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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 6/28/91 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,

8EHQ-92-11976
INIT 10/27/92

Mark H. Christman
Counsel
Legal D-7158
1007 Market Street
Wilmington, DE 19898
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88920010226

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[2]. 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).

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[2]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".

[3]A comparison of the 1978 Statement of Interpretation and the 1992 "Reporting Guide" is a 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 intent[4], 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.
- othe "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];
- 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 reporing criteria not previously found in the 1978 Statement of Interpretation/Enforcement Policy .

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[4]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.

[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 Environemntal 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]

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[6] 43 Fed Reg at 11114, comment 14:

"This policy statements directs the reporitng of specifiec effects when unknown to the Administrator. Many routine tests are based on a knowledge of toxicity associated with a chemicalL 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."

[7] Guide at pp.22, 29-31.

[8] Guide at pp-34-36.

[9] Guide at pp-34-36.

[10] Guide at pp-34-36.

[11] Guide at pp-22; 36-37.

[12] Guide at pp-22

[13] 43 Fed Reg at 11112

"Birth Defects" listed.

[14] Guide at pp-22

NEUROTOXICITY	N	Y[15]
CARCINOGENICITY	Y[16]	Y[17]
MUTAGENICITY		
In Vitro	Y}[18]	Y} [19]
In Vivo	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

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[15] Guide at pp-23; 33-34.

[16] 43 Fed Reg at 11112
"Cancer" listed

[17] Guide at pp-21.

[18] 43 Fed Reg at 11112; 11115 at Comment 15
"Mutagenicity" listed/ *in vivo* vs *invitro* discussed; discussion of "Ames test".

[19] Guide at pp-23.

[20] 43 Fed Reg at 11112; 11115 at Comment 16.

CAS # 123-72-8
Chem: Butyraldehyde
Title: Vapor Inhalation by Dogs and Rats for 14 and 13 weeks, respectively
Date: 6/11/79
Summary of Effects: squamous metaplasia

J-6165

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.

Project Report 42-50
324 Pages
June 11, 1979
Tel: (412) 327-1020

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HASKELL LAB.

CHEMICAL HYGIENE FELLOWSHIP
Carnegie-Mellon Institute of Research
Carnegie-Mellon University
4400 Fifth Avenue
Pittsburgh, PA 15213

Butyraldehyde
Vapor Inhalation by Dogs and Rats for 14 and 13 Weeks, Respectively

Initiated: Jan. 16, 1978 Completed: April 18, 1978

Sponsor: Union Carbide Corporation

* * * * *

Summary

Male beagle dogs and male and female Sprague-Dawley rats were exposed 6 hours per day, 5 days per week for up to 14 and 13 weeks, respectively, to butyraldehyde vapor concentrations of 5.44, 1.36, and 0.34 mg/liter (2000, 500 and 125 ppm). The measured parameters for toxic response included body and organ weights, urinalysis, blood chemistry, pathology, ophthalmologic and hematologic examinations.

Rats at all levels tested had a significant incidence of squamous metaplasia of the nasal cavities. Dogs exposed to 2000 ppm had significant microscopic lesions of the upper respiratory tract, including mucosal cell hyperplasia, inflammation, and squamous metaplasia. Exposed dogs at 500 and 125 ppm had goblet cell hyperplasia within the nasal mucosa. There were no other significant differences found between test and control groups which could be related to inhalation of butyraldehyde vapor concentrations.

This study was designed to examine toxic response in dogs and rats subjected to repeated inhalation of atmospheres containing butyraldehyde vapor. All raw data are being held at the Chemical Hygiene Laboratory of Carnegie-Mellon Institute of Research for future reference.

Sample

Ten 55-gallon drums of anhydrous butyraldehyde were received from South Charleston on 1/4/78. They were randomly assigned CHF sample numbers 41-2a through 41-2j. The butyraldehyde sample was taken from a unit make tank and placed in polyethylene-lined drums purged with nitrogen before loading to prevent reaction. Each drum was analysed as being typical of normal production. Results of compositional analysis for the two drums of butyraldehyde used for the subchronic inhalation study are presented in Table 42-1. Pertinent physico-chemical properties are presented in Table 42-2. The drum of sample assigned CHF No. 41-2a was used for the first 8 weeks of the inhalation study. Drum No. 41-2b was used for the final 6 weeks.

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The butyraldehyde used for the subchronic inhalation study was transferred to 1-gallon glass bottles and blanketed with nitrogen. Approximately 6 gallons of sample were used each week. The drum from which the butyraldehyde was withdrawn was blanketed with nitrogen following each sample collection to prevent reaction with the air. Samples taken from the two drums of butyraldehyde during exposure weeks 1, 3, 4, 7, 8, 9, 11, 12 and 13 were analyzed for butyric acid by gas chromatography to insure that no change in sample composition had occurred. Chromatographic analysis of liquid samples did not show any apparent changes in sample composition throughout the inhalation study.

Some of the samples obtained for one week of exposure and each week thereafter throughout the subchronic inhalation study were rust-colored and contained some granular sediment. The other 1-gallon samples appeared normal. Chromatographic analysis of these rust-colored samples showed no apparent changes in composition; therefore, with the exception of the rust-colored 1-gallon samples, all samples were used for the inhalation exposure. As a further insurance to sample stability the following samples of butyraldehyde were sent back to UCC, South Charleston for compositional analysis: (a) drum 41-2a, third exposure week, both clear and rust-colored samples; (b) drum 41-2b, 6 weeks following the end of the 14-week inhalation study, a rust-colored sample (darker in color than that obtained throughout the 14-week study); drum 41-2h (unused drum), 7 weeks following the end of the inhalation study, a clear sample. Results of these compositional analyses are given in Table 42-3. The compositional analysis for drum 41-2b showed a high butyric acid percent by weight as compared to the other drums analyzed.

Methods

Animal Species and Source

Sprague-Dawley rats of both sexes were received from Hilltop Laboratories, Inc., Scottdale, PA. The 3- to 4-week old rats were identified by standard toe-clipping techniques following arrival at the Laboratory.

Male beagle dogs were received from White Eagle Farms, Incorporated, Doylestown, PA. The dogs were 9.5 to 12 months of age when received. The supplier had marked each dog for identification with a number tattooed on the inner surface of the right ear. Corresponding Chemical Hygiene Fellowship animal identification numbers were also assigned to each dog.

Animal Quarantine

Within one day following arrival, a visual examination of the health and ophthalmological status of all rats was made and a randomly selected group was examined for intestinal parasites by zinc sulfate flotation of fecal samples. Body weight and physical condition were observed for 2 weeks prior to placement into exposure groups.

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One month prior to the start of the inhalation study all dogs 15.5 to 18 months of age were examined for abnormalities in physical appearance, behavior, hematology, parasitology and clinical chemistry. Dogs were weighed once each week and food consumption, body functions and general behavior were monitored daily for each dog for a 2-week period preceding random assignment into test groups.

Randomization and Care of Animals

Animals were assigned to one of four groups using a random number system. Following the 2-week quarantine, rats were randomized and assigned to one of four groups consisting of twenty Sprague-Dawley rats per sex. Sixteen dogs were randomly assigned to one of four groups of four dogs each following quarantine. 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 abnormalities in hematology, parasitology or blood chemistry profiles was rejected.

Animal Husbandry

Rats separated by test group and sex were housed 3 rats per cage in stainless steel cages with a wire-mesh front and bottom. Rats were kept in an air-conditioned room maintained at a mean temperature of 21°C, with an actual range of 18 to 24°C. The mean relative humidity of the holding room was 43% with an actual range of 35 to 49%. Water was supplied *ad libitum* by an automatic watering system and Wayne Lab Blox® F-6 was also available *ad libitum*. (During the final week of exposure the remaining 5 rats per sex per exposure level received powdered Purina Formulab Chow® 5008 prior to determination of 24-hour urine volume and water consumption.) A layer of Deodised Animal Care Board® was placed under each shelf of cages and changed at least three times per week. For the daily inhalation, rats were caged in all-mesh stainless steel cages with solid galvanized steel tops. The rats and cages were numbered so that the animals were always in the same nonexposure cage and inhalation cage to minimize risk of spreading infections. Nonexposure carriers and feeders were cleaned once each week. Shelf pan and carriers were cleaned with hot water while feeders were first washed in Aura® and then rinsed with hot water. Exposure cages were washed with hot water following each 6-hour exposure period.

Dogs were housed individually in galvanized steel cages within a room that was separate from the rats. For the first 4.5 weeks of the inhalation study dogs were kept in a room maintained at a mean temperature of 17°C with an actual range of 12 to 21°C. The mean relative humidity of the room was 42% with an actual range of 34 to 53%. For the remainder of the 14-week study, due to renovation of the building in the proximity of the above holding room, the dogs were relocated. The second holding room was maintained at a mean temperature of 22°C with an actual range of 20 to 24°C. The mean relative humidity of this holding room was 49% with an actual range of 40 to 57%. Nonexposure cages were

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cleaned daily and washed with hot water every second week. ARBOR-DRY® hardwood bedding produced by Lab Products, Inc., was placed daily in dog nonexposure cages. Dogs were fed 3 cups of Purina Formula Chow (Canine Diet 5006) daily, at the conclusion of each 6-hour exposure period and at a similar time on weekends. Water was available ad libitum from bottles when dogs were not in the inhalation chambers. The feed pans and water bottles were cleaned daily in hot water. For the inhalation exposure, each dog was transferred to an exposure cage. Dogs and cages were numbered so that the dog was always placed in the same exposure cage and returned to the same nonexposure cage. Following transfer of dogs to nonexposure cages after each 6-hour exposure period, the exposure cages were washed with hot water.

Target Chamber Concentrations

Target concentrations of 2,000, 500 and 125 ppm were selected for the study based upon the results of a preliminary 9-day inhalation study described in Special Report 41-39 issued in 1976.

Vapor Generation

Butyraldehyde vapor concentrations were generated by metering the liquid down the inside of an electrically heated Pyrex® tube previously described by Carpenter, et al., (1975). 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 counter-current air stream that entered the bottom of the tube, and passed directly into the chamber. The desired concentration was produced by controlling the amount of liquid vaporized into the metered air stream. Liquid flow of butyraldehyde was adjusted to produce measured target chamber concentrations of 2,000, 500, and 125 ppm in the chamber. If analyzed chamber concentrations deviated more than ± 10% from target concentrations, conditions of vapor generation were adjusted. Air was exhausted from the chamber at a rate of 1,000 liter/min. With the chamber door sealed, all air entered the chamber through the vaporizer. To compensate for any possible but undetected variation in vapor distribution within the chamber, the location of the animals within the chamber was changed on a routine basis. Dog and rat carriers were alternately placed in the front or rear of the chamber on a two-exposure-day interval. The position of male and female rats, each sex placed in four cages, were alternated from the top half of the chamber to the bottom half of the chamber daily.

