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8EHQ-0586-0594S
89-8680233 FLWP

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

Re: 8EHQ-0386-0594 S, Octyltin Ester Mixture, Supplemental Submission

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.

On March 21, 1986, [ ] 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 "[ ], 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 15 and 30 mg/kg and the NOEL was determined to be [illegible].5 mg/kg. DOTC similarly shows a statistically significant thymus weight reduction at 10 and 25 mg/kg but not at 2[illegible] 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 "[ ], Toxicity Studies on Young Male Rats" is enclosed.

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

Yours truly,

[

]

[ ]
Enc.

Sanitized

8EHQ-0586-0594S
89-8680233 FLWP

Translated from German Part 2

[ ]*

TOXICOLOGY

MAY 1 1986

[Octyltin Ester Mixture]

TOXICITY STUDIES ON YOUNG MALE RATS

[ ]

sgd. [ ]
Dr. phil. nat.

sgd. [ ]
M.D.

August 22, 1979/jc

Animal species:	Rat, [ ]
Test substance:	[ ] Internal product No. [ ]
Positive controls:	DOTC (di-n-octyl-tin-dichloride) Internal product No. [ ] Manufactured by Schering AG Batch 1279/78
Sponsor:	[ ]
Test system No.	[ ]
Project No.	[ ] Positive control Project No. [ ]
Mode of administration:	Oral, through metal esophageal tube, once a day
Dosage in mg/kg per day:	Test substance 4.3 / 13 / 30 DOTC: 2.5 / 10 / 25
Solvent:	Peanut oil (Oleum Arachidis, PHH VI, Siegfried)
Inception of study:	July 26, 1979
Date of report:	August 22, 1979

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* All Confidential Business Information is Bracketed

SUMMARY AND EVALUATION

[ ] an organic tin stabilizer, was tested by comparison with DOTC as 'positive control' for toxic activity in the rat, specifically for a potential thymolytic effect. To this end, the test substance was dissolved in peanut oil and administered orally by intubation to young male albino rats, once a day for ten days. Three dosage levels were chosen, to wit 4.3, 13 and 30 mg/kg per day.

The rats in the intermediate and high dosage groups evidenced a significant (dose-dependent) reduction of the weight of the thymus.

The remaining investigations, consisting of spleen and liver weighing and macroscopic inspection of the organs, disclosed no deviations vis-a-vis the controls.

At a dosage of 10 and 25 mg/kg, DOTC brought about a distinct reduction of thymus weight.

MATERIALS AND METHODS

Young male albino rats [ ] were reared under SPF conditions and separated from the dams on Day 24 after parturition and weaning. Thereafter, the offspring were reared under standardized conditions in macrolon cages, five to a group, on a bedding of standardized wood chips, fed Nafag 890 rations and bottled water at will. Ambient temperature was kept at 21 $\pm$ 1°C. Air moisture 60% $\pm$ 5%, light exposure 10 hours per day (7 a.m. to 5 p.m.).

Beginning on Day 25 after birth, and for ten consecutive days, the animals were treated orally once a day by intubation.

Peanut oil was used as a solvent. The quantity of fluid administered in each instance was 0.5 ml per 100 g of body weight. One control group received the solvent only.

There were 15 rats in each dosage group and control group. So-called 'positive controls' were treated with DOTC [ ]

A daily record of the body weight was kept throughout the treatment period. Signs of intolerance to the product were also noted.

On Day 11, that is one day after the last treatment, the rats were dissected, bled, and weighed. The thymus gland, spleen and liver were weighed and major abdominal and pulmonary cavity organs were examined macroscopically.

The raw data relating to body weight and the weight of the organs were compiled as an appendix to this report.

FINDINGS (cf. Table 1 and 2)

In the intermediate and high dosage groups, there was a dose-related significant reduction of the thymus weight as compared to controls.

Similar findings were noted in the 'positive control' group (cf. Table 2). In addition, these animals displayed a reduced rate of weight gain.

TABLE 1.

Group	% weight gain	Weight of organs as a percentage of body weight		
		Thymus	Spleen	Liver
4.3 mg/kg	+ 50.1	0.37	0.35	5.45
13 mg/kg	+ 51.9	0.25*	0.39	5.29
30 mg/kg	+ 51.7	0.11*	0.37	5.42
Controls	+ 52.3	0.38	0.36	5.52

*) Significant reduction compared to controls (one-way t test; $P < 0.01$).

TABLE 2. (Positive controls, DOTC)

Group	% weight gain	Weight of organs as a percentage of body weight		
		Thymus	Spleen	Liver
2.5 mg/kg	+ 50.2	0.36	o.34	5.70
10 mg/kg	+ 48.5	0.20*	0.37	5.64
25 mg/kg	+ 45.0	0.08*	0.29	5.76
Controls	+ 52.3	0.38	0.36	5.52

*) Significant reduction compared to controls (one-way t test, $P < 0.01$).

