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August 10, 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/CAP Agreement, E.I. Du Pont de Nemours and Co. hereby submits (*in triplicate*) the attached studies. Submission of this information is voluntary and is occasioned by unilateral changes in EPA's standard as to what EPA now considers as reportable information. Regulatee's submission of information is made solely in response to the new EPA §8(e) reporting standards and is not an admission: (1) of TSCA violation or liability; (2) that Regulatee's activities with the study compounds reasonably support a conclusion of substantial health or environmental risk or (3) that the studies themselves reasonably support a conclusion of substantial health or environmental risk.

For Regulatee,

Mark H. Christman
Counsel
Legal D-7058
1007 Market Street
Wilmington, DE 19898
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ATTACHMENT 1

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

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

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

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

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

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

- even though EPA expressly disclaims each "status report" as being preliminary evaluations that should not be regarded as final EPA policy or intent⁴, the "Reporting Guide" gives the "status reports" great weight as "sound and adequate basis" from which to determine mandatory reporting obligations. ("Guide" at page 20).
- the "Reporting Guide" contains a matrix that establishes new numerical reporting "cutoff" concentrations for acute lethality information ("Guide" at p. 31). Neither this matrix nor the cutoff values therein are contained in the Statement of Interpretation. The regulated community was not made aware of these cutoff values prior to issuance of the "Reporting Guide" in June, 1991.
- the "Reporting Guide" states new specific definitional criteria with which the Agency, for the first time, defines as 'distinguishable neurotoxicological effects'; such criteria/guidance not expressed in the 1978 Statement of Interpretation.⁵
- the "Reporting Guide" provides new review/ reporting criteria for irritation and sensitization studies; such criteria not previously found in the 1978 Statement of Interpretation/Enforcement Policy.
- the "Reporting Guide" publicizes certain EPA Q/A criteria issued to the Monsanto Co. in 1981 which are not in the Statement of Interpretation; have never been published in the Federal Register or distributed by the EPA to the Registrants. Such Q/A establishes new reporting criteria not previously found in the 1978 Statement of Interpretation/Enforcement Policy.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

APPENDIX

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

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

¹43 Fed Reg at 11114, comment 14:

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

²Guide at pp.22, 29-31.

³Guide at pp-34-36.

⁴Guide at pp-34-36.

⁵Guide at pp-34-36.

⁶Guide at pp-22; 36-37.

⁷Guide at pp-22

⁸43 Fed Reg at 11112

Only the term "Birth Defects" is listed.

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

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

¹⁰Guide at pp-23; 33-34.

¹¹43 Fed Reg at 11112

Only the term "Cancer" listed.

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

¹³43 Fed Reg at 11112; 11115 at Comment 15

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

¹⁴Guide at pp-23.

¹⁵43 Fed Reg at 11112; 11115 at Comment 16.

Attachment 2

Study Summary and Report

) CAS #123-39-7

Chem: Formamide, N-Methyl-

Title: Subacute Inhalation Toxicity Study in Rats

Date 5-3-83

Summary of Effects: Severe weight loss; liver effects

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Copies to: K. D. Dastur (1)
J. C. Watts (1)
J. K. Kosak (1)

E. I. du Pont de Nemours and Co., Inc.
Haskell Laboratory for Toxicology and Industrial Medicine
Elkton Road, P. O. Box 50,
Newark, Delaware 19711

HASKELL LABORATORY REPORT NO. 162-83 MR NO. 4378-001

Material Tested
Formamide, N-methyl-

Haskell No.
14,513

SUBACUTE INHALATION TOXICITY STUDY IN RATS

Summary: Groups of 15 male Crl:CD[®] rats were exposed 6 hours/day, 5 days/week for 2 weeks to concentrations of either 0.12, 0.32, or 0.97 mg/L of N-methylformamide (MHF) in air. A control group was simultaneously exposed to air only. Blood and urine samples were collected for clinical analysis, and sacrifices were performed for pathologic examination at the end of the exposure period and 13 days post-exposure. Urine samples were collected for MHF analysis on exposure days 1, 4, and 9 and on recovery days 3, 6, and 13.

Clinical observations of rats exposed to 0.12 mg/L were indistinguishable from controls throughout the study. Rats exposed to 0.32 mg/L had significantly lower body weights during the first week and the latter part of the second week of exposure. Gain during the recovery phase was parallel to that of controls. Rats exposed to 0.97 mg/L had significantly lower body weights throughout the study with severe weight depression during the exposure phase and weight gain at a rate parallel to that of controls during the recovery phase.

Clinical chemistry measurements made at the end of the exposure period showed no compound-related effects in rats exposed to 0.12 mg/L. Rats exposed to 0.32 and 0.97 mg/L had increased serum cholesterol concentrations. Rats exposed to 0.97 mg/L also had decreased serum urea nitrogen concentrations, decreased serum alkaline phosphatase activities, and increased serum ALT/GPT and AST/GOT activities. These changes were interpreted to be evidence of treatment-related effects on the integrity and function of hepatic tissue. All compound-related effects observed at the end of the exposure period were absent 14 days later.

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Pathologic examination revealed no compound-related macroscopic lesions in any rats. Microscopically, there were compound-related effects following exposure in the livers of rats exposed to 0.32 and 0.97 mg/L. Lesions included pale cytoplasm, increase in the number of mitotic figures, and cytoplasmic lipid vacuolation. These changes were interpreted as being degenerative and regenerative in nature. Fourteen days following exposure, partial recovery at the high level and complete recovery at the intermediate level had occurred. The low level was a histologic no-effect level.

A comparison of organ weights between test rats and controls showed no changes in rats exposed to 0.12 mg/L. Following 10 exposures, mean absolute weights of the heart, lung, spleen, and thymus were significantly lower in rats exposed to 0.97 mg/L than in controls. On a relative basis, rats exposed to 0.32 and 0.97 mg/L had increased liver/body weight ratios and rats exposed to 0.97 had increased testis/body weight ratios. Fourteen days following exposure, there were no differences between test rats and controls.

MMF was excreted in a dose-dependent fashion in the urine of exposed rats. It was detected in the urine of rats exposed to 0.32 and 0.97 mg/L on Day 1 and in rats exposed to 0.12 mg/L on Day 4. In all test groups, urinary levels of MMF generally increased throughout the exposure period and then decreased throughout the recovery period. At the end of the recovery period, MMF was still detectable in rats exposed to 0.32 and 0.97 mg/L but not in rats exposed to 0.12 mg/L.

Based on parameters evaluated in this study, 0.12 mg/L of MMF is a no-effect level. The intermediate and high levels are definite and dose-dependent effect levels with primary effects on the liver.

