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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 6/28/91CAP 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



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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 standard<sup>2</sup>. This is particularly troublesome as the "Reporting Guide" states criteria, applied retroactively, which expands upon and conflicts with the Statement of Interpretation.<sup>3</sup> 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).

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<sup>2</sup>In 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".

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

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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 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 intent<sup>4</sup>, 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.<sup>5</sup>
- othe "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.
- othe "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.

<sup>4</sup>The '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.

<sup>5</sup> 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?
<b>ACUTE LETHALITY</b>		
Oral	N}	Y}
Dermal	N}	Y}
Inhalation (Vapors)	} <sup>6</sup>	} <sup>7</sup>
aerosol	N}	Y}
dusts/ particles	N}	Y}
SKIN IRRITATION	N	Y <sup>8</sup>
SKIN SENSITIZATION (ANIMALS)	N	Y <sup>9</sup>
EYE IRRITATION	N	Y <sup>10</sup>
SUBCHRONIC (ORAL/DERMAL/INHALATION)	N	Y <sup>11</sup>
REPRODUCTION STUDY	N	Y <sup>12</sup>
DEVELOPMENTAL TOX	Y <sup>13</sup>	Y <sup>14</sup>

<sup>6</sup>43 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."

<sup>7</sup>Guide at pp.22, 29-31.

<sup>8</sup>Guide at pp-34-36.

<sup>9</sup>Guide at pp-34-36.

<sup>10</sup>Guide at pp-34-36.

<sup>11</sup>Guide at pp-22; 36-37.

<sup>12</sup>Guide at pp-22

<sup>13</sup>43 Fed Reg at 11112

"Birth Defects" listed.

<sup>14</sup>Guide at pp-22

NEUROTOXICITY	N	Y <sup>15</sup>
CARCINOGENICITY	Y <sup>16</sup>	Y <sup>17</sup>
<b>MUTAGENICITY</b>		
<i>In Vitro</i>	Y <sup>18</sup>	Y <sup>19</sup>
<i>In Vivo</i>	Y}	Y}
<b>ENVIRONMENTAL</b>		
Bioaccumulation	Y}	N
Bioconcentration	Y <sup>20</sup>	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
<b>AVIAN</b>		
Acute	N	N
Reproductive	N	N
Reprodcutive	N	N

<sup>15</sup>Guide at pp-23; 33-34.

<sup>16</sup>43 Fed Reg at 11112  
"Cancer" listed

<sup>17</sup>Guide at pp-21.

<sup>18</sup>43 Fed Reg at 11112; 11115 at Comment 15

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

<sup>19</sup>Guide at pp-23.

<sup>20</sup>43 Fed Reg at 11112; 11115 at Comment 16.

**CAS # 75-87-6**

**Chem: Chloral**

**Title: Two-week subacute vapor inhalation toxicity  
study with chloral in albino rats**

**Date: 2/23/73**

**Summary of Effects: Mortality at 0.08 mg/L**

REPORT TO

E. I. du PONT de NEMOURS & COMPANY

TWO-WEEK SUBACUTE VAPOR INHALATION  
TOXICITY STUDY WITH  
CHLORAL  
IN ALBINO RATS

FEBRUARY 23, 1973

IBT NO. T2459

I. Introduction

A sample identified as Chloral was received from E. I. du Pont de Nemours & Company on October 16, 1972, for the purpose of conducting a two-week subacute vapor inhalation toxicity study using male albino rats as experimental animals. Exposures were initiated November 6, 1972, and terminated November 17, 1972.

## II. Summary

Twenty male albino rats were selected and divided into two equal groups designated Test and Untreated Control. The test group was exposed to vapor of Chloral at an average nominal concentration of 0.08 mg/L air. Inhalation exposures were four hours per day, five days per week, for a two-week period (a total of ten exposures).

Observations were made with respect to incidence of mortality, reactions displayed, and body weight effects. A schedule was arranged to sacrifice half of the rats from each group within a few hours after the last inhalation exposure and to sacrifice the remaining animals after a two-week recovery period. Gross and microscopic pathologic studies were performed on each animal (including any rats which died during the investigational period). In addition, organ weights were recorded and subjected to statistical analyses.

Six test group rats died during the two-week exposure period, and body weight losses were noted in all surviving test animals. Untoward behavioral reactions included sneezing, ptosis, dyspnea, and weakness. These reactions were slight during the first three test days; however, they gradually increased in severity with each exposure until extreme weakness or death occurred.

