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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 6/28/91 CAP Agreement, E.I. Du Pont de Nemours and Co. hereby submits (*in triplicate*) the attached studies. Submission of this information is voluntary and is occasioned by unilateral changes in EPA's standard as to what EPA now considers as reportable information. Regulatee's submission of information is made solely in response to the new EPA §8(e) reporting standards and is not an admission: (1) of TSCA violation or liability; (2) that Regulatee's activities with the study compounds reasonably support a conclusion of substantial health or environmental risk or (3) that the studies themselves reasonably support a conclusion of substantial health or environmental risk.

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

For Regulatee,

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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).

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

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

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

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

- o even though EPA expressly disclaims each "status report" as being preliminary evaluations that should not be regarded as final EPA policy or intent⁴, the "Reporting Guide" gives the "status reports" great weight as "sound and adequate basis" from which to determine mandatory reporting obligations. ("Guide" at page 20).
- o the "Reporting Guide" contains a matrix that establishes new numerical reporting "cutoff" concentrations for acute lethality information ("Guide" at p. 31). Neither this matrix nor the cutoff values therein are contained in the Statement of Interpretation. The regulated community was not made aware of these cutoff values prior to issuance of the "Reporting Guide" in June, 1991.
- o the "Reporting Guide" states new specific definitional criteria with which the Agency, for the first time, defines as 'distinguishable neurotoxicological effects'; such criteria/guidance not expressed in the 1978 Statement of Interpretation.⁵;
- o the "Reporting Guide" provides new review/ reporting criteria for irritation and sensitization studies; such criteria not previously found in the 1978 Statement of Interpretation/Enforcement Policy.
- o the "Reporting Guide" publicizes certain EPA Q/A criteria issued to the Monsanto Co. in 1989 which are not in the Statement of Interpretation; have never been published in the Federal Register or distributed by the EPA to the Regulatee. Such Q/A establishes new reporting criteria not previously found in the 1978 Statement of Interpretation/Enforcement Policy .

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

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

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

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

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

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

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

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

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

(1977). [Section 8(e) findings require "extraordinary exposure to a chemical substance...which critically imperil human health or the environment"].

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

If an overall weight-of-evidence analysis indicates that this classification is unwarranted, reporting should be unnecessary under §8(e) because the available data will not "reasonably support the conclusion" that the chemical presents a substantial risk of serious adverse consequences to human health.

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

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

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

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

Attachment

Comparison:

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

TEST TYPE	1978 POLICY CRITERIA EXIST?	New 1991 GUIDE CRITERIA EXIST?
ACUTE LETHALITY		
Oral	N}	Y}
Dermal	N}	Y}
Inhalation (Vapors)	} ⁶	} ⁷
aerosol	N}	Y}
dusts/ particles	N}	Y}
SKIN IRRITATION	N	Y ⁸
SKIN SENSITIZATION (ANIMALS)	N	Y ⁹
EYE IRRITATION	N	Y ¹⁰
SUBCHRONIC (ORAL/DERMAL/INHALATION)	N	Y ¹¹
REPRODUCTION STUDY	N	Y ¹²
DEVELOPMENTAL TOX	Y ¹³	Y ¹⁴

⁶43 Fed Reg at 11114, comment 14:

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

⁷Guide at pp.22, 29-31.

⁸Guide at pp-34-36.

⁹Guide at pp-34-36.

¹⁰Guide at pp-34-36.

¹¹Guide at pp-22; 36-37.

¹²Guide at pp-22

¹³43 Fed Reg at 11112

"Birth Defects" listed.

¹⁴Guide at pp-22

NEUROTOXICITY	N	Y ¹⁵
CARCINOGENICITY	Y ¹⁶	Y ¹⁷
MUTAGENICITY		
<i>In Vitro</i>	Y ¹⁸	Y ¹⁹
<i>In Vivo</i>	Y}	Y}
ENVIRONMENTAL		
Bioaccumulation	Y}	N
Bioconcentration	Y ²⁰	N
Oct/water Part. Coeff.	Y}	N
Acute Fish	N	N
Acute Daphnia	N	N
Subchronic Fish	N	N
Subchronic Daphnia	N	N
Chronic Fish	N	N
AVIAN		
Acute	N	N
Reproductive	N	N
Reprodcutive	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 # 123-72-8

Chem: Butyraldehyde vapor

Title: Nine-day repeated vapor inhalation toxicity study

Date: 3/9/78

Summary of Effects: Coordination loss, anesthesia at 6400ppm

CONFIDENTIAL: Not to be released outside UCC without the written consent of the C&P Medical Director, Occupational Health Team Operations Manager, or Product Safety Director.

J-6185
Project Report 41-39
21 Pages
March 9, 1978
Tel: (412) 327-1020

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CHEMICAL HYGIENE FELLOWSHIP
Carnegie-Mellon Institute of Research
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HASKELL LAB.

Butyraldehyde

Nine-Day Repeated Vapor Inhalation Toxicity Study

Sponsor: *Union Carbide Corporation*

Summary

Rats, mice, guinea pigs, rabbits and dogs were exposed to butyraldehyde vapor 6 hours/day, 5 days/week for 9 days over a two-week period. The measured concentrations for the 3 test levels were 6400, 3100 and 2000 ppm. Definite signs of eye and respiratory irritation, and statistically significantly lower body weight findings were observed in most species inhaling 6400 and 3100 ppm of butyraldehyde. Other signs observed in most animals at 6400 ppm included coordination loss, anesthesia and death. At 3100 ppm these effects were observed only in the beagle dog. Only some eye and respiratory irritation and statistically significantly lower body weight effects were observed among animals inhaling 2000 ppm of butyraldehyde. Scattered organ weight effects were found in rats for both test groups (3100 and 2000 ppm) surviving the 9-day inhalation treatment. (Further interpretation of these organ weight findings will probably be forthcoming in the following 13 week study.) No pathologically significant treatment related gross lesions were found among animals inhaling 3100 or 2000 ppm of butyraldehyde. One male Sprague-Dawley rat that had been exposed to 6400 ppm had bilateral hemorrhage of the ethmoturbinates.

