



E. I. DU PONT DE NEMOURS & COMPANY
INCORPORATED
WILMINGTON, DELAWARE 19898

8EHQ-0992-13174
Contains No CBI

92 SEP 22 AM 9:57

19

LEGAL DEPARTMENT

8EHQ-92-13174
INIT
88920010977

No CBI

**Certified Mail
Return Receipt Requested**

(A)

September 11, 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 6/28/91 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.

COPY
8E CAP

For Regulatee,

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

3/24/95

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*.

TEST TYPE	1978 POLICY CRITERIA EXIST?	New 1991 GUIDE CRITERIA EXIST?
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 *in vitro* discussed; discussion of "Ames test".

¹⁹Guide at pp-23.

²⁰43 Fed Reg at 11112; 11115 at Comment 16.

CAS #92-36-4

Chem: Benzothiazole,2-(4-aminophenyl)-6-methyl

Title: Subacute Inhalation Toxicity Study in Rats

Date: January 18, 1980

Summary of Effects: compound related effects in liver, spleen and kidneys;
liver effects were not reversible during 14 day recovery period.

Copies to: S. N. Boye (2)
 W. H. Darnell (1)
 J. C. Watts (1)
 J. L. Riggs (1)
 R. N. Dion (1)
 J. F. Schwantes (1)

E. I. du Pont de Nemours and Company
 Haskell Laboratory for Toxicology and Industrial Medicine
 Elkton Road, Newark, Delaware 19711

HASKELL LABORATORY REPORT NO. 838-79

MR NO. 2992-001

Material Tested	Haskell No.	Other Codes	Study Initiated/ Completed	Material Submitted by
Benzothiazole, 2-(4-amino-phenyl)-6-methyl-	12,325	1932C2-2000 Charge No. 697	10/23/78-11/17/78	J. P. Schwantes Chemicals, Dyes & Pigments Dept. Chambers Works

SUBACUTE INHALATION TOXICITY STUDY IN RATS

4

Introduction: This experiment was conducted to investigate the subacute inhalation toxicity of Benzothiazole, 2-(4-amino-phenyl)-6-methyl- (DHPT). The Approximate Lethal Concentration was 3.00 mg/l (HLR 719-78). Design levels were 0.0 and 0.6 mg/l DHPT.

Procedure: Twenty Chr-CD₁ male rats (250-300 grams) were placed in 20-liter battery jars designed as test chambers. The test material was weighed (40-50 grams) and placed in a three-neck heated Instatherm flask and heated to a maximum of 260°C. Nitrogen (3.5 liters/minute) was passed through the flask to blow vapors into the exposure chamber. The test chamber temperature was maintained at $\leq 28^{\circ}\text{C}$ and the oxygen concentration was maintained at $\sim 20\%$. Chamber samples were collected on Gelman glass fiber filters at ~ 20 -30 minute intervals. Any particulate or vapor that passed through the filters was trapped in midjet impingers filled with acetone that were placed in the sampling line behind the filters. Test material collected in the filters was weighed and test material in the impinger was analyzed by gas chromatography (FID-6' glass column, 1/4 CD filled with 10% SE-30 on 60/80 W-HWDMCS). The values for the two analytical methods were combined to give chamber concentration results. Results are given as a Time-Weighted Average (TWA) for the 6-hour exposures. A Brinks cascade impactor was used to determine the mass median diameter of particles generated. The rats (10 each at 0 and 0.6 mg/l desior. were subjected to 10 6-hour exposures over a 2-week period. After 10 exposures, half of each group was examined pathologically; the remaining half was allowed a 14-day recovery period and was examined pathologically. Urine analysis was conducted on 5 rats from each exposure level after 9 exposures and on all remaining rats after 14-days recovery. Hematology and clinical blood chemistry examinations were conducted on the same rats from each group. All rats were weighed and observed daily (except weekends) during the exposure and recovery period. Food and water were available ad libitum at all times other than during actual exposure.

Analytical Summary Table

Exposure No.	TWA DHPT Concentration, Range (mg/l)		Mass Median Particle Diameter (u)		Clinical Observations
	0.55,	0.14-1.41	7.0		
1	0.38,	0.15-0.59	>10		During exposure, rats showed salivation, pawing and chewing motions, lacrimation, sporadic cases of closing of the eyes, fasciculations, rapid respiration and red nasal discharge. Clinical signs for the 14-day recovery period were similar.
2	0.55,	0.02-0.85	7.2		
3	0.58,	0.30-0.81	>10		
4	0.63,	0.01-1.13	4.0		
5	0.70,	0.35-1.01	8.0		
6	0.82,	0.62-1.32	9.0		
7	0.84,	0.06-1.11	9.0		
8	0.91,	0.55-1.42	6.2		
9	0.84,	0.35-1.12	1.8		
10					
Average =	0.68 mg/l		7.2 u		

DHPT-exposed rats showed a loss of body weight during the exposure period (Figure 1). Exposed rats showed normal weight gain during recovery; however, their final body weights were 10% less than those of the controls.

