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E. I. DU PONT DE NEMOURS & COMPANY

INCORPORATED

WILMINGTON, DELAWARE 19898

LEGAL DEPARTMENT

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August 10, 1992

Document Processing Center (TS-790)
Office of Pollution Prevention and Toxics
Environmental Protection Agency
401 M Street., S.W.
Washington, D.C. 20460
Attn: Section 8(e) Coordinator (CAP Agreement)

Dear Coordinator:

8ECAP-0025

On behalf of the Regulatee and pursuant to Unit II B.1.b. and Unit II C of the 6/28/CAP Agreement, E.I. Du Pont de Nemours and Co. hereby submits (*in triplicate*) the attached studies. Submission of this information is voluntary and is occasioned by unilateral changes in EPA's standard as to what EPA now considers as reportable information. Regulatee's submission of information is made solely in response to the new EPA §8(e) reporting standards and is not an admission: (1) of TSCA violation or liability; (2) that Regulatee's activities with the study compounds reasonably support a conclusion of substantial health or environmental risk or (3) that the studies themselves reasonably support a conclusion of substantial health or environmental risk.

For Regulatee,

Mark H. Christman
Counsel
Legal D-7058
1007 Market Street
Wilmington, DE 19898
(302) 774-6443

3/30/95

ATTACHMENT 1

Submission of information is made under the 6/28/91 CAP Agreement, Unit II. This submission is made voluntarily and is occasioned by recent changes in EPA's TSCA §8(e) reporting standard; such changes made, for the first time in 1991 and 1992 without prior notice and in violation of Regulatee's constitutional due process rights. Regulatee's submission of information under this changed standard is not a waiver of its due process rights; an admission of TSCA violation or liability, or an admission that Regulatee's activities with the study compounds reasonably support a conclusion of substantial risk to health or to the environment. Regulatee has historically relied in good faith upon the 1978 Statement of Interpretation and Enforcement Policy criteria for determining whether study information is reportable under TSCA §8(e), 43 Fed Reg 11110 (March 16, 1978). EPA has not, to date, amended this Statement of Interpretation.

After CAP registration, EPA provided the Regulatee the June 1, 1991 "TSCA Section 8(e) Reporting Guide". This "Guide" has been further amended by EPA, EPA letter, April 10, 1992. EPA has not indicated that the "Reporting Guide" or the April 1992 amendment supersedes the 1978 Statement of Interpretation. The "Reporting Guide" and April 1992 amendment substantively lowers the Statement of Interpretation's TSCA §8(e) reporting standard². This is particularly troublesome as the "Reporting Guide" states criteria, applied retroactively, which expands upon and conflicts with the Statement of Interpretation.³ Absent amendment of the Statement of Interpretation, the informal issuance of the "Reporting Guide" and the April 1992 amendment clouds the appropriate standard by which regulated persons must assess information for purposes of TSCA §8(e).

Throughout the CAP, EPA has mischaracterized the 1991 guidance as reflecting "longstanding" EPA policy concerning the standards by which toxicity information should be reviewed for purposes of §8(e) compliance. Regulatee recognizes that experience with the 1978 Statement of Interpretation may cause a review of its criteri. Regulatee supports and has no objection to the Agency's amending reporting criteria *provided that* such amendment is not applied to the regulated community in an unfair way. However, with the unilateral announcement of the CAP under the auspices of an enforcement proceeding, EPA has wrought a terrific unfairness since much of the criteria EPA has espoused in the June 1991 Reporting Guide and in the Agency's April 2, 1992 amendment is new criteria which does not exist in the 1978 Statement of Interpretation and Enforcement Policy.

²In sharp contrast to the Agency's 1977 and 1978 actions to soliciting public comment on the proposed and final §8(e) Policy, EPA has unilaterally pronounced §8(e) substantive reporting criteria in the 1991 Section 8(e) Guide without public notice and comment, See 42 Fed Reg 45362 (9/9/77), "Notification of Substantial Risk under Section 8(e): Proposed Guidance".