Introduction

The 9-day inhalation test was performed to evaluate the toxic responses in multiple species due to repeated inhalation of atmospheres containing butyraldehyde. Results of the 9-day study are used to establish exposure levels and yield information regarding toxic effects for a subsequent 13-week subchronic inhalation study. The 13-week inhalation study is designed to serve as an indicator of the possible chronic toxic effects of butyraldehyde inhalation. Based on the results of the 9-day study target vapor concentrations of 2000, 500 and 125 ppm have been chosen for the 13-week subchronic study. The dog and Sprague-Dawley rat have been selected as species to be used for evaluation of the possible chronic effects of butyraldehyde inhalation.

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Sample

Two 5-gallon drums of butyraldehyde, representative of regular production grade, were received from South Charleston on 11-10-77. The sample was assigned CHF sample no. 40-412 (A & B). Pertinent physical properties are presented in Table 41-1.

Before starting the 9-day inhalation study, the sample was transferred to 1-gallon glass bottles and purged and blanketed with nitrogen. Each 1-gallon bottle contained the amount of sample needed for completion of a 6-hour exposure period for each test group.

ProcedureExposure Groups

The 9-day inhalation study was utilized for determination of differences in responses of various species and to provide data for assigning levels for a 13-week subchronic study. Animals assigned to each of the three test levels and a control level included 5 male and 5 female Fischer 344 rats, 5 male and 5 female Sprague-Dawley rats, 5 male Swiss-Wabster mice, 3 male English smooth-haired guinea pigs (albino), one New Zealand white rabbit, and one male beagle dog. The source and age of all animal species is presented in Table 41-2. Following a 1-week quarantine, animals were randomly assigned to one of four groups. At the time of randomization only those animals with body weight within two standard deviations of the mean were accepted for the study. Any animal that lost weight or was found to have poor muscle tone during the quarantine period and any dog with physical abnormalities was rejected.

Test Concentrations and Exposure Regimen

Target concentrations of 8000, 4000 and 2000 ppm were selected for the study based upon the results of preliminary acute range-finding tests on rats at these concentrations. Beginning on a Monday, the animals were subjected to 6 hours per day of inhalation of the assigned vapor/air concentration in a 547-liter masonite chamber for 5 consecutive days. After being rested over the weekend, the survivors were subjected to inhalation of the vapor for an additional 4 consecutive days. Control animals were dealt with and housed in an identical manner to the dosed groups, but were subjected only to room air adjusted to conform to the highest temperature in any of the exposure chambers.

Vapor Generation

Butyraldehyde vapor concentrations were generated by metering the liquid down the inside of a spirally corrugated surface of an electrically heated one-inch diameter Pyrex[®] tube. Maximum temperature of the vaporizer was limited to that required to effect complete vaporization of the liquid butyraldehyde. Resultant vapors were carried into the chamber by a countercurrent air stream that entered the bottom of the tube, and passed directly into the chamber. Air was exhausted from the chamber at a metered rate (150 liters/min) to produce 15 air changes per hour. To compensate for any possible but undetected variation in vapor distribution within the chamber, the location of the animals within the chamber was rotated routinely.

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Analytical Method

A Perkin-Elmer model 3920B gas chromatograph was used employing conditions of operation are presented in Table 41-3. The gas chromatograph was operated under temperature programmed conditions using a flame ionization detector. The program was started at 170°C then raised to 190°C at 2°C/min, with a hold at 190°C for 2 min. If testing for butyric acid a hold at 190°C for 8 min was employed. (The gas chromatographic analysis of butyraldehyde was carried out in a manner that butyric acid would be detected.) The analytical procedure is based on measurement of peak height. Calibration curves were constructed from solutions of known weight per unit of volume of butyraldehyde dissolved in water. Microliter samples were injected into the chromatograph at three or more concentrations covering the range of analysis. Vapor-air samples, taken volumetrically from the chambers, were injected directly into the chromatograph by means of gas-tight syringes, one for each chamber. Test vapor concentrations were analyzed at least 3 times each day and control chambers and room air 2 times each day. Samples were taken from various ports located in the front of the chamber. Standards were run each day to verify the analytical reproducibility of the calibration curves, and new curves were constructed as necessary. Reference chromatograms were filed in the Chemical Hygiene Laboratory of Carnegie-Mellon Institute of Research.

Criteria of Toxic Response Monitored

Animals were closely observed for signs indicative of toxic effect during each 6-hour inhalation period and during the individual transfer of each animal between nonexposure cage and exposure cage preceding and following exposure. The corneas of all rabbits were examined on exposure days 1, 2, 5, 6, 7 and at sacrifice using the aqueous fluorescein staining technique (on exposure days 1, 5 and 6 corneal examinations were made immediately pre- and post-exposure; on exposure days 2 and 7 examinations were only made prior to exposure). The body weight of each animal was measured and recorded preceding the 1st, 2nd, 5th, 6th and 7th day of exposure and again preceding sacrifice. Moribund animals or animals that died during the 9-day inhalation regimen were subjected to necropsy as they were found. All survivors were sacrificed for necropsy on the morning following the 9th or final day of the exposure regimen. Tissues were only taken at necropsy from selected animals where abnormalities or clinical signs were observed that warranted further investigation. The livers and kidneys of all rats were weighed at sacrifice.