APPENDIX

Individual readings: Body weight of rats on day of dissection

Weight of thymus gland

Weight of spleen

Weight of liver

[ ]

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MAR 17 1986

[ ]

[Octyltin Ester Mixture]

UNTERSUCHUNGEN ZUR TOXIZITÄT AN

JUNGEN MÄNNLICHEN RATTEN

TOXICOLOGY

MAR 18 1986

[ ]

[ ]

[ ]

[ ]

-2. August 1979 / jc

[ ] TOXIZITÄT AN JUNGEN MÄNNLICHEN RATTEN

Tierspezies:	Ratte, [ ]
Testsubstanz:	[ ] [ ] Interne Produkt-Nr.: [ ]
Positiv-Kontrolle:	Di-n-octylzinn-dichlorid (DOTC) Interne Produkt-Nr.: [ ] Herkunft: Schering AG Charge: 1279/78
Sponsor:	[ ]
Testsystem-Nr.:	[ ]
Projekt-Nr.:	[ ] (Projekt-Nr. Positiv-Kontrolle: [ ].
Art der Verabfolgung:	oral (Metallschlundsonde), einmal täglich
Dosierung (mg/kg/Tag):	Testsubstanz: 4,3 / 13 / 30 DOTC: 2,5 / 10 / 25
Lösungsmittel:	Erdnussöl (Oleum Arachidis, PHH VI, Siegfried)
Beginn der Studie:	26. Juli 1979
Berichterstattung:	22. August 1979

ZUSAMMENFASSUNG UND BEURTEILUNG

Der Organozinnstabilisator [ ] wurde, vergleichend mit DOTC als "Positiv-Kontrolle", auf toxische Wirkungen bei der Ratte geprüft, namentlich unter dem Aspekt eines möglichen thymolytischen Effekts. Hierzu wurde die Testsubstanz in Erdnussöl gelöst und peroral durch Intubation an junge männliche Albinoratten einmal täglich während 10 Tagen verabfolgt. Es kamen folgende drei Dosierungen zur Anwendung: 4,3; 13 und 30 mg/kg/Tag.

Die Ratten der mittleren und hohen Dosisgruppe zeigten eine (dosisabhängige) signifikante Verminderung des Thymusgewichts.

Die übrigen Untersuchungen (Gewicht von Milz und Leber, makroskopische Inspektion der Organe) ergaben keine Abweichungen von der Kontrolle.

DOTC führte in einer Dosierung von 10 bzw. 25 mg/kg zu einer deutlichen Reduktion des Thymusgewichts.

MATERIAL UND METHODE

Junge männliche Albinoratten [ ] wurden unter SPF-Bedingungen aufgezogen und nach der Entwöhnung am 24. Tag post partum von den Muttertieren getrennt. Die Haltung der Jungtiere erfolgte dann unter konventionellen Bedinungen (5er-Gruppen) in den üblichen Makrolonschalen, Einstreu: standardisiertes Holzgranulat, Futter (Nafag Nr. 890) und Wasser (Trinkflaschen) ad libitum. Temperatur im Tierhaltungsraum: 21° C ± 1° C, Luftfeuchtigkeit: 60 % ± 5 %, Beleuchtungsdauer: 10 Std. täglich (07.00-17.00 Uhr).

Die Tiere erhielten während 10 Tagen einmal täglich, beginnend am Tag 25 post partum, die Testsubstanz peroral mit der Schlundsonde verabfolgt.

Als Lösungsmittel diente Erdnussöl. Die verabfolgte Flüssigkeitsmenge betrug jeweils 0,5 ml/100 g Körpergewicht. Eine Kontrollgruppe erhielt nur das Lösungsmittel.

Pro Gruppe (Dosisgruppen und Kontrolle) wurden 15 Ratten angesetzt.

Als "Positiv-Kontrolle" diente DOTC [ ]

Während der Behandlungsperiode wurde täglich das Körpergewicht registriert. Symptome einer Produktunverträglichkeit wurden notiert.

Die Sektion der Ratten erfolgte am 11. Versuchstag, d.h. einen Tag nach der letzten Behandlung. Das Körpergewicht wurde am entbluteten Tier festgestellt und die Gewichte von

Thymus, Milz und Leber wurden bestimmt. Die Hauptorgane von Brust- und Bauchhöhle wurden makroskopisch beurteilt.

Die Rondaten bezüglich Körpergewicht und Organgewichte sind in einem Anhang zum vorliegenden Bericht dargestellt.