³A comparison of the 1978 Statement of Interpretation and the 1992 "Reporting Guide" is appended.

The following examples of new criteria contained in the "Reporting Guide" that is not contained in the Statement of Interpretation follow:

- even though EPA expressly disclaims each "status report" as being preliminary evaluations that should not be regarded as final EPA policy or intent⁴, the "Reporting Guide" gives the "status reports" great weight as "sound and adequate basis" from which to determine mandatory reporting obligations. ("Guide" at page 20).
- the "Reporting Guide" contains a matrix that establishes new numerical reporting "cutoff" concentrations for acute lethality information ("Guide" at p. 31). Neither this matrix nor the cutoff values therein are contained in the Statement of Interpretation. The regulated community was not made aware of these cutoff values prior to issuance of the "Reporting Guide" in June, 1991.
- the "Reporting Guide" states new specific definitional criteria with which the Agency, for the first time, defines as 'distinguishable neurotoxicological effects'; such criteria/guidance not expressed in the 1978 Statement of Interpretation.⁵

- the "Reporting Guide" provides new review/ reporting criteria for irritation and sensitization studies; such criteria not previously found in the 1978 Statement of Interpretation/Enforcement Policy.
- the "Reporting Guide" publicizes certain EPA Q/A criteria issued to the Monsanto Co. in 1989 which are not in the Statement of Interpretation; have never been published in the Federal Register or distributed by the EPA to the Regulatee. Such Q/A establishes new reporting criteria not previously found in the 1978 Statement of Interpretation/Enforcement Policy.

In discharging its responsibilities, an administrative agency must give the regulated community fair and adequate warning to as what constitutes noncompliance for which penalties may be assessed.

Among the myriad applications of the due process clause is the fundamental principle that statutes and regulations which purport to govern conduct must give an adequate warning of what they command or forbid.... Even a regulation which governs purely economic or commercial activities, if its violation can engender penalties, must be so framed as to provide a constitutionally adequate warning to those whose activities are governed.

⁴The 'status reports' address the significance, if any, of particular information reported to the Agency, rather than stating EPA's interpretation of §8(e) reporting criteria. In the infrequent instances in which the status reports contain discussion of reportability, the analysis is invariably quite limited, without substantial supporting scientific or legal rationale.

⁵ See, e.g. 10/2/91 letter from Du Pont to EPA regarding the definition of 'serious and prolonged effects' as this term may relate to transient anesthetic effects observed at lethal levels; 10/1/91 letter from the American Petroleum Institute to EPA regarding clarification of the Reporting Guide criteria.

Diebold, Inc. v. Marshall, 585 F.2d 1327, 1335-36 (D.C. Cir. 1978). See also, Rollins Environmental Services (NJ) Inc. v. U.S. Environmental Protection Agency, 937 F. 2d 649 (D.C. Cir. 1991).

While neither the are rules, This principle has been applied to hold that agency 'clarification', such as the Statement of Interpretation, the "Reporting Guide" nor the April 1992 amendments will not applied retroactively.

...a federal court will not retroactively apply an unforeseeable interpretation of an administrative regulation to the detriment of a regulated party on the theory that the post hoc interpretation asserted by the Agency is generally consistent with the policies underlying the Agency's regulatory program, when the semantic meaning of the regulations, as previously drafted and construed by the appropriate agency, does not support the interpretation which that agency urges upon the court.

Standard Oil Co. v. Federal Energy Administration, 453 F. Supp. 203, 240 (N.D. Ohio 1978), aff'd sub nom. Standard Oil Co. v. Department of Energy, 596 F.2d 1029 (Em. App. 1978):