Test group rats which died during the two-week exposure period displayed severe edema and severe diffuse red discoloration of the lungs. In addition, most of these rats showed reduced organ sizes

and empty gastrointestinal tracts. Animals surviving the inhalation exposures and the two-week recovery period showed white foci on the lungs with no occurrences of red discoloration. Histopathologic examination of the lungs did not reveal any changes which could be directly attributed to inhalation of Chloral vapors.

Statistical analyses of organ weights revealed several differences between control and test group animals. Organs noted as showing effects included lungs, spleen, liver, kidneys, heart, and gonads.

Respectfully submitted,

INDUSTRIAL BIO-TEST LABORATORIES, INC.

Report prepared by:

Victor M. Bowers

Victor M. Bowers, B.A.  
Assistant Toxicologist  
Inhalation Toxicity

Report approved by:

Kenneth J. Schadeberg

Kenneth J. Schadeberg, B.S.  
Senior Group Leader  
Inhalation and Pharmacology

John W. Goode

John W. Goode, Ph. D.  
Manager  
Decatur Research Laboratories

M. L. Keplinger

M. L. Keplinger, Ph. D.  
Manager, Toxicology

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### III. Procedure

#### A. Experimental Animals

Young male albino rats of the Sprague-Dawley strain\* were used as test animals. Twenty rats were selected after having been observed for at least five days to insure their general health and suitability for testing. The rats were divided into two groups, designated Test and Untreated Control. All rats were housed individually in stock cages and permitted a standard laboratory diet\*\* plus water ad libitum, except during inhalation exposures.

#### B. Exposure Schedule

The test group was exposed four hours per day, five days per week, for a two-week period (ten exposures). Inhalation exposures were initiated November 6, 1972, and terminated November 17, 1972.

#### C. Experimental Apparatus

Test group animals were exposed in a specially constructed Plexiglas inhalation chamber having a capacity of 700 liters. Each animal was caged separately during exposure to minimize filtration of inspired air by animal fur.

Vapor was generated by bubbling a stream of clean dry air (-40°C dewpoint) through the undiluted test material. The resulting air-vapor mixture was introduced into the exposure chamber at the

\* ARS/Sprague-Dawley, Madison, Wisconsin.

\*\* Purina Rat Chow, Ralston Purina Company, St. Louis, Missouri.

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top center, dispersed by a baffle plate and exhausted at the bottom of the chamber. The vapor generator was all-glass construction and was linked to the exposure chamber by a short length of Tygon tubing. Air flow rate through the system (0.13 L/min at 29.92 inches Hg and 25°C) was measured with a rotameter, connected upstream of the generator. The rotameter was calibrated with a bubble meter before each exposure. In order to achieve the desired final vapor concentration, an additional stream of clean dry air was supplied at the top of the chamber. This larger air flow was measured by a hot-wire anemometer\*. The additional air was maintained at 537 L/min ( $\pm 20$  L/min). The average daily nominal vapor concentration was calculated by dividing the weight loss of the vapor generator by the total volume of air used for each exposure. The overall average concentration was found to be 0.08 mg/L air.

#### D. Mortality and Reactions

All rats were observed daily for incidence of mortality and reactions displayed.

#### E. Body Weight Effects

The body weight of each rat was determined and recorded on the first test day. Thereafter, individual weighings were conducted weekly and the data recorded as an index to body weight effects.

\* Alnor Instrument Company, Chicago, Illinois; Type FE-AVM.

F. Pathologic Studies

Arrangements were made to subject any animal which might die during the test to a gross autopsy. Also, in those instances when postmortem changes were not advanced, sections of representative tissues and organs were to be taken for histopathologic study. Before exposures were initiated, a schedule was set to sacrifice five rats from each group of animals within a few hours after the last inhalation exposure. The remaining animals were to be sacrificed after a two-week recovery period. In the event of significant mortality (seven or more rats per group) during the two weeks of inhalation exposures, it was decided that all surviving rats would not be sacrificed until after the two-week recovery period. Also, for each animal sacrificed, a complete set of tissues and organs was removed and preserved in ten percent buffered formalin solution (pH 7.0).

Weights of the liver, kidneys, spleen, heart, gonads, brain, lungs, thyroid glands, and adrenal glands were determined and recorded for each control and test animal. Statistical analyses, viz. an Analysis of Variance and "t"-tests, were conducted on the absolute organ weights and on the organ to body weight and organ to brain weight ratios.

Histopathologic examinations were conducted on all test and control rats. The following tissues and organs were included: adrenal gland, brain, gonads, heart, kidney, liver, lung, lymph nodes (cervical, peribronchial, and mesenteric), spleen, trachea, and thyroid gland.