Statistical Analysis

The results of the quantitative continuous variables, such as body weight changes, were intercompared for the dosage groups and the controls by the use of the following tests: Bartlett's homogeneity of variance, analysis of variance, rank sum (Snedecor and Cochran, 1967), and Duncan's multiple range (Duncan, 1955, 1957; Harter, 1960). The latter was used, if F for analysis of variance was significantly high, to delineate which groups differed from the controls. If Bartlett's test indicated heterogeneous variances, the F test was used for each group versus the control. If these individual F tests were not significant, Student's t test was used; if significant, the means were compared by the Cochran t test (Snedecor and Cochran, 1967) or the rank sum test. Correlation coefficients were calculated when necessary to determine if statistically significant findings were indicative of a dose-response.

In general, only criteria that differed significantly ($P < 0.05$) from the control group are discussed. Omission of comment is indicative that no statistically significant differences were found. Some of the data presented in this report has been rounded off to reflect the limits of significant figures.

Results

Chamber Concentration

Gas chromatographic analysis of target chamber concentrations of 6400 and 2000 ppm of butyraldehyde vapor/air mixtures yielded mean measured concentrations of 6400, 3100 and 2000 ppm (18.9, 9.1 and 5.9 mg/liter) as indicated in Table 41-4.

A minor peak eluting from the gas chromatograph at the same time as butyraldehyde was detected when control chamber air was sampled for one of the analyses. This peak, equivalent to a butyraldehyde concentration of 0.05 ppm, actually appears to represent low level contamination of control chamber air by butyraldehyde vapor. Because analysis of room air near the test chamber indicated a concentration of 0.4 ppm of butyraldehyde vapor for one of the analyses, it is likely that general contamination of air in the room housing the 4 inhalation chambers was the source of this insignificant control chamber contamination.

No observable amount of butyric acid was detected in any of the analyses. Measured concentrations of butyric acid were $\leq 1\%$ of measured butyraldehyde concentrations; the lower level of detection of butyric acid was 1%.

Toxicity Findings

A summary of significant signs observed for the 6400, 3100 and 2000 ppm test groups for each species compared to the control group is given in Tables 41-5 to 41-8. At sacrifice, marked multifocal interstitial pneumonia was observed in treated and control Fischer rats. Since control rats were affected as severely as treated rats, it is concluded that this pneumonia was not in any way caused or associated with butyraldehyde treatment. This pathologic condition may be reflected in the toxicity findings observed for these rats.

Mortality. Exposure to a vapor concentration of 6400 ppm resulted in the death of all animals within 9 days, with the exception of one male Sprague-Dawley rat. The day of death for each animal is given in Tables 41-5 thru 41-8. One male beagle dog, at this concentration, was considered to be moribund by a clinical veterinarian following the first 6-hour exposure. This animal was therefore euthanized for necropsy following this exposure.

The beagle dog was the only death that occurred for the 3100 ppm exposure group. This dog died overnight following the 3rd day of exposure. No mortality occurred for the 2000 ppm exposure level.

Appearance and demeanor. As indicated from Tables 41-5 thru 41-8, definite signs of eye and respiratory irritation, as well as coordination loss and anesthesia were observed in all species at 6400 ppm. The signs of irritation observed for each species at this concentration included lacrimation, salivation, nasal discharge, audible respiration, dullness or opacity of the cornea and labored breathing.

At 3100 ppm, several definite signs of eye and respiratory irritation (salivation, lacrimation, nasal discharge and audible respiration) were again observed in all species with the exception of the mice. Only some slight salivation was observed in mice at this concentration on exposure day one. Other signs observed only among the dog, rabbit and guinea pigs at 3100 ppm included labored breathing, conjunctivitis, coordination loss, and anesthesia in the dog; conjunctivitis, iritis, and dullness of the cornea in the rabbit; and labored breathing in the guinea pigs.

As shown in Tables 41-5 thru 41-8, some lacrimation, salivation, nasal discharge, conjunctivitis (dog only) and other sporadic signs were observed among animals at the 2000 ppm exposure level. In the rabbit and in rats, the irritation noted was slight and was only observed during the last 5 days of exposure. More definite signs of irritation were observed in the guinea pigs and dogs. In guinea pigs the clinical abnormalities observed were sporadic. In the dog, definite lacrimation and slight conjunctivitis were observed on all exposure days. No abnormalities in appearance or demeanor were observed in mice at this concentration.

Corneal examination (fluorescein staining technique). Corneal examinations were made for the 6400 ppm rabbit on exposure days 1, 2 and 5. During each examination dullness and 25 to 80% necrosis of the cornea was observed. Corneas of rabbits for the remaining exposure groups were examined on exposure days 1, 2, 5, 6, 7 and at sacrifice. Some indication of corneal damage (cornea slightly dull with 5-10% necrosis) was observed in the rabbit at 3100 ppm on exposure day 5 and at sacrifice. No signs of corneal injury were observed in the 2000 ppm or control group rabbits.

Body weight. Mean body weight values for all species and all exposure levels are given in Tables 41-9 to 41-12. Statistically significant lower body weight as compared to control were found for rats, guinea pigs and mice for both the 6400 and 3100 ppm exposure groups. Body weights for the dog and rabbit at these concentrations were also lower than control, but were not compared statistically due to the small sample size. At 2000 ppm, statistically significant differences in body weight compared to control (again lower) were observed only for the Fischer rat (both sexes). This finding may be a reflection of the multifocal interstitial pneumonia found in these rats.

Organ weight. Mean liver and kidney weight findings obtained for the Sprague-Dawley and Fischer rat (for the 3100 and 2000 ppm test groups surviving the 9-day butyraldehyde treatment, and control) are given in Table 41-13. Statistically significant differences in mean liver weight values compared to the mean control values were found for the Sprague-Dawley (both sexes) and male Fischer rat at 3100 ppm. Mean kidney weight values were different from control for the Fischer rat (both sexes) at 3100 ppm and for the female Sprague-Dawley rat at 3100 and 2000 ppm.