The 1978 Statement of Interpretation does not provide adequate notice of, and indeed conflicts with, the Agency's current position at §8(e) requires reporting of all 'positive' toxicological findings without regard to an assessment of their relevance to human health. In accordance with the statute, EPA's 1978 Statement of Interpretation requires the regulated community to use scientific judgment to evaluate the significance of toxicological findings and to determining whether they reasonably support a conclusion of a substantial risk. Part V of the Statement of Interpretation urges persons to consider "the fact or probability" of an effect's occurrence. Similarly, the 1978 Statement of Interpretation stresses that an animal study is reportable only when "it contains reliable evidence ascribing the effect to the chemical." 43 Fed Reg. at 11112. Moreover, EPA's Statement of Interpretation defines the substantiality of risk as a function of both the seriousness of the effect and the probability of its occurrence. 43 Fed Reg 11110 (1978). Earlier Agency interpretation also emphasized the "substantial" nature of a §8(e) determination. See 42 Fed Reg 45362, 45363 (1977). [Section 8(e) findings require "extraordinary exposure to a chemical substance...which critically imperil human health or the environment"].

The recently issued "Reporting Guide" and April 1992 Amendment guidance requires reporting beyond and inconsistent with that required by the Statement of Interpretation. Given the statute and the Statement of Interpretation's explicit focus on substantial human or environmental risk, whether a substance poses a "substantial risk" of injury requires the application of scientific judgment to the available data on a case-by-case basis.

If an overall weight-of-evidence analysis indicates that this classification is unwarranted, reporting should be unnecessary under §8(e) because the available data will not "reasonably support the conclusion" that the

chemical presents a substantial risk of serious adverse consequences to human health.

Neither the legislative history of §8(e) nor the plain meaning of the statute support EPA's recent lowering of the reporting threshold that TSCA §8(e) was intended to be a sweeping information gathering mechanism. In introducing the new version of the toxic substances legislation, Representative Eckhart included for the record discussion of the specific changes from the version of H. R. 10318 reported by the Consumer Protection and Finance Subcommittee in December 1975. One of these changes was to modify the standard for reporting under §8(e). The standard in the House version was changed from "causes or contributes to an unreasonable risk" to "causes or significantly contributes to a substantial risk". This particular change was one of several made in TSCA §8 to avoid placing an undue burden on the regulated community. The final changes to focus the scope of Section 8(e) were made in the version reported by the Conference Committee.

The word "substantial" means "considerable in importance, value, degree, amount or extent". Therefore, as generally understood, a "substantial risk" is one which will affect a considerable number of people or portion of the environment, will cause serious injury and is based on reasonably sound scientific analysis or data. Support for the interpretation can be found in a similar provision in the Consumer Product Safety Act. Section 15 of the CPSA defines a "substantial product hazard" to be:

"a product defect which because of the pattern of defect, the number of defective products distributed in commerce, the severity of the risk, or otherwise, creates a substantial risk of injury to the public."

Similarly, EPA has interpreted the word 'substantial' as a quantitative measurement. Thus, a 'substantial risk' is a risk that can be quantified, *See*, 56 Fed Reg 32292, 32297 (7/15/91). Finally, since information pertinent to the exposure of humans or the environment to chemical substances or mixtures may be obtained by EPA through Sections 8(a) and 8(d) regardless of the degree of potential risk, §8(e) has specialized function. Consequently, information subject to §8(e) reporting should be of a type which would lead a reasonable man to conclude that some type action was required immediately to prevent injury to health or the environment.

APPENDIX

Comparison: Criteria found in the 1978 "Statement of Interpretation/ Enforcement Policy", 43 Fed Reg 11110 (3/16/78) and the June 1991 Section 8(e) Guide.

<u>TOXICITY TEST TYPE</u>	<u>1978 POLICY CRITERIA EXIST?</u>	<u>New 1991 GUIDE CRITERIA EXIST?</u>
ACUTE LETHALITY		
Oral	N)	Y)
Dermal	N)	Y)
Inhalation (Vapors)) ¹) ²
aerosol	N)	Y)
dusts/ particles	N)	Y)
SKIN IRRITATION	N	Y ³
SKIN SENSITIZATION	N	Y ⁴
EYE IRRITATION	N	Y ⁵
SUBCHRONIC (ORAL/DERMAL/INHALATION)	N	Y ⁶
REPRODUCTION STUDY	N	Y ⁷
DEVELOPMENTAL TOX	Y ⁸	Y ⁹

¹43 Fed Reg at 11114, comment 14:

"This policy statements directs the reporting of specified effects when unknown to the Administrator. Many routine tests are based on a knowledge of toxicity associated with a chemical unknown effects occurring during such a range test may have to be reported if they are those of concern tot he Agency and if the information meets the criteria set forth in Parts V and VII."

