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October 15, 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 6/28/91CAP 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

mm
2/17/95

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# 95-80-7

Chem: 2,4-Toluenediamine and Chlorotoluenediamine Mixture

**Title: Long-Term Oral Administration of 2,4-Toluenediamine
(MTD) and Chlorotoluenediamine Mixture (C1-MTD) in
Rats and Dogs**

Date: 1972

Summary of Effects: Liver tumor

LONG-TERM ORAL ADMINISTRATION OF 2,4-TOLUENEDIAMINE
(MTD) AND CHLOROTOLUENEDIAMINE MIXTURE (Cl-MTD) IN RATS AND DOGS

Haskell Laboratory Report No. 72-76

Medical Research Project No. 5078

SUMMARY

The addition of 1000→500→250 ppm MTD to the diet of Chr-CD rats for up to 15 months resulted in a statistically significant increase in liver and mammary tumor development in both sexes, together with a significant increase in lung tumors in males. Other prominent changes found were: a marked depression in body weight gain together with splenic atrophy in both sexes, and an increase in the mortality rate and testicular atrophy in males.

The addition of 4000→2000 ppm Cl-MTD to the diet of Chr-CD rats for up to 15 months resulted in a statistically significant increase in liver tumor formation in both sexes. Other prominent changes were: a marked depression in body weight gain in both sexes, and an increase in the mortality rate together with testicular atrophy in males.

The addition of 1000 ppm Cl-MTD to the diet of Chr-CD rats for up to 15 months resulted in a statistically significant increase in liver tumor development in both sexes which was less severe than that found at the 4000→2000 ppm dosage. There was, in addition, a marked depression in body weight gain in both sexes.

Intragastric administration of 100 mg MTD/kg body weight for 10 doses over a 30-day period, with a subsequent 9-month observation period, resulted in mammary tumor development in female Sprague-Dawley rats. A comparative test with 300 mg Cl-MTD/kg body weight also resulted in a neoplastic response in the mammary gland.

Oral dosing by capsule of 100→50 mg Cl-MTD/dog daily to 6 female beagle dogs for up to 8 months resulted in a loss of body weight and ascites in one dog, together with cholangiofibrosis in the liver of all dogs. As cholangiofibrosis was a frequent finding with Cl-MTD administration in rats, it appears that there is much similarity in the response of the liver to Cl-MTD in both rats and dogs. The dog test should not be considered to be an adequate test of carcinogenic potential because of the short test period of eight months.

LONG-TERM ORAL ADMINISTRATION OF 2,4-TOLUENEDIAMINE (MTD) AND CHLOROTOLUENEDIAMINE MIXTURE (Cl-MTD) IN RATS AND DOGS

Haskell Laboratory Report No. 72-76

Medical Research Project No. 5078

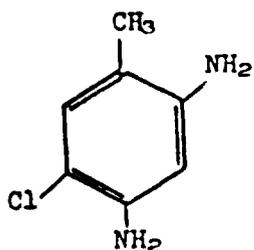
INTRODUCTION

This report completes the work that was started under Medical Research Project No. 1214. This study was designed to evaluate the long-term toxicity potential of chlorotoluene diamine mixture, Cl-MTD, which was being considered as a replacement for Moca[®]; 2,4-toluenediamine (MTD) was used as a positive control.

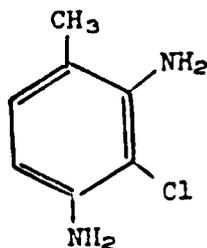
The oral AID of Cl-MTD in male rats was 1500 mg/kg body weight (Haskell Laboratory Report No. 27-69). The oral ALD in rats of MTD was 500 mg/kg body weight (Toxic Substances List, H. E. Christensen, Ed., NIOSH, 1973). MTD was found to be a liver carcinogen when fed to male Wistar rats at 600 and 1000 ppm in the diet for 9 months (Ito, N. et al., Cancer Res. 29:1137-1145, 1969). There was, in addition, a marked reduction in body weight gain.