Clinical Pathology: The clinical laboratory measurements on samples of blood and urine from rats exposed ten times to DHPT suggested a hemolytic anemia and injury to the liver and kidneys. Recovery to normal was not complete after 14 days recovery. (Detailed report, Appendix A.)

Organ/Body Weight Evaluations: After 0 recovery days the test rats had mean absolute and relative organ weights that were significantly different from the control group; these differences were likely related to severe weight loss. After 14 recovery days, the test rats showed mean absolute spleen weight and mean relative spleen, testis, and liver weights that were significantly larger than controls. (Appendix B)

Pathology: There was a compound-related effect detected in the livers, spleens and kidneys of the rats exposed to DHPT. The effects in the livers appeared not to be reversible. (Detailed Report, Appendix C.)

Summary: Groups of 10 male rats inhaled atmospheric concentrations of either 0 or 0.6 mg/l of Benzothiazole, 2-(4-aminophenyl)-6-methyl- (DHPT) for 10 6-hour exposures over a 2-week period.

DHPT-exposed rats showed a loss of body weight during the exposure period. Exposed rats showed normal weight gain during recovery; however, their final body weights were 10% less than those of the controls.

BEST COPY AVAILABLE

The clinical laboratory measurements on samples of blood and urine from rats exposed ten times to DHPF suggested a hemolytic anemia and injury to the liver and kidneys. Recovery to normal was not complete after 14 days recovery.

There was a compound-related effect detected in the livers, spleens and kidneys of the rats exposed to DHPF. The effects in the livers appeared not to be reversible.

* Synonym: DHPF

Other Name: Dehydrothio-p-Toluidine

Report by:

Faye F. Watson
Faye F. Watson
Technician

Approved by:

Geyald L. Kennedy
Geyald L. Kennedy
Chief, Acute Investigations Section

FFW:vlm

Date Issued: January 18, 1980

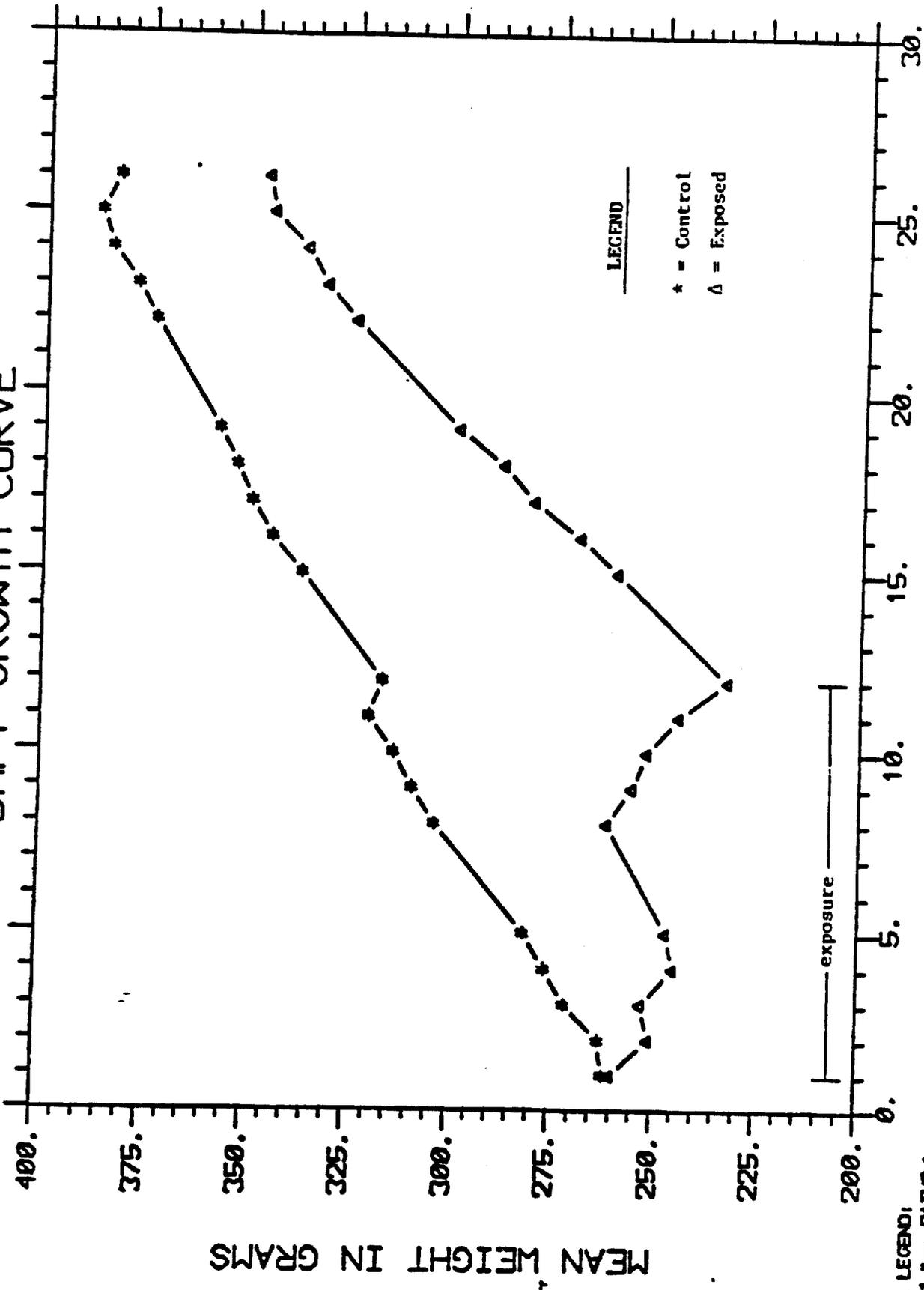
N.B. E-18670, p. 74-123

Report No. 838-79



FIG. 1

DHPT GROWTH CURVE



MEAN WEIGHT IN GRAMS

FILE LEGEND:
PATH1 *— PATH2 ▲—

— exposure —

DAYS ON TEST

APPENDIX A

SUBACUTE INHALATION TOXICITY STUDY IN RATS
EXPOSED TO DEHYDROTHIO-p-TOLUIDINE (DHPT)

Medical Research Project No. 2992

Haskell No. 12325

Clinical Pathology Report

January 12, 1979

Procedure:

Blood was taken from two groups of ten male rats for hematologic and clinical chemistry measurements. One group was exposed to 0.60 mg/L dehydrothio-p-toluidine (DHPT) for ten times while the remaining group was unexposed and served as controls. Overnight urine samples were collected from both groups for examination after the ninth exposure. Five animals from each group were sacrificed for pathology after the tenth exposure. The remaining animals were sampled after a recovery period of 14 days.

The examination of the blood and urine included the following:

Hematology - Erythrocyte count (RBC), hemoglobin (Hb), hematocrit (Hc), total leukocyte count (WBC) and differential leukocyte count. The indices, mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), and mean corpuscular hemoglobin concentration (MCHC) were calculated from these data.

Urinalysis - A measure of the volume, osmolality and pH; a semi-quantitative test for sugar, acetone, urobilinogen and protein; a test for blood and bilirubin; a microscopic examination of the urinary sediment from pooled specimens.

Chemistry - Alkaline phosphatase (AP), glutamic-pyruvic transaminase (GPT), glutamic-oxalacetic transaminase (GOT), gamma-glutamyl transpeptidase (GGTP), bilirubin (BILRN), urea nitrogen (BUN), and total protein (TP).

The data were analyzed statistically by a two variable crossed and nested analysis of variance. Significance was judged at the 0.05 probability level.

Results:

The results of the clinical laboratory measurements are summarized in Table 1; the statistical analysis in Table 2. Measurements on individual animals are listed in the computer print-out attached to the report.

The erythrocyte count, hematocrit and relative number of lymphocytes were lower in the rats exposed ten times to DHPT than in the controls. The relative number of neutrophils was higher than the controls. Fourteen days after the last exposure the hematocrit had returned to the normal range, but the erythrocyte and lymphocyte counts remained lower and the neutrophils higher in the five exposed rats than in the controls. The decrease in

erythrocytes and hematocrit also resulted in an effect on the calculated indices, MCH and MCHC.

The rats exposed to DHPT excreted a larger volume of less concentrated urine that contained a higher concentration of urobilinogen than the controls. Fourteen days after the last exposure the remaining rats in this group continued to excrete a dilute urine, but the amount of urobilinogen was within the normal range.

The plasma bilirubin was increased and the total protein decreased in the rats exposed to DHPT. Fourteen days after the last exposure the total protein was normal, but the bilirubin, alkaline phosphatase, GPT, and GOT were elevated in the rats remaining in the group.

Summary:

The clinical laboratory measurements on samples of blood and urine from rats exposed ten times to DHPT indicate that the compound may have caused a hemolytic anemia and injury to the liver and kidneys. Recovery to normal was not complete fourteen days after the last exposure.

Report by: Walter B. Konecki
Walter B. Konecki
Clinical Chemist

Approved by: John R. Barnes
John R. Barnes
Chief, Clinical Pathology

WBK:JRB:ljm

BEST COPY AVAILABLE

TABLE 1

SUMMARY OF CLINICAL LABORATORY MEASUREMENTS
ON RATS EXPOSED TO DEHYDROTHIO-p-TOLUIDINE (DHPT)