I. Introduction: The purpose of this study was to determine the effects of monomethylformamide (MMF) on male rats after repeated inhalation exposure. In range-finding work, rats exposed to 5.6 and 10 mg/L showed severe initial weight loss followed by weight gain with no deaths occurring.

II. Procedure:

- A. Animals: Male Crl:CD® rats were housed 2/cage in 8" x 8" x 14" stainless-steel, wire-mesh cages and provided Purina Certified Rodent Chow® #5002 and water ad libitum. Rats were observed for general suitability for 1 week prior to testing.
- B. Exposure Protocol: Groups of 15 rats each, 7-8 weeks old and weighing 207-242 grams, were exposed nose-only to different concentrations of 0, 0.1, 0.3 or 1.0 mg/L. Rats were exposed 6 hours/day, 5 days/week for 2 weeks. All rats were weighed and observed daily (excluding weekends) through the exposure period and for 14 days post-exposure.

C. Generation: The liquid test material was syringe-driven into a heated (180°C) 3-neck flask, where it flash evaporated. Unheated dilution air passed through the flask and carried vapors to the exposure chamber.

D. Analytical: Atmospheric concentrations were analyzed on a Hewlett-Packard 5730A Gas Chromatograph (GC) with a flame ionization detector. The column used was a 1/8" ID x 3' long glass coil packed with 10% Carbowax® 20M and 5% KOH on 60/80 mesh Chromosorb® P HMDS.

Standards were prepared by quantitative dilution of the test material in acetone. The GC was calibrated daily by injection of the liquid standards. Chambers were sampled at 30-minute intervals by drawing atmosphere through a glass impinger containing acetone. The mean and standard deviation were calculated for each exposure and for the overall 2-week exposure. Chamber temperature was monitored with a thermometer during each exposure.

E. Test Material:

Purity: 99.5%

Contaminants: N,N-Dimethylformamide 0.2%
Water 0.2%
Five higher boiling unknowns 0.1%

Synonyms: • Monomethylformamide
• MMF

Other Codes: N.B. E-25416-74C

Submitted by: J. R. Kosak
Chemicals & Pigments Department

F. Clinical Measurements: Clinical laboratory measurements were made on urine samples collected overnight following the 9th exposure and the 13th day of recovery. Analyses included quantitative measures of the volume, osmolality and pH, and semiquantitative tests for occult blood, protein, sugar, bilirubin, acetone, and urobilinogen. Each specimen was noted for color and appearance and the sediment from pooled specimens was examined microscopically.

Blood samples were taken from the rats' tails after the 10th exposure and the 14th day of recovery for measurement of the following: hemoglobin concentration; mean corpuscular volume, counts of erythrocytes, platelets, and leukocytes; and relative numbers of neutrophils, lymphocytes, eosinophils, monocytes, and basophils. Hematocrit, mean corpuscular hemoglobin, and mean corpuscular hemoglobin concentration were calculated from these data. In addition to hematologic parameters, serum concentrations

of alkaline phosphatase, glutamic-pyruvic transaminase, glutamic-oxaloacetic transaminase, urea nitrogen, creatinine, total protein and cholesterol were also measured.

- G. Pathology: After the 10th exposure, 3 rats from each group were selected at random and sacrificed for gross and histopathological examination. Five of the remaining rats were sacrificed on the 14th day of recovery for identical examination. Organs and tissues examined included adrenal glands, thyroid gland, esophagus, stomach, duodenum, pancreas, jejunum, ileum, cecum, colon, liver, spleen, thymus, mediastinal lymph nodes, eye, brain, trachea, heart, nose, urinary bladder, lungs, sternum, kidneys, testes and epididymides.
- H. Organ and Weight Analysis: At each sacrifice organ weights and organ to body weight ratios were determined for heart, liver, lungs, kidneys, spleen, testes and thymus.
- I. Urine Analysis for MUF: Of the 15 rats/group exposed to the test material, 5/group were used solely for collection of urine samples for MUF analysis. Urine samples were collected overnight from these rats on exposure days 1, 4, and 9 and on recovery days 3, 6, and 13. Samples were analyzed by gas chromatography. A Hewlett-Packard 5880A GC equipped with a nitrogen-phosphorus detector and a 10' x 1/8" I.D. stainless-steel column packed with Chromosorb® 103, 80/100 mesh was used for the analysis.

III. Results: Chamber temperature was maintained at 27-34°C.

A. Exposure Data

Exposure No.	Design Level - 0.1 mg/L			Design Level - 0.3 mg/L		
	Mean	S.D.	Range	Mean	S.D.	Range
1	0.06	0.02	0.04-0.08	0.33	0.03	0.28-0.36
2	0.10	0.05	0.04-0.19	0.31	0.08	0.21-0.46
3	0.17	0.02	0.14-0.21	0.38	0.06	0.29-0.51
4	0.09	0.01	0.07-0.12	0.29	0.08	0.16-0.50
5	0.14	0.03	0.08-0.18	0.33	0.04	0.26-0.39
6	0.12	0.01	0.10-0.15	0.27	0.02	0.25-0.31
7	0.14	0.01	0.11-0.15	0.30	0.03	0.26-0.33
8	0.14	0.03	0.09-0.21	0.32	0.05	0.24-0.41
9	0.13	0.01	0.12-0.15	0.34	0.03	0.31-0.39
10	0.09	0.02	0.06-0.11	0.30	0.04	0.03-0.36
Overall	0.12	0.04	0.04-0.21	0.32	0.06	0.03-0.51

Exposure No.	Design Level - 1.0 mg/L		
	Mean	S.D.	Range
1	0.81	0.20	0.61-1.3
2	0.87	0.19	0.63-1.1
3	0.88	0.17	0.69-1.2
4	0.94	0.22	0.60-1.1
5	1.0	0.15	0.76-1.2
6	1.1	0.22	0.69-1.4
7	1.1	0.15	0.82-1.4
8	1.1	0.30	0.74-1.8
9	1.0	0.15	0.78-1.3
10	0.96	0.28	0.67-1.6
Overall†	0.97	0.22	0.60-1.8

†Mean of all samples from 10 exposures.

- B. Clinical Observations: Clinical observations of rats exposed to MTF were indistinguishable from controls throughout the study.
- C. Clinical Chemistry(1): Statistical analysis of the data indicated that following the exposure period, rats exposed to 0.32 and 0.97 mg/L had increased serum cholesterol concentrations. Rats exposed to 0.97 mg/L also had decreased serum urea nitrogen concentrations, decreased serum alkaline phosphatase activities, and increased serum ALT/GPT and AST/GOT activities. These changes were interpreted to be evidence of treatment-related effects on the integrity and function of hepatic tissue.