MATERIALS AND METHODS

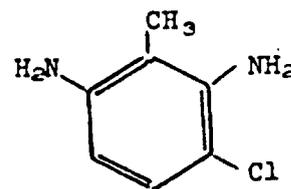
Some physical characteristics of MTD and Cl-MTD are presented in Table 18. The composition of Cl-MTD mixture was as follows:



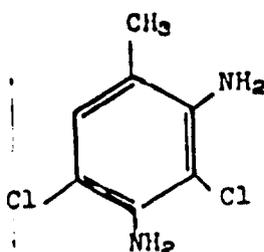
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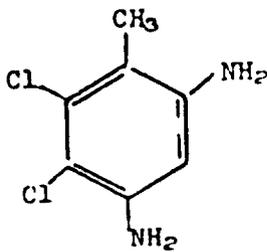
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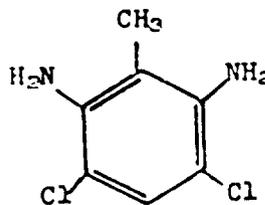
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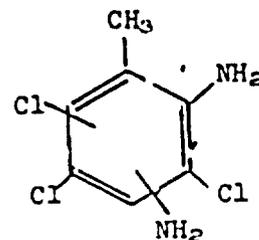
ca. 10.0%



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0.4%

Cl-MTD was added to the diet of 36 male and 36 female Chr-CD rats, starting when 30 days of age for up to 15 months when the test was terminated as shown in Tables 5 and 6. The high level was 4000 ppm Cl-MTD and was lowered to 2000 ppm after two weeks until the end of the test. A lower level of 1000 ppm Cl-MTD was fed continuously to 36 male and 36 female Chr-CD rats for up to 15 months as shown in Tables 3 and 4. Thirty-six male and 36 female Chr-CD rats were kept as negative controls and terminated after 15 months on test (Tables 1 and 2). In addition, 36 male and 36 female Chr-CD rats were kept as positive controls and were terminated after 15 months on test; these were fed a diet containing MTD, the level was 1000 ppm for two weeks, 500 ppm for 5.5 months and 250 ppm for 9.0 months (Tables 7 and 8).

The following organs were examined histologically unless indicated otherwise in the tables: brain, heart, liver, kidney, lung, trachea, esophagus, aorta, stomach, small intestine, cecum, large intestine, pancreas, salivary glands, exorbital lacrimal gland, eye, lymph nodes, thymus, spleen, bone marrow, sternal bone, sciatic nerve with adjacent muscle, testis, epididymis, prostate, bladder, ovaries, uterus, mammary gland, skin, and all masses and gross lesions.

Six rats per group were sacrificed after one year on test for an interim evaluation. All dead rats and those found in extremis were necropsied and the tissues saved if not autolyzed.

The Clinical Laboratory Report concerning the above rats was completed on November 17, 1970.

In addition to our conventional oral toxicity test using Chr-CD rats, a "short-term" carcinogenicity test as proposed by Griswald et al. was carried out (Cancer Res. 28:928, 1969). In this test female Sprague-Dawley rats, 45 days of age, were given 10 intragastric doses over a 30-day period; the test was terminated after an additional 9-month observation period. Development of mammary tumors was the indicator of carcinogenicity. MTD and Cl-MTD were administered as indicated in Tables 12, 13, 15 and 15. Only mammary tissue was examined histologically.

In addition to the rat tests, Cl-MTD was administered orally, by capsule, to 6 female beagle dogs, about one year of age, as shown in Table 17. This test was terminated after 8 months as clinical signs of Cl-MTD toxicity were observed. The same tissues were examined histologically as listed for the Chr-CD rats above.

RESULTS

A. CONVENTIONAL CHR-CD RAT STUDY (Tables 1 through 11), (Fig. 1, 2).

1. MTD: Both sexes exhibited a marked reduction in body weight gain as shown in Fig. 1 and 2. There was an increased mortality rate in males (Table 11). The Clinical Laboratory Report indicated that the rats fed MTD developed a slight anemia and leucocytosis. Histologically, hemosiderin was found in various tissues in amounts greater than found in controls. Male rats excreted a larger volume

of a more dilute urine than seen in controls. Males fed MTD developed proteinuria and glucosuria. Histologically, males fed MTD showed inflammation of renal pelvis more frequently than found in controls. Urine urobilinogen was elevated in both sexes fed MTD. The serum alkaline phosphatase, glutamic-pyruvic transaminase and bilirubin levels were higher in rats fed MTD than in controls: the effect being greater in males. These changes are consistent with those found histologically in the liver: focal liver cell alteration, cystic bile ducts, cholangitis, cholangiofibrosis, hematopoiesis and hemosiderin. Males fed MTD had an elevated blood glucose after 9 months on test. Histologically, there was a slight vacuolation of the Islets of Langerhans; however, this change does not appear to be sufficient to explain the elevated glucose as due to damage to the islets. A more likely explanation for the elevated blood glucose is a stress response with increased glucocorticoid production. Severe atrophy of the spleen was seen in both sexes fed MTD. Severe testicular atrophy with granulomata formation was a consistent finding in males fed MTD.