Inhalation Chambers

Chambers were of 3,800 liters volume, constructed of tempered masonite and contained glass windows for observation of animals. Internal chamber walls were coated with sodium silicate and joints were sealed with transparent Silastic®. The internal dimensions of each chamber were 2.1 meters long, 2.0 meters high and 0.9 meters wide.

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lytical Method

A Perkin-Elmer model 39203 chromatograph equipped with a flame ionization
tector was used. Conditions of operation are presented in Table 42-4.
tially the analytical procedure depended solely upon measurement of peak
ght. Calibration curves were constructed from solutions of known weight per
t of volume of butyraldehyde in water. Microliter samples were injected into
chromatograph at 3 or more concentrations covering the entire range of
lysis. On the 6th day of the study, a second PE 39203 chromatograph
ipped with a Spectra Physics series 4000 central processor, data interface
printer/plotter was employed. Conditions of operation for this
omatograph are presented in Table 42-5.

The KF value for the integrator was calculated by averaging the KF's of 3 or
e concentrations covering the range of analysis. From this date to the
ination of the exposure, data from both chromatographic systems was
orted. Vapor-air samples, taken volumetrically from the chambers, were
ected directly into the chromatograph by means of gas-tight syringes. Test
or concentrations were analyzed at least 3 times each day and control
mbers 2 times each day. Samples were taken from a single port. Standards
e run each day to verify the analytical reproducibility of the calibration
ve and new curves were constructed as necessary. On a regular basis, samples
the unused 55-gallon drums of butyraldehyde were analyzed for butyric acid
ng the conditions given in Tables 42-4 and 42-5.

teria of Toxic Response Monitored

The criteria of toxic response monitored for each species is summarized in
le 42-6. Sprague-Dawley rats used for urine, blood and histopathologic
luation during the study were selected by stratified randomization from each
t and control group prior to each sacrifice. Five additional Sprague-Dawley
per sex per exposure group were included to serve as replacements for those
study in the event of deaths or to obtain additional data during the study.

Daily observations. All animals were observed daily prior to, during and
lowing exposure for any abnormalities in appearance, body tone or general
avior. Animals were observed at least four times during each 6-hour exposure
ed for signs indicative of toxic effect.

Food consumption. Food consumption was measured only for dogs. The
tity (cups) of food remaining was measured and recorded daily each week for
dog by a technician.

Body weight. Body weight was measured and recorded for all animals
diately preceding the first and second days of exposure and once each week
eafter. Both absolute body weight and change in body weight from
exposure for treated animals were statistically compared with controls.

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Blood analysis. For dogs, hematological and blood chemistry tests were performed prior to the start of the inhalation study and again after both 27 and 39 days of exposure. Similar tests were performed on blood obtained from five Sprague-Dawley rats per sex per exposure level at 6 and 13 weeks of exposure. Additional blood analyses were made for dogs where results indicated the need for further experimental data.

Hematological evaluation included determination of hemoglobin, total erythrocyte count, packed cell volume, mean corpuscular volume, leucocyte count, tabulation of mean corpuscular hemoglobin, and mean corpuscular hemoglobin concentration. Blood smears were reviewed for differential counts if deemed necessary. Hematologic determinations were based on those described by Schalm, Jain and Carrol (1975) and Davidson and Henry (1974). Biochemical analysis included albumin, alkaline phosphatase, total bilirubin, blood urea nitrogen (BUN), calcium, cholinesterase, creatinine, creatine phosphokinase (CPK), glucose, gamma-glutamyl transpeptidase (GGT), alpha-hydroxybutyric dehydrogenase (HBDH), lactic dehydrogenase-L to P (LDH-L), total protein, serum glutamic oxaloacetic transaminase (SGOT), serum glutamic pyruvic transaminase (SGPT), and serum hemoglobin.

All animals had free access to water and food prior to collection of blood from randomly designated animals. For dogs, a 4- to 5-ml sample of blood was drawn from the jugular or cephalic vein using a 5-ml Vacutainer® tube and a 22-gauge needle. Rats were anesthetized with methoxyflurane and 2 to 3 ml of blood was obtained from the orbital sinus using a plain micro-hematocrit capillary tube. Blood was collected in glass tubes coated with heparin for biochemical analyses or with EDTA (ethylenediaminetetraacetic acid) for hematologic analyses. Following blood collection rats were sacrificed.

Urinalysis

Urine from all dogs was examined prior to the start of the inhalation study and again after 26 and 37 days of exposure. Urine was collected and analysed from each of five and ten Sprague-Dawley rats per sex per exposure level at 6 and 13 weeks of exposure, respectively. Urinalysis included determination of color, turbidity, volume, bilirubin, glucose, ketones, nitrite, pH, protein, sediment (microscopic examination), specific gravity (refractive index), urobilinogen and occult blood. Additional urinalyses were made for dogs where results indicated the need for further experimental data. At 14 weeks of exposure the five rats per sex per exposure level included in the event of need for additional experimental data were used for evaluation of 24-hour urine volume and water consumption.

For urinalysis at 6 and 13 weeks rats were placed in wire-bottomed stainless steel metabolism cages for one to three hours. A piece of fine gauze was placed over the funnel spout in each cage to prevent passage of fecal material into the urine collection bottle attached to the bottom of the cage funnel. On the day preceding urinalysis, each dog was placed in a galvanized steel metabolism

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cage and urine was collected, overnight (16-17 hours). A tuft of glass wool was placed in the funnel spout of the metabolism cages to filter out fecal material and hair. One preservative tablet of Sodium Fluoride-Thymol was placed in urine collection containers for dogs as a preservative. Although water was available to both species ad libitum, food was removed. For the 24-hour urine collection the extra rats used were switched to a diet of powdered feed one week prior to the urine collection. These rats were placed in the metabolism cages immediately following the 69th or final day of the inhalation regimen. Both water and powdered feed were available ad libitum to rats for the 24-hour urine collection.

At six weeks of exposure a misinterpretation of the study protocol resulted in the use of a preservative (Sodium Fluoride-Thymol; used for collection of 17-24 hour urine samples) for collection of urine in the male Sprague-Dawley rats. The use of this preservative [illegible] the small urine volume collected in 1 to 3 hours resulted in the urinalysis data being rendered useless. Therefore, a second group of 5 male rats per exposure level were randomly selected and urine was collected and analyzed. Following urinalysis rats were returned to their exposure groups.

Ophthalmological Evaluation

The eyes of all animals were examined prior to the start of the inhalation study for any signs of gross corneal opacities. Rats found with corneal opacities were culled prior to the start of the inhalation study. If corneal changes were observed in dogs prior to the inhalation study, they were examined with an ophthalmoscope to determine if there were any internal changes. If clinical signs of eye irritation became evident during the study, the animals involved were examined immediately following the conclusion of the 6-hour exposure period for that day. The eyes of rats sacrificed at 6 and 13 weeks were examined at necropsy by a wet microscope slide technique, within 3 minutes following sacrifice. All dogs were examined preceding necropsy at 14 weeks with an ophthalmoscope by a clinical veterinarian.

Organ Weights

Kidneys and liver were removed and weighed at necropsy after 6 and 13 weeks of exposure from Sprague-Dawley rats and at 14 weeks from dogs. Both absolute organ weight and organ weight expressed as percentage of total body weight for treated animals were statistically compared with controls.

Pathology

Groups of 5 and 10 Sprague-Dawley rats per sex per treatment group were sacrificed after 6 and 13 weeks of exposure, respectively, for collection of tissues. All dogs were sacrificed after 14 weeks of exposure. Rats were killed by severing the brachial blood vessels following anesthesia with methoxyflurane. Dogs were anesthetized with sodium pentobarbital and exsanguinated via the brachial arteries. Animals were sacrificed in a random sequence.

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A list of tissues taken for microscopic examination from Sprague-Dawley rats at each sacrifice interval and from beagles after 14 weeks of exposure is presented in Table 42-7. All tissues taken from animals at the 2,000 ppm and control groups were submitted to the veterinary pathologist for microscopic examination. Tissues taken from animals at the two intermediate target concentration levels, 500 and 125 ppm, were to be examined only if treatment-induced lesions were observed in the 2,000 ppm group. No tissues were taken from the Sprague-Dawley rats used for evaluation of urine volume after 14 weeks.

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, (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_{max} test was used for each group versus the control. If these individual F_{max} 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 to reflect the limits of significant figures.

Chamber Concentration

Gas chromatographic analysis of target chamber concentrations of 2000, 500, and 125 ppm butyraldehyde vapor/air mixtures yielded mean measured concentrations of 1852, 462, and 117 ppm (5.44, 1.36, and 0.34 mg/liter) as indicated in Table 42-8.

A peak that elutes from the gas chromatograph at the same position as butyraldehyde was detected when control chamber air was samples. This peak was detected in many of the analyses and appears to actually represent low level contamination of control chamber air by butyraldehyde vapor. Analysis of control chamber air indicated butyraldehyde concentration of 0.05 ppm (the limit of detection). 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 all 4 inhalation chambers was the source of this insignificant control chamber contamination.

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No observable amount of butyric acid was detected in any of the analyses (measured concentrations of butyric acid were < 1% of measured butyraldehyde concentrations: the lower level of detection of butyric acid as 1% of the butyraldehyde concentration being measured).

Toxicity Findings

Appearance and Demeanor

Signs of eye and respiratory irritation were observed in both species at all three exposure levels. These signs included lacrimation, salivation, and nasal discharge.

Mortality

One male Sprague-Dawley rat from the 2000 ppm exposure group was found dead preceding the 37th exposure day. This rat appeared normal on previous days with no apparent body weight loss (cause of death was not determined. Pathology performed on animal gave no evidence of a cause). Aside from this sole exception, no animals of either species died during the course of the study.

Statistically Significant Findings

Body Weight

No instance of statistically significant differences in body weight were found between test and control groups in the beagles (Table 42-9). Three isolated instances of significant differences were found in the Sprague-Dawley rats. In the male rats, the weights of the 2000 and 500 ppm (Table 42-10) were significantly lower on the first day of exposure ($0.001 > p$ for the 2000 and $0.01 > p > 0.001$ for the 500 ppm group). In the female Sprague-Dawley rats, a single instance of statistically significant ($0.05 > p$) lower body weight was seen in the 2000 ppm animals on day 36 (Table 42-11).

Blood Analysis

The analyses of blood samples taken from dogs assigned to each concentration level and control one week prior to the first day of exposure and again on exposure days 27 and 59 are given in Table 42-12 (blood chemistry) and 42-13 (hematology). In the blood chemistry parameters monitored (Table 42-12), mean albumin levels for both the 500 and 125 ppm concentrations were significantly higher ($0.05 > p > 0.01$) than the mean for the control group (on day 27). The hematological parameters monitored (Table 42-13) were not significantly different between test and control groups.