Hematology	10 Treatment		Recovery	
	Control	0.60 mg/L DHPT	Control	0.60 mg/L DHPT
Erythrocytes, $\times 10^6/\text{mm}^3$	6.05	5.72	6.46	5.99
Hemoglobin, g%	15.5	15.0	15.2	14.8
Hematocrit %	50	45	47	46
MCV μ^3	82	79	73	77
MCH ng	26	26	24	25
MCHC %	31	33	32	32
Leukocytes $\times 10^3/\text{mm}^3$	14.98	23.37	13.27	16.75
Neutrophils %	12	29	16	32
Lymphocytes %	85	69	82	61
Eosinophils %	0.8	0.4	0.8	0.2
Monocytes %	2.1	1.3	1.2	7.0
Basophils %	0	0	0	0
<u>Urinalysis</u>				
Volume ml	8	27	11	18
. molality mOs	2187	674	1918	1398
pH	6.5	6.8	6.8	7.0
Blood, no. positive	0	0	0	0
Sugar, no. abnormal	0	0	0	0
Protein, no. abnormal	0	0	0	0
Urobilinogen E.U.	1.0	5.2	1.0	1.0
Bilirubin, no. positive	0	1	0	0
Microscopic, no. abnormal	0	0	0	0
Acetone, no. positive	0	0	0	0
<u>Chemistry</u>				
AP, I.U.	210	164	191	486
GPT, I.U.	18	17	16	29
GOT, I.U.	52	65	45	63
GGTP, I.U.	0.7	0.7	2.0	2.9
Bilirubin, mg%	0.4	1.4	0.3	0.5
Urea Nitrogen, mg%	15	19	17	20
Total Protein g%	6.8	5.8	6.7	6.0

TABLE 2

SUMMARY OF STATISTICAL DATA
F: RATIO OF VARIANCES

Test	10-Day Treatment 0.6 mg/L DHPT	Recovery 14-Day Post-Exposure
Erythrocytes $\times 10^6/\text{mm}^3$	6.4 ^b	10.8 ^b
Hemoglobin gms %	1.4	2.2
Hematocrit %	14.5 ^b	0.8
NCV μ^3	2.1	2.0
MCH $\mu\text{-g}$	0.6	10.9 ^a
MCHC %	6.7 ^b	0.0
Leukocytes $\times 10^3/\text{mm}^3$	3.2	1.1
Neutrophils %	6.8 ^a	10.0 ^a
Lymphocytes %	6.0 ^b	15.7 ^b
Eosinophils %	1.8	2.0
Monocytes %	1.6	19.3 ^a
Basophils %	-	-
Urine Volume ml/24 hrs.	10.3 ^a	14.6 ^a
Urine Osmolality mOa	51.4 ^b	10.6 ^b
AP I.U.	2.5	4.9 ^a
GPT I.U.	0.2	4.9 ^a
GOT I.U.	2.9	4.5 ^a
GGTP I.U.	0.0	0.4
Bilirubin mg%	33.4 ^a	9.7 ^a
Urea Nitrogen mg%	1.4	0.9
Total Protein g%	18.2 ^b	2.7

a = Significantly higher than controls, $p < 0.05$

b = Significantly lower than controls, $p < 0.05$

NEAR ABSOLUTE ORGAN AND BODY WEIGHTS OF MALE RATS EXPOSED TO
DHPT [10 EXPOSURES 0-RECOVERY DAYS]

GROUP	FIN. BODY WT.	HEART	LUNGS	LIVER	SPLEEN	
I	314.6000	1.0660	1.7400	11.9680	0.6160	
II	222.4000+	0.7900+	1.3860+	8.6840+	0.8300	
	F RATIO(1)	30.164*	13.098*	18.494*	13.085*	2.603
	LSD(2)	38.7120	0.1759	0.1898	2.0935	0.3059
	DUNNETT(3)	38.7791	0.1762	0.1902	2.0971	0.3064
	WMS(4)	704.5500	0.0145	0.0169	2.0605	0.0440

GROUP	KIDNEY	TESTIS	THYMUS	
I	2.4580	2.7840	0.7160	
II	2.0200+	2.8700	0.4300+	
	F RATIO(1)	5.852*	0.422	10.078*
	LSD(2)	0.4175	0.3051	0.2077
	DUNNETT(3)	0.4183	0.3056	0.2081
	WMS(4)	0.0820	0.0438	0.0203

(1) RATIO OF AMONG- TO WITHIN-GROUP VARIATION--ONE-FACTOR ANALYSIS OF VARIANCE.

(2) LEAST SIGNIFICANT DIFFERENCE--GIVEN A SIGNIFICANT (ALPHA=0.05) F RATIO. ANY TWO MEANS DIFFERING BY MORE THAN THE LSD ARE SIGNIFICANTLY DIFFERENT WITH A VARIABLE-WISE FALSE POSITIVE (ALPHA) ERROR RATE OF 0.05.

(3) DUNNETT TEST--ANY TREATMENT MEAN DIFFERING FROM THE CONTROL MEAN BY MORE THAN THE DUNNETT STATISTIC IS SIGNIFICANTLY DIFFERENT FROM THE CONTROL MEAN WITH A VARIABLE-WISE FALSE POSITIVE (ALPHA) ERROR RATE OF 0.05.

(4) WITHIN-GROUP MEAN SQUARE.

+ SIGNIFICANTLY DIFFERENT (P<0.05) FROM CONTROL GROUP BY LSD.