#### IV. Results

##### A. Mortality

One test animal died after the sixth inhalation exposure. A second death occurred after the seventh exposure. Four test animals died during the last (tenth) inhalation period. One test animal was sacrificed immediately after the final exposure to insure at least one set of fresh tissues for accurate histological examination. Three of the ten test rats survived the two-week test period and the following two-week observation or recovery period.

##### B. Body Weight Effects

Inhalation of the test material vapor caused large weight losses in all of the test rats over the two-week testing period. The three surviving rats gained a considerable amount of weight during the two-week observation period, but their final weights were still lower than those of the untreated control rats. Individual body weights and weight gain data are presented in Table 1.

TABLE I

TEST MATERIAL: Chloral

Two-Week Subacute Vapor Inhalation: Toxicity Study - Albino Rats

Individual Body Weight and Weight Gain Data

Group	Animal Number	Individual Body Weights (grams)			Two-Week Body Weight Gain		Four-Week Body Weight Gain	
		0	1	2	Final	Body Weight Gain	Body Weight Gain	
Untreated Control	1	150	209	243	-	93	-	-
	2	166	224	258	-	92	-	-
	3	176	234	263	-	87	-	-
	4	150	216	199	-	49	-	-
	5	170	228	256	-	86	-	-
	6	153	98	156	195	257	3	104
	7	169	207	255	290	311	86	142
	8	165	225	258	280	310	93	145
	9	155	218	250	282	306	95	151
	10	164	240	269	304	335	105	171
Test	11	168	151	137	209	268	-31	100
	12	158	155	143	183	255	-15	97
	13	176	144	119	-	-	-57	-
	14	184	142	-	-	-	-	-
	15	168	147	119	-	-	-49	-
	16	162	177	141	-	-	-21	-
	17	168	178	152	208	262	-16	94
	18	167	150	134	-	-	-33	-
	19	174	156	113	-	-	-61	-
	20	170	155	-	-	-	-	-

Animal died or was sacrificed.

C. Behavioral Reactions

The first outward behavioral reaction noted was sneezing after 30 minutes of exposure. After 60 minutes, all animals exhibited ptosis, and after 90 minutes a few animals showed dyspnea. All of these reactions continued with progressive increases in severity with each daily exposure to the Chloral vapors until either death or extreme weakness occurred. The three surviving rats showed normal behavior within three days after the last inhalation exposure.

D. Pathology

1. Gross Pathologic Findings

Necropsy examination of the test rats which died during the two-week test period and of those which were sacrificed after the two-week observation period revealed a general stunting of growth of all the organs. This effect was more pronounced in the rats which died during the test period. In addition, all rats that died displayed severe edema and severe diffuse red discoloration of the lungs. No food was found in the gastrointestinal tract in any of the test animals which died during the test period. Necropsy examination of rats surviving the two-week recovery period revealed only white foci on the lungs of each animal. Necropsy examination of control animals did not reveal any gross pathologic findings in any of the tissues and organs examined during either the interim or final sacrifice.

2. Organ Weight Data

Organ weights and organ weight ratios varied considerably between test and control animals at the interim sacrifice. Organs showing effects included lungs, brain, adrenal glands, gonads, heart, kidneys, liver, and spleen. Most of these effects are probably attributable to starvation (as indicated by empty gastrointestinal tract).

Significant differences were observed in organ weights and organ weight ratios in the lungs and adrenal glands only of the animals sacrificed after the two-week observation period.

The organ weight and organ weight ratios are presented in Tables II through X. It should be noted that the comparisons made were between control and test animals which died or were sacrificed at the end of the two-week exposure period and between control and test animals surviving the two-week recovery period.

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TABLE II

## TEST MATERIAL: Chloral

Two-Week Subacute Vapor Inhalation Toxicity Study - Albino Rats

Mean Organ Weight and Ratio Data

Organ: Lungs

Group	Absolute Organ Weight (g)	Organ/Body Weight Ratio (g/100 g)	Organ/Brain Weight Ratio (g/g)
Interim Control	1.307	0.538	0.815
Interim Test	3.039**	2.520***	1.970**
Final Control	1.537	0.505	0.900
Final Test	1.980	0.774*	1.175*

\* Statistically significant difference at the 95 percent confidence level.

\*\* Statistically significant difference at the 99 percent confidence level.