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Blood samples for five and ten rats per sex per exposure level were taken prior to sacrifice at 6 and 13 weeks of exposure, respectively. In the male rats, alkaline phosphatase was the sole blood chemistry parameter yielding statistical significance. It was significantly lower ($0.05 > p > 0.01$) in the 500 ppm animals than in the control animals on days 61 and 62 (Males being done on day 61, females on day 62, Table 42-14). None of the hematologic or differential blood count parameters in the males produced statistically significant results (Tables 42-15 and 42-16, respectively).

In the female rats, some scattered incidences of statistical significance were found. For the blood chemistry analysis, the mean albumin levels were significantly higher ($0.01 > p > 0.001$) in the 125 ppm animals than in the control animals (on day 63 and 64), BUN levels were significantly higher ($0.05 > p > 0.01$) in the 2000 and 125 ppm animals as compared to the control animals (on day 29), and the mean total protein was significantly higher ($0.05 > p > 0.01$) in the 125 ppm group than in the control group on day 29 (Table 42-17). In the hematologic findings, the mean RBC level and the mean Hct level were significantly higher ($0.01 > p > 0.001$) in the 125 ppm animals than in the control animals on days 63 and 64 (Table 42-18). The differential blood count calculations yielded two cases of statistical significance. In both the 2000 and 125 ppm animals, the mean for monocytes was significantly higher ($0.05 > p > 0.01$) than for the control animals on days 63 and 64 (Table 42-19).

A few individual rats had abnormally elevated clinical chemistry values. This may be an explanation for some of the most significant differences found in the blood chemistry analyses. There was no clear histologic alteration to account for these elevated clinical chemistry values. The contributory role of the nasal cavity inflammation in elevating clinical chemistry values is not known. With this in mind, and in view of the erratic and infrequent occurrence of statistical significance in both the blood chemistry and hematological analyses, it is probable that the few significant differences found in these blood studies are statistical artifacts and do not represent a biologically significant response to treatment.

Organ Weight

The mean liver and kidney weights for the groups of five female and five male Sprague-Dawley rats per exposure level sacrificed after six weeks of exposure are presented in Table 42-20. Mean liver and kidney weights for the Sprague-Dawley rats and Beagle dogs sacrificed after thirteen and fourteen weeks, respectively, are presented in Table 42-21. No statistically significant differences were found between test and control rat groups at six or thirteen exposure weeks. Likewise, no statistically significant differences in organ weights were found between test and control dog groups at fourteen weeks of exposure.

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Ophthalmologic Examination

No ophthalmologic abnormalities were observed in any of the rats sacrificed throughout the study. Slight conjunctivitis was observed in all dogs from the 2000 ppm concentration level and in one dog from the 500 ppm concentration level.

Urinalysis

Throughout the study, no statistically significant differences between test and control groups were found during urinalysis in either rats or dogs. However, signs of a possible relationship between urine volume and urogenital fur discoloration and wetness existed. Due to this possible relationship, a 24-hour urine collection test was done with the five remaining rats per concentration level at the end of the study. Upon this closer examination, it was determined that there was no statistical significance for urine volume between test and control groups.

Pathology

The complete pathology report can be found in Appendix A.

All sixteen male beagles (four groups, four animals per group) were sacrificed after fourteen weeks of exposure to butyraldehyde. Dogs exposed at the 2000 ppm concentration level had clinical signs consisting of lacrimation, and slight conjunctivitis and redness of the sclera. In these same animals, significant microscopic lesions were limited to the upper respiratory tract (Table 42-22). These changes consisted of moderate to marked rhinitis with mucosal cell hyperplasia, inflammation and squamous metaplasia. In at least one dog in the 2000 ppm group, squamous metaplasia was also present within the larnyx and trachea (and possibly in the laryngeal region of the other three animals in this group).

Clinical signs observed in the 2000 ppm group were also observed at the 500 and 125 ppm concentration levels, however, they were not as prevalent and were only observed following exposure. Changes in the respiratory tract of the 125 and 500 ppm-exposed dogs consisted primarily of goblet cell hyperplasia within the nasal mucosa.

In conclusion, under the conditions of this study, inhalation of butyraldehyde vapor by dogs at the 2000 ppm level resulted in upper respiratory mucosal damage leading to chronic rhinitis, ulceration of the nasal mucosa and an alteration of the normal respiratory mucosa within the nose and possibly within the larnyx and trachea to the squamous type. At the 500 and 125 ppm levels, inhalation of butyraldehyde vapor resulted in hyperplasia of the goblet cells within the nasal mucosa but did not, over a fourteen week period in the dog, in significant mucosal damage.

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Five male and five female rats from each concentration level were sacrificed after six weeks of exposure to butyraldehyde. At this time, clinical signs for animals at the 2000 ppm concentration level consisted of a yellow-brown fur discoloration of the urogenital region and a slight red fur discoloration of the dorsal cervical region. After thirteen weeks of exposure to butyraldehyde, ten male and five female rats from each concentration level were sacrificed. The clinical signs for the 2000 ppm group were consistent with those observed during the six week sacrifice. The aforementioned fur discoloration occurred infrequently and to a lesser degree in animals at the 500 and 125 ppm concentration levels. The only other clinical signs observed were a sporadic wetness about the nares and moistened eyes in the 2000 ppm concentration level.

The six week necropsy findings showed minor sporadic lesions in both treated and control rats, however, these lesions were not considered biologically significant by the attending pathologist. The necropsy findings of the thirteen week sacrifice yielded multiple (punctate to 2 mm in diameter) foci of varied colorations, disseminated over the surface of the lungs in approximately 64% of both treated and control rats. One rat at the 500 ppm concentration level had bilateral hydronephrosis in the kidneys, and unilateral hydronephrosis (right kidney) was observed in one male rat at the 500 ppm concentration level and one male and one female rat at the 125 ppm concentration level.

Both male and female rats had treatment-related histopathologic changes in the nasal cavity indicative of a response to chronic upper respiratory tract irritation (Tables 42-23, -24). These changes were present in most animals exposed to 2000, 500 and 125 ppm of butyraldehyde vapor. Histologic alterations consisted of squamous metaplasia of mucosal epithelium, rhinitis and initial goblet cell atrophy followed by goblet cell hyperplasia. These alterations were more severe in rats sacrificed after six weeks of exposure than in those sacrificed after thirteen weeks of exposure. It is concluded that, under the conditions of this study, inhalation of butyraldehyde vapor for six to thirteen weeks results in irritation to the upper respiratory passageways and the development of histopathologic changes at all concentrations.

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Table 42-1

Compositional Analyses of

Anhydrous Butyraldehyde Drums

Drum Identification Number	Analysis Drum Number	CHF # Assigned	Butyr* Wt. %	Ethanol Wt. %	Lights Wt. %	Unknowns Wt. %	Water Wt. %	Acid Wt. %	Gravity 20/20°C	Iron Wt. %	Color Pt-Co	Distill IBP	Distill Dry Pt.
389	1	41-2j	99.60	0.19	0.02	0.01	0.18	0.24	.8049	less 1 ppm	3	73.3	76.1
397	2	41-2a	99.53	0.21	0.03		0.23	0.50	.8044		3	73.8	75.1
387	3	41-2e	99.35	0.21		0.22	0.22	0.21	.8045	"	3	73.1	75.2
400	4	41-2d	99.48	0.22		0.11	0.19	0.31	.8056	"	5	73.0	75.2
428	5	41-2f	99.32	0.22		0.24	0.22	0.15	.8055	"	5	72.8	75.0
420	6	41-2b	99.24	0.20		0.34	0.22	0.16	.8062	"	5	73.1	74.7
404	7	41-2i	99.61	0.19		0.03	0.17	0.27	.8054	"	8	72.8	75.9
399	8	41-2g	99.59	0.22		0.05	0.14	0.35	.8055	"	8	72.8	75.1
408	9	41-2c	99.63	0.20		0.01	0.16	0.34	.8050	"	5	72.5	75.3
415	10	41-2h	99.56	0.20	0.01	0.03	0.20	0.25	.8052	"	5	73.3	75.2

Notes: Butyraldehyde, ethanol, lights, and unknowns by gas chromatograph.

Identification of lights and unknowns was not possible by regular laboratory methods.

Water by Fisher Reagent titration.

Acid by Potassium hydroxide titration using nitrogen purge

* Butyraldehyde

Table 42-2

Physical Properties of Butyraldehyde

Butyraldehyde Synonyms:	Butanal, Butaldehyde, Butylaldehyde, n-Butylaldehyde, 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 42-3

Compositional Analyses of Four

Anhydrous Butyraldehyde Drums

CHF # Assigned	Purity % by Weight	Water % by Weight, ppm	Butyric Acid % by Weight
41-2a Clear	99.52	0.30	0.40
41-2a Rust	99.41	0.30	0.66
41-2b Rust	98.92	0.30	5.10
41-2h Clear	99.46	0.30	0.97

Table 42-4

Butyraldehyde

Conditions of Operation: Perkin-Elmer 3920B Chromatograph

Used for Inhalation Exposures 1 thru 45

Detector	Flame Ionization
Column	4.5 ft 1/4" Stainless Steel Tubing Chromosorb 101 Temperature programmed from 170°C to 190°C
Column Temperature*	Rate 2°/min 8 Minute Upper Limit Hold
Injection Temperature	200°C
Detector Temperature	200°C
Carrier, Flow Rate	60 ml/min
Hydrogen Flow Rate	26 psi at Chromatograph
Air Flow Rate	50 psi at Chromatograph
Sample Size	0.5 cc to 5 cc
Retention Time	4 min
Attenuation	16
Range	100
Solvent for Standards	Water
Chart Speed	30 cm/hr

* The 8 minute upper limit hold is necessary only when checking for butyric acid.

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Table 42-5

Butyraldehyde

Conditions of Operation: Perkin-Elmer 3920B Chromatograph

Used for Inhalation Exposures 46 thru 69

Detector	Flame Ionization
Column	10 ft 1/4" Stainless Steel Tubing Chromosorb 101 Temperature programmed from 170°C to 190°C
Column Temperature*	Rate 2°/min 16 min Upper Limit Hold
Injection Temperature	200°C
Detector Temperature	200°C
Carrier, Flow Rate	60 ml/min
Hydrogen Flow Rate	25 psi at Chromatograph
Air Flow Rate	50 psi at Chromatograph
Sample Size	1 cc to 5 cc
Retention Time	5.5 min
Attenuation	32
Range	100
Solvent for Standards	Water
Chart Speed	30 cm/hr
KF **	18200

* The 16 minute upper limit hold is necessary only when checking for butyric acid.