Pathology. In the opinion of the veterinary pathologist, there were no pathologically significant treatment-related gross lesions among rats, mice, guinea pigs, rabbits or dogs that inhaled either 3100 or 2000 ppm of butyraldehyde. One male Sprague-Dawley rat that had been exposed to 6400 ppm had bilateral hemorrhage of the ethmoturbinates.

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The majority of animals exposed to 6400 ppm of butyraldehyde died prior to termination of the 9-day repeated inhalation test. As judged from gross findings, the principal cause of death in these animals was respiratory failure. In the opinion of the veterinary pathologist, "events leading to respiratory failure may have involved either one or both of two possible pathogenetic mechanisms. Nasal cavity obstruction in obligatory nose-breathing species leads to the inability of the animal to get sufficient air into the lungs. The result is asphyxiation. An alternative pathogenetic mechanism results from swallowing of air as the animal reflexively and repeatedly gasps. This may occur with or without nasal cavity obstruction. As a result of swallowing air, the stomach and intestines become distended with gas. This increases intraabdominal pressure and thereby prevents proper functioning of the diaphragm. If the diaphragm cannot move posteriorly into the abdominal cavity space due to increased pressure from a gastrointestinal tract distended with air, then insufficient negative pressure develops in the thoracic cavity and air cannot be inhaled. The result is asphyxiation."

As previously mentioned, marked multifocal interstitial pneumonia was observed in treated and control Fischer rats at the termination of the study. Since control rats were affected equally with treated rats, the veterinary pathologist suggests that this pneumonia was not in any way causally associated with butyraldehyde treatment. The Fischer rats, being specific pathogen free and barrier reared, probably had limited inherent resistance to the causative agents which may have been carried by other more resistant species occupying the same exposure chambers and animal holding room. Alternatively, these rats may have been latent carriers of the causative agents.

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Chromatographic analysis

S. J. Kozbelt, B.A.
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Date: March 28, 1978

Typed: djp

Table 41-1

Physical Properties of Butyraldehyde

Butyraldehyde Synonyms:	Butanal, Butaldehyde, Butylaldehyde, n-Butyl aldehyde, Butyral, Butyrylaldehyde, Butanaldehyde, Butal.
Molecular Formula:	C_4H_8O
Molecular Weight:	72.11
Specific Gravity at 20/20°C:	0.803 gm/ml
Boiling Point at 760 mm Hg:	74.8°C
Vapor Pressure at 20°C: (air saturated at 20°C contains @ 125,000 ppm)	91.5 mm Hg
Flash Point (open cup)	20°F
@ 25°C and 760 mm Hg:	1 mg/liter = 340 ppm 1 ppm = 0.00294 mg/liter

Table 41-2

Animal Species Used for Nine-Day Butyraldehyde Inhalation Study

Sample Size ¹	Species	Stock or Strain	Sex	Age (at start)
3	Guinea Pigs (albino)	H1a: English A(SR)	male	9-1/2 to 10-1/2 weeks
5	Mice (albino)	H1a: (SW) BR	male	7 weeks
1	Rabbit	Thr: (NZW)	male	11 - 13 weeks
1	Dog	Deagle (AKC registered)	male	2-1/3 - 7 years
5	Rats	F344/11a1 BR	male	46 - 50 days
5	Rats	F344/11a1 BR	female	46 - 50 days
5	Rats	H1a (SD)	male	43 - 47 days
5	Rats	H1a (SD)	female	43 - 47 days

Source: Sprague-Dawley rats, mice and guinea pigs - Hilltop Laboratories, Inc., Scottdale, Pa.
 Fischer 344 rats - Microbiological Associates, Walkersville, Md.
 Dogs - White Eagle Laboratories. Two dogs 2-1/3 to 2-1/2 years of age were obtained from White Eagle Laboratories, Inc., Doylestown, Pa. Two dogs 6 to 7 years of age were bred at the Chemical Hygiene Fellowship.
 Rabbits - Three Springs Kennel Company, Zelienople, Pa.

¹ Number of animals per exposure group.

Table 41-3

Butyraldehyde

Conditions of Operation: Perkin-Elmer 3920B Chromatograph

Column	Stainless Steel 1/4 in. o.d. X 4-1/2 ft.
Support	Chromosorb 101
Conditions	Initial column temperature 170°C, then raised to final temperature of 190°C at a rate of 2°C/min., with a hold at 190°C for 2 min. Temperature of injection port 180°C and detector 240°C
Solvent for calibration	Water
Carrier Gas	Nitrogen, 30 ml/min
Burner	Hydrogen at 45 ml/min, air at 550 ml/min
Vapor sample size	1 ml
Lower limit of detection	0.5 PPM
Detector	Flame ionization

Table 41-4

Gas Chromatographic Analyses of Butyraldehyde Vapor Concentrations
For 9-Day Inhalation Study

Number of samples	36	31	29	23
Target Concentration, ppm	8000	4000	2000	0
Measured Concentration, ppm	6400	3100	2000	0.0 ^a
Measured Concentration, mg/l	18.9	9.1	5.9	0.0 ^a
Measured as % of Target Concentration	80	78	100	-
95% Confidence Limits for Measured Concentrations, mg/l	6.3 to 31.5	5.2 to 14.3	4.7 to 7.1	0.0 to 0.0 ^b
Coefficient of Variation	32.8	20.3	10.0	-

^a = Median value given because distribution of control values skewed to the left.