SIGNIFICANTLY DIFFERENT (P<0.05) FROM CONTROL GROUP BY DUNNETT TEST.

* SIGNIFICANT AT THE 0.05 PROBABILITY LEVEL.

MEAN RELATIVE ORGAN AND BODY WEIGHTS OF MALE RATS EXPOSED TO
 [DPT [10 EXPOSURES 0-RECOVERY DAYS]

GROUP	HEART	LUNGS	LIVER	SELEEN	KIDNEY
I	0.3392	0.5528	3.8008	0.1962	0.781
II	0.3563	0.6315	3.8829	0.3685+	0.9129
F RATIO(1)	0.608	4.448	0.233	12.017*	5.319
LSD(2)	0.0506	0.0860	0.3925	0.1146	0.1314
DUNNETT(3)	0.0506	0.0862	0.3932	0.1148	0.1316
WMS(4)	0.0012	0.0035	0.0724	0.0062	0.0081

GROUP	TESTIS	THYMUS
I	0.8874	0.2288
II	1.3052+	0.1859
F RATIO(1)	34.340*	1.726
LSD(2)	0.1644	0.0754
DUNNETT(3)	0.1647	0.0755
WMS(4)	0.0127	0.0027

(1) RATIO OF AMONG- TO WITHIN-GROUP VARIATION--ONE-FACTOR ANALYSIS OF VARIANCE.

(2) LEAST SIGNIFICANT DIFFERENCE--GIVEN A SIGNIFICANT (ALPHA=0.05) F RATIO, ANY TWO MEANS DIFFERING BY MORE THAN THE LSD ARE SIGNIFICATLY DIFFERENT WITH A VARIABLE-WISE FALSE POSITIVE (ALPHA) ERROR RATE OF 0.05.

(3) DUNNETT TEST--ANY TREATMENT MEAN DIFFERING FROM THE CONTROL MEAN BY MORE THAN THE DUNNETT STATISTIC IS SIGNIFICANTLY DIFFERENT FROM THE CONTROL MEAN WITH A VARIABLE-WISE FALSE POSITIVE (ALPHA) ERROR RATE OF 0.05.

(4) WITHIN-GROUP MEAN SQUARE.

+ SIGNIFICANTLY DIFFERENT (P<0.05) FROM CONTROL GROUP BY LSD.

* SIGNIFICANTLY DIFFERENT (P<0.05) FROM CONTROL GROUP BY DUNNETT TEST.

† SIGNIFICANT AT THE 0.05 PROBABILITY LEVEL.

MEAN ABSOLUTE ORGAN AND BODY WEIGHTS OF MALE RATS EXPOSED TO
DHPT [10 EXPOSURES 14-RECOVERY DAYS]

GROUP	FIN. BODY WT.	HEART	LUNGS	LIVER	SELEEN
I	383.0000	1.2820	1.9460	15.0040	0.7480
II	346.8000	1.2180	1.9000	17.4980	1.0540+
F RATIO(1)	2.844	0.334	0.041	3.784	13.319*
LSD(2)	49.5033	0.2552	0.5217	2.9566	0.1933
DUNNETT(3)	49.5892	0.2556	0.5226	2.9617	0.1937
WMS(4)	1152.1000	0.0306	0.1279	4.1096	0.0176

GROUP	KIDNEY	TESTIS	THYMUS
I	3.2560	3.1440	0.8000
II	3.0180	3.3960	0.7160
F RATIO(1)	0.828	1.571	0.389
LSD(2)	0.6033	0.4636	0.3107
DUNNETT(3)	0.6044	0.4644	0.3113
WMS(4)	0.1711	0.1011	0.0454

(1) RATIO OF AMONG- TO WITHIN-GROUP VARIATION--ONE-FACTOR ANALYSIS OF VARIANCE.

(2) LEAST SIGNIFICANT DIFFERENCE--GIVEN A SIGNIFICANT (ALPHA=0.05) F RATIO, TWO MEANS DIFFERING BY MORE THAN THE LSD ARE SIGNIFICANTLY DIFFERENT WITH A VARIABLE-WISE FALSE POSITIVE (ALPHA) ERROR RATE OF 0.05.

(3) DUNNETT TEST--ANY TREATMENT MEAN DIFFERING FROM THE CONTROL MEAN BY MORE THAN THE DUNNETT STATISTIC IS SIGNIFICANTLY DIFFERENT FROM THE CONTROL MEAN WITH A VARIABLE-WISE FALSE POSITIVE (ALPHA) ERROR RATE OF 0.05.

(4) WITHIN-GROUP MEAN SQUARE.

* SIGNIFICANTLY DIFFERENT (P<0.05) FROM CONTROL GROUP BY LSD.

* SIGNIFICANTLY DIFFERENT (P<0.05) FROM CONTROL GROUP BY DUNNETT TEST.

* SIGNIFICANT AT THE 0.05 PROBABILITY LEVEL.