** Calibration Factor

Tab'a 42-7

Rat and Beagle Dog Tissues
Taken at Necropsy for Histopathological Examination
For 90-Day Formaldehyde Inhalation Study

:s lesions
:mals
:ZB
:u and bone marrow
(femoral, sternal, vertebral)
:ain - brain stem, cerebellum,
:erebrum
:vix
:s
:ididymus
:phagus
:s
:lopian tubes
:rt
:estine - large (3 levels)
small (3 levels)
:neys
:rimal glands
:ynx
:er
:ns
:ph nodes (cervical, mesenteric,
:horacic, bronchial)

mammary tissue
nasal turbinates
nerve - sciatic
ovaries
pancreas
parathyroids
pituitary
prostate (and associated accessory sex glands)
salivary glands
skeletal muscle (thigh)
skin (flank)
spinal cord (lumbo-sacral section)
spleen
stomach
testes
thymus
thyroids
trachea
urinary bladder
uterus
vagina
zymbal glands

:sacrifice all tissues listed above were examined grossly and fixed for possible future
:mination. Underlined tissues are termed "selected organs" and were prepared for histo-
:gic evaluation. Histopathologic examinations were performed for all "selected organs"
the control and high level group(s) in order to delineate specific target organs.
:se target organs were examined in animals from the remaining groups.

Table 42-8

Gas Chromatographic Analyses of Butraldehyde Vapor Concentration for 14-Week Inhalation Study

of Samples	254	265	267	170
Concentration, ppm	2000	500	125	0
ed Concentration, ppm	1852	462	117	0[a]
ed Concentration, mg/liter	5.44	1.36	0.34	0[a]
ed as % of Target Concentration	92	92	93	-
ducial Limits for Measured ncentrations, mg/liter	4.22-6.67	1.00-1.71	0.26-0.43	0.00-0.00[b]
cient of Variation	11.43	13.29	12.30	-

an value given because distribution of control values skewed to the left.

to third quartile limits (Q_1-Q_3).

Table 42-9

Mean Body Weight, kg: Male Beagles

Calendar Days	Butyraldehyde Concentration, mg/liter							
	5.44		1.36		0.34		0	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
0	11.50	1.54	11.55	0.90	11.48	1.16	11.32	1.13
1	11.52	1.45	11.72	0.97	11.45	1.15	11.32	0.97
9	11.55	1.66	11.75	0.90	11.30	1.07	11.38	0.93
16	11.50	1.51	11.62	0.92	11.40	0.99	11.32	1.14
23	11.50	1.47	11.72	0.79	11.70	0.50	11.30	1.05
30	11.55	1.45	11.82	0.86	11.45	0.91	11.30	1.05
36	11.10	1.56	11.48	0.73	11.18	0.99	10.75	1.01
44	11.10	1.58	11.42	0.73	10.88	0.97	10.80	1.06
51	10.98	1.64	11.60	0.75	11.22	0.99	11.02	0.98
58	11.12	1.66	11.58	0.91	11.22	1.18	11.10	0.96
65	11.02	1.66	11.75	0.79	11.28	1.09	11.02	0.97
72	10.90	1.54	11.92	0.74	11.32	0.93	11.15	0.92
79	10.73	1.50	11.82	0.58	11.12	1.15	11.15	0.95
84	11.10	1.79	11.98	0.71	11.30	0.96	11.05	0.98

SD = Standard Deviation

Table 42-10

Mean Body Weight Change - Male Sprague-Dawley Rats

Calendar Days	Butyraldehyde Concentration, mg/liter: 5.44 Mean	5.44 SD	1.36 Mean	1.36 SD	0.34 Mean	0.34 SD	0 Mean	0 SD
	Mean Body Weight, gm							
0	256.7	18.5	262.6	15.5	266.8	21.8	260.8	10.2
	Mean Body Weight Change From Exposure Day 0, gm							
1	-1.2[c]	3.2	1.5[b]	2.9	3.0	4.5	5.0	2.8
9	48.4	6.8	50.8	11.5	54.9	12.7	51.4	8.6
16	77.8	10.8	85.6	17.9	89.6	18.0	82.9	13.6
23	104.9	15.2	115.6	25.1	120.7	23.4	111.8	18.4
30	132.2	19.8	143.9	29.7	151.2	28.8	135.6	20.9
36	151.7	23.5	163.4	34.4	172.4	31.9	155.2	23.3
44	163.5	22.7	185.7	42.3	188.1	34.0	176.3	23.7
51	177.4	27.9	203.2	46.2	203.5	38.4	190.2	26.7
58	194.8	29.5	220.5	50.5	220.5	40.8	206.3	30.1
65	209.3	32.2	234.8	52.4	233.9	43.1	218.4	33.2
72	225.1	34.3	250.7	53.4	246.6	46.1	231.1	35.2
79	233.1	35.7	261.9	57.0	256.7	47.6	243.2	37.1
84	242.9	37.6	269.3	58.5	264.7	48.4	251.0	38.6

[b] = 0.01 > P > 0.001

[c] = 0.001 > P

SD = Standard Deviation

Table 42-11

Mean Body Weight Change - Female Sprague-Dawley Rats

Calendar Day	Butyraldehyde Concentration, mg/liter 5.44 Mean	SD	1.36 Mean	SD	0.34 Mean	SD	0 Mean	SD
0	191.6	12.6	187.6	14.1	188.2	13.3	192.8	7.8
	Mean Body Weight Change From Exposure Day 0, gm							
1	-0.6	4.4	-0.9	3.2	1.9	3.2	0.4	2.9
9	26.1	7.8	22.3	7.7	26.8	6.8	26.7	6.2
16	43.4	8.1	41.9	9.8	45.9	10.3	48.5	8.7
23	59.0	9.9	57.8	10.6	62.7	10.7	62.3	10.8
30	73.0	13.3	72.5	12.2	80.0	13.1	79.0	12.2
36	81.0[a]	13.1	82.9	15.7	89.6	13.7	91.8	12.6
44	94.3	17.6	89.0	10.9	97.1	15.6	102.5	16.7
51	99.9	18.1	97.3	14.3	108.3	16.7	108.4	15.4
58	109.3	20.6	106.5	11.4	116.7	17.0	114.9	16.0
65	117.6	22.4	112.8	14.4	125.9	21.2	123.6	20.4
72	124.3	24.0	121.1	15.2	131.1	23.3	129.1	19.6
79	127.8	22.0	125.0	15.1	135.3	23.9	133.5	21.8
84	130.8	24.0	130.1	15.8	139.9	23.1	134.4	20.8

D = Standard Deviation
a = 0.05 > p

Table 42-12

Mean Blood Chemistry Analyses for Groups of Four Male Beagles That Inhaled Butyraldehyde Vapor for 14 Weeks

Parameter	Days of Exposure	Butyraldehyde Concentration, mg/liter (ppm): 5.44 (1852) Mean	SD	1.36 (462) Mean	SD	0.34 (117) Mean	SD	0 (0) Mean	SD
Albumin (gm/dl)	Pre-exposure	3.60	0.18	3.70	0.14	3.58	0.13	3.48	0.17
	27	2.92	0.15	3.10[a]	0.08	3.15[a]	0.24	2.72	0.28
	59	3.18	0.17	3.15	0.21	3.20	0.08	2.98	0.15
Alkaline phosphatase (u/l)	Pre-exposure	51.5	31.8	34.2	4.7	32.5	12.6	34.5	11.7
	27	46.5	24.4	36.2	5.6	28.8	14.1	31.8	10.9
	59	60.0	27.7	41.8	12.1	31.2	18.8	34.8	14.4
Bilirubin total (mg/dl)	Pre-exposure	0.30	0.00	0.10	0.20	0.00	0.00	0.00	0.00
	27	0.05	0.06	0.10	0.20	0.10	0.12	0.02	0.05
	59	0.40	0.08	0.28	0.10	0.40	0.10	0.35	0.10
BUN (mg/dl)	Pre-exposure	16.5	2.9	14.5	2.6	18.5	3.5	18.2	4.5
	27	19.2	6.2	16.0	1.6	21.0	3.2	23.0	7.2
	59	19.8	3.4	14.5	1.7	18.2	4.1	18.5	5.2
Calcium (mg/dl)	Pre-exposure	10.98	0.38	10.95	0.26	11.25	0.67	10.80	0.35
	27	10.98	0.33	11.05	0.19	10.90	0.35	10.65	0.31
	59	10.82	0.35	11.20	0.34	10.85	0.33	10.85	0.37
Cholinesterase (u/l)	Pre-exposure	1476.5	131.6	1688.8	218.8	1536.2	213.2	1849.0	290.7
	27	1660.5	185.8	1964.2	267.3	1790.2	327.3	2215.5	436.1
	59	1718.8	154.2	2141.2	171.2	1937.2	355.0	2358.0	521.4
CPK (u/l)	Pre-exposure	66.0	22.0	55.5	3.5	84.2	62.0	60.5	11.4
	27	68.5	28.8	53.5	9.5	119.8	128.4	59.0	22.4
	59	298.8	456.7	52.5	7.9	60.0	17.4	65.5	19.8
Creatinine (mg/dl)	Pre-exposure	0.68	0.09	0.70	0.18	0.78	0.15	0.75	0.10
	27	0.80	0.08	0.78	0.12	0.80	0.18	0.80	0.08
	59	0.75	0.06	0.70	0.14	0.80	0.14	0.85	0.17

(Continued)

Parameter	Days of Exposure	Butyraldehyde Concentration, mg/liter (ppm) 5.44 (1852) Mean	SD	1.36 (462) Mean	SD	0.34 (117) Mean	SD	0 (0) Mean	SD
Glucose (mg/dl)	Pre-exposure	106.5	8.7	108.2	7.3	109.8	8.2	105.8	10.1
	27	114.0	6.0	110.8	10.5	116.8	7.9	102.2	4.3
	59	94.5	15.2	101.5	4.8	110.8	6.4	106.2	8.9
GGT (u/l)	Pre-exposure	1.5	1.7	1.5	1.7	0.8	1.6	2.5	0.8
	27	2.2	1.2	3.2	1.2	2.8	0.5	3.5	0.6
	59	3.2	1.0	4.2	1.2	3.5	0.6	4.2	0.5
Hemoglobin[1] (mg/dl)	59	3.75	0.96	2.25	1.89	5.25	3.30	2.00	1.41
ECH (u/l)	Pre-exposure	47.8	18.2	68.0	26.3	42.5	17.0	37.0	7.2
	27	44.2	28.5	50.2	21.4	56.7	30.2	51.2	23.8
	59	62.5	34.2	32.8	7.5	57.0	20.7	35.2	12.8
LDH (u/l)	Pre-exposure	33.8	15.9	48.5	18.1	31.5	17.1	25.8	5.7
	27	44.5	38.1	40.2	17.4	44.8	25.4	42.2	23.2
	59	59.5	41.8	29.5	2.6	47.8	17.5	29.5	10.8
Total protein (gm/dl)	Pre-exposure	6.40	0.16	6.15	0.21	6.05	0.53	6.12	0.43
	27	6.35	0.21	6.18	0.22	6.28	0.17	6.02	0.17
	59	6.45	0.26	6.32	0.55	6.38	0.22	6.02	0.15
SGOT (mu/l)	Pre-exposure	25.2	4.6	20.5	5.2	26.5	8.3	27.0	1.8
	27	72.5	107.2	16.5	3.9	25.2	11.3	29.5	20.9
	59	32.5	16.4	22.2	3.3	25.2	5.0	26.5	6.1
SGPT	Pre-exposure	36.8	3.1	37.2	17.7	36.5	5.8	39.8	9.1
	27	113.5	169.7	38.0	16.3	53.2	44.6	52.5	44.2
	59	33.2	1.7	37.5	21.3	34.8	2.6	34.8	14.6

SD = Standard Deviation

1 Serum hemoglobin data for pre-exposure and at 27 exposure days are not included in the table because the reproducibility study of the measurement for the serum hemoglobin using tetramethylbenzidine as a chromogen was not completed.

