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October 15, 1992

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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 6/28/91 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.

The "Reporting Guide" creates new TSCA 8(e) reporting criteria which were not previously announced by EPA in its 1978 Statement of Interpretation and Enforcement Policy, 43 Fed Reg 11110 (March 16, 1978). The "Reporting Guide states criteria which expands upon and conflicts with the 1978 Statement of Interpretation. Absent amendment of the Statement of Interpretation, the informal issuance of the "Reporting Guide" raises significant due processes issues and clouds the appropriate reporting standard by which regulated persons can assure TSCA Section 8(e) compliance.

For Regulatee,

Mark H. Christman
Counsel
Legal D-7158
1007 Market Street
Wilmington, DE 19898
(302) 774-6443

3/29/95

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).

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.

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 OCM 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.

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

- o 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).
- o 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.
- o 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;
- o 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.
- o 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.

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.

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.

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.

Attachment

Comparison:

Reporting triggers 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>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)	} ⁶	} ⁷
aerosol	N}	Y}
dusts/ particles	N}	Y}
SKIN IRRITATION	N	Y ⁸
SKIN SENSITIZATION (ANIMALS)	N	Y ⁹
EYE IRRITATION	N	Y ¹⁰
SUBCHRONIC (ORAL/DERMAL/INHALATION)	N	Y ¹¹
REPRODUCTION STUDY	N	Y ¹²
DEVELOPMENTAL TOX	Y ¹³	Y ¹⁴

⁶43 Fed Reg at 11114, comment 14:

"This policy statements directs the reporting of specific 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 to the Agency and if the information meets the criteria set forth in Parts V and VII."

⁷Guide at pp.22, 29-31.

⁸Guide at pp-34-36.

⁹Guide at pp-34-36.

¹⁰Guide at pp-34-36.

¹¹Guide at pp-22; 36-37.

¹²Guide at pp-22

¹³43 Fed Reg at 11112

"Birth Defects" listed.

¹⁴Guide at pp-22

NEUROTOXICITY	N	Y ¹⁵
CARCINOGENICITY	Y ¹⁶	Y ¹⁷
MUTAGENICITY		
<i>In Vitro</i>	Y ¹⁸	Y ¹⁹
<i>In Vivo</i>	Y	Y
ENVIRONMENTAL		
Bioaccumulation	Y}	N
Bioconcentration	Y ²⁰	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

¹⁵Guide at pp-23; 33-34.

¹⁶43 Fed Reg at 11112
"Cancer" listed

¹⁷Guide at pp-21.

¹⁸43 Fed Reg at 11112; 11115 at Comment 15
"Mutagenicity" listed/ *in vivo* vs *invitro* discussed; discussion of "Ames test".

¹⁹Guide at pp-23.

²⁰43 Fed Reg at 11112; 11115 at Comment 16.

CAS #21232-47-3

Chem: 3,3',4,4'-tetrachloroazobenzene

Title Approximate Lethal Concentration (ALC)

Date: 7/30/76

Summary of Effects: ALC 0.92 mg/L

Copies to: C. W. Maynard, Jr. (6)
M. H. Krackov (1)

E. I. du Pont de Nemours and Company
Haskell Laboratory for Toxicology and Industrial Medicine

HASKELL LABORATORY REPORT NO. 529-76 MR NO. 2320-001

<u>Test Material</u>	<u>Haskell No.</u>	<u>Other Codes</u>	<u>Sample Ready for Testing</u>	<u>Submitted by</u>
3,3',4,4'-Tetrachloroazobenzene	9731	TCAB	6-18-76	M. H. Krackov, Organic Chemicals Department, Chambers Works.

APPROXIMATE LETHAL CONCENTRATION (ALC)

Introduction: In the distillation of 3,4-dichloroaniline (3,4-DCA) at Chambers Works, a tarry by-product is produced containing a small amount of TCAB. Although the toxicity of TCAB is low on an acute dermal absorption basis, repeated dermal exposure results in cumulative toxicity and chloracne (Part I of MR-2320, report forthcoming).

In order to establish proper handling procedures for such materials, the following acute inhalation toxicity study on TCAB was conducted.

Generation Procedure and Test Design: A one-liter, round-bottom flask containing TCAB was placed in a Glas-Cob heating mantle and the top portion wrapped with insulating material. A glass delivery arm (1" in diameter), wrapped with wetting tape connected the flask to the top of a 20-liter cylindrical (12" diameter) exposure chamber. The flask and delivery arm were heated to temperatures of 300 to 340°C and 210 to 280°C, respectively (depending on exposure concentration), and monitored by thermocouples attached to their surfaces. House-line air was then passed through the flask and delivery arm carrying volatilized TCAB into the top of the exposure chamber where a baffle dispersed the incoming atmosphere. Concentration control was achieved by varying the ratio of dilution to generation air or by changing generation apparatus temperatures. Lastly, the chamber atmosphere was vacuum exhausted from the bottom of the chamber for scrubbing.

Exposures were conducted on test groups of six male C57-CD rats of initial body weight between 240 and 270 grams. Each exposure was four hours in duration, followed by a 14-day recovery period after which the remaining rats were sacrificed.

Analytical Method: A Du Pont Instruments 830 High Pressure Liquid Chromatograph was employed for sample analysis. Liquid samples were obtained by scrubbing the chamber atmosphere through fritted glass midget impingers, using n-heptane as the trapping solvent. Injections were made by use of a 10 μ l sample loop into a 2' x 1/4" Permaphase® ETH column with n-heptane as the mobile phase. Standards were prepared with 99.5% TCAB in n-heptane.