MEAN RELATIVE ORGAN AND BODY WEIGHTS OF MALE RATS EXPOSED TO
DHPT [10 EXPOSURES 14-RECOVERY DAYS]

GROUP	HEART	LUNGS	LIVER	SPLEEN	KIDNEY
I	0.3346	0.5085	3.9196	0.1955	0.8497
II	0.3494	0.5487	5.0540+	0.3060+	0.8684
F RATIO(1)	1.022	0.486	21.579*	25.308*	0.203
LSD(2)	0.0340	0.1328	0.5631	0.0506	0.0956
DUNNETT(3)	0.0340	0.1330	0.5641	0.0507	0.0958
WMS(4)	0.0005	0.0083	0.1491	0.0012	0.0043

GROUP	TESTIS	THYMUS
I	0.8212	0.2087
II	0.9809+	0.2043
F RATIO(1)	45.022*	0.016
LSD(2)	0.0549	0.0789
DUNNETT(3)	0.0550	0.0790
WMS(4)	0.0014	0.0029

(1) RATIO OF AMONG- TO WITHIN-GROUP VARIATION--ONE-FACTOR ANALYSIS OF VARIANCE.

(2) LEAST SIGNIFICANT DIFFERENCE--GIVEN A SIGNIFICANT (ALPHA=0.05) F RATIO, ANY TWO MEANS DIFFERING BY MORE THAN THE LSD ARE SIGNIFICANTLY DIFFERENT WITH A VARIABLE-WISE FALSE POSITIVE (ALPHA) ERROR RATE OF 0.05.

(3) DUNNETT TEST--ANY TREATMENT MEAN DIFFERING FROM THE CONTROL MEAN BY MORE THAN THE DUNNETT STATISTIC IS SIGNIFICANTLY DIFFERENT FROM THE CONTROL MEAN WITH A VARIABLE-WISE FALSE POSITIVE (ALPHA) ERROR RATE OF 0.05.

(4) WITHIN-GROUP MEAN SQUARE.

* SIGNIFICANTLY DIFFERENT (P<0.05) FROM CONTROL GROUP BY LSD.

SIGNIFICANTLY DIFFERENT (P<0.05) FROM CONTROL GROUP BY DUNNETT TEST.

• SIGNIFICANT AT THE 0.05 PROBABILITY LEVEL.

APPENDIX C

PATHOLOGY REPORT NO. 11-79

DEHYDROTHIO-P- TOLUIDINE(DHPT)

H-12325 - NR-2992-001 - Chemicals, Dyes and Pigments Department

Two-Week Inhalation Toxicity Study - ChR-CD Rats

May 23, 1979

Summary and Conclusion

Ten young adult male rats were exposed to Dehydrothio-p-toluidine, (DHPT), at a concentration of 0.6 mg/l for 6 hours/day, 5 days/week for 2 weeks. After the two-week exposure period, five animals were sacrificed for pathological evaluation. The other five were allowed to survive for a 14-day recovery period and were then sacrificed for the same purpose. An equal number of animals were exposed to air and served as a negative control. At necropsy, the animals were examined grossly, and selected organs and tissues were saved for histological evaluation. Those saved included external ear, abdominal skin, trachea, lungs*, thyroid*, adrenals, thymus*, mediastinal tissue, spleen*, sternbrae with bone marrow, stomach, small and large intestines, liver, testes*, epididymides, kidneys*, brain and eyes.

The results of pathologic findings are summarized in Table I. There were effects of the compound observed in the livers and spleens of all rats in the kidneys of two rats after 10 exposures to the compound. The effects still persisted in the livers and spleens of all animals and the kidney of one animal after a two-week recovery period. The changes in the liver were characterized by hypertrophic hepatocytes and proliferation of bile duct epithelial cells. The spleen showed congestion of red pulp with excessive amounts of hemosiderin which was possibly indicative of intravascular hemolysis. These compound-induced changes, especially the bile duct epithelial cell proliferation which progressed to a marked change in rats (2/5) after 14 days recovery. The liver change was also accompanied by the presence of basophilic hepatocytes and the occurrence of pericholangitis. A mild scattering of focal necrosis in the liver was seen in only one rat (R240917) after 10 exposures to the compound, and this change was also considered as a compound-induced lesion. A mild degree of kidney tubular degeneration was seen in 3 out of 5 rats in the treated group following dosing and in 1 out of 5 after 14 days recovery.

There were thymus necrosis and depletion of lymphocytes observed in 2 rats (2/5) after 10 exposures to the compound and vacuolization of the adrenal medullary cord cells observed in 2 rats (2/5) after 10 exposures to the compound with a 14-day recovery period. The significance of these changes in relation of the compound, however, is not clear. All of the other pathological findings listed in the table are believed to be spontaneous lesions or the result of intercurrent disease.