Other changes which were not interpreted as being treatment related include: decreased serum urea nitrogen concentrations and decreased urinary solute concentrations in rats exposed to 0.12 and 0.32 mg/L; and decreased mean corpuscular volumes, increased serum creatinine concentrations, and increased urine excretion in rats exposed to 0.97 mg/L. Following 14 days recovery, the only difference between test rats and controls was excretion of a more alkaline urine in rats exposed to 0.32 mg/L.

The serum urea nitrogen concentrations in rats exposed to 0.12 and 0.32 mg/L were not interpreted to be treatment related because the mean concentrations for these groups maintained their quantitative differences from the control mean following the 14-day observation period. The statistically-significant changes in mean corpuscular volumes and serum creatinine concentrations observed in rats exposed to 0.97 mg/L were within the expected range of biological variation and therefore not considered compound related. The biological significance of the changes in urinary parameters could not be determined because of specimen contamination.

(1)Matarrese, Catherine C. and Raymond M. Everett, Clinical Pathology Report No. 28-82, MR-4378-001, H-14,513, November 3, 1982.

All compound-related effects observed at the end of the exposure period were absent 14 days later.

The 0.12 mg/L exposure concentration was a no-effect level for the hematologic and clinical chemical parameters measured in this study.

- D. Pathology(2): Examination revealed no compound-related macroscopic lesions in any rats. Microscopically, there were compound-related effects following exposure in the livers of rats exposed to 0.32 and 0.97 mg/L. Lesions included pale cytoplasm, increase in the number of mitotic figures, and cytoplasmic lipid vacuolation. These changes were interpreted as being degenerative and regenerative in nature. Fourteen days following exposure, partial recovery at the high level and complete recovery at the intermediate level had occurred. The low-level was a histologic no-effect level.

Other changes which were not considered compound related include mild, sporadic lung and testicular changes observed in control as well as test rats.

- E. Body and Organ Weight Analysis: Body weights of rats exposed to 0.12 mg/L were indistinguishable from controls throughout the study. Rats exposed to 0.32 mg/L had significantly lower body weights during the first week and the latter part of the second week of exposure. Gain during the recovery phase was parallel to that of controls. Rats exposed to 0.97 had significantly lower body weights throughout the study with severe weight depression during the exposure phase and weight gain at a rate parallel to that of controls during the recovery phase (Figure I, Appendix I).

A comparison of organ weights between test rats and controls showed no changes in rats exposed to 0.12 mg/L. Following 10 exposures, mean absolute weights of the heart, lung, spleen, and thymus were significantly lower in rats exposed to 0.97 mg/L than in controls. On a relative basis, rats exposed to 0.32 and 0.97 mg/L had increased liver/body weight ratios and rats exposed to 0.97 mg/L had increased testis/body weight ratios. Fourteen days following exposure there were no differences between test rats and controls (Appendix II).

(2)Stula, E. F. and William C. Krauss, Pathology Report No. 81-82, MR-4378-001, H-14,513, November 23, 1982.

F. Urine Analysis for MMF (3): MMF was excreted in a dose-dependent fashion in the urine of exposed rats. It was first detected in urine of intermediate and high level rats on Day 1 and in low level rats on Day 4. In all test groups, urinary levels of MMF generally increased throughout the exposure period and then decreased throughout the recovery period. At the end of the recovery period, MMF was still detectable in intermediate and high level rats but not in low level rats (Figure II). Specific data are presented in the following table.

Test Group	Urinary MMF (mg/16 hours)		
	Day 1	Day 4	Day 11
Control	N.D.*	N.D.	N.D.
0.12 mg/L	N.D.	0.04 ± 0.07	0.20 ± 0.06
0.32 mg/L	0.65 ± 0.36**	0.24 ± 0.19	2.1 ± 0.95
0.97 mg/L	2.0 ± 0.61	4.3 ± 6.5	9.9 ± 3.2
Test Group	Day 15	Day 18	Day 25
Control	N.D.	N.D.	N.D.
0.12 mg/L	0.07 ± 0.02	0.10 ± 0.06	N.D.
0.32 mg/L	0.15 ± 0.13	0.12 ± 0.03	0.07 ± 0.03
0.97 mg/L	0.23 ± 0.14	0.13 ± 0.04	0.03 ± 0.04

*N.D. = None detected with a minimum detection limit of 0.01 mg/mL of urine.

**Includes data from 3/5 samples; peaks unresolved in 2/5.

Based on parameters evaluated in this study, 0.12 mg/L of MMF is a no-effect level. The intermediate and high levels are definite and dose-dependent effect levels with primary effects on the liver.

(3) Sullivan, Ruth E. and Norman W. Henry, Haskell Analytical Report No. HA-82-184, MR-4372-001, November 19, 1992.