Results: As with the "Still Heel Tars" exposures (HIR No. 528-76), the atmosphere resulting from this type of generation consisted of a fine particulate cloud which, in this case, turned out to be pure TCAB by analysis. The results are presented below:

<u>TWA Concentration</u> <u>(mg TCAB/l Air)</u>	<u>Standard Deviation</u> <u>(mg TCAB/l Air)</u>	<u>Fractional Mortality</u> <u>(No. Deaths/No. Exposed)</u>
0.59	0.24	0/6
0.88	0.23	0/6
0.92	0.38	6/6
0.97	0.27	2/6

Clinical signs observed were limited to respiratory effects ranging from labored respiration to gasping. Buildup of the fine yellow particulate was observed, especially around the rat nostrils.

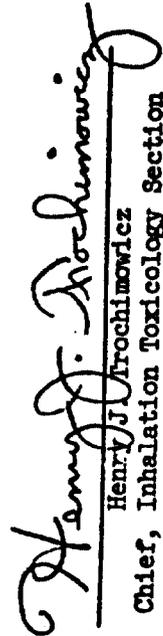
Gross pathologic examination revealed white plaques, red focal spots and edema of the lungs. In addition, the lungs were slightly heavy, probably due to yellow particulate observed in the trachea and lungs.

Summary: The acute inhalation toxicity of TCAB was investigated in four-hour exposures using male Chr-CD rats. Under these experimental conditions, the Approximate Lethal Concentration (AIC) for TCAB was 0.92 mg/liter.

Report by:


Bruce A. Burgess
Assistant Toxicologist

Approved by:


Henry J. Trochimowicz
Chief, Inhalation Toxicology Section

BAE/aph

N.B. E-9126, page 60

Report No. 529-76

Date Issued: July 30, 1976

Triage of 8(e) Submissions

Date sent to triage: 2/5/96

NON-CAP

CAP

Submission number: 12325 A

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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CHC/ATS/RIAGE TRACKING DBASE ENTRY FORM

CONTACT NO. 014-11035 SEQ. 2

TYPE INT. SUPP. FLWP

SUBMITTER NAME: Amgen

Amgen, Inc. Comp IV

IND. DATE: 10/28/92

OTB DATE: 10/28/92

CSRAD DATE: 08/29/95

Chemical Name

Amgen, Inc. Comp IV

Case

21232-47-3

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INFORMATION CODE	P.F.C.	DESCRIPTION	P.F.C.	INFORMATION TYPE	P.F.C.
0001	01 02 04	ONCO (HUMAN)	0006	TOXICITY	01 02 04
0002	01 02 04	ONCO (ANIMAL)	0007	HUMAN EXPOS (REGO CONTAM)	01 02 04
0003	01 02 04	CHL. TRIPS (IN VITRO)	0008	HUMAN EXPOS (ACCIDENTAL)	01 02 04
0004	01 02 04	DATA (IN VITRO)	0009	HUMAN EXPOS (MONITORING)	01 02 04
0005	01 02 04	DATA (IN VIVO)	0010	TOXICOLOGY	01 02 04
0006	01 02 04	REPRODUCTION (HUMAN)	0011	ENV. OCCURRENCE	01 02 04
0007	01 02 04	REPRODUCTION (ANIMAL)	0012	RISK ENCL OF ENV CONTAM	01 02 04
0008	01 02 04	NEURO (HUMAN)	0013	ELECTRIC SIGNAL RELAY	01 02 04
0009	01 02 04	NEURO (ANIMAL)	0014	PRODUCTION RATIONALE	01 02 04
0010	01 02 04	ACUTE TOX (HUMAN)	0015	PRODUCTION RATIONALE	01 02 04
0011	01 02 04	ACUTE TOX (ANIMAL)	0016	COX - INITIAL	01 02 04
0012	01 02 04	SUB ACUTE TOX (HUMAN)	0017	ALLERGIC REACT	01 02 04
0013	01 02 04	SUB ACUTE TOX (ANIMAL)	0018	ALLERG (ANIMAL)	01 02 04
0014	01 02 04	SUB CHRONIC TOX (ANIMAL)	0019	METAPHARMACO (ANIMAL)	01 02 04
0015	01 02 04	CHRONIC TOX (ANIMAL)	0020	METAPHARMACO (HUMAN)	01 02 04

- NON-INITIAL ACTIONS
- 0001 ACTION NOT FOR IT D
 - 0002 VIEWS PLANNED (SINCE 01/91)
 - 0003 INITIATION OF WORK (SINCE 01/91)
 - 0004 LABEL ASSESS (SINCE 01/91)
 - 0005 PROFESSIONAL INFO CHANGE S
 - 0006 APPROVE DISCONTINUED
 - 0007 PRODUCTION DISCONTINUED
 - 0008 CONFIDENTIAL

REGISTRATION	RESEARCH/DEVELOPMENT	CONFORMS TO GMP	STATUS	TOXICOLOGICAL CONCERN	USE	PRODUCTION
CAS SR	YES	YES (DROPH/REFFA)	RAT	LOW		
	NO	NO (CONTINUE)		MED Acute Inhalation Toxicity		
	IN TRAINING	REFFA		HIGH		

#12335A

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Acute inhalation toxicity is of medium concern based on an approximate lethal concentration of 0.92 g/m^3 in rats exposed for 4 hours. Mortality and corresponding doses (g/m^3) were 0/6 (0.59, 0.88), 6/6 (0.92) and 2/6 (0.97). Clinical signs included breathing abnormalities; pathological examination revealed white plaques, red focal spots and edema of the lungs.