BEFUND (vgl. Tabellen 1 und 2)

Dosisabhängig fand sich bei der mittleren und hohen Dosisgruppe eine signifikante Verminderung des Thymusgewichts im Vergleich mit der Kontrolle.

Ein entsprechender Befund wurde für die "Positiv-Kontrolle" (Tabelle 2) erhoben. Hier war überdies eine Reduktion der Körpergewichtszunahme zu verzeichnen.

TABELLE 1

Gruppe	Körpergewichts-zunahme in %	Organgewichte in % Körpergewicht		
		Thymus	Milz	Leber
4,3 mg/kg	+ 50,1	0,37	0,35	5,45
13 mg/kg	+ 51,9	0,25*	0,39	5,29
30 mg/kg	+ 51,7	0,11*	0,37	5,42
Kontrolle	+ 52,3	0,38	0,36	5,52

*Im Vergleich zur Kontrolle signifikant vermindert (t Test, einseitig; $P < 0,01$)

TABELLE 2 ("Positiv-Kontrolle": DOTC)

Gruppe	Körpergewichts-zunahme in %	Organgewichte in % Körpergewicht		
		Thymus	Milz	Leber
2,5 mg/kg	+ 50,2	0,36	0,34	5,70
10 mg/kg	+ 48,5	0,20*	0,37	5,64
25 mg/kg	+ 45,0	0,08*	0,29	5,76
Kontrolle	+ 52,3	0,38	0,36	5,52

*Im Vergleich zur Kontrolle signifikant vermindert (t Test, einseitig, $P < 0,01$)

ANHANG

Einzeldaten: Körpergewicht der Ratten am Sektionstag

Thymusgewicht

Milzgewicht

Lebergewicht

TESTSUBSTANZ :

Dosis (mg/kg/Tag) : 4,3

Körpergewicht (g)	Organgewichte (g) Thymus	Milz	Leber
104.00000	0.42700	0.32300	5.93400
104.00000	0.40700	0.32600	5.37800
106.00000	0.38800	0.35400	6.30800
92.00000	0.13500	0.44000	4.80000
107.00000	0.44500	0.35500	5.69800
112.00000	0.39500	0.39800	6.30800
136.00000	0.50100	0.55900	7.01300
116.00000	0.45200	0.33900	6.82400
143.00000	0.44300	0.43700	8.07000
127.00000	0.47400	0.41300	6.47100
99.00000	0.44000	0.37700	4.88800
113.00000	0.47600	0.37000	5.71200
121.00000	0.46500	0.42900	6.72900
94.00000	0.40000	0.42200	5.39900
108.00000	0.41600	0.32100	6.06700
X-MEAN	X-MEAN	X-MEAN	X-MEAN
VARIANCE	VARIANCE	VARIANCE	VARIANCE
STANDARD DEVIATION	STANDARD DEVIATION	STANDARD DEVIATION	STANDARD DEVIATION
112.13333	0.41793	0.39087	6.10667
211.26667	0.00721	0.00396	0.74067
14.53502	0.08490	0.06292	0.86062
STANDARD ERROR OF X MEAN	STANDARD ERROR OF X MEAN	STANDARD ERROR OF X MEAN	STANDARD ERROR OF X MEAN
3.75292	0.02192	0.01625	0.22221
SUM OF XSQR	SUM OF XSQR	SUM OF XSQR	SUM OF XSQR
SUM OF X	SUM OF X	SUM OF X	SUM OF X
N	N	N	N
1.91566	2.72094	2.34709	569.74010
1632.00000	6.26900	5.86300	91.60000
15.00000	15.00000	15.00000	15.00000

TESTSUBSTANZ :

Dosis (mg/kg/Tag) : 13

Körpergewicht (g)	Organgewichte (g) Thymus	Milz	Leber
108.00000	0.37100	0.51500	5.55900
98.00000	0.32200	0.34000	5.72400
96.00000	0.28100	0.43100	5.74500
98.00000	0.34700	0.36300	5.23000
111.00000	0.35600	0.41200	5.51500
96.00000	0.22400	0.37600	4.59200
117.00000	0.22200	0.38000	5.90300
96.00000	0.17700	0.37600	5.35300
105.00000	0.19300	0.35200	5.54100
102.00000	0.31300	0.43100	5.09700
123.00000	0.15100	0.50700	6.70600
102.00000	0.18400	0.39600	5.44100
92.00000	0.18300	0.34200	4.97800
90.00000	0.20700	0.33500	4.39100
86.00000	0.20500	0.35300	4.56600
X-MEAN	X-MEAN	X-MEAN	X-MEAN
VARIANCE	VARIANCE	VARIANCE	VARIANCE
STANDARD DEVIATION	STANDARD DEVIATION	STANDARD DEVIATION	STANDARD DEVIATION
101.33333	0.24907	0.39393	5.35607
101.80952	0.00557	0.00320	0.34866
10.09007	0.07462	0.05659	0.59048
STANDARD ERROR OF X MEAN	STANDARD ERROR OF X MEAN	STANDARD ERROR OF X MEAN	STANDARD ERROR OF X MEAN
2.60525	0.01927	0.01461	0.15246
SUM OF XSQR	SUM OF XSQR	SUM OF XSQR	SUM OF XSQR
SUM OF X	SUM OF X	SUM OF X	SUM OF X
N	N	N	N
1.55452	1.00846	2.37258	435.19302
1520.00000	3.73600	5.90900	80.34100
15.00000	15.00000	15.00000	15.00000