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Work by: Robert T. Turner
Robert T. Turner
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Supervision & Report by: Rayanne L. Fergis
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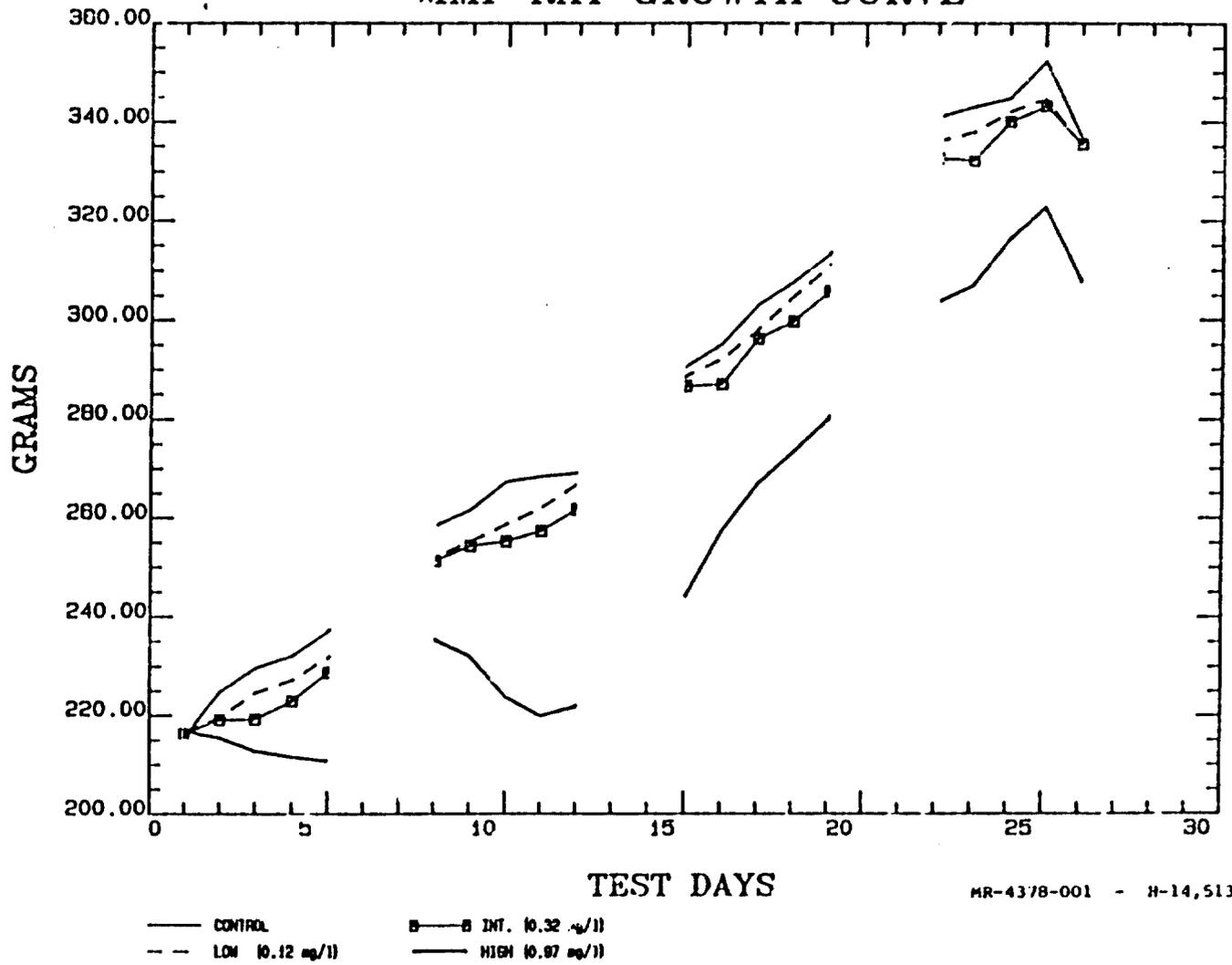
RLF:rac:WP:3.10
Study Initiated/Completed: 7/12/82-8/6/82
Date Issued: May 3, 1983
Notebook E-28336, pp. 1-134
Haskell Lab. Report No. 162-83
Number of pages in this report: 18

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FIGURE I

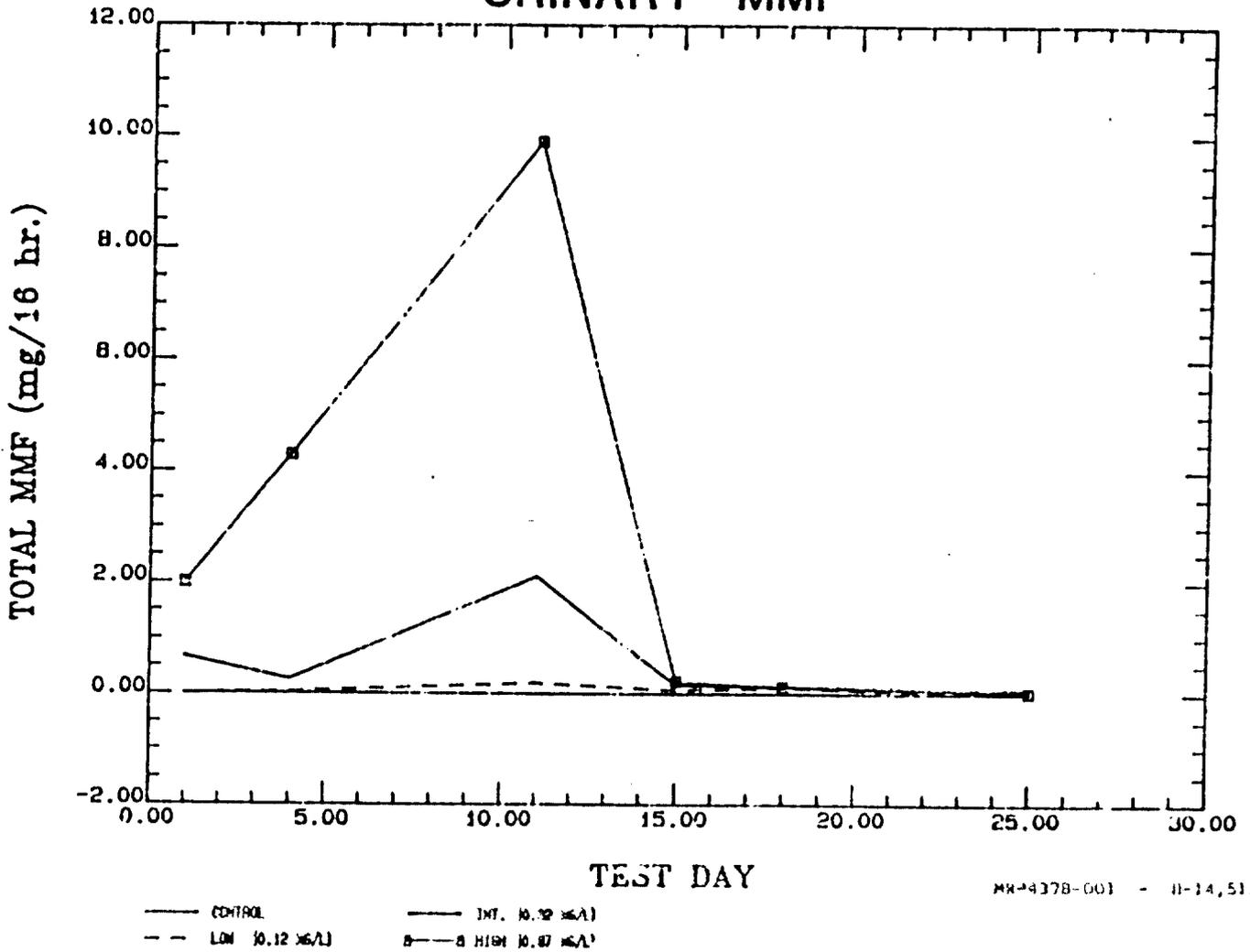
MMF RAT GROWTH CURVE



MR-4378-001 - H-14,513

FIGURE 11

URINARY MMF





E. I. DU PONT DE NEMOURS & COMPANY
INCORPORATED

HASKELL LABORATORY FOR TOXICOLOGY
AND INDUSTRIAL MEDICINE
ELKTON ROAD, NEWARK, DELAWARE 19711

CENTRAL RESEARCH AND DEVELOPMENT DEPARTMENT

PATHOLOGY REPORT NO. 81-82

Formamide, N-Methyl; N-Methylformamide (MMF)

MR-4378 - H-14513 - Biochemicals Department

Subacute Inhalation Test in Crl:CD® Male Rats

November 23, 1982

Summary

Rats were exposed to MMF by inhalation six hours/day for 10 days at the following concentrations: 0.00 mg/L (Group I - control); 0.10 mg/L (Group II, low level); 0.30 mg/L (Group III, intermediate level); and 1.00 mg/L (Group IV, high level). Each group consisted of 10 rats; 5 rats of each group were sacrificed after the last exposure and 5 rats were sacrificed after a 14-day recovery period.