^b = Semi-interquartile range

Butyraldehyde Concentration, ppm

	6400	3100	2000
Male Beagle	<p>Lacrimation, excessive salivation, clear nasal discharge, labored breathing, coordination loss, cornea dull, conjunctivitis, anesthesia (exposure day 1); sacrificed following exposure day 1.</p>	<p>Lacrimation, excessive salivation, clear nasal discharge, some conjunctivitis (exposure days 1 thru 3); anesthesia, labored breathing; audible respiration, death (exposure day 3).</p>	<p>Lacrimation, slight conjunctivitis (exposure days 1 thru 9).</p>
Male Rabbit	<p>Lacrimation, salivation, clear nasal discharge, audible respiration (exposure days 1 thru 5); labored breathing (exposure days 3 thru 5); conjunctivitis, iritis, ocular discharge, cornea dull or opaque with 25 to 80% necrosis (when examined on exposure days 1, 2 and 5); death (exposure day 5).</p>	<p>Lacrimation, salivation, clear nasal discharge, audible respiration (most exposure days); conjunctivitis, slight ocular discharge (when examined on exposure days 1, 6, 7 and prior to sacrifice); iritis, cornea dull with 5 to 10% necrosis (when examined on exposure days 5, and at sacrifice).</p>	<p>Slight lacrimation and salivation (exposure days 7 and 9); clear nasal discharge (exposure day 8).</p>

Response of the Guinea Pig and Mice to Inhalation of Butyraldehyde Vapors for 9-Days

Butyraldehyde Concentration, ppm	
6400	2000
<p>Male Guinea Pigs</p> <p>Lacrimation, salivation, conjunctivitis (exposure days 1 thru 5); corneal opacity, red-black nasal discharge (exposure days 2 thru 5); labored breathing; audible respiration (exposure days 4 and 5); body weight statistically significantly lower than control (exposure day 5); deaths (one on exposure day 5, two prior to exposure day 6).</p>	<p>Lacrimation (exposure days 7 thru 9); excessive salivation (exposure days 8 and 9); audible respiration (two on exposure day 5, one on exposure day 9); clear nasal discharge (exposure day 5).</p>
3100	
<p>Lacrimation, salivation, clear or yellow-brown nasal discharge (exposure days 1 thru 9); slight audible respiration (exposure days 2 thru 9); labored breathing (exposure day 6); body weight statistically significantly lower than control (exposure days 5, 6, 7 and at sacrifice).</p>	
<p>Lacrimation, salivation, anesthesia or poor coordination (exposure days 1 thru 9); audible, labored respiration, some corneal opacity (exposure days 5 thru 9); deaths (three on exposure day 1, one on exposure days 7 and 9).</p>	<p>Nothing remarkable observed.</p>
<p>Lacrimation, salivation (exposure day 1); body weight statistically significantly lower than control (exposure day 5 and at sacrifice).</p>	

Butyraldehyde Concentration, ppm

6400

Male Sprague-Dawley Rats

Lacrimation, salivation, clear or red-black crusty nasal discharge, audible respiration (exposure days 2, 5, 6 and 9); some corneal opacity (exposure days 7 thru 9); coordination loss (exposure days 6 and 7); anesthesia (exposure days 7 and 8); deaths (two on exposure day 6, one on exposure days 7 and 9); body weight statistically significantly lower than control (exposure days 2, 5, 6 and 7).

3100

Lacrimation, salivation (exposure days 1 thru 9); clear or red-black crusty nasal discharge (exposure days 1, 6, 7, 8 and 9); audible respiration (exposure days 4 thru 9); body weight statistically significantly lower than control (exposure days 5 and 7); absolute and relative liver weight statistically significantly lower than control.

2000

Slight lacrimation (exposure day 5); clear nasal discharge (exposure days 8 and 9).

Female Sprague-Dawley Rats

Lacrimation, salivation, clear or red-black crusty nasal discharge (exposure days 1 thru 9); audible respiration (exposure days 4 thru 6); labored breathing (exposure days 5 and 6); anesthesia (exposure day 6); deaths (one on exposure day 5, four on exposure day 6); body weight statistically significantly lower than control (exposure day 2, 5 and 6).

Lacrimation, salivation (exposure days 1 thru 9); clear or red-black crusty nasal discharge (exposure days 1, 6, 7, 8 and 9); audible respiration (exposure days 8 and 9); body weight statistically significantly lower than control (exposure days 5, 6, 7 and at sacrifice); absolute liver and kidney weight statistically significantly lower than control.

Slight lacrimation (exposure days 5 thru 9); salivation (exposure day 5); clear nasal discharge (exposure day 8); audible respiration (exposure day 9); absolute kidney weight statistically significantly lower than control.

Response of the Fischer 344 Rat to Inhalation of Butyraldehyde Vapors for 9-Days

Butyraldehyde Concentration, ppm

	6400	3100	2000
Male Fischer 344/Maf Rats ¹	Lacrimation, salivation (exposure days 1 thru 7); clear or red-black crusty nasal discharge (exposure days 1 thru 5); audible respiration (exposure days 1, 4 and 6); labored breathing (exposure days 2 thru 7); some corneal opacity (exposure days 3, 6 and 7); anesthesia (exposure days 2 thru 4); deaths (one on exposure days 4 and 7, two on exposure day 5); body weight change statistically significantly lower than control (exposure day 2).	Lacrimation, salivation (exposure days 1 thru 9); clear or red-black nasal discharge (exposure days 1, 7 and 9); audible respiration (exposure days 6 thru 9); body weight statistically significantly lower than control (exposure days 2, 5, 6, 7 and at sacrifice); absolute and relative liver weight, absolute kidney weight statistically significantly lower than control; relative kidney weight statistically significantly higher than control.	Slight lacrimation, salivation, clear nasal discharge (exposure days 5 thru 8); body weight statistically significantly lower than control (exposure day 5 and at sacrifice).
Female Fischer 344/Maf Rats ¹	Lacrimation, salivation, clear or red-black crusty nasal discharge (exposure days 1 thru 5); audible respiration, labored breathing, some corneal opacity (exposure days 3 to 5); deaths (one on exposure days 1 and 2, two on exposure day 5, one prior to exposure day 6); body weight statistically significantly lower than control (exposure day 2).	Lacrimation, salivation (exposure days 1 thru 9); clear or red-black crusty nasal discharge (exposure days 1, 7 and 9); audible respiration (exposure days 5 and 9); body weight statistically significantly lower than control (exposure days 2, 5, 6, 7 and at sacrifice); relative kidney weight statistically higher than control.	Slight lacrimation, salivation (exposure days 5 thru 8); body weight statistically significantly lower than control (at sacrifice).