$\alpha = 0.05 > p > 0.01$

Table 42-13

Hematological Findings for Groups of Four Male Beagles

That Inhaled Butyraldehyde Vapor for 14 Weeks

Parameter	Days of Exposure	Butyraldehyde Concentration, mg/liter (ppm) 5.44 (1852) Mean	SD	1.36 (462) Mean	SD	0.34 (117) Mean	SD	0 (0) Mean	SD
RBC (millions/mm^3)	Pre-exposure	8.197	0.570	8.442	0.456	8.002	0.729	7.907	0.167
	27	7.285	0.324	7.332	0.613	7.162	0.356	6.870	0.242
	59	7.590	0.302	7.568	0.664	7.418	0.232	7.242	0.761
WBC (thousands/mm^3)	Pre-exposure	9.120	0.970	8.050	1.130	8.950	1.540	8.680	0.760
	27	8.620	1.590	8.900	0.365	9.500	1.560	10.080	2.200
	59	9.220	2.220	9.100	0.870	9.280	1.110	9.620	2.140
Ht (%)	Pre-exposure	54.0	2.2	55.0	2.4	54.2	5.1	53.0	1.8
	27	48.0	1.4	48.5	3.7	48.8	2.1	46.8	1.7
	59	51.0	2.2	51.0	4.8	51.2	1.5	49.5	4.4
Hb (gm/dl)	Pre-exposure	17.95	1.04	18.92	0.88	18.10	1.48	17.95	0.59
	27	17.72	0.46	17.82	1.65	18.12	0.83	17.08	0.62
	59	18.72	1.08	18.88	1.44	18.90	0.50	17.82	1.61
MCV (μ^3)	Pre-exposure	67.2	3.0	66.5	2.1	69.2	1.5	68.2	1.5
	27	66.0	3.9	66.0	3.2	68.0	1.8	68.0	1.6
	59	67.0	1.2	67.0	2.2	68.8	1.0	67.8	1.2
MCH (mu/gm)	Pre-exposure	21.8	0.5	22.2	0.5	22.8	0.5	22.8	0.5
	27	24.5	0.6	24.0	0.8	25.2	0.5	25.0	0.8
	59	24.5	0.6	25.0	0.8	25.8	0.5	24.5	1.3
MCHC (%)	Pre-exposure	33.2	1.0	34.5	0.6	33.5	1.0	33.8	1.0
	27	36.8	1.2	37.0	0.8	37.5	0.6	36.5	0.6
	59	36.8	1.0	37.0	0.8	37.0	0.8	36.0	1.4
Neutrophils /mm^3	Pre-exposure	5620	610	5700	1200	5150	910	5420	930
	27	5820	1450	6000	240	5180	910	6350	2700
	59	6280	2090	5850	730	5120	190	5920	2060

(Continued)

Parameter	Days of Exposure	Butyraldehyde Concentration, mg/liter (ppm) 5.44 (1852) Mean	SD	1.36 (462) Mean	SD	0.34 (117) Mean	SD	0 (0) Mean	SD
Lymphocytes /mm^3	Pre-exposure	1700	370	1900	290	2420	470	2150	380
	27	1780	780	2120	380	2980	1230	2600	560
	59	2220	490	2450	380	2950	620	2880	320
Monocytes /mm^3	Pre-exposure	780	260	320	150	650	460	550	60
	27	690	220	540	310	620	340	520	190
	59	520	270	220	170	410	460	490	220
Basophils /mm^3	Pre-exposure	25	50	0	0	100	82	0	0
	27	0	0	0	0	180	360	20	40
	59	0	0	0	0	100	200	0	0
Eosinophils /mm^3	Pre-exposure	420	210	150	130	480	500	380	360
	27	280	280	250	280	480	290	370	340
	59	140	130	510	400	570	410	370	260
Bands /mm^3	Pre-exposure	420	470	0	0	120	190	180	170
	27	60	70	20	40	80	50	0	0
	59	60	70	70	50	50	100	0	0
Enclosted RBC's /mm^3	Pre-exposure	0	0	0	0	0	0	0	0
	27	0	0	0	0	0	0	98	195
	59	0	0	0	0	0	0	0	0

SD = Standard Deviation

Table 42-14

Mean Blood Chemistry Analysis for Groups of Five and Ten Male Sprague-Dawley Rats That Inhaled Butyraldehyde Vapor for Approximately 6 and 13 Weeks, Respectively

Parameter	Days of Exposure	Butyraldehyde Concentration, mg/liter (ppm): 5.44 (1852) Mean	SD	1.36 (462) Mean	SD	0.34 (117) Mean	SD	0 (0) Mean	SD
Albumin (gm/Dl)	28	3.76	0.13	3.86	0.11	3.92	0.18	3.94	0.11
	61 and 62	3.78	0.15	3.81	0.13	3.88	0.10	3.87	0.16
Alkaline Phosphatase (U/L)	28	314.8	61.6	245.8	48.2	290.8	82.8	287.8	85.0
	61 and 62	226.5	46.8	180.2[a]	62.1	249.2	60.5	242.1	60.6
Bilirubin Total (mg/Dl)	28	0.10	0.07	0.00	0.00	0.06	0.13	0.02	0.04
	61 and 62	0.10	0.12	0.05	0.11	0.15	0.07	0.13	0.10
BUN (mg/Dl)	28	19.2	1.5	18.0	3.7	18.4	0.5	18.6	1.5
	61 and 62	19.4	2.4	19.5	1.8	19.3	2.6	18.7	1.7
Calcium (mg/Dl)	28	11.58	0.15	11.48	0.22	11.70	0.37	11.84	0.22
	61 and 62	10.21	0.37	10.32	0.50	10.37	0.45	10.20	0.32
Cholinesterase (U/L)	28	460.8	179.6	350.6	52.4	418.0	66.7	386.2	54.8
	61 and 62	530.2	189.6	519.1	177.9	450.0	101.5	436.5	160.4
CPK (U/L)	28	260.2	257.5	316.0	292.9	177.2	142.9	162.4	49.8
	61 and 62	80.3	44.7	147.6	118.9	156.9	106.2	164.4	166.0
Creatinine (mg/Dl)	28	0.48	0.04	0.38	0.11	0.50	0.12	0.54	0.15
	61 and 62	0.50	0.10	0.48	0.10	0.48	0.08	0.52	0.06
Glucose (mg/Dl)	28	181.6	33.5	171.6	28.1	169.2	14.1	172.6	9.6
	61 and 62	151.1	11.7	158.3	21.9	163.4	19.6	163.6	16.1
GGT (U/L)	28	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
	61 and 62	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Hemoglobin (mg/Dl)	28	3.74	3.49	5.64	3.13	3.10	1.79	1.06	0.85
	61 and 62	4.22	1.74	3.87	1.01	5.39	2.18	5.02	3.41

(Continued)

Table 42-14 (continued)

Parameter	Days of Exposure	Butyraldehyde Concentration, mg/liter (ppm) 5.44 (1852) Mean	SD	1.36 (462) Mean	SD	0.34 (117) Mean	SD	0 (0) Mean	SD
HBDH (U/L)	28	176.8	96.2	464.2	330.4	252.0	217.1	190.2	153.1
	61 and 62	111.4	68.5	86.1	34.8	121.7	65.4	120.2	89.5
LDH (U/L)	28	163.0	85.7	433.4	296.6	239.4	204.5	273.2	135.2
	61 and 62	113.0	61.8	83.0	29.8	122.8	71.7	213.8	79.2
Total Protein (gm/Dl)	28	6.20	0.23	6.12	0.42	6.28	0.25	6.32	0.25
	61 and 62	6.30	0.27	6.31	0.31	6.31	0.22	6.16	0.39
SGOT (U/L)	28	66.0	14.2	78.8	25.2	62.4	17.9	69.6	16.9
	61 and 62	55.7	6.1	54.9	7.6	59.8	15.0	62.2	19.5
SGPT (U/L)	28	28.4	8.1	29.6	7.9	25.3	2.6	30.0	6.8
	61 and 62	20.0	2.7	19.5	3.9	22.6	9.6	21.9	3.6

SD = Standard Deviation
$a = 0.05 > p > 0.01$

Table 42-15

Mean Hematologic Findings for Groups of 5 and 10 Male Sprague-Dawley Rats That Inhaled Butyraldehyde Vapor for Approximately 6 and 13 Weeks, Respectively

Parameter	Days of Exposure	Butyraldehyde Concentration, mg/liter (ppm) 5.44 (1852) Mean	SD	1.36 (462) Mean	SD	0.34 (117) Mean	SD	0 (0) Mean	SD
RBC (millions/mm^3)	28	7.388	0.248	7.238	0.312	7.414	0.345	7.092	0.352
	61 and 62	6.454	0.268	6.687	0.285	6.570	0.261	6.545	0.472
WBC (thousands/mm^3)	28	6.140	1.820	5.680	1.930	7.000	1.000	8.100	2.170
	61 and 62	6.060	1.160	7.140	1.560	6.850	1.770	6.420	1.070
Ht (0/0)	28	41.2	0.8	40.4	1.5	40.6	1.9	41.0	2.2
	61 and 62	38.9	1.9	40.1	2.0	39.8	2.0	39.4	3.1
Hb (gm/dl)	28	15.06	0.49	14.80	0.57	15.00	0.62	14.88	0.40
	61 and 62	15.16	0.30	15.47	0.42	15.61	0.60	15.59	0.62
MCV (μ^3)	28	55.6	1.5	55.8	0.8	54.8	2.4	58.0	2.0
	61 and 62	60.2	1.2	60.0	0.7	60.6	1.2	60.2	0.6
[illegible] (pm)	28	20.2	0.4	20.4	0.5	20.2	0.4	21.0	0.7
	61 and 62	23.4	1.1	23.2	0.9	23.7	0.7	23.8	1.1
MCHC (%)	28	36.6	0.9	36.6	1.1	37.2	1.3	36.4	1.1
	61 and 62	38.9	2.0	38.7	1.7	39.3	1.5	39.6	2.1