Histologically, test compound-related effects were found only in the liver, at the high level (zero and 14 days recovery) and at the intermediate level (zero days recovery only). The lesions in hepatocytes were degenerative and regenerative in nature with partial recovery at the high level and complete recovery at the intermediate level. The low level was a histologic no-effect level.

Discussion

At necropsy, a statistically significant mean final body weight reduction, when compared to controls, was found only at the high level, at both zero and 14 days recovery time. A significant decrease in mean absolute weight of the thymus, spleen, heart and lung, was found at the

high level (zero days recovery only). The mean testes to body weight and liver to body weight ratios were significantly increased at the high level (zero days recovery only). At the intermediate level with zero days recovery the mean liver to body weight ratio was significantly increased. At necropsy, there were no gross lesions that were considered to be test compound-related. Microscopic observations of various tissues for individual rats together with a summary of the incidence of the various observations are presented in Table I. Test compound-related lesions in hepatocytes were as follows: pale cytoplasm, increase in the number of mitotic figures, and cytoplasmic lipid vacuolation. These changes were interpreted as being degenerative and regenerative in nature. All other changes recorded in Table I were considered to be due to natural causes or artifacts in tissue preparation and unrelated to the test chemical exposure.

Report by: E. F. Stula
E. F. Stula, D.V.M., Ph.D.
Senior Research Pathologist

Approved by: William C. Krauss
W. C. Krauss, D.V.M.
Manager, Pathology Division

EFS:WCK:ljm

CODES FOR TABLE I

Mode of Death Code

SD = Sacrificed by design

Tissue Accounting Code

N = No change observed

L = Change observed

O = No tissue present

Lesion Codes

- = Change not observed

1 = Slight degree of change observed

2 = Moderate degree of change observed

3 = Marked degree of change observed

TABLE I - MICRO OBSERVATIONS

MMF - INHALATION, SUBACUTE

C&P

HN-14513

HC-17

MR-4378

SPECIES: RAT

DOSE: CONTROL

SEX: MALE

GROUP: I

TISSUES/OBSERVATIONS	DAYS ON TEST:		12		12		26		26			
	SD	SD	SD	SD	SD	SD	SD	SD	SD	SD		
	MODE OF DEATH:		327		327		327		327			
	ANIMAL NUMBER:		096	100	103	131	132	083	099	123	126	140
	DAYS ON RECOVERY:		0	0	0	0	0	14	14	14	14	14
ESOPHAGUS	N	N	N	N	N	N	N	N	N	N	N	N
URINARY BLADDER CYSTITIS	-	-	-	-	-	-	-	-	-	-	-	-
BRAIN	N	N	N	N	N	N	N	N	N	N	N	N
STOMACH	N	N	N	N	N	N	N	N	N	N	N	N
DUODENUM	N	N	N	N	N	N	N	N	N	N	N	N
JEJUNUM	N	N	N	N	N	N	N	N	N	N	N	N
ILEUM	N	N	N	N	N	N	N	N	N	N	N	N
CECUM	N	N	N	N	N	N	N	N	N	N	N	N
COLON	N	N	N	N	N	N	N	N	N	N	N	N
MESENTERIC LYMPH NODES	N	N	N	N	N	N	N	N	N	N	N	N
PANCREAS	N	N	N	N	N	N	N	N	N	N	N	N
TESTES	N	N	N	N	N	N	N	N	N	L	N	N
GERMINAL CELL ATROPHY, FOCAL, BILATERAL	-	-	-	-	-	-	-	-	-	2	-	-
GERMINAL CELL ATROPHY, UNILATERAL	-	-	-	-	-	-	-	-	-	-	-	-
HEMORRHAGE, FOCAL	-	-	-	-	-	-	-	-	-	-	-	-
EPIDIDYIMIDES	N	N	N	N	N	N	N	N	N	N	N	N
STERNUM	N	N	N	N	N	N	N	N	N	N	N	N
EYES	N	N	N	N	N	N	N	N	N	N	N	N
NOSE	N	N	N	N	N	N	N	N	N	N	N	N

*** END OF GROUP I

TABLE I - MICRO OBSERVATIONS

MMF - INHALATION, SUBACUTE

C&P

HN-14513

HC-17

MR-4378

SPECIES: RAT

DOSE: LOW

SEX: MALE

GROUP: II

TISSUES/OBSERVATIONS	DAYS ON TEST:					MODE OF DEATH:					ANIMAL NUMBER:					DAYS ON RECOVERY:									
	12	12	12	12	12	SD	SD	SD	SD	SD	327	327	327	327	327	086	087	091	102	109	079	084	104	108	111
ESOPHAGUS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
URINARY BLADDER CYSTITIS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	-	-	-	-	-	-	-	-	-	-
BRAIN	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
STOMACH	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
DUODENUM	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
JEJUNUM	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
ILEUM	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
CECUM	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
COLON	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
MESENTERIC LYMPH NODES	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
PANCREAS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
TESTES	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
GERMINAL CELL ATROPHY, FOCAL, BILATERAL	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
GERMINAL CELL ATROPHY, UNILATERAL	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
HEMORRHAGE, FOCAL	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
EPIDIDYMIDES	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
STERNUM	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
EYES	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
NOSE	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N

*** END OF GROUP II

TABLE I - MICRO OBSERVATIONS

MMF - INHALATION, SUBACUTE

C&P

HN-14513
HC-17
MR-4378

SPECIES: RAT DOSE: INTERMEDIATE

SEX: MALE GROUP: III

DAYS ON TEST:	12	12	12	12	12	26	26	26	26	26
MODE OF DEATH:	SD									
ANIMAL NUMBER:	327	327	327	327	327	327	327	327	327	327
TISSUES/OBSERVATIONS	080	095	101	112	137	085	094	098	135	138
DAYS ON RECOVERY:	0	0	0	0	0	14	14	14	14	14

