Substances (WH-557)
Environmental Protection Agency
401 M Street, S.W.
Washington, D. C. 20460

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

SANITIZED COPY

Re: BEHQ-0386-0594 S, Octyltin Ester Mixture, Supplemental Submission

Dear Madam/Sir:

CIBA-GEIGY Corporation requests that all information shown in brackets in this letter and the attached toxicity study be treated as Confidential Business Information. We enclose a sanitized copy of this letter and the toxicity study for the public file.

On March 21, 1986, CIBA-GEIGY Corporation submitted a TSCA Section 8(e) notice describing certain results, consistent with dioctyltin immuno-suppression effects observed in a 90-day dietary study in rats with the subject octyltin ester mixture.

We have subsequently received another report, in German, for this mixture, entitled "TK 10 315 [], Untersuchungen Zur Toxizität an Jungen Männlichen Ratten" and commissioned the English translation of the report (except for the individual data tables which are understandable without translation). The subject mixture was compared in this study against dioctyltin chloride (DOTC), a well characterized immunosuppressant in the rat. The main scope of the study was to detail the weight changes in the thymus, spleen and liver. The test substances were administered orally by intubation for 10 days and the animals were necropsied on day 11.

The present study confirms the thymus atrophy reported in our 8(e) submission of March 21, 1986. The subject mixture shows a statistically significant thymus weight reduction which was dose related at 13 and 30 mg/kg and the NOEL was determined to be 4.3 mg/kg. DOTC similarly shows a statistically significant thymus weight reduction at 10 and 25 mg/kg but not at 2.5 mg/kg. Spleen and liver weights were not significantly different from the control at any dose level tested for either the subject mixture or DOTC.

A copy of the new report cited above, and its English translation, entitled "TK 10 315 [], Toxicity Studies on Young Male Rats" is enclosed.

We are in the process of gathering the information requested in Frank D. Kover's letter of April 16, 1986 and will respond to that request separately.

Yours truly,

A. Di Battista

A. Di Battista
manager, Toxic Substances Compliance
Safety, Health & Ecology

ADB19:gg:06
enc.

We are in the process of gathering the information requested in Frank D. Kover's letter of April 16, 1986 and will respond to that request separately.

Yours truly,

A. Di Battista

A. Di Battista
manager, Toxic Substances Compliance
Safety, Health & Ecology

ADB19:gg:06
Enc.

CIBA-GEIGY Corporation
Ardley, New York 10502-2699
Telephone 914 478 3131

CIBA-GEIGY

attach 3

May 21, 1986

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

Document Control Officer (TS-790)
Att: 8(e) Coordinator
Information Management Division
Office of Toxic Substances
U. S. Environmental Protection Agency
401 "M" Street, S.W.
Washington, D.C. 20460

SANITIZED COPY

Re: 8EHQ-0386-0594S, Octyltin Ester Mixture,
Follow-Up of EPA Requested Information

Dear Madam/Sir:

CIBA-GEIGY Corporation requests that all information shown in brackets in this letter and the attached Material Safety Data Sheet (MSDS) be treated as Confidential Business Information. We enclose a sanitized copy of this letter and the MSDS.

This is in reply to your letter of April 16, 1986, which we received April 23, 1986.

1. Copies of our Material Safety Data Sheet and label for [] that have been revised to reflect the reported toxicologic findings are enclosed. [] is the 8(e) reported octyltin ester mixture.
2. The studies listed below were run with the minor component in []. Chemically, the minor component is octyltin tris (thioglycolic acid, 2-ethylhexyl ester, CAS No. 27107-89-7. A description of the studies and the available results are as follows:
 - a) Acute oral LD 50, rat; January 9, 1973: 5000 (3760-6650) mg/kg.
 - b) Acute oral LD 50, rat; April 23, 1980: 5189(3436-12090) mg/kg.
 - c) 90-Day rat feeding study: Dietary levels of 0, 20, 100, and 500 ppm, equivalent to 0, 1.3, 6.2, and 30.3 mg/kg. A slight dose related increase in adrenal weights in male animals was seen; this effect was reversible. -It was attributed to a non-specific stress-induced adrenal hypertrophy caused by the extremely unpleasant smell of the test substance. The NOEL was concluded to be 500 ppm.

d) The only other study we are aware of is a 2-year carcinogenicity study run in France using 20 male and 20 female rats at a single dose level of 100 mg/kg. This study has just been received. We will describe it to the Agency after we have it translated into English.

Very truly yours,

A. Di Battista

A. Di Battista
Manager, Toxic Substances Compliance
Safety, Health & Ecology]

ADB19:gg:18
Enc.