TABLE III

TEST MATERIAL: Chloral

Two-Week Subacute Vapor Inhalation Toxicity Study - Albino Rats

Mean Organ Weight and Ratio Data

Organ: Thyroid Glands

Group	Absolute Organ Weight (g)	Organ/Body Weight Ratio (g/100 g)	Organ/Brain Weight Ratio ( $\frac{\mu}{\mu}$ )
Interim Control	0.018	0.005	0.012
Interim Test	0.012	0.011	0.008
Final Control	0.019	0.006	0.011
Final Test	0.018	0.007	0.011

TABLE IV  
 TEST MATERIAL: Chloral  
 Two-Week Subacute Vapor Inhalation Toxicity Study - Albino Rats  
 Mean Organ Weight and Ratio Data

Group	Absolute Organ Weight (g)	Organ: Spleen	
		Organ/Body Weight Ratio (g/100 g)	Organ/Brain Weight Ratio (g/g)
Interim Control	0.692	0.282	0.431
Interim Test	0.194**	0.160**	0.128**
Final Control	0.721	0.238	0.425
Final Test	1.184	0.446	0.702

\*\* Statistically significant difference at the 99 percent confidence level.

TABLE V

TEST MATERIAL: Chloral

Two-Week Subacute Vapor Inhalation Toxicity Study - Albino Rats

Mean Organ Weight and Ratio Data

Organ: Liver

Group	Absolute Organ Weight (g)	Organ/Body Weight Ratio (g/100 g)	Organ/Brain Weight Ratio (g/g)
Interim Control	9.683	3.929	6.023
Interim Test	4.699**	3.908	3.083**
Final Control	11.465	3.778	6.752
Final Test	10.100	3.889	5.992

\*\* Statistically significant difference at the 99 percent confidence level.

TABLE VI

## TEST MATERIAL: Chloral

Two-Week Subacute Vapor Inhalation Toxicity Study - Albino Rats

Mean Organ Weight and Ratio Data

Organ: Kidneys

Group	Absolute Organ Weight (g)	Organ/Body Weight Ratio (%/100 g)	Organ/Brain Weight Ratio (g/g)
Interim Control	1.985	0.816	1.237
Interim Test	1.164**	0.978**	0.770
Final Control	2.319	0.757	1.364
Final Test	1.930	0.748	1.145

\*\* Statistically significant difference at the 99 percent confidence level.

TABLE VII

TEST MATERIAL: Chloral

Two-Week Subacute Vapor Inhalation Toxicity Study - Albino Rats

Mean Organ Weight and Ratio Data

Organ: Heart

Group	Absolute Organ Weight (g)	Organ./Body Weight Ratio (g/100 g)	Organ./Brain Weight Ratio (g/g)
Interim Control	0.811	0.334	0.506
Interim Test	0.524**	0.439**	0.346**
Final Control	1.045	0.343	0.617
Final Test	0.930	0.361	0.552

\*\* Statistically significant difference at the 99 percent confidence level.

TABLE VIII

TEST MATERIAL: Chloral

Two-Week Subacute Vapor Inhalation Toxicity Study - Albino Rats

Mean Organ Weight and Ratio Data

Organ: Gonads

Group	Absolute Organ Weight (g)	Organ/Body Weight Ratio (g/100 g)	Organ/Brain Weight Ratio (g/g)
Control	3.981	1.646	2.485
Low Dose Test	2.127**	1.774	1.402**
High Dose Control	4.435	1.448	2.560
High Dose Test	3.545	1.372	2.103

Statistically significant difference at the 99 percent confidence level.

TABLE IX

TEST MATERIAL: Chloral

Two-Week Subacute Vapor Inhalation Toxicity Study - Albino Rats

Mean Organ Weight and Ratio Data

Organ: Adrenal Glands

Group	Absolute Organ Weight (g)	Organ/Body Weight Ratio (g/100 g)	Organ/Brain Weight Ratio (g/g)
Interim Control	0.048	0.020	0.031
Interim Test	0.056	0.047**	0.037
Final Control	0.048	0.016	0.029
Final Test	0.057*	0.022#	0.034

\* Statistically significant difference at the 95 percent confidence level.

# Statistically significant difference at the 99 percent confidence level.

TABLE X  
 TEST MATERIAL: Chloral  
 Two-Week Subacute Vapor Inhalation Toxicity Study - Albino Rats  
 Mean Organ Weight and Ratio Data

Group	Organ: Brain	
	Absolute Organ Weight (g)	Organ/Body Weight Ratio (g/100 g)
Interim Control	1.603	0.664
Interim Test	1.514	1.269**
Final Control	1.703	0.561
Final Test	1.684	0.655

\*\* Statistically significant difference at the 99 percent confidence level.

3. Microscopic Pathologic Findings

The histopathologic evaluation did not reveal any changes that could be attributed to the test material. The changes described in the lung and other tissues from control and test animals at the interim and final sacrifices are regarded as manifestations of naturally occurring disease or related to the method of sacrifice.

Individual histopathologic findings are listed in Table XI.