BEST COPY AVAILABLE

PART II

II-12329
NR-2992

TABLE I
PATHOLOGIC FINDINGS IN MALE CHR-CD RATS
EXPOSED TO DIETHYLSTIBO-*p*-TOLUIDINE (DEPT)

Animal No.	Group	Dose (mg/l)	Days on test	Recovery days	Lung: Chronic murine pneumonia, early stage	Liver: Non-specific microgranuloma/extramedullary hemopoiesis	Liver: Hypertrophy of hepatocytes, perportal	Liver: Scattered focal necrosis	Liver: Basophilic foci of hepatocytes	Liver: Pericholangitis	Liver: Bile duct epithelial cell proliferation	Kidney: Chronic progressive nephropathy, early stage	Kidney: Hydropic degeneration, diffuse	Testis: Degeneration and necrosis of spermatogonia, seminiferous tubules	Adrenal: Vacuolation, medullary cords	Spleen: Congested red pulp	Spleen: Excessive hemosiderin pigmentation, red pulp	Thymus: Necrosis and depletion of lymphocytes	External: Focal proliferation of fibroblasts, subcutis, (old scar)
R240912	II	0.6	10	0	2	1	2	1	1	1	1	1	1	1	3	1	1	1	1
R240913	II	0.6	10	0	1	1	2	1	1	1	1	1	1	1	3	1	1	1	1
R240916 ^a	II	0.6	10	0	1	1	2	1	1	1	1	1	1	1	3	1	1	1	1
R240917	II	0.6	10	0	1	1	2	1	1	1	1	1	1	1	3	1	1	1	1
R240918	II	0.6	10	0	1	1	2	1	1	1	1	1	1	1	3	1	1	1	1
R240919	II	0.6	10	14	1	1	1	1	1	1	2	1	1	1	3	1	1	1	1
R240928	II	0.6	10	14	1	1	3	1	1	1	1	1	1	1	1	1	1	1	1
R240929	II	0.6	10	14	1	1	3	1	2	2	4	1	1	1	2	2	1	1	1
R240932	II	0.6	10	14	1	1	1	1	2	2	4	1	1	1	1	1	1	1	1
R240934	II	0.6	10	14	3	1	1	1	1	1	2	1	1	1	1	1	1	1	1

Code: 0 = No change 1 = Very mild change 2 = Slight change 3 = Moderate change 4 = Marked change P = Present
 1 = Liver (basophilic normal) but not available for histologic section R240916: Thyroid R240917: Thyroid and skin



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

Mark H. Christman
Counsel
E. I. Du Pont De Nemours and Company
Legal D-7010-1
1007 Market Street
Wilmington, Delaware 19898

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

MAY 08 1995

EPA acknowledges the receipt of information submitted by your organization under Section 8(e) of the Toxic Substances Control Act (TSCA). For your reference, copies of the first page(s) of your submission(s) are enclosed and display the TSCA §8(e) Document Control Number (e.g., 8EHQ-00-0000) assigned by EPA to your submission(s). Please cite the assigned 8(e) number when submitting follow-up or supplemental information and refer to the reverse side of this page for "EPA Information Requests".

All TSCA 8(e) submissions are placed in the public files unless confidentiality is claimed according to the procedures outlined in Part X of EPA's TSCA §8(e) policy statement (43 FR 11110, March 16, 1978). Confidential submissions received pursuant to the TSCA §8(e) Compliance Audit Program (CAP) should already contain information supporting confidentiality claims. This information is required and should be submitted if not done so previously. To substantiate claims, submit responses to the questions in the enclosure "Support Information for Confidentiality Claims". This same enclosure is used to support confidentiality claims for non-CAP submissions.

Please address any further correspondence with the Agency related to this TSCA 8(e) submission to:

Document Processing Center (7407)
Attn: TSCA Section 8(e) Coordinator
Office of Pollution Prevention and Toxics
U.S. Environmental Protection Agency
Washington, D.C. 20460-0001

EPA looks forward to continued cooperation with your organization in its ongoing efforts to evaluate and manage potential risks posed by chemicals to health and the environment.

Sincerely,

Terry R. O'Bryan
Terry R. O'Bryan
Risk Analysis Branch

Enclosure

13174A



Recycled/Recyclable
Printed with Soy/Canola Ink on paper that
contains at least 50% recycled fiber

Triage of 8(e) Submissions

Date sent to triage: MAY 09 1995

NON-CAP

CAP

Submission number: 13174A

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)

~~ATC~~

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:

THIS IS THE ORIGINAL 8(e) SUBMISSION; PLEASE REFILE AFTER TRIAGE DATABASE ENTRY

		For Contractor Use Only			
entire document:	<u>0</u>	1	2	pages 1, 1st TAB	pages <u>1, 7 TABS</u>
Notes:					
Contractor reviewer:	<u>PRZ</u>			Date:	<u>4/26/95</u>

CECATS/TRIAGE TRACKING DBASE ENTRY FORM

CECATS DATA: Submission # BEHQ-0992-13174 SEQ. A
 TYPE: (INT) SUPP FLWT
 SUBMITTER NAME: F. I. Dupont de Nemours and Company