¹ At sacrifice, marked multifocal interstitial pneumonia (not related to treatment) was observed in both treated and control rats. This pathologic condition may be reflected in the toxicity findings for these rats.

Table 41-9
Mean Body Weights and Body Weight Changes (gm) for Dogs and Rabbits
That Inhaled Butyraldehyde Vapors for 9 Days

Species	Calendar Day	Butyraldehyde Concentration, ppm											
		6400			3100			2000			0		
		Body Weight	Body Weight Change	Body Weight	Body Weight Change	Body Weight	Body Weight Change	Body Weight	Body Weight Change	Body Weight	Body Weight Change	Body Weight	Body Weight Change
Male Beagles	0	10400	--	12300	--	12600	--	10500	--	10500	--	10500	--
	1	--	--	11800	-600	13000	400	11200	700	11200	400	11200	700
	4	--	--	11100	-1200	12900	300	11000	500	11000	300	11000	500
	7	--	--	--	--	12700	100	10800	300	10800	100	10800	300
	8	--	--	--	--	13100	500	11000	500	11000	500	11000	500
	11	--	--	--	--	13300	700	11100	600	11100	700	11100	600
Male Rabbits	0	2246	--	2254	--	2210	--	2110	--	2110	--	2110	--
	1	2200	-46	2202	-52	2150	-60	2080	-30	2080	-60	2080	-30
	4	1995	-51	2185	-69	2158	-52	2145	35	2145	-52	2145	35
	7	--	--	2255	1	2205	-5	2152	42	2152	-5	2152	42
	8	--	--	2220	-34	2160	-50	2162	52	2162	-50	2162	52
	11	--	--	2240	-14	2180	-30	2160	50	2160	-30	2160	50

Body weights for the dog and rabbit were not compared statistically due to the small sample size.

Table 41-10

Mean Body Weights and Body Weight Changes (gm) for Guinea Pigs and Mice
That Inhaled Butyraldehyde Vapors for 9-Days

Species	Calendar Day	Butyraldehyde Concentration, ppm							
		6400		3100		2000		0	
		Body Weight	Body Weight Change	Body Weight	Body Weight Change	Body Weight	Body Weight Change	Body Weight	Body Weight Change
Male Swiss Webster Mice	0	33.6	-	33.2	-	35.0	-	33.2	-
	1	28.5 ¹	-5.1 ¹	32.2	-1.0	34.6	-0.4	33.0	-0.2
	4	25.5 ¹	-8.1 ¹	29.8	-3.4 ^b	34.0	-1.0	32.6	-0.6
	7	24.0 ¹	-9.6 ¹	32.0	-1.2	35.0	0.0	33.6	0.4
	8	24.0 ¹	-9.6 ¹	31.4	-1.8	35.0	0.0	32.8	-0.4
	11	-	-	31.6	-1.6 ^a	35.6	0.6	33.6	0.4
Male Guinea Pigs	0	632.3	-	637.3	-	631.6	-	632.3	-
	1	602.0	-30.3	605.6	-31.6	623.6	-8.0	627.0	-5.3
	4	482.3 ^b	-150.0 ^c	576.6	-60.7 ^b	613.6	-18.0	640.6	8.3
	7	-	-	600.0	-37.3 ^b	636.3	4.7	656.0	23.7
	8	-	-	580.3	-57.0 ^b	629.6	-2.0	661.6	29.3
	11	-	-	567.6	-69.6 ^c	635.0	3.3	671.6	39.3

Statistical analysis was not made for groups containing less than three animals.

a = 0.05 > P > 0.01

b = 0.01 > P > 0.001

c = 0.001 > P

¹ Mean value based on the two remaining mice

Mean Body Weight and Body Weight Changes (gm) for Sprague-Dawley Rats

That Inhaled Butyraldehyde Vapors for 9-Days

Butyraldehyde Concentration, ppm

Species	Calendar Day	6400			3100			2000			0		
		Body Weight	Body Weight Change	Body Weight	Body Weight Change	Body Weight	Body Weight Change	Body Weight	Body Weight Change	Body Weight	Body Weight Change		
Female Sprague Dawley Rats	0	193.6	-	188.8	-	190.8	-	194.2	-	196.2	-	194.2	-
	1	185.2	-8.4 ^b	187.0	-1.8 ^b	193.4	2.6	196.2	2.6	208.2	14.0	196.2	2.0
	4	189.0 ¹	-4.6 ^c	192.0	3.2 ^b	198.6	7.8	208.2	7.8	217.4	23.2	208.2	14.0
	7	190.3 ¹	-0.8 ^{1,c}	207.0	18.2 ^a	207.2	16.4	217.4	16.4	221.0	26.8	217.4	23.2
	8	-	-	205.2 ^b	16.4 ^a	209.0	18.2	221.0	18.2	227.6	33.4	221.0	26.8
	11	-	-	212.0 ^b	23.2	215.6	24.8	227.6	24.8	287.4	-	227.6	33.4
Male Sprague Dawley Rats	0	280.0	-	284.2	-	285.0	-	287.4	-	286.2	-	287.4	-
	1	258.4 ^a	-21.6 ^c	277.4 ^a	-6.8 ^b	283.2	-1.8	286.2	-1.8	304.6	17.2	286.2	-1.2
	4	248.6 ^c	-31.4 ^c	283.4 ^a	-0.8 ^b	295.8	10.8	304.6	10.8	324.2	36.8	304.6	17.2
	7	262.0 ^c	-18.0 ^c	308.6 ^a	24.4 ^a	320.8	33.8	324.2	33.8	326.6	39.2	324.2	36.8
	8	245.6 ^{2,c}	-31.6 ³	302.4 ^a	18.2 ^c	316.2	31.2	326.6	31.2	339.2	51.8	326.6	39.2
	11	194.0 ³	-65.0 ³	311.4 ^a	29.2 ^b	332.2	47.2	339.2	47.2				