²Guide at pp.22, 29-31.

³Guide at pp-34-36.

⁴Guide at pp-34-36.

⁵Guide at pp-34-36.

⁶Guide at pp-22; 36-37.

⁷Guide at pp-22

⁸43 Fed Reg at 11112

Only the term "Birth Defects" is listed.

NEUROTOXICITY	N	Y ¹⁰
CARCINOGENICITY	Y ¹¹	Y ¹²
MUTAGENICITY		
<i>In Vitro</i>	Y ¹³	Y ¹⁴
<i>In Vivo</i>	Y	Y
ENVIRONMENTAL		
Bioaccumulation	Y	N
Bioconcentration	Y ¹⁵	N
Oct/water Part. Coeff.	Y	N
Acute Fish	N	N
Acute Daphnia	N	N
Subchronic Fish	N	N
Subchronic Daphnia	N	N
Chronic Fish	N	N
AVIAN		
Acute	N	N
Reproductive	N	N
Reproductive	N	N

⁹Guide at pp-2122. Includes new detailed criteria regarding statistical treatment, specific observations and the §8(e)-significance of maternal toxicity.

¹⁰Guide at pp-23; 33-34.

¹¹43 Fed Reg at 11112

Only the term "Cancer" listed.

¹²Guide at pp-21. Includes new criteria regarding biological significance and statistical treatment.

¹³43 Fed Reg at 11112; 11115 at Comment 15

"Mutagenicity" listed/ *in vivo* vs *invitro* discussed; discussion of "Ames test".

¹⁴Guide at pp-23.

¹⁵43 Fed Reg at 11112; 11115 at Comment 16.

Attachment 2

Study Summary and Report

CAS #5593-70-4

Chem: 1, Butanol, titanium (4+) salt

Title: Approximate Lethal Dose (ALD) of tetrabutyl titanate in Rats

Date: 4-22-85

Summary of Effects: Ataxia

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cc: K. D. Dastur (1)
J. C. Watts (1)
R. A. Halling (1)

E. I. du Pont de Nemours and Co., Inc.
Haskell Laboratory for Toxicology and Industrial Medicine
Elkton Road, P. O. Box 50,
Newark, Delaware 19714

HASKELL LABORATORY REPORT NO. 106-85 MR NO. 7317-001

<u>Material Tested</u>	<u>Haskell No.</u>
1-Butanol, titanium(4+) salt	15,538

8072 7004

APPROXIMATE LETHAL DOSE (ALD) OF TETRABUTYL TITANATE IN RATS

SUMMARY

Tetrabutyl titanate (95-100% pure) was administered as a single oral dose by intragastric intubation to male rats. Under the conditions of this test the ALD was greater than 25,000 mg/kg of body weight, which was the maximum practical dose. Clinical signs of toxicity were observed in dosed animals. No deaths were observed. This material is considered to have very low toxicity when administered as a single oral dose (i.e., ALD greater than 5,000 mg/kg).

INTRODUCTION

The purpose of this test was to determine an approximate lethal dose of tetrabutyl titanate when administered as a single oral dose. The ALD was defined as the lowest dose administered which caused death either on the day of dosing or within 14 days post exposure.

MATERIALS AND METHODS

A. Animal Husbandry

Male, 7-week old, Crl:CD®(SD)BR rats were received from Charles River Breeding Laboratories, Kingston, NY. Rats were housed singly in

suspended, stainless steel, wire-mesh cages. Each rat was assigned a unique identification number which was recorded on a card affixed to the cage. Purina Certified Rodent Chow® #5002 and water were available ad libitum. Rats were quarantined, weighed, and observed for general health for approximately one week prior to testing. Animal rooms were maintained on a timer-controlled, 12 hour/12 hour light/dark cycle; temperatures ranged from 23-25°C and relative humidity from 31-65%.