ESOPHAGUS	N	N	N	N	N	N	N	N	N	N
URINARY BLADDER CYSTITIS	N	N	N	N	N	N	N	N	N	N
BRAIN	-	-	-	-	-	-	-	-	-	-
STOMACH	N	N	N	N	N	N	N	N	N	N
DUODENUM	N	N	N	N	N	N	N	N	N	N
JEJUNUM	N	N	N	N	N	N	N	N	N	N
ILEUM	N	N	N	N	N	N	N	N	N	N
CECUM	N	N	N	N	N	N	N	N	N	N
COLON	N	N	N	N	N	N	N	N	N	N
MESENTERIC LYMPH NODES	N	N	N	N	N	N	N	N	N	N
PANCREAS	N	N	N	N	N	N	N	N	N	N
TESTES	N	N	N	N	N	N	N	N	L	N
GERMINAL CELL ATROPHY, FOCAL, BILATERAL	-	-	-	-	-	-	-	-	-	-
GERMINAL CELL ATROPHY, UNILATERAL	-	-	-	-	-	-	-	-	2	-
HEMORRHAGE, FOCAL	-	-	-	-	-	-	-	-	-	-
EPIDIDYMIDES	N	N	N	N	N	N	N	N	N	N
STERNUM	N	N	N	N	N	N	N	N	N	N
EYES	N	N	N	N	N	N	N	N	N	N
NOSE	N	N	N	N	N	N	N	N	N	N

*** END OF GROUP III

TABLE I - MICRO OBSERVATIONS

MMF - INHALATION, SUBACUTE

C&P

HN-14513

HC-17

MR-4378

SPECIES: RAT

DOSE: HIGH

SEX: MALE

GROUP: IV

TISSUES/OBSERVATIONS	DAYS ON TEST:		MODE OF DEATH:		ANIMAL NUMBER:		DAYS ON RECOVERY:	
	12	26	SD	SD	089	117	120	122
	12	26	SD	SD	081	082	105	118
	12	26	327	327	121	121	121	121
	0	0	0	0	0	14	14	14
ESOPHAGUS	N	N	N	N	N	N	N	N
URINARY BLADDER CYSTITIS	-	-	-	-	-	-	-	-
BRAIN	N	N	N	N	N	N	N	N
STOMACH	N	N	N	N	N	N	N	N
DUODENUM	N	N	N	N	N	N	N	N
JEJUNUM	N	N	N	N	N	N	N	N
ILEUM	N	N	N	N	N	N	N	N
CECUM	N	N	N	N	N	N	N	N
COLON	N	N	N	N	N	N	N	N
MESENTERIC LYMPH NODES	N	N	N	N	N	N	N	N
PANCREAS	N	N	N	N	N	N	N	N
TESTES -	N	N	N	L	N	N	N	N
GERMINAL CELL ATROPHY, FOCAL, BILATERAL	-	-	-	-	-	-	-	-
GERMINAL CELL ATROPHY, UNILATERAL	-	-	-	1	-	-	-	-
HEMORRHAGE, FOCAL	-	-	-	-	-	-	-	-
EPIDIDYMIDES	N	N	N	N	N	N	N	N
STERNUM	N	N	N	N	N	N	N	N
EYES	N	N	N	N	N	N	N	N
NOSE	N	N	N	N	N	N	N	N

*** END OF GROUP IV

SUMMARY TABLE

PART 3

HN-14513

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D-4378

INCIDENCES OF NON-NEOPLASTIC LESIONS
 SPECIES: RAT COMPOUND: MHF - INHALATION, SUBACUTE
 TABLE I - MICRO OBSERVATIONS

MALES (days-on-test from 1 to 12)

TISSUE/LESION:	GROUP DESIGNATION:	I	II	III	IV
	DOSE (MG/L):	0.00	0.10	0.30	1.00
	NUMBER IN GROUP:	10	10	10	10
=====					
LIVER		5	5	5	5
CENTRIOBULAR CYTOPLASMIC VACUOLATION		-	-	-	-
HEMATOPOIESIS, FOCAL		-	1	1	-
LIPID VACUOLATION, CYTOPLASMIC, HEPATOCELLULAR		-	-	1	5
MITOTIC FIGURE INCREASE, CENTRIOBULAR		-	-	3	2
PALE CYTOPLASM, HEPATOCELLULAR		-	-	3	-
PALE CYTOPLASM, HEPATOCELLULAR, CENTRIOBULAR		-	-	2	5
KIDNEYS		5	5	5	5
CYTOPLASMIC VACUOLATION, PROXIMAL TUBULES		-	-	-	-
NEPHROPATHY, CORTICAL, TUBULAR, FOCAL		-	-	-	-
PYELITIS, BILATERAL		-	-	-	-
LUNG		5	5	5	5
EDEMA		-	-	-	-
EMPHYSEMA		-	-	-	-
EPITHELIAL HYPERPLASIA, ALVEOLAR/BRONCHIOLAR		-	-	-	-
FIBROSING ALVEOLITIS		-	-	-	-
FIBROSIS, ALVEOLAR, FOCAL		-	-	-	-
HEMORRHAGE, ALVEOLAR LUMEN, FOCAL		-	-	-	1
MACROPHAGE, FOCI, INTRABRONCHIOLAR		-	-	-	-
MACROPHAGES, FOCI, INTRAALVEOLAR		2	-	-	-
MURINE PNEUMONIA		-	-	-	-
OSSEOUS METAPLASIA, ALVEOLAR, FOCAL		-	-	-	-
PLEURITIS		-	-	-	-
HEART		5	5	5	5
SPLEEN		5	5	5	5
THYMUS		5	5	5	5
LYMPHOID CELL ATROPHY		-	-	-	-
ADRENALS		5	5	5	5
THYROID		5	5	5	5
TRACHEA		5	5	5	5
ESOPHAGUS		5	5	5	5

SUMMARY TABLE

PART:

HN-14513
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INCIDENCES OF NON-NEOPLASTIC LESIONS
SPECIES: RAT COMPOUND: MMF - INHALATION, SUBACUTE
TABLE I - MICRO OBSERVATIONS