Statistical analysis was not made for groups containing less than three animals.

a = 0.05 > P > 0.01 b = 0.01 > P > 0.001 c = 0.001 > P

- 1 Mean value based on the 4 remaining rats
- 2 Mean value based on the 3 remaining rats
- 3 Mean value based on the 1 remaining rat

Table 41-12

Mean Body Weights and Body Weight Changes (gm) for Fischer 344 Rats
That Inhaled Butyraldehyde Vapors for 9-Days

Species	Calendar Day	Butyraldehyde Concentration, ppm											
		6400			3100			2000			0		
		Body Weight	Body Weight Change	Body Weight	Body Weight Change	Body Weight	Body Weight Change	Body Weight	Body Weight Change	Body Weight	Body Weight Change	Body Weight	Body Weight Change
Female Fischer 344 Rats ⁴	0	113.0	-	116.8	-	114.2	-	114.6	-	114.6	-	114.6	-
	1	96.2	-15.3 ^{1,c}	111.4	-5.4 ^b	114.2	0.0	114.8	0.2	114.8	0.2	114.8	0.2
	4	82.0 ¹	-31.0 ³	112.2	-4.6 ^c	115.6	1.4	119.4	4.8	119.4	4.8	119.4	4.8
	7	-	-	119.6	2.8 ^b	120.8	6.6	124.4	9.8	124.4	9.8	124.4	9.8
	8	-	-	118.2	1.4 ^b	120.6	6.4	126.8	12.2	126.8	12.2	126.8	12.2
	11	-	-	119.6 ^a	2.8 ^b	120.6 ^a	6.4 ^a	128.6	14.0	128.6	14.0	128.6	14.0
Male Fischer 344 Rats ⁴	0	153.6	-	146.6	-	152.8	-	157.4	-	157.4	-	157.4	-
	1	133.8 ^c	19.8 ^c	139.6 ^c	-7.0 ^c	154.6	1.8	158.8	1.4	158.8	1.4	158.8	1.4
	4	126.5 ²	-33.5 ²	145.0	-1.6 ^c	157.4	4.6 ^a	167.4	10.0	167.4	10.0	167.4	10.0
	7	149.0 ³	-32.0 ³	157.4	10.8 ^b	171.6	16.8	180.6	23.2	180.6	23.2	180.6	23.2
	8	135.0 ³	-46.0 ³	155.8 ^a	9.2 ^c	172.0	19.2	182.6	25.2	182.6	25.2	182.6	25.2
	11	-	-	156.0 ^c	9.4 ^c	177.4 ^c	24.6 ^a	191.0	33.6	191.0	33.6	191.0	33.6

Statistical analysis was not made for groups containing less than three animals.

a = 0.05 > P > 0.01

b = 0.01 > P > 0.001

c = 0.001 > P

1 Mean value based on the 4 remaining rats

2 Mean value based on the 2 remaining rats

3 Mean value based on the 1 remaining rat

4 At sacrifice, marked multifocal interstitial pneumonia (not related to treatment) was observed in both treated and control rats. This pathologic condition may be reflected in the body weight findings for these rats.

Table 41-13

Mean Organ Weight (gm) for Rats Inhaling Butyraldehyde Vapor for 9 Days

Rats Sex and Strain	Organ, Basis	Butyraldehyde Concentration, ppm					
		3100		2000		Control	
		Mean	S.D.	Mean	S.D.	Mean	S.D.
Female Fischer 344 1	Liver, absolute	4.78	0.26	4.43	0.22	4.93	0.42
	Liver, % body wt	4.00	0.13	3.67	0.13	3.83	0.16
	Kidney, absolute	1.02	0.06	1.00	0.03	1.01	0.08
	Kidney, % body wt	0.85 [ⓐ]	0.04	0.83	0.04	0.78	0.03
Sprague-Dawley	Liver, absolute	7.90 ^b	0.51	8.32	1.30	9.24	0.18
	Liver, % body wt	3.73	0.23	3.84	0.31	4.06	0.11
	Kidney, absolute	1.63 ^c	0.05	1.56 ^c	0.04	1.79	0.05
	Kidney, % body wt	0.77	0.03	0.73	0.07	0.79	0.03
Male Fischer 344 1	Liver, absolute	6.36 ^b	0.83	7.55	0.97	8.39	0.64
	Liver, % body wt	4.07 ^b	0.19	4.24	0.17	4.39	0.07
	Kidney, absolute	1.29 ^a	0.10	1.41	0.13	1.49	0.07
	Kidney, % body wt	0.83 [ⓐ]	0.04	0.80	0.01	0.78	0.02
Male Sprague-Dawley	Liver, absolute	11.11 ^b	0.81	13.12	0.45	14.30	1.73
	Liver, % body wt	3.57 ^b	0.11	3.95	0.10	4.20	0.36
	Kidney, absolute	2.31	0.11	2.38	0.18	2.52	0.14
	Kidney, % body wt	0.74	0.04	0.72	0.06	0.74	0.13

Circled superscripts indicate that mean values are greater than control.

a = 0.05 > P > 0.01

b = 0.01 > P > 0.001

c = 0.001 > P

1 At sacrifice, marked multifocal interstitial pneumonia (not related to treatment) was observed in both treated and control rats. This pathologic condition may be reflected in the organ weight findings for these rats.