TESTSUBSTANZ : _____

Dosis (mg/kg/Tag) : 30

Körpergewicht (g)	Organgewichte (g) Thymus	Milz	Leber
84.00000	0.07400	0.22000	4.64900
91.00000	0.12800	0.32000	5.17600
100.00000	0.11900	0.37400	5.97000
101.00000	0.12700	0.41300	5.90300
93.00000	0.12600	0.32600	5.43500
84.00000	0.08300	0.25500	4.06600
93.00000	0.08100	0.40300	4.79800
78.00000	0.08200	0.25500	4.50200
94.00000	0.11000	0.37500	4.73500
68.00000	0.07600	0.26800	3.56200
91.00000	0.08800	0.36000	4.64100
85.00000	0.11300	0.30400	4.45500
78.00000	0.07800	0.28100	4.14700
82.00000	0.07400	0.36400	4.24100
82.00000	0.08500	0.29800	4.44800
X-MEAN	X-MEAN	X-MEAN	X-MEAN
VARIANCE	VARIANCE	VARIANCE	VARIANCE
STANDARD DEVIATION	STANDARD DEVIATION	STANDARD DEVIATION	STANDARD DEVIATION
86.93333	0.09627	0.32107	4.71520
79.49524	0.00045	0.00346	0.44404
8.91601	0.02132	0.05883	0.66636
STANDARD ERROR OF X MEAN	STANDARD ERROR OF X MEAN	STANDARD ERROR OF X MEAN	STANDARD ERROR OF X MEAN
2.30210	0.00551	0.01519	0.17205
SUM OF XSQR	SUM OF XSQR	SUM OF XSQR	SUM OF XSQR
SUM OF X	SUM OF X	SUM OF X	SUM OF X
N	N	N	N
1.14474	0.14537	1.59471	339.71324
1304.00000	1.44400	4.81600	70.72800
15.00000	15.00000	15.00000	15.00000

Versuchsnr.: Lösungsmittel Kontrolle

Dosis (mg/kg/Tag) : –

Körpergewicht (g)	Organgewichte (g) Thymus	Milz	Leber
94.00000	0.35300	0.28700	5.12100
120.00000	0.44000	0.40700	6.46200
103.00000	0.41100	0.38100	6.05600
110.00000	0.35700	0.31900	6.20700
98.00000	0.35800	0.33300	6.38700
115.00000	0.40800	0.36300	5.80200
95.00000	0.35200	0.39400	5.48100
107.00000	0.37600	0.46000	6.16300
110.00000	0.41900	0.39500	5.82500
112.00000	0.40700	0.36000	5.77400
86.00000	0.39000	0.30800	4.79000
104.00000	0.45400	0.34200	5.43100
85.00000	0.34400	0.38800	4.57300
96.00000	0.37300	0.35300	5.12900
106.00000	0.43700	0.41200	5.83100
X-MEAN	X-MEAN	X-MEAN	X-MEAN
VARIANCE	VARIANCE	VARIANCE	VARIANCE
STANDARD DEVIATION	STANDARD DEVIATION	STANDARD DEVIATION	STANDARD DEVIATION
102.73333	0.39193	0.36680	5.66880
104.92381	0.00130	0.00205	0.32605
10.24323	0.03603	0.04524	0.57101
STANDARD ERROR OF X MEAN	STANDARD ERROR OF X MEAN	STANDARD ERROR OF X MEAN	STANDARD ERROR OF X MEAN
2.64479	0.00930	0.01168	0.14743
SUM OF XSQR	SUM OF XSQR	SUM OF XSQR	SUM OF XSQR
SUM OF X	SUM OF X	SUM OF X	SUM OF X
N	N	N	N
1.59781	2.32235	2.04678	486.59407
1541.00000	5.87900	5.50200	85.03200
15.00000	15.00000	15.00000	15.00000

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