INFORMATION REQUESTED: FLWT DATE
 0501 NO INFO REQUESTED
 0502 INFO REQUESTED (TECH)
 0503 INFO REQUESTED (VOL ACTIONS)
 0504 INFO REQUESTED (REPORTING RATIONAL F)
 DISPOSITION:
REFR TO CHEMICAL SCREENING
REFR CAP NOTICE

VOLUNTARY ACTIONS:
 0401 NO ACTION REPORTED
 0402 STUDIES PLANNED (IN H W A)
 0403 NOTIFICATION (H WINK) REPORTED
 0404 LABEL/MSDS (TIAN) IS
 0405 PROCESS/MSDI (ING) (TIAN) IS
 0406 APP USE DISCONTINUED
 0407 PRODUCTION DISCONTINUED
 0408 CONFIDENTIAL

SUB. DATE: 09/11/92 OTR DATE: 09/22/92 CSRAD DATE: 03/24/95
 CHEMICAL NAME: _____
 CASE: 92-36-4

INFORMATION TYPE:	P F C	INFORMATION TYPE:	P F C	INFORMATION TYPE:	P F C
0201 ONCO (HUMAN)	01 02 04	0216 EPICLON	01 02 04	0241 IMMUNO (ANIMAL)	01 02 04
0202 ONCO (ANIMAL)	01 02 04	0217 HUMAN EXPOS (PROD CONTAM)	01 02 04	0242 IMMUNO (HUMAN)	01 02 04
0203 CELL TRANS (IN VITRO)	01 02 04	0218 HUMAN EXPOS (ACCIDENTAL)	01 02 04	0243 CHEMPHYS PROP	01 02 04
0204 MUTA (IN VITRO)	01 02 04	0219 HUMAN EXPOS (MONITORING)	01 02 04	0244 CLASTO (IN VITRO)	01 02 04
0205 MUTA (IN VIVO)	01 02 04	0220 ECOAQUA TOX	01 02 04	0245 CLASTO (ANIMAL)	01 02 04
0206 REPRO/TERATO (HUMAN)	01 02 04	0221 ENV. OCCURENCE/FATE	01 02 04	0246 CLASTO (HUMAN)	01 02 04
0207 REPRO/TERATO (ANIMAL)	01 02 04	0222 EMER INCI OF ENV CONTAM	01 02 04	0247 DNA DAMREPAIR	01 02 04
0208 NEURO (HUMAN)	01 02 04	0223 RESPONSE REQUEST DELAY	01 02 04	0248 PRODUSE/PROC	01 02 04
0209 NEURO (ANIMAL)	01 02 04	0224 PROD/COMP/CHEM ID	01 02 04	0251 MSDS	01 02 04
0210 ACUTE TOX. (HUMAN)	01 02 04	0225 REPORTING RATIONALE	01 02 04	0259 OTHER	01 02 04
0211 CHR. TOX. (HUMAN)	01 02 04	0226 CONFIDENTIAL	01 02 04		
0212 ACUTE TOX. (ANIMAL)	01 02 04	0227 ALLERG (HUMAN)	01 02 04		
0213 SUB ACUTE TOX (ANIMAL)	01 02 04	0228 ALLERG (ANIMAL)	01 02 04		
0214 SUB CHRONIC TOX (ANIMAL)	01 02 04	0229 METAB/PHARMACO (ANIMAL)	01 02 04		
0215 CHRONIC TOX (ANIMAL)	01 02 04	0240 METAB/PHARMACO (HUMAN)	01 02 04		

TRIAL/DATA: NON-OR INVENTORY
 YES (DROPPED/REFER) NO (CONTINUE) REFTR
 SPECIES: RAT
 TOXICOLOGICAL CONCERN: LOW MED HIGH
 USE: _____
 PRODUCTION: _____

-CPSS- 0927952113

0 0 0 0 0 0 0 0 0 0 0

> <ID NUMBER>

8(E)-13174A

> <TOX CONCERN>

L

> <COMMENT>

SUBACUTE INHALATION TOXICITY IN MALE RATS IS LOW CONCERN WITH AN ALC OF 3.00 MG/L. 10 ANIMALS WERE EXPOSED TO 0.68 MG/L OF TEST MATERIAL FOR 10 6-HOUR EXPOSURES OVER A 2-WEEK PERIOD. CLINICAL SIGNS INCLUDED SALIVATION, PAWING AND CHEWING MOTIONS, LACRIMATION, SPORADIC CASES OF CLOSING OF THE EYES, FASCICULATION, RAPID RESPIRATION, AND RED NASAL DISCHARGE. PATHOLOGY CHANGES INCLUDED HEMOLYTIC ANEMIA AND INJURY TO THE LIVER, SPLEEN, AND KIDNEYS. AFTER RECOVERY PERIOD ANIMALS EXHIBITED LARGER MEAN ABSOLUTE SPLEEN WEIGHT, AND MEAN RELATIVE SPLEEN, TESTIS, AND LIVER WEIGHTS.

\$\$\$\$