TISSUE/LESION:	MALES (days-on-test from 1 to 12)				
	GROUP DESIGNATION:	I	II	III	IV
	DOSE (MG/L):	0.00	0.10	0.30	1.00
NUMBER IN GROUP:	10	10	10	10	
URINARY BLADDER	<u>5</u>	<u>5</u>	<u>5</u>	<u>5</u>	
CYSTITIS	-	-	-	-	
BRAIN	<u>5</u>	<u>5</u>	<u>5</u>	<u>5</u>	
STOMACH	<u>5</u>	<u>5</u>	<u>5</u>	<u>5</u>	
DUODENUM	<u>5</u>	<u>5</u>	<u>5</u>	<u>5</u>	
JEJUNUM	<u>5</u>	<u>5</u>	<u>5</u>	<u>5</u>	
ILEUM	<u>5</u>	<u>5</u>	<u>5</u>	<u>5</u>	
CECUM	<u>5</u>	<u>5</u>	<u>5</u>	<u>5</u>	
COLON	<u>5</u>	<u>5</u>	<u>5</u>	<u>5</u>	
MESENTERIC LYMPH NODES	<u>5</u>	<u>5</u>	<u>5</u>	<u>5</u>	
PANCREAS	<u>5</u>	<u>5</u>	<u>5</u>	<u>5</u>	
TESTES	<u>5</u>	<u>5</u>	<u>5</u>	<u>5</u>	
GERMINAL CELL ATROPHY, FOCAL, BILATERAL	-	-	-	-	
GERMINAL CELL ATROPHY, UNILATERAL	-	-	-	1	
HEMORRHAGE, FOCAL	-	-	-	-	
EPIDIDYMIDES	<u>5</u>	<u>5</u>	<u>5</u>	<u>5</u>	
STERNUM	<u>5</u>	<u>5</u>	<u>5</u>	<u>5</u>	
EYES	<u>5</u>	<u>5</u>	<u>5</u>	<u>5</u>	
NOSE	<u>5</u>	<u>5</u>	<u>5</u>	<u>5</u>	

NOTES:

- o THE NUMBER OF ORGANS EXAMINED FOR EACH GROUP IS UNDERLINED.

SUMMARY TABLE

PART

HN-14513
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INCIDENCES OF NON-NEOPLASTIC LESIONS
 SPECIES: RAT COMPOUND: MMF - INHALATION, SUBACUTE
 TABLE I - MICRO OBSERVATIONS

MALES (days-on-test from 13 to 26)

TISSUE/LESION:	GROUP DESIGNATION: DOSE (MG/L): NUMBER IN GROUP:	I 0.00 10	II 0.10 10	III 0.30 10	IV 1.00 10
LIVER		5	5	5	5
CENTRILOBULAR CYTOPLASMIC VACUOLATION		1	4	1	-
HEMATOPOIESIS, FOCAL		1	-	-	-
LIPID VACUOLATION, CYTOPLASMIC, HEPATOCELLULAR		-	-	-	-
MITOTIC FIGURE INCREASE, CENTRILOBULAR		-	-	-	-
PALE CYTOPLASM, HEPATOCELLULAR		-	-	1	5
PALE CYTOPLASM, HEPATOCELLULAR, CENTRILOBULAR		-	-	-	-
KIDNEYS		5	5	5	5
CYTOPLASMIC VACUOLATION, PROXIMAL TUBULES		-	-	-	-
NEPHROPATHY, CORTICAL, TUBULAR, FOCAL		-	-	-	1
PYELITIS, BILATERAL		-	-	-	-
LUNG		5	5	5	5
EDEMA		-	-	-	-
EMPHYSEMA		-	-	-	-
EPITHELIAL HYPERPLASIA, ALVEOLAR/BRONCHIOLAR		-	-	-	-
FIBROSING ALVEOLITIS		-	-	-	-
FIBROSIS, ALVEOLAR, FOCAL		-	-	-	-
HEMORRAGE, ALVEOLAR LUMEN, FOCAL		-	-	1	-
MACROPHAGE, FOCI, INTRABRONCHIOLAR		-	-	-	1
MACROPHAGES, FOCI, INTRAALVEOLAR		1	-	-	-
MURINE PNEUMONIA		-	1	-	-
OSSEOUS METAPLASIA, ALVEOLAR, FOCAL		-	-	-	-
PLEURITIS		-	-	-	-
HEART		5	5	5	5
SPLEEN		5	5	5	5
THYMUS		5	5	5	5
LYMPHOID CELL ATROPHY		-	-	-	-
ADRENALS		5	5	5	5
THYROID		5	5	5	5
TRACHEA		5	5	5	5
ESOPHAGUS		5	5	5	5

SUMMARY TABLE

PART:

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INCIDENCES OF NON-NEOPLASTIC LESIONS
 SPECIES: RAT COMPOUND: MMF - INHALATION, SUBACUTE
 TABLE I - MICRO OBSERVATIONS

TISSUE/LESION:	MALES				
	(days-on-test from 13 to 26)				
	GROUP DESIGNATION:	I	II	III	IV
	DOSE (MG/L):	0.00	0.10	0.30	1.00
NUMBER IN GROUP:	10	10	10	10	
URINARY BLADDER	<u>5</u>	<u>5</u>	<u>5</u>	<u>5</u>	
CYSTITIS	-	-	-	-	
BRAIN	<u>5</u>	<u>5</u>	<u>5</u>	<u>5</u>	
STOMACH	<u>5</u>	<u>5</u>	<u>5</u>	<u>5</u>	
DUODENUM	<u>5</u>	<u>5</u>	<u>5</u>	<u>5</u>	
JEJUNUM	<u>5</u>	<u>5</u>	<u>5</u>	<u>5</u>	
ILEUM	<u>5</u>	<u>5</u>	<u>5</u>	<u>5</u>	
CECUM	<u>5</u>	<u>5</u>	<u>5</u>	<u>5</u>	
COLON	<u>5</u>	<u>5</u>	<u>5</u>	<u>5</u>	
MESENTERIC LYMPH NODES	<u>5</u>	<u>5</u>	<u>5</u>	<u>5</u>	
PANCREAS	<u>5</u>	<u>5</u>	<u>5</u>	<u>5</u>	
TESTES	<u>5</u>	<u>5</u>	<u>5</u>	<u>5</u>	
GERMINAL CELL ATROPHY, FOCAL, BILATERAL	1	-	-	-	
GERMINAL CELL ATROPHY, UNILATERAL	-	-	1	-	
HEMORRHAGE, FOCAL	-	-	-	-	
EPIDIDYMIDES	<u>5</u>	<u>5</u>	<u>5</u>	<u>5</u>	
STERNUM	<u>5</u>	<u>5</u>	<u>5</u>	<u>5</u>	
EYES	<u>5</u>	<u>5</u>	<u>5</u>	<u>5</u>	
NOSE	<u>5</u>	<u>5</u>	<u>5</u>	<u>5</u>	

NOTES:

o THE NUMBER OF ORGANS EXAMINED FOR EACH GROUP IS UNDERLINED.



UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
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Wilmington, Delaware 19898

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

APR 18 1995

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Sincerely,

Terry R. O'Bryan

Terry R. O'Bryan
Risk Analysis Branch

Enclosure

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Triage of 8(e) Submissions

Date sent to triage: AUG 24 1985

NON-CAP CAP

Submission number: 12042A

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:

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

For Contractor Use Only

entire document: 0 1 2 pages 1,151 NIB pages 1,770 BS

Notes:

Contractor reviewer: POZ Date: 3/21/95

CECATSTRIDGE TRACKING DBASE ENTRY FORM

CECATS DATA: Submission # SEHO-1092-12092 SEQ. A

TYPE: (INT) SUPP FLWP

SUBMITTER NAME: E.I. Dupont de Nemours and Company

SUB. DATE: 08/10/92 OTR DATE: 10/27/92 CSRAD DATE: 01/25/95

CHEMICAL NAME: _____
CASE: 123-39-7

INFORMATION REQUESTED: FLWT DATE: _____
0501 NO INFO REQUESTED
0502 INFO REQUESTED (TECH)
0503 INFO REQUESTED (VOL ACTIONS)
0504 INFO REQUESTED (REPORTING RATIONALE)
DEPOSITE: _____
0510 REFER TO CHEMICAL SCREENING
0510 CAP NOTICE

VOLUNTARY ACTIONS:
0401 NO ACTION REPORTED
0402 STUDIES PLANNED (MINIMUM 6 M) _____
0403 MUTAGENICITY (MINIMUM 3) _____
0404 LARPLASIDS (TIAMINIS) _____
0405 PROCELLANDI ING. (TIAMINIS) _____
0406 APPAUSE DISCONTINUED
0407 PRODUCTION DISCONTINUED
0408 CONFIDENTIAL

INFORMATION TYPE:	L.F.C.	INFORMATION TYPE:	L.F.C.	INFORMATION TYPE:	L.F.C.
0201 ONCO (HUMAN)	01 02 04	0216 EPICLIN	01 02 04	0241 BAMBINO (ANIMAL)	01 02 04
0202 ONCO (ANIMAL)	01 02 04	0217 HUMAN EXPOS (PROD CONTAM)	01 02 04	0242 BAMBINO (HUMAN)	01 02 04
0203 CELL TRANS (IN VITRO)	01 02 04	0218 HUMAN EXPOS (ACCIDENTAL)	01 02 04	0243 CHEMOPHYS 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 REPROTERATO (HUMAN)	01 02 04	0221 ENV. OCCUREL/FATE	01 02 04	0246 CLASTO (HUMAN)	01 02 04
0207 REPROTERATO (ANIMAL)	01 02 04	0222 EMER INCI OF ENV CONTAM	01 02 04	0247 DNA DAMAGE/PAIR	01 02 04
0208 NEURO (HUMAN)	01 02 04	0223 RESPONSE ROBUST DELAY	01 02 04	0248 PRODUSE/PROC	01 02 04
0209 NEURO (ANIMAL)	01 02 04	0224 PRODUCE/PROC 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 METABPHARMACOD (ANIMAL)	01 02 04		
0215 CHRONIC TOX (ANIMAL)	01 02 04	0230 METABPHARMACOD (HUMAN)	01 02 04		

TRADE NAME: _____ NON-ORI INVENTORY: _____
 YES (DROP/REFER) NO (CONTINUE) REPT-R
 CAS SR: _____
 YES NO IN PENDING
 SPECIES: RAT TOXICOLOGICAL CONCERN: LOW (circled) ~~MED~~ HIGH
 USE: _____ PRODUCTION: _____

1-123-39-7

-CPSS- 0301960919

0 0 0 0 0 0 0 0 0 0 0
> <ID NUMBER>
8(E)-12042A

> <TOX CONCERN>
L

> <COMMENT>

SUBACUTE INHALATION TOXICITY IN MALE CRL:CD RATS IS OF LOW CONCERN. REPEAT 6-HOUR EXPOSURES 5 DAYS PER WEEK FOR 2 WEEKS AT CONCENTRATIONS OF 0.12, 0.32 OR 0.97 MG/L ADMINISTERED TO GROUPS OF 15 EACH MALE RATS WERE ASSOCIATED WITH DOSE-RELATED DEGENERATIVE LIVER CHANGES THAT WERE RESOLVED BY THE END OF 14- DAY POST-TREATMENT OBSERVATION. ALL MEASURED PARAMETERS RELATED TO A 0.12 MG/L EXPOSURE REGIMEN WERE INDISTINGUISHABLE FROM THOSE OF CONTROLS. CLINICAL SIGNS OF TOXICITY IN ANIMALS OF 0.32 AND 0.97 MG/L EXPOSURES INCLUDED REDUCED WEIGHT GAINS WITH INCREASED MEAN ABSOLUTE LIVER WEIGHTS. MEAN ABSOLUTE ORGAN WEIGHTS WERE ALSO SIGNIFICANTLY REDUCED FOR HEART, LUNG, SPLEEN AND THYMUS IN ANIMALS OF THE 0.97 MG/L EXPOSURES WITH INCREASED TESTIS/BODYWEIGHT RATIOS. MICROPATHOLOGY OBSERVED IN THE LIVER OF ANIMALS RECEIVING EXPOSURES TO 0.32 AND 0.97 MG/L WAS CHARACTERIZED AS BOTH DEGENERATIVE AND REGENERATIVE IN NATURE AND INCLUDED PALE CYTOPLASM, INCREASED NUMBER OF MITOTIC FIGURES AND CYTOPLASMIC LIPID VACUOLATION. RECOVERY FROM LIVER-SPECIFIC EFFECTS WAS COMPLETE AT THE 0.32 MG/L LEVEL OF EXPOSURE AND NEARLY COMPLETE IN THE 0.97 MG/L LEVEL OF EXPOSURE BY THE END OF 14-DAY OBSERVATION; BODYWEIGHT GAINS NORMALIZED DURING OBSERVATION AS WELL. CHEMISTRY INDICATORS OF LIVER-SPECIFIC TOXICITY INCLUDED INCREASED SERUM CHOLESTEROL IN ANIMALS OF 0.32 MG/L REGIMEN, WHILE RATS OF THE 0.97 MG/L EXPOSURES ALSO DEMONSTRATED DECREASED SERUM UREA NITROGEN CONCENTRATIONS, DECREASED SERUM ALKALINE PHOSPHATASE ACTIVITY AND INCREASED SERUM ALT/GPT AND AST/GOT ACTIVITY. THESE CHANGES WERE ATTENUATED, ALTHOUGH THE TEST SUBSTANCE WAS STILL FOUND IN THE URINE OF 0.97 MG/L EXPOSED ANIMALS AT STUDY END.

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-CPSS-

> <ID NUMBER>

8(E)-12042A

> <TOX CONCERN>

L

> <COMMENT>

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