MTD feeding resulted in a statistically significant increase in tumor formation in the liver, mammary gland and lung in males, together with liver and mammary tumors in females. These results are presented in Tables 1, 2, 7, 8 and are summarized in Tables 9 and 10. In the diagnosis of liver lesions a recommended classification was used (Squire, R. A. and Levitt, M. H., *Cancer Res.* 35: 3214-3223, 1975). There was, in addition, an increase in various tumors found in organs other than the liver, lung and mammary gland in male rats fed MTD when compared with controls, however, a larger group size with complete microscopic examination of tissues would have to be used to determine if this increase is significant (Table 10).

2. C1-MTD: Both sexes at the high and low level of C1-MTD feeding exhibited a marked reduction in body weight gain (Fig. 1, 2). Only males at the high level showed an increase in mortality rate (Table 11). Clinical laboratory findings with high level C1-MTD feeding were similar, but less marked when compared with MTD, except that the elevation of blood glucose and bilirubin was not seen with C1-MTD. Also, proteinuria with an increase in urine volume with a low osmolarity was not seen with C1-MTD. The urine urobilinogen was elevated at both levels of C1-MTD feeding in both sexes. Testicular atrophy was found as a result of feeding C1-MTD at the high level. The feeding of two levels of C1-MTD resulted in liver tumor development in both sexes (Table 9). The carcinogenic effect was more severe at the highest level in both sexes. Males were more severely affected by liver neoplasia than females at the high level; this difference was not seen at the low level. The non-neoplastic liver changes seen with C1-MTD were similar to that found with MTD.

B. SPRAGUE-DAWLEY FEMALE RAT STUDY

The results of the intragastric dosing for one month, followed by an observation period of 9 additional months, are presented in Tables 12, 13, 14 and 15; these data are summarized in Table 16. As mammary tumors were found in at least 23% of the rats dosed with either C1-MTD or MTD, this "short-term" test was effective in demonstrating the neoplastic

effect of these chemicals. None of 20 control rats dosed with acetone/corn oil developed mammary tumors.

C. FEMALE BEAGLE DOG STUDY

The dosage of Cl-MTD, the initial and final body weights, together with the results of the histologic examination of tissues is presented in Table 17. The dosing was intermittent as no dosing was done if the dogs would not eat. As Dog No. 1028 showed a decrease in body weight and had ascites, she was sacrificed, in extremis, after seven months on test. At necropsy, Dog No. 1028 had about 500 ml of clear fluid in the peritoneal cavity and a nodular liver. At necropsy, the other 5 dogs had a slight nodularity of the liver suggestive of fibrosis. Histologically, cholangitis and cholangiofibrosis were the principal lesions attributable to Cl-MTD ingestion.

DISCUSSION

The acute toxicity of MTD (ALD = 500 mg/kg/body weight) is greater than that of Cl-MTD (ALD = 1500 mg/kg/body weight). Likewise, the chronic toxicity, including carcinogenicity, is greater with MTD than with Cl-MTD. In making a comparison of carcinogenic potential, however, mortality and severity of pathologic change in certain organs, is a major consideration. Ideally, in making a judgement of comparative carcinogenicity, the overall toxicity should be of the same order of magnitude. In the above comparison the overall toxicity was greater with MTD than with Cl-MTD in the Chr-CD rat test.

That mammary and lung tumors appeared after MTD feeding in our test and were not found by Ito et al. may be explained by the longer test period (15 months vs. 9 months). Other factors such as strain of rat, age at start of test and diet may also be important.