SD = Standard Deviation

Table 42-16

Mean Differential Blood Count Calculations for Groups of Five and Ten Male Sprague-Dawley Rats That Inhaled Butyraldehyde Vapor for Approximately 6 and 13 Weeks, Respectively

		Butyraldehyde Concentration, mg/liter (ppm)							
		5.44 (1852)		1.36 (462)		0.34 (117)		0 (0)	
Parameter	Days of Exposure	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Neutrophils /mm^3	28	1200	680	1060	220	1280	540	1080	520
	61 and 62	1040	420	1000	480	960	370	960	460
Lymphocytes /mm^3	28	4640	1440	4380	1820	5400	780	6660	1690
	61 and 62	4780	1060	5610	1390	5500	1400	5010	760
Monocytes /mm^3	28	192	201	198	165	222	178	254	259
	61 and 62	174	120	361	243	276	296	398	246
Basophils /mm^3	28	0	0	0	0	0	0	0	0
	61 and 62	0	0	0	0	0	0	0	0
Eosinophils /mm^3	28	82	39	44	67	60	83	104	106
	61 and 62	40	42	126	97	106	88	113	161
Bands /mm^3	28	0	0	0	0	14	31	0	0
	61 and 62	0	0	20	46	10	32	0	0
Nucleated RBC's /mm^3	28	0	0	0	0	0	0	0	0
	61 and 62	0	0	0	0	0	0	0	0

SD = Standard Deviation

Table 42-17

Mean Blood Chemistry Analysis for Groups of Five and Ten Female Sprague-Dawley Rats That Inhaled Butyraldehyde Vapor for Approximately 6 and 13 Weeks, Respectively

Parameter	Days of Exposure	Butyraldehyde Concentration, mg/liter (ppm) 5.44 (1852) Mean	SD	1.36 (462) Mean	SD	0.34 (117) Mean	SD	0 (0) Mean	SD
Albumin (gm/Dl)	29	3.84	0.21	3.94	0.09	4.02	0.15	3.92	0.08
	63 and 64	3.90	0.12	4.04	0.18	4.18[b]	0.09	3.98	0.20
Alkaline Phosphatase (U/L)	29	261.6	110.4	264.4	125.3	301.2	66.3	235.4	68.9
	63 and 64	246.8	65.3	234.5	102.3	208.6	54.9	286.7	57.0
Bilirubin Total (mg/Dl)	29	0.18	0.13	0.18	0.11	0.24	0.26	0.22	0.16
	63 and 64	0.21	0.17	0.40	0.25	0.25	0.23	0.35	0.23
BUN (mg/Dl)	29	29.4[a]	2.3	18.4	4.5	19.2[a]	0.8	16.8	1.5
	63 and 64	19.1	3.2	19.9	2.8	18.7	2.4	18.9	3.6
Calcium (mg/Dl)	29	11.10	0.16	11.08	0.37	11.22	0.27	10.92	0.29
	63 and 64	10.22	0.38	10.40	0.24	10.42	0.37	10.30	0.31
Cholinesterase (U/L)	29	592.4	188.3	838.2	516.9	501.0	351.6	576.0	310.0
	63 and 64	1112.6	748.9	1015.2	851.2	724.2	711.6	1055.3	807.8
CPK (U/L)	29	329.0	326.7	102.4	62.1	104.2	56.4	164.6	140.9
	63 and 64	111.2	113.6	175.7	332.2	78.6	41.8	114.7	195.3
Creatinine (mg/Dl)	29	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
	63 and 64	0.54	0.12	0.55	0.11	0.51	0.10	0.51	0.09
Glucose (mg/Dl)	29	161.0	13.6	161.6	14.2	165.4	23.4	164.2	13.3
	63 and 64	166.4	18.9	173.8	17.9	173.2	12.3	170.7	13.4
GGT (U/L)	29	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
	63 and 64	0.1	0.3	0.1	0.3	0.1	0.3	0.0	0.0
Hemoglobin (mg/Dl)	29	12.84	5.33	8.36	5.37	25.48	30.24	17.44	17.02
	63 and 64	6.37	4.47	8.83	6.10	6.54	3.23	7.83	4.29

(Continued)

Table 42-17 (continued)

Parameter	Days of Exposure	Butyraldehyde Concentration, mg/liter (ppm) 5.44 (1852) Mean	SD	1.35 (462) Mean	SD	0.34 (117) Mean	SD	0 (0) Mean	SD
SGOT (U/L)	29	302.0	208.6	146.6	64.7	152.0	51.2	219.0	128.6
	63 and 64	116.8	84.1	175.1	177.3	147.0	104.3	97.3	56.8
LDH (U/L)	29	275.0	192.4	144.8	67.5	154.4	54.6	203.6	126.7
	63 and 64	116.9	83.4	167.9	162.7	150.9	102.1	99.2	54.4
Total Protein (gm/Dl)	29	6.84	0.36	7.12	0.24	7.24[a]	0.26	6.78	0.24
	63 and 64	6.46	0.20	6.47	0.35	6.68	0.43	6.34	0.21
SGOT (U/L)	29	72.8	18.9	59.8	6.3	53.2	8.5	59.4	4.7
	63 and 64	51.4	7.0	60.7	16.0	52.1	12.8	55.2	6.4
SGPT (U/L)	29	18.6	3.4	17.4	4.2	18.0	3.1	19.8	2.2
	63 and 64	14.3	2.4	17.8	3.4	16.0	2.9	17.6	4.1

SD = Standard Deviation

a = $0.05 > p > 0.01$

b = $0.01 > p > 0.001$

Table 42-18

Mean Hematologic Findings for Groups of Five and Ten Female Sprague-Dawley Rats That Inhaled Butyraldehyde Vapor for Approximately 6 and 13 Weeks, Respectively

Parameter	Days of Exposure	Butyraldehyde Concentration, mg/liter (ppm) 5.44 (1852) Mean	SD	1.36 (462) Mean	SD	0.34 (117) Mean	SD	0 (0) Mean	SD
RBC (millions/mm^3)	29	6.248[1]	0.292	6.328	0.508	6.228	0.145	6.346	0.320
	63 and 64	6.258	0.194	6.288	0.231	6.556[b]	0.211	6.171	0.265
WBC (thousands/mm^3)	29	4.750[1]	1.500	5.020	1.430	5.260	1.630	5.280	1.070
	63 and 64	5.080	2.120	4.850	2.110	4.120	0.720	3.730	1.130
Ht (%)	29	37.2[1]	1.0	39.2	1.3	38.0	1.0	37.6	1.1
	63 and 64	38.5	1.3	38.5	2.0	40.7[b]	1.4	38.1	1.8
Hb (gm/[illegible])	29	14.20[1]	0.50	14.38	0.38	13.94	0.22	14.16	0.34
	63 and 64	14.54	0.56	14.59	0.50	13.03	0.35	14.30	0.43
MCV (μ^3)	29	59.8[1]	1.7	62.2	4.5	61.2	2.2	59.4	1.9
	63 and 64	61.3	0.7	61.4	1.0	61.8	0.4	61.5	0.5
MCH ($\mu\mu$g/gm)	29	22.5[1]	0.6	22.6	1.3	22.4	0.5	22.2	0.8
	63 and 64	23.2	0.6	23.1	0.6	22.8	0.6	23.1	0.7
MCHC (%)	29	38.2[1]	1.2	36.6	0.9	36.8	0.8	37.6	1.1
	63 and 64	37.5	0.8	37.9	0.9	36.8	0.9	37.6	1.4

1 Mean based on 4 rats. Blood taken from the fifth was clotted.

b = $0.01 > p > 0.001$

Table 42-19

Mean Differential Blood Count Calculations for Groups of Five and Ten Female Sprague-Dawley Rats That Inhaled Butyraldehyde Vapor for Approximately 6 and 13 Weeks, Respectively

Parameter	Days of Exposure	Butyraldehyde Concentration, mg/liter (ppm) 5.44 (1852) Mean	SD	1.36 (462) Mean	SD	0.34 (117) Mean	SD	0 (0) Mean	SD
Neutrophils /mm^3	29	780[1]	250	960	320	670	120	600	290
	63 and 64	810	820	780	480	720	340	570	330
Lymphocytes /mm^3	29	3680[1]	1160	3840	1230	4360	1240	4580	1030
	63 and 64	4060	1390	3750	1390	3220	880	3020	910
Monocytes /mm^3	29	140[1]	130	142	113	164	119	52	56
	63 and 64	144[a]	57	249	420	165[a]	110	69	70
Basophils /mm^3	29	0.0[1]	0.0	0.0	0.0	0.0	0.0	0.0	0.0
	63 and 64	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Eosinophils /mm^3	29	105[1]	90	66	72	72	86	38	52
	63 and 64	77	58	32	40	69	51	71	39
Bands /mm^3	29	15[1]	30	18	40	0	0	0	0
	63 and 64	0	0	14	24	11	18	0	0
Nucleated RBC's /mm^3	29	0[1]	0	10	22	0	0	0	0
	63 and 64	0	0	0	0	0	0	0	0

SD = Standard Deviation

[a] = 0.05 > P > 0.01

[1] Mean based on 4 rats. Blood taken from the fifth rat was clotted.