0 0 3 1

TABLE XI

TEST MATERIAL: Chloral

Two-Week Subacute Vapor Inhalation Toxicity Study - Albino Rats

Histopathologic Data

Group	Animal Number	Organ	Findings	Grade
Untreated Control	1	Lung	Chronic murine pneumonia (peribronchiolar and perivascular lymphoid infiltrations)	1.0
			Focal emphysema (agonal)	1.0
		Spleen	Extramedullary hematopoiesis	1.0
	2	Lung	Chronic murine pneumonia (peribronchiolar and perivascular lymphoid infiltrations)	1.0
			Focal emphysema (agonal)	1.0
	3	Lung	Focal emphysema (agonal)	1.0
	4	Lung	Focal emphysema (agonal)	1.0
	5	Lung	Focal emphysema (agonal)	1.0
		Liver	Focal lymphoid infiltrations	1.0
		Spleen	Extramedullary hematopoiesis	1.5
	6	Lung	Chronic murine pneumonia (peribronchial and perivascular lymphoid infiltrations)	1.0
			Focal emphysema (agonal)	1.5
Kidneys		Tubular nephrosis (focal)	1.0	
Spleen		Extramedullary hematopoiesis	1.5	

0 0 3 2

TABLE XI continued

TEST MATERIAL: Chloral

Two-Week Subacute Vapor Inhalation Toxicity Study - Albino Rats

## Histopathologic Data

Group	Animal Number	Organ	Findings	Grade
Untreated Control	7	Lung	Chronic murine pneumonia (peribronchial and perivascular lymphoid infiltrations)	1.0
			Subacute focal bronchopneumonia	2.0
			Acute focal inflammatory edema	2.0
			Alveolar macrophages (focal)	2.0
			Focal emphysema	1.5
	8	Lung	Chronic focal interstitial pneumonia	1.0
			Chronic focal bronchopneumonia	2.0
			Alveolar macrophages (focal)	1.0
			Focal emphysema	1.0
		Kidney	Tubular nephrosis (focal)	1.0
	9	Lung	Chronic murine pneumonia (peribronchiolar and perivascular lymphoid infiltrations)	1.5
			Focal emphysema	1.5
10	Lung	Chronic murine pneumonia (peribronchiolar and perivascular lymphoid infiltrations)	1.0	
	Kidney	Tubular nephrosis (focal)	1.0	
		Focal lymphoid infiltrations	1.0	
Test	11	Lung	Chronic murine pneumonia (peribronchiolar and perivascular lymphoid infiltrations)	1.0
			Alveolar macrophages (focal)	1.0
			Focal emphysema	1.5

TABLE XI continued

TEST MATERIAL: Chloral

Two-Week Subacute Vapor Inhalation Toxicity Study - Albino Rats

Histopathologic Data

Group	Animal Number	Organ	Findings	Grade	
Test	12	Lung	Chronic focal interstitial pneumonia	1.5	
			Chronic bronchopneumonia	1.5	
			Alveolar macrophages (focal)	1.5	
			Focal emphysema	1.5	
			Kidney	Congestion	1.0
			Spleen	Extramedullary hematopoiesis	1.0
		13	Lung	Chronic focal interstitial pneumonia	2.0
	Acute focal inflammatory edema			2.5	
	Alveolar macrophages			2.0	
			Kidney	Congestion (agonal)	2.0
			Liver	Congestion (agonal)	2.0
		15	Lung	Focal emphysema (agonal)	1.5
		17	Lung	Diffuse congestion	2.5
	Acute focal inflammatory edema			2.0	
Alveolar macrophages	2.0				
		Kidney	Diffuse congestion	2.0	
		Brain	Diffuse congestion	2.0	
	18	Lung	Chronic focal interstitial pneumonia	2.0	
Acute focal bronchopneumonia			1.5		
Inflammatory edema			2.0		
Alveolar macrophages			2.0		
		Kidney	Congestion (agonal)	2.0	
		Liver	Congestion (agonal)	1.5	

## TABLE XI continued

## TEST MATERIAL: Chloral

## Two-Week Subacute Vapor Inhalation Toxicity Study - Albino Rats

## Histopathologic Data

Group	Animal Number	Organ	Findings	Grade
Test	19	Lung	Diffuse congestion	1.5
			Alveolar macrophages	1.0
			Focal emphysema	2.0
		Kidney	ongestion (agonal)	2.0
		Liver	Congestion (agonal)	2.0

Note: Animal Nos. 14, 16, and 20 were too badly decomposed for histopathologic examination.

Grading System

0.5 = minimal

1.0 = slight

2.0 = mild

3.0 = moderate

4.0 = severe

5.0 = extreme

0 0 3 5