Orthotoluidine, structurally related to MTD, was found to produce urinary bladder and subcutaneous tumors after feeding in rats (Russfield et al. Abstr. of Annual Meeting Soc. Tox. p. 15, 1973). These workers also found that feeding paratoluidine to mice resulted in hepatoma development; however, metatoluidine feeding in mice and rats did not result in tumor formation.

Hemangiosarcoma of various organs was found after 4-chloro-ortho-toluidine-HCl feeding mice (Homburger et al. Abstr. Annual Meeting Soc. Tox. p. 9, 1972). This material has structural resemblance to Cl-MTD.

The Du Pont Company has over 48 years of experience in the manufacture of MTD. Because MTD may cause methemoglobinemia, the MTD manufacturing operation has been included in the program to biologically monitor exposure to cyanogenic aromatic nitro and amino chemicals (Du Pont Trade Bulletin No. 42575; 4-30-75).

Triage of 8(e) Submissions

Date sent to triage: 2/5/96

NON-CAP

CAP

Submission number: ~~12002A~~
12002A

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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Date sent to triage: 2/5/96

NON-CAP

CAP

Submission number: ~~12002A~~

TSCA Inventory: Y N D

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ECO AQUATO

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ATOX SBTOX SEN w/NEUR

Group 3 - Elizabeth Margosches (1 copy each)

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

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Triage of 8(e) Submissions

Date sent to triage: 2/5/96

NON-CAP CAP

Submission number: ~~12002A~~
12002A

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 SETOX SEN w/NEUR

Group 3 - Elizabeth Margosches (1 copy each)

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STOX/ONCO CTOX/ONCO IMMUNO CYTO NEUR

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entire document: 0 1 <u>(2)</u> pages <u>1, 1st tab</u>	pages <u>1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, 100</u>
Notes:	<u>12/6/95</u>
Contractor reviewer: <u>[Signature]</u>	Date: <u>12/6/95</u>



CECATS/TRIAGE TRACKING DBASE ENTRY FORM

CECATS DATA: Submission # BEHQ 1092-12002 SEQ. A
 TYPE: INT SUPP FLWP
 SUBMITTER NAME: E. I. DuPont de Nemours and Company

INFORMATION REQUESTED: FLWP DATE
 0501 NO INFO REQUESTED
 0502 INFO REQUESTED (TECH)
 0503 INFO REQUESTED (VOL ACTIONS)
 0504 INFO REQUESTED (REPORTING RATIONALE)
 DISPOSITION: REFER TO CHEMICAL SCREENING (6678) CAP NOTICE

INFORMATION REQUESTED: FLWP DATE
 0401 NO ACTION REPORTED
 0402 STUDIES PLANNED/IN PROGRESS
 0403 NOTIFICATION OF WORKING CONDITIONS
 0404 LABELING/MSDS CHANGES
 0405 PROCESS/ANALYSIS CHANGES
 0406 APP/USE DISCONTINUED
 0407 PRODUCTION DISCONTINUED
 0408 CONFIDENTIAL

SUB. DATE: 10/15/92 OTS DATE: 10/27/92 CSRAD DATE: 02/17/95
 CAS#: 95-80-7
 CHEMICAL NAME: 2,4-Toluene diamine
Chlorotoluene diamine mixture
None

INFORMATION TYPE:	P F C	INFORMATION TYPE:	P F C
0201 ONCO (HUMAN)	01 02 04	EPICLIN	01 02 04
0202 ONCO (ANIMAL)	01 02 04	HUMAN EXPOS (PROD CONTAM)	01 02 04
0203 CELL TRANS (IN VITRO)	01 02 04	HUMAN EXPOS (ACCIDENTAL)	01 02 04
0204 MUTA (IN VITRO)	01 02 04	HUMAN EXPOS (MONITORING)	01 02 04
0205 MUTA (IN VIVO)	01 02 04	ECO/AQUA TOX	01 02 04
0206 REPRO/TERATO (HUMAN)	01 02 04	ENV. OCCUR/REL/FATE	01 02 04
0207 REPRO/TERATO (ANIMAL)	01 02 04	EMER INCI OF ENV CONTAM	01 02 04
0208 NEURO (HUMAN)	01 02 04	RESPONSE REQUEST DELAY	01 02 04
0209 NEURO (ANIMAL)	01 02 04	PROD/COMP/CHEM ID	01 02 04
0210 ACUTE TOX. (HUMAN)	01 02 04	REPORTING RATIONALE	01 02 04
0211 CHR. TOX. (HUMAN)	01 02 04	CONFIDENTIAL	01 02 04
0212 ACUTE TOX. (ANIMAL)	01 02 04	ALLERG (HUMAN)	01 02 04
0213 SUB ACUTE TOX (ANIMAL)	01 02 04	ALLERG (ANIMAL)	01 02 04
0214 SUB CHRONIC TOX (ANIMAL)	01 02 04	METAB/PHARMACO (ANIMAL)	01 02 04
0215 CHRONIC TOX (ANIMAL)	01 02 04	METAB/PHARMACO (HUMAN)	01 02 04