Table 42-20

Mean Organ Weight: Groups of Five Male and Five Female Sprague-Dawley Rats Sacrificed After Approximately Six Exposure Weeks

Organ, Sex	Butyraldehyde Concentration, mg/liter							
	5.44		1.35		0.34		0	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Male Sprague-Dawley Rats								
Mean body weight, gm	429.6	40.1	417.6	17.6	456.6	53.9	405.8	39.1
Liver, absolute, gm	13.4956	2.5266	13.0346	0.4685	15.3770	2.3675	13.7658	2.2702
Liver, % body wt.	3.1280	0.3957	3.1248	0.1513	3.3638	0.3091	3.3766	0.2485
Kidney, absolute, gm	2.7400	0.3370	2.8338	0.1841	3.0382	0.4612	2.8712	0.2873
Kidney, % body wt.	0.6376	0.0490	0.6800	0.0610	0.6638	0.0497	0.7078	0.0305
Female Sprague-Dawley Rats								
Mean body weight, gm	265.0	15.0	270.6	22.4	276.2	18.0	288.0	7.2
Liver, absolute, gm	8.4144	0.2424	8.7762	1.2825	9.1094	1.4486	8.8654	1.2874
Liver, % body wt.	3.1886	0.1303	3.2398	0.3080	3.2840	0.3246	3.0730	0.3805
Kidney, absolute, gm	1.8878	0.0838	1.9524	0.2121	1.9066	0.0984	1.9672	0.0897
Kidney, % body wt.	0.7146	0.0587	0.7202	0.0322	0.6916	0.0374	0.6836	0.0349

SD - Standard Deviation

Table 42-21

Table 42-21

Mean Organ Weight: Sprague-Dawley Rats and Beagle Dogs

Sacrificed After Approximately 13 and 14 Exposure Weeks, Respectively

Organ, Basis	Butyraldehyde Concentration, mg/liter							
	5.44		1.36		0.34		0	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Male Sprague-Dawley Rats								
Mean body weight, gm	501.9	47.8	510.4	68.5	537.1	75.2	517.3	61.4
Liver, absolute, gm	14.5194	1.6610	15.3674	2.8755	15.9561	3.0412	15.4664	2.4344
Liver, % body wt.	2.8931	0.1815	2.9974	0.2070	2.9586	0.2137	2.9809	0.2055
Kidney, absolute, gm	3.0181	0.2571	3.2242	0.3222	3.2065	0.3341	3.1756	0.2640
Kidney, % body wt.	0.6029	0.0366	0.6362	0.0575	0.6006	0.0412	0.6174	0.0458
Female Sprague-Dawley Rats								
Mean body weight, gm	322.8	36.7	312.2	25.4	324.9	32.5	326.3	24.3
Liver, absolute, gm	8.9518	1.3373	9.2433	1.1624	9.3653	1.3004	9.0590	1.0360
Liver, % body wt.	2.7720	0.2838	2.9550	0.2047	2.8833	0.2943	2.7745	0.2086
Kidney, absolute, gm	1.9978	0.2076	1.8999	0.2478	1.9281	0.1545	2.0201	0.1669
Kidney, % body wt.	0.6215	0.0538	0.6083	0.0500	0.5939	0.0462	0.6199	0.0393
Male Beagle Dogs								
Mean Body Weight, gm	11080	1700	11950	870	11220	1330	11020	990
Liver, absolute, gm	298.0	11.5	329.0	50.9	292.2	47.6	320.0	27.7
Liver, % body wt.	2.7412	0.4417	2.7742	0.5639	2.5962	0.1656	2.9242	0.3960
Kidney, absolute, gm	60.8	6.2	65.8	8.0	56.8	7.4	59.0	10.2
Kidney, % body wt.	0.5530	0.0562	0.5505	0.0564	0.5100	0.0822	0.5348	0.0698

SD = Standard Deviation

Table 42-12

Frequency of Histologic Findings: Beagle Dogs

Sacrificed After [illegible] Fourteen

Weeks of Inhalation to Butyraldehyde

ORGANS/Findings	Males: ppm of Butyraldehyde 2000	500	125	Control
NASAL CAVITY, Normal	0/4[a]	0/4[a]	1/4	3/4
/Rhinitis, moderate	3/4	0/4	0/4	0/4
/Rhinitis, marked	1/4	0/4	0/4	0/4
/Mucosal cell hyperplasia, slight-moderate	4/4	2/4	0/4	1/4
/Squamous metaplasia	3/4	0/4	0/4	0/4
/Goblet cell hyperplasia	0/4	3/4	3/4	1/4
/Mucosal gland hyperplasia	4/4[a]	0/4	0/4	0/4
LUNGS**, Normal	2/4	0/1	0/3	1/4
/Interstitial pneumonitis	1/4	1/1	0/3	0/4
/Granulomatous pneumonitis	1/4	0/1	1/3	0/4
/Peribronchial pneumonitis	0/4	0/1	0/3	1/4
/Peribronchial lymphocytic infiltrates	0/4	1/1	0/3	0/4
/Capsular fibrosis	1/4	0/1	0/3	0/4
/Interstitial fibrosis	0/4	0/1	0/3	1/4
/Bronchiectasis	1/4	0/1	0/3	0/4
/Emphysema	1/4	0/1	1/3	1/4
/Smooth muscle hyperplasia	1/4	0/1	0/3	0/4
/Hemorrhage, agonal	0/4	0/1	1/3	0/4
TRACHEA, Normal	3/4	-	-	4/4
/Squamous metaplasia	1/4	-	-	0/4
LARYNX, Normal	2/4	-	-	4/4
/Laryngitis	1/4	-	-	0/4
/Squamous metaplasia	1/4	-	-	0/4
PITUITARY, Normal	4/4	-	-	3/4
/Cyst	0/4	-	-	1/4
THYROIDS, Normal	1/4	-	-	3/4
/Lymphocytic thyroiditis	1/4	-	-	0/4
/Parafollicular cell hyperplasia	3/4	-	-	1/4
/Follicular cyst	0/4	-	-	1/4
HEART, Normal	2/4	-	-	4/4
/Cyst	1/4	-	-	0/4
/Mural thrombus	1/4	-	-	0/4
SPLEEN**, Normal	0/4	0/4	0/3	0/4
/Hemorrhage/hemangioma	4/4	2/4	3/3	1/4
/Capsular siderosis	2/4	2/4	1/3	2/4
/Capsular fibrosis	0/4	0/4	0/3	1/4
/Hemosiderosis	1/4	2/4	0/3	2/4
/Congestion/hemorrhage	0/4	1/4	0/3	0/4
KIDNEYS, Normal	1/4	-	-	4/4
/Dystrophic mineralization	2/4	-	-	0/4
/Venous and lymphatic dilation	1/4	-	-	0/4
STOMACH, Normal	3/4	-	-	3/4
/Lymphocytic infiltrates, nodular	1/4	-	-	0/4
/Dystrophic mineralization	0/4	-	-	1/4

(Continued)

Table 42-22

(Continued)

ORGANS/Findings	Males ppm of Butyraldehyde 2000	500	125	Control
LIVER**, Normal	3/4	0/1	0/1	4/4
/Hemosiderosis	1/4	1/1	1/1	0/4
BRAIN**, Normal	2/4	0/1	1/2	4/4
/Hydrocephalus	0/4	1/1	1/2	0/4
/Meningeal fibrosis	1/4	0/1	0/2	0/4
/Purkinje neuron loss	1/4	0/1	0/2	0/4
/Microhemorrhages	1/4	0/1	0/2	0/4
PARATHYROIDS, Normal	4/4	-	-	3/3
ADRENALS, Normal	4/4	-	-	4/4
TESTES, Normal	4/4	-	-	4/4
EPIDIDYMIDES, Normal	4/4	-	-	4/4
PROSTATE, Normal	4/4	-	-	4/4
EYES, Normal	4/4	-	-	4/4
PANCREAS, Normal	4/4	-	-	4/4

[a]$0.05 > p > 0.01$

*Numerator equals number of dogs with specified finding.
Denominator equals number of dogs for which specified organ was examined.

**Examined in 500 and 125 ppm groups only if gross lesion was present.

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Frequency of Histologic Findings: Sprague - Dawley Rats

Sacrificed After Six Weeks of Exposure to Butyraldehyde

ORGANS/Findings	Males: ppm of Butyraldehyde 2000	500	125	Control	Females: ppm of Butyraldehyde 2000	500	125	Control
NASAL CAVITY, Normal	0/5[a,b]	1/5[a]	2/5	5/5	0/5[b]	0/5[b]	3/5	5/5
/Rhinitis, marked	1/5	0/5	0/5	0/5	0/5	0/5	0/5	0/5
/Rhinitis, moderate	3/5	0/5	0/5	0/5	3/5	0/5	0/5	0/5
/Rhinitis, mild	1/5	4/5[a]	1/5	0/5	2/5	3/5	1/5	0/5
/Squamous metaplasia, marked	0/5	0/5	0/5	0/5		1/5	0/5	0/5
/Squamous metaplasia, moderate	3/5	1/5	1/5	0/5	2/5	2/5	0/5	0/5
/Squamous metaplasia, mild	2/5	0/5	0/5	0/5	2/5	1/5	0/5	0/5
/Exhaustion atrophy of goblet cells, severe	0/5	0/5	0/5	0/5	1/5	0/5	0/5	0/5
/Exhaustion atrophy of goblet cells, marked	1/5	2/5	1/5	0/5	4/5[a]	3/5	0/5	0/5
/Exhaustion atrophy of goblet cells, moderate	3/5	0/5	1/5	0/5	0/5	2/5	0/5	0/5
/Exhaustion atrophy of goblet cells, mild	1/5	2/5	1/5	0/5	0/5	0/5	0/5	0/5
/Goblet cell hyperplasia, mild	0/5	0/5	0/5	0/5	0/5	0/5	2/5	0/5
LUNG, Normal	3/5	3/4	3/4	3/5	1/5[a]	1/4	1/2	5/5
/Perivasculitis, marked	0/5	0/4	0/4	0/5	1/5	0/4	0/2	0/5
/Perivasculitis, moderate	0/5	0/4	0/4	1/5	1/5	0/4	1/2	0/5
/Perivasculitis, mild	2/5	1/4	1/4	1/5	1/5	3/4	0/2	0/5
/Interstitial pneumonia, marked	0/5	0/4	0/4	0/5	1/5	0/4	0/2	0/5
/Interstitial pneumonia, moderate	0/5	0/4	0/4	1/5	0/5	0/4	0/2	0/5
/Interstitial pneumonia, mild	1/5	1/4	0/4	1/5	3/5	2/4	1/2	0/5
KIDNEY, Normal	3/5	-	-	5/5	5/5	-	-	5/5
/Hydronephrosis, Unilateral	2/5	-	-	0/5	0/5	-	-	0/5
LIVER, Normal	5/5	-	-	5/5	4/5	-	-	2/5
/Hepatitis	0/5	-	-	0/5	1/5	-	-	3/5
PANCREATICO-SPLENIC LYMPH NODE								
/Hemorrhagic drainage reaction	-	-	-	1/1	-	-	-	1/1
PITUITARY, Normal	5/5	-	-	5/5	5/5	1/1	-	5/5
THYROIDS, Normal	5/5	-	-	5/5	5/5	-	-	5/5
PARATHYROIDS, Normal	5/5	-	-	5/5	5/5	-	-	3/3
ADRENALS, Normal	5/5	-	-	5/5	5/5	-	-	5/5
HEART, Normal	5/5	-	-	5/5	5/5	-	-	5/5
SPLEEN, Normal	5/5	-	-	5/5	5/5	-	-	5/5
LARYNX, Normal	5/5	-	-	5/5	5/5	-	-	5/5
TRACHEA, Normal	5/5	-	-	5/5	-	-	-	-
TESTES, Normal	5/5	-	-	5/5				

(Continued)

Table 42-23

(Continued)

ORGANS/Findings	Males				Female			
	ppm of Butyraldehyde				ppm of Butyraldehyde			
	2000	500	125	Control	2000	500	125	Control
EPIDIDYMIDES, Normal	5/5	-	-	5/5	-	-	-	-
PROSTATE, Normal	5/5	-	-	4/4	-	-	-	-
OVARIES, Normal	-	-	-	-	5/5	-	-	5/5
OVIDUCT, Normal	-	-	-	-	5/5	-	-	5/5
UTERUS, Normal	-	-	-	-	5/5	-	-	5/5
ESOPHAGUS, Normal	5/5	-	-	5/5	5/5	-	-	5/5
STOMACH, Normal	5/5	-	-	5/5	5/5	-	-	5/5
PANCREAS, Normal	5/5	-	-	5/5	5/5	-	-	5/5
BRAIN, Normal	5/5	-	-	5/5	5/5	-	-	5/5
EYES, Normal	5/5	-	-	5/5	5/5	-	-	5/5
FEMUR, Normal	5/5	-	-	5/5	5/5	-	-	5/5

[a]Numerator equals number of rats with specified finding.
Denominator equals number of rats for which specified organ was examined.