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

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TSCA Inventory: Y N D

Study type (circle appropriate):

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ECO AQUATO

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ATOX SBTOX SEN w/NEUR

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CECATS DATA:
Submission # BEHQ-1092-12365 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:
0639 REFER TO CHEMICAL SCREENING
0678 CAP NOTICE

VOLUNTARY ACTIONS:
0401 NO ACTION REPORTED
0402 STUDIES PLANNED/IN PROGRESS
0403 NOTIFICATION OF WORKER CONCERNS
0404 LABEL/MSDS CHANGES
0405 PROCESS/HANDLING CHANGES
0406 APP. USE DISCONTINUED
0407 PRODUCTION DISCONTINUED
0408 CONFIDENTIAL

SUB. DATE: 10/15/92 OTS DATE: 10/27/92 CSRAD DATE: 02/02/95

CHEMICAL NAME:

CAS#

123-72-8

<u>INFORMATION TYPE:</u>	<u>P F C</u>	<u>INFORMATION TYPE:</u>	<u>P F C</u>	<u>INFORMATION TYPE:</u>	<u>P F C</u>
0201 ONCO (HUMAN)	01 02 04	0216 EPI/CLIN	01 02 04	0241 IMMUNO (ANIMAL)	01 02 04
0202 ONCO (ANIMAL)	01 02 04	0217 HUMAN EXPOS (PROD CONTAM)	01 02 04	0242 IMMUNO (HUMAN)	01 02 04
0203 CELL TRANS (IN VITRO)	01 02 04	0218 HUMAN EXPOS (ACCIDENTAL)	01 02 04	<u>0243</u> CHEM/PHYS 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 ECO/AQUA TOX	01 02 04	0245 CLASTO (ANIMAL)	01 02 04
0206 REPRO/TERATO (HUMAN)	01 02 04	0221 ENV. OCC/REL/FATE	01 02 04	0246 CLASTO (HUMAN)	01 02 04
0207 REPRO/TERATO (ANIMAL)	01 02 04	0222 EMER INCI OF ENV CONTAM	01 02 04	0247 DNA DAM/REPAIR	01 02 04
0208 NEURO (HUMAN)	01 02 04	0223 RESPONSE REQEST DELAY	01 02 04	0248 PROD/USE/PROC	01 02 04
0209 NEURO (ANIMAL)	01 02 04	0224 PROD/COMP/CHEM ID	01 02 04	0251 MSDS	01 02 04
0210 ACUTE TOX. (HUMAN)	01 02 04	0225 REPORTING RATIONALE	01 02 04	0299 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		
<u>0213</u> SUB ACUTE TOX (ANIMAL)	<u>01 02 04</u>	0228 ALLERG (ANIMAL)	01 02 04		
<u>0214</u> SUB CHRONIC TOX (ANIMAL)	<u>01 02 04</u>	0239 METAB/PHARMACO (ANIMAL)	01 02 04		
0215 CHRONIC TOX (ANIMAL)	01 02 04	0240 METAB/PHARMACO (HUMAN)	01 02 04		

<u>TRIAGE DATA:</u>	<u>NON-CBI INVENTORY</u>	<u>ONGOING REVIEW</u>	<u>SPECIES</u>	<u>TOXICOLOGICAL CONCERN:</u>	<u>USE:</u>	<u>PRODUCTION:</u>
	<u>YES</u>	<u>YES (DROP/REFER)</u>	<u>RAT</u>	<u>LOW</u>		
<u>CAS SR</u>	<u>NO</u>	<u>NO (CONTINUE)</u>	<u>MSD</u>	<u>MED</u>		
	<u>IN TITUMINI</u>	<u>REFER</u>	<u>GP</u>	<u>HIGH</u>		
			<u>RBT</u>			
			<u>DOG</u>			

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SUBCHRONIC INHALATION TOXICITY IN MICE, RATS, GUINEA PIGS, RABBITS AND DOGS IS OF LOW CONCERN. REPEAT WHOLE-BODY EXPOSURES OF 6 HOURS/DAY, 5 DAYS/WEEK FOR 2 WEEKS (9 TOTAL EXPOSURES) AT CONCENTRATIONS OF 2000, 3100 OR 6400 PPM TO 1 EACH MALE RABBIT AND DOG, GROUPS OF 3 EACH MALE GUINEA PIGS, 5 EACH MALE MICE, AND 15 EACH MALE AND 5 EACH FEMALE SPRAGUE-DAWLEY AND FISCHER RATS WERE ASSOCIATED WITH ADDITIVE DOSE-DEPENDENT SIGNS OF RESPIRATORY TOXICITY AND MORTALITY. CLINICAL SIGNS OF TOXICITY GRADUATED WITH EXPOSURE LEVEL FROM OCULAR IRRITATION, LACRIMATION, SALIVATION AND AUDIBLE RESPIRATION WITH NASAL DISCHARGE TO CORNEAL OPACITY, IRITIS, LABORED BREATHING, ANESTHESIA, LOSS OF COORDINATION AND DEATH AT LETHAL CONCENTRATIONS. RESPIRATORY DISTRESS WORSENERD WITH REPEAT EXPOSURES. ALL ANIMALS OF A 6400 PPM EXPOSURE DIED OR WERE SACRIFICED IN MORIBUND CONDITION WITHIN THE 9-DAY TREATMENT PERIOD. THE MALE DOG OF A 3100 PPM EXPOSURE SACRIFICED AFTER DAY 1 IN MORIBUND CONDITION WAS THE ONLY MORTALITY ATTRIBUTED TO TREATMENT AT THIS EXPOSURE LEVEL. BODY WEIGHTS WERE SIGNIFICANTLY LOWER RELATIVE TO CONTROL IN RATS, MICE AND GUINEA PIGS AT EXPOSURE LEVELS OF 3100 AND 6400 PPM. LIVER AND KIDNEY WEIGHTS WERE REDUCED IN RATS SURVIVING 9 TOTAL EXPOSURES AT 2000 AND 3100 PPM. NO GROSS PATHOLOGY WAS NOTED INDICATING ORGAN-SPECIFIC TOXICITY.

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