INFORMATION TYPE: IMMUNO (ANIMAL) 0241
 IMMUNO (HUMAN) 0242
 CHEM/PHYS PROP 0243
 CLASTO (IN VITRO) 0244
 CLASTO (ANIMAL) 0245
 CLASTO (HUMAN) 0246
 DNA DAM/REPAIR 0247
 PROD/USE/PROC 0248
 MSDS 0251
 OTHER 0299

INFORMATION TYPE: TOXICOLOGICAL CONCERN: LOW
 SPECIES: RAT
DOG
 MED
 HIGH

ONCO (HUMAN) 01 02 04
 ONCO (ANIMAL) 01 02 04
 CELL TRANS (IN VITRO) 01 02 04
 MUTA (IN VITRO) 01 02 04
 MUTA (IN VIVO) 01 02 04
 REPRO/TERATO (HUMAN) 01 02 04
 REPRO/TERATO (ANIMAL) 01 02 04
 NEURO (HUMAN) 01 02 04
 NEURO (ANIMAL) 01 02 04
 ACUTE TOX. (HUMAN) 01 02 04
 CHR. TOX. (HUMAN) 01 02 04
 ACUTE TOX. (ANIMAL) 01 02 04
 SUB ACUTE TOX (ANIMAL) 01 02 04
 SUB CHRONIC TOX (ANIMAL) 01 02 04
 CHRONIC TOX (ANIMAL) 01 02 04

ONCO (HUMAN) 01 02 04
 ONCO (ANIMAL) 01 02 04
 CELL TRANS (IN VITRO) 01 02 04
 MUTA (IN VITRO) 01 02 04
 MUTA (IN VIVO) 01 02 04
 REPRO/TERATO (HUMAN) 01 02 04
 REPRO/TERATO (ANIMAL) 01 02 04
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 NEURO (ANIMAL) 01 02 04
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 ACUTE TOX. (ANIMAL) 01 02 04
 SUB ACUTE TOX (ANIMAL) 01 02 04
 SUB CHRONIC TOX (ANIMAL) 01 02 04
 CHRONIC TOX (ANIMAL) 01 02 04

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 REPRO/TERATO (ANIMAL) 01 02 04
 NEURO (HUMAN) 01 02 04
 NEURO (ANIMAL) 01 02 04
 ACUTE TOX. (HUMAN) 01 02 04
 CHR. TOX. (HUMAN) 01 02 04
 ACUTE TOX. (ANIMAL) 01 02 04
 SUB ACUTE TOX (ANIMAL) 01 02 04
 SUB CHRONIC TOX (ANIMAL) 01 02 04
 CHRONIC TOX (ANIMAL) 01 02 04

#12002A

L

Subacute oral toxicity for MTD is of low concern based on no mortality in female rats exposed by gavage to 100 mg/kg for 10 doses over 30 days.

L

Subacute oral toxicity for Cl-MTD is of low concern based on no mortality in female rats exposed by gavage to 300 mg/kg for 10 doses over 30 days.

H 2,4-toluene diamine (250, 500, & 1000 ppm in the diet) caused liver and mammary tumors in

CHR-CD rats.

Intragastric administration of 2,4-toluene diamine (100 mg/kg) ^{10 doses of} over a period of 30 days resulted in mammary tumors in Sprague-Dawley rats

for 15 months

H Administration of a chlorotoluene diamine mixture (intragastric administration of 300 mg/kg in 10 doses over 30 days) resulted in mammary tumors in Sprague-Dawley rats.

It also causes liver tumors in CHR-D rats when administered in feed (1000, 2000, & 4000 ppm).