B. Protocol

The test material as a suspension in Mazola® corn oil was administered to one rat per dose level by intragastric intubation. Dose levels administered ranged from 2,250 to 25,000 mg/kg in increments of approximately 50%. Additionally, one rat was dosed at 690 mg/kg. The dosing day was considered to be day 1; postexposure day 14 was test day 15. Following administration of the dose, rats were observed for clinical signs of toxicity. Surviving rats were weighed and observed daily until signs of toxicity subsided, and then at least every other day (weekends and holidays excluded) throughout the 14-day recovery period.

C. Test Material

Physical Form:	Yellow liquid
Purity:	95-100%
Composition:	25 Wt% Tetrabutyl titanate 75 Wt% Kerosene
Contaminants:	Possibly 0-5% 1-butanol
Synonyms:	Tetrabutyl titanate
Other Codes:	TLF-6171 Lot 1
CAS Registry No.:	5593-70-4
Stability:	The test material was assumed to be stable under the conditions of administration.
Submitted By:	Robert A. Halling Chemical and Pigments Department Jackson Laboratory

D. Records Retention

All raw data and the final report will be stored in the archives of Haskell Laboratory for Toxicology and Industrial Medicine, E. I. du Pont de Nemours and Co., Newark, Delaware or in the Du Pont Hall of Records, Wilmington, Delaware.

RESULTS

A. Dosage and Mortality Data

The dosage regimen and the mortality resulting over the 15-day test period are detailed below. There were no mortalities associated with any of the doses given.

<u>Dose (mg/kg)</u>	<u>Dose (mL)</u>	<u>Suspension Concentration (mg/kg)</u>	<u>Initial Body Weight (g)</u>	<u>Mortality</u>
690	1.1	150	240	no
2,250	3.9	150	260	no
3,500	1.4	600	243	no
4,900	2.2	600	269	no
7,500	3.2	600	256	no
11,000	4.8	600	263	no
17,000	6.7*	600	237	no
25,000	9.4*	600	225	no

* Administered in two portions, 15 minutes apart.

B. Clinical Signs

Slight to severe body weight losses (i.e., 1-12% of body weight) were observed for 1-3 days after dosing, followed by normal weight gain. Clinical signs included lethargy, wet and/or yellow stained perineum, low posture, ataxia, limpness, clear discharge from the eyes, lung noise, salivation and dry red discharge from the nose or mouth.

CONCLUSION

Under the conditions of this study, the ALD for tetrabutyl titanate was greater than 25,000 mg/kg of body weight, which was the maximum practical dose. This material is considered to have very low toxicity when administered in single oral doses (i.e., ALD greater than 5,000 mg/kg).

Work and Report By:

Calvin N. Wylie
Calvin N. Wylie
Technician

Study Director:

David B. Warheit 4/15/85
David B. Warheit, Ph.D.
Research Toxicologist

Approved By:

Nancy C. Chromey 4/22/85
Nancy C. Chromey, Ph.D.
Section Supervisor,
Acute Investigations Section

CNW:DBW:cgs

Date Issued: APRIL 22, 1985

Study Initiated/Completed: 11/29/84-1/28/85

Notebook: E-35964, pp. 83-89

Haskell Laboratory Report No. 106-85

Number of pages in this report: 4

Triage of 8(e) Submissions

Date sent to triage: 2/5/96

NON-CAP

CAP

Submission number: 12337A

TSCA Inventory:

Y N D

Study type (circle appropriate):

Group 1 - Dick Clements (1 copy total)

ECO AQUATO

Group 2 - Ernie Falke (1 copy total)

ATOX SBTOX SEN w/NEUR

Group 3 - Elizabeth Margosches (1 copy each)

STOX CTOX EPI RTOX GTOX
STOX/ONCO CTOX/ONCO IMMUNO CYTO NEUR

Other (FATE, EXPO, MET, etc.): _____

Notes:

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entire document: 0 1 2 pages 1/1st TAB pages [REDACTED]

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CECATS/TRADE TRACKING DBASE ENTRY FORM