[a]$0.05 > P > 0.01$ [b]$0.01 > P > 0.001$

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Table 42-24

Frequency of Histologic Findings: Sprague - Dawley Rats

Sacrificed After Thirteen Weeks of Exposure to Butyraldehyde

ORGANS/Findings	Males				Females			
	ppm of Butyraldehyde				ppm of Butyraldehyde			
	2000	500	125	Control	2000	500	125	Control
NASAL CAVITY, Normal	1/10[ab]	2/10[b]	1/10[b]	9/10	1/10[c]	0/10[c]	1/10[c]	10/10
/Rhinitis, severe	0/10	0/10	0/10	0/10	1/10	0/10	0/10	0/10
/Rhinitis, marked	0/10	0/10	0/10	0/10	1/10	0/10	0/10	0/10
/Rhinitis, moderate	5/10[a]	1/10	0/10	0/10	4/10	0/10	2/10	0/10
/Rhinitis, mild	4/10[a]	3/10	2/10	0/10	3/10	1/10	2/10	0/10
/Squamous metaplasia, severe	0/10	0/10	0/10	0/10	1/10	0/10	0/10	0/10
/Squamous metaplasia, marked	0/10	0/10	0/10	0/10	0/10	0/10	1/10	0/10
/Squamous metaplasia, moderate	6/10[a]	2/10	1/10	0/10	5/10[a]	1/10	2/10	0/10
/Squamous metaplasia, mild	3/10	4/10	8/10[c]	0/10	2/10	9/10[c]	6/10[a]	0/10
/Goblet cell hyperplasia, marked	0/10	1/10	0/10	0/10	0/10	1/10	1/10	0/10
/Goblet cell hyperplasia, moderate	0/10	2/10	2/10	0/10	0/10	3/10	2/10	0/10
/Goblet cell hyperplasia, mild	1/10	2/10	7/10[b]	0/10	0/10	3/10	5/10[a]	0/10
/Goblet cell fusion, mild	0/10	0/10	0/10	1/10	0/10	0/10	1/10	0/10
/Submucosal edema, mild	0/10	0/10	0/10	0/10	0/10	0/10	1/10	0/10
LUNGS, Normal	2/10	1/6	1/7	2/10	0/10[b]	0/4	0/5[a]	7/10
/Perivasculitis, severe	0/10	0/6	0/7	0/10	0/10	0/4	1/5	0/10
/Perivasculitis, marked	1/10	0/6	0/7	0/10	1/10	0/4	0/5	0/10
/Perivasculitis, moderate	0/10	1/6	3/7	3/10	1/10	2/4	2/5	1/10
/Perivasculitis, mild	7/10	3/6	3/7	5/10	8/10[a]	1/4	2/5	2/10
/Interstitial pneumonia, severe	0/10	0/6	0/7	0/10	0/10	0/4	1/5	0/10
/Interstitial pneumonia, marked	0/10	0/6	0/7	0/10	0/10	1/4	0/5	0/10
/Interstitial pneumonia, moderate	1/10	1/6	0/7	2/10	1/10	0/4	2/5	0/10
/Interstitial pneumonia, mild	6/10	3/6	5/7	5/10	4/10	3/4	0/5	2/10
/Lymphoid hyperplasia, mild	1/10	0/6	0/7	0/10	0/10	0/4	0/5	0/10
/Pleuritis, mild	0/10	1/6	0/7	0/10	0/10	1/4	2/5	0/10
/Pleural fibrosis, mild	0/10	0/6	0/7	0/10	1/10	1/4	0/5	0/10
TRACHEA, Normal	10/10	–	–	9/10	10/10	–	–	10/10
/Submucosal gland dilation, mild	0/10	–	–	1/10	0/10	–	–	0/10
CERVICAL LYMPH NODES, Normal	–	0/1	–	–	–	–	–	–
/Hemorrhage, mild	–	1/1	–	–	–	–	–	–
/Lymphoid hyperplasia, moderate	–	1/1	–	–	–	–	–	–
HEART, Normal	6/10	–	–	4/10	10/10	–	–	10/10
/Myocarditis, moderate	0/10	–	–	1/10	0/10	–	–	0/10
/Myocarditis, mild	1/10	–	–	2/10	0/10	–	–	0/10
/Arteriosclerosis, mild	3/10	–	–	4/10	0/10	–	–	0/10

(Continued)

(Continued)

ORGANS/Findings	Males				Females			
	ppm of Butyraldehyde				ppm of Butyraldehyde			
	2000	500	125	Control	2000	500	125	Control
KIDNEYS**, Normal	2/10	0/1	0/2	3/10	8/10	-	1/1	9/10
/Interstitial nephritis, mild	1/10	0/1	0/2	0/10	0/10	-	0/1	1/10
/Glomerular adhesions, moderate	2/10	0/1	0/2	1/10	0/10	-	0/1	0/10
/Glomerular adhesions, mild	6/10	1/1	0/2	4/10	2/10	-	0/1	0/10
/Tubular hyperplasia, mild	1/10	0/1	0/2	2/10	0/10	-	0/1	0/10
/Hydronephrosis, moderate, unilateral	0/10	1/1	1/2	0/10	0/10	-	0/1	0/10
/Hydronephrosis, mild, unilateral	0/10	0/1	1/2	0/10	0/10	-	0/1	0/10
PROSTATE, Normal	9/10	-	-	8/10	-	-	-	-
/Prostatitis, moderate	0/10	-	-	1/10	-	-	-	-
/Prostatitis, mild	1/10	-	-	0/10	-	-	-	-
/Edema, marked	0/10	-	-	1/10	-	-	-	-
LIVER, Normal	9/10	-	-	10/10	9/10	-	-	9/10
/Hepatitis, mild	0/10	-	-	0/10	0/10	-	-	1/10
/Triditis, mild	1/10	-	-	0/10	1/10	-	-	0/10
PANCREATICO-SPLENIC LYMPH NODE**, Normal	-	-	-	0/2	-	-	-	-
/Hemorrhagic drainage reaction, mild	-	-	-	2/2	-	-	-	-
/Hemosiderosis, mild	-	-	-	1/2	-	-	-	-
STOMACH, Normal	8/10	-	-	9/10	8/10	-	-	10/10
/Mucosal gland dilation, mild	1/10	-	-	1/10	2/10	-	-	0/10
/Gastritis, mild	1/10	-	-	0/10	0/10	-	-	0/10
BRAIN, Normal	9/10	-	-	10/10	10/10	-	-	10/10
/Cystic area	1/10	-	-	0/10	0/10	-	-	0/10
EYES, Normal	10/10	-	-	10/10	9/10	-	-	10/10
/Iridal cyst	0/10	-	-	0/10	1/10	-	-	0/10
PITUITARY, Normal	10/10	-	-	10/10	10/10	-	-	9/10
/Cysts	0/10	-	-	0/10	0/10	-	-	1/10
THYROIDS, Normal	10/10	-	-		10/10	-	-	9/9
PARATHYROIDS, Normal	10/10	-	-	9/9	9/9	-	-	8/8
ADRENALS, Normal	10/10	-	-	10/10	10/10	-	-	10/10
SPLEEN, Normal	10/10	-	-	10/10	10/10	-	-	10/10
LARYNX, Normal	10/10	-	-	10/10	10/10	-	-	10/10
OVARIES, Normal	-	-	-	-	10/10	-	-	10/10
OVIDUCT, Normal	-	-	-	-	10/10	-	-	10/10
UTERUS, Normal	-	-	-	-	10/10	-	-	10/10
TESTES, Normal	10/10	-	-	10/10	-	-	-	-
EPIDIDYMIDES, Normal	10/10	-	-	10/10	-	-	-	-

(Continued)

Table 42-24

(Continued)

ORGANS/Findings	Males ppm of Butyraldehyde 2000	500	125	Control	Females ppm of Butyraldehyde 2000	500	125	Control
ESOPHAGUS, Normal	10/10	-	-	10/10	10/10	-	-	10/10
PANCREAS, Normal	10/10	-	-	10/10	10/10	-	-	10/10
FEMUR, Normal	10/10	-	-	10/10	10/10	-	-	10/10

[a]0.05 > P > 0.01 [b]0.01 > P > 0.001 [c]P < 0.001

*Numerator equals number of rats with specified finding.
Denominator equals number of rats for which specified organ was examined.

**Examined in 500 and 125 ppm groups only if gross lesion was present.

***Examined only if gross lesion was present.

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Pages 47 through 322 of this report contained individual pathology data sheets for each animal. Those sheets have not been included in this report in order to decrease costs of reproduction and distribution of reports. A copy of the report containing the individual data sheets was distributed to the Project Initiator and the original is on file in the Chemical Hygiene Fellowship Archives.

Quality Assurance Unit Study Inspection Summary

Test Substance: Butyraldehyde

Study: Vapor Inhalation by Dogs and Rats for 14 and 13 Weeks Respectively

Project Manager: S. C. Gad

The Quality Assurance Unit conducted the following inspections and reported the results to the Project Manager and to Management on the dates indicated.

Inspection		QAU Date Report Issued	
Date	Type	To Project Mgr.	To Management
3-28 to 4-23-79	Final Ongoing Raw Data	4-23-79	5-17-79
5-31 to 6-4-79	Final Report	6-5-79	6-8-79

Daniel P. Leary 6/8/79

Quality Assurance Officer Date

LJC/dcm
1-29-79