CECATS DATA: 123337 SEQ. A

TYPE/INT. SUPP. FLWP

SUBMITTER NAME: Dupont

Company

DATE: 03/27/92

OTO DATE: 10/27/92

CSRAD DATE: 03/30/95

CHEMICAL NAME:

CAE

5593-70-4

- OPTIONAL ACTIONS**
- 0401 NOT ACTIVE (PORT 1)
 - 0402 STUDIES PLANNED (IND. HWAY)
 - 0403 PARTICIPATION IN WORK (IND. HWAY)
 - 0404 LARGE AMOUNTS (TRANS. S)
 - 0405 PROCEEDING (IND. TRANS. S)
 - 0406 APPROUSE DISCONTINUED
 - 0407 PRODUCTION DISCONTINUED
 - 0408 CONFIDENTIAL

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INFORMATION TYPE	P F C	INFORMATION TYPE	P F C	INFORMATION TYPE	P F C
0101 ONCO (HUMAN)	01 02 04	0216 SPECIES	01 02 04	0241 DRUGS (ANIMAL)	01 02 04
0102 ONCO (ANIMAL)	01 02 04	0217 HUMAN EXPOS (PROG CONTAM)	01 02 04	0242 DRUGS (HUMAN)	01 02 04
0103 CELL TRANS (IN VITRO)	01 02 04	0218 HUMAN EXPOS (ACCIDENTAL)	01 02 04	0243 CHEM/YS PROP	01 02 04
0104 MUTA (IN VITRO)	01 02 04	0219 HUMAN EXPOS (MONITORING)	01 02 04	0244 CLASTO (IN VITRO)	01 02 04
0105 MUTA (IN VIVO)	01 02 04	0220 ECOTOXIC TOX	01 02 04	0245 CLASTO (ANIMAL)	01 02 04
0106 REPRODUCTION (HUMAN)	01 02 04	0221 ENV. OCCURRENCE	01 02 04	0246 CLASTO (HUMAN)	01 02 04
0107 REPRODUCTION (ANIMAL)	01 02 04	0222 ENV. SOIL OF ENV CONTAM	01 02 04	0247 DNA DAMAGE/REPAIR	01 02 04
0108 NEURO (HUMAN)	01 02 04	0223 ENV. SOURCE REQUEST DELAY	01 02 04	0248 PRODUCE/PROC	01 02 04
0109 NEURO (ANIMAL)	01 02 04	0224 FUNDING/NUMBER 12	01 02 04	0249 MSDS	01 02 04
0110 ACUTE TOX (HUMAN)	01 02 04	0225 REPORTING RATIONALE	01 02 04	0250 OTHER	01 02 04
0111 CHL TOX (HUMAN)	01 02 04	0226 CONFIDENTIAL	01 02 04		
0112 ACUTE TOX (ANIMAL)	01 02 04	0227 ALLERGIC TOXICANT	01 02 04		
0113 SUB ACUTE TOX (ANIMAL)	01 02 04	0228 ALLERGIC ANIMAL	01 02 04		
0114 SUB CHRONIC TOX (ANIMAL)	01 02 04	0229 METABOLISM/ACC (ANIMAL)	01 02 04		
0115 CHRONIC TOX (ANIMAL)	01 02 04	0230 METAPHARMACO (HUMAN)	01 02 04		

TOXICITY	NON-ORAL/INHALATORY	REVIEW	SPECIES	TOXICOLOGICAL CONCERN	USE	PRODUCTION
CAS SR	YES	YES (DROPPABLE)	RAT	LOW Acute Oral Toxicity		
	NO	NO (CONTINUE)		MED		
	IN FORMING	RE-PA		HIGH		

UNCLASSIFIED

#12337A

L

Acute oral toxicity is of low concern based on no mortality in rats (1/group) exposed to doses of 690, 2250, 3500, 4900, 7500, 11000, 17000 and 25000 mg/kg. Clinical signs included lethargy, low posture, ataxia, limpness, lung noises and slight to severe weight loss (doses not reported).