NTP TECHNICAL REPORT

ON THE

TOXICOLOGY AND CARCINOGENESIS

STUDIES OF GLUTARALDEHYDE

(CAS NO. 111-30-8)

IN F344/N RATS AND B6C3F$_1$ MICE

(INHALATION STUDIES)

NATIONAL TOXICOLOGY PROGRAM
P.O. Box 12233
Research Triangle Park, NC 27709

September 1999

NTP TR 490

NIH Publication No. 99-3980

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
National Institutes of Health

FOREWORD

The National Toxicology Program (NTP) is made up of four charter agencies of the U.S. Department of Health and Human Services (DHHS): the National Cancer Institute (NCI), National Institutes of Health; the National Institute of Environmental Health Sciences (NIEHS), National Institutes of Health; the National Center for Toxicological Research (NCTR), Food and Drug Administration; and the National Institute for Occupational Safety and Health (NIOSH), Centers for Disease Control and Prevention. In July 1981, the Carcinogenesis Bioassay Testing Program, NCI, was transferred to the NIEHS. The NTP coordinates the relevant programs, staff, and resources from these Public Health Service agencies relating to basic and applied research and to biological assay development and validation.

The NTP develops, evaluates, and disseminates scientific information about potentially toxic and hazardous chemicals. This knowledge is used for protecting the health of the American people and for the primary prevention of disease.

The studies described in this Technical Report were performed under the direction of the NIEHS and were conducted in compliance with NTP laboratory health and safety requirements and must meet or exceed all applicable federal, state, and local health and safety regulations. Animal care and use were in accordance with the Public Health Service Policy on Humane Care and Use of Animals. The prechronic and chronic studies were conducted in compliance with Food and Drug Administration (FDA) Good Laboratory Practice Regulations, and all aspects of the chronic studies were subjected to retrospective quality assurance audits before being presented for public review.

These studies are designed and conducted to characterize and evaluate the toxicologic potential, including carcinogenic activity, of selected chemicals in laboratory animals (usually two species, rats and mice). Chemicals selected for NTP toxicology and carcinogenesis studies are chosen primarily on the bases of human exposure, level of production, and chemical structure. The interpretive conclusions presented in this Technical Report are based only on the results of these NTP studies. Extrapolation of these results to other species and quantitative risk analyses for humans require wider analyses beyond the purview of these studies. Selection *per se* is not an indicator of a chemical's carcinogenic potential.

Listings of all published NTP reports and ongoing studies are available from NTP Central Data Management, NIEHS, P.O. Box 12233, MD E1-02, Research Triangle Park, NC 27709 (919-541-3419). The Abstracts and other study information for 2-year studies are also available at the NTP's World Wide Web site: http://ntp-server.niehs.nih.gov.

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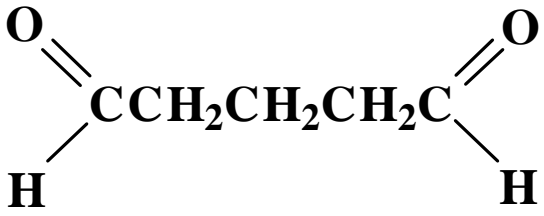
CONTENTS

ABSTRACT



GLUTARALDEHYDE

CAS No. 111-30-8

Chemical Formula: $C_5H_8O_2$ Molecular Weight: 100.13

Synonyms: 1,3-Diformylpropane; glutaral; glutardialdehyde; glutaric dialdehyde; 1,5-pentanedial; 1,5-pentanedione; potentiated acid glutaraldehyde
Trade names: Cidex; Sonacide

Glutaraldehyde is used in large volume in a variety of industries as a disinfectant, preservative, fixative and cross-linking agent, and as a chemical intermediate in the synthesis of pharmaceuticals and pesticides. Glutaraldehyde was nominated by the National Cancer Institute, the Occupational Safety and Health Administration, and the National Institute of Environmental Health Sciences for carcinogenicity studies because of potential occupational exposure. Male and female F344/N rats and B6C3F$_1$ mice were exposed to glutaraldehyde (25% aqueous solution) (approximately 93% pure) by inhalation for 2 years. *In vitro* genetic toxicology studies were conducted in *Salmonella typhimurium*, L5178Y mouse lymphoma cells, and cultured Chinese hamster ovary cells; *in vivo* studies were conducted to measure sex-linked recessive lethal mutations in *Drosophila melanogaster*, chromosomal aberrations and micronucleated erythrocytes in mouse bone marrow, and micronucleated erythrocytes in mouse peripheral blood. The results of 13-week inhalation studies with glutaraldehyde were reported previously (NTP, 1993).

2-YEAR STUDY IN RATS

Groups of 50 male and 50 female F344/N rats were exposed to 0, 250, 500, or 750 ppb glutaraldehyde vapor by inhalation, 6 hours per day, 5 days per week, for 104 weeks. Survival of 500 and 750 ppb female rats was less than that of the chamber controls. Mean body weights of all exposed groups of male rats and 500 and 750 ppb female rats were generally less than those of the chamber controls. Some female rats exposed to 750 ppb were thin to emaciated at the time they were killed moribund. Increased incidences of nonneoplastic nasal lesions occurred primarily within the anterior section of the nose in 500 and 750 ppb rats and to a lesser extent in 250 ppb rats. The more significant lesions included hyperplasia and

inflammation of the squamous and respiratory epithelia and squamous metaplasia of the respiratory epithelium.

2-YEAR STUDY IN MICE

Groups of 50 male and 50 female B6C3F$_1$ mice were exposed to 0, 62.5, 125, or 250 ppb glutaraldehyde vapor by inhalation, 6 hours per day, 5 days per week, for 104 weeks. Survival of exposed mice was similar to that of the chamber controls. Mean body weights of female mice exposed to 250 ppb were generally less than those of the chamber controls throughout the study. Incidences of squamous metaplasia of the respiratory epithelium were increased in 250 ppb males and females and 125 ppb females. Incidences of hyaline degeneration of the respiratory epithelium were increased in all exposed groups of females. The incidence of inflammation of the nose was marginally increased in 250 ppb females.

GENETIC TOXICOLOGY

In genetic toxicity studies, glutaraldehyde was mutagenic with and without S9 metabolic activation in *S. typhimurium* strains TA100, TA102, and TA104. Glutaraldehyde was mutagenic in mouse L5178Y lymphoma cells in the absence of S9 and induced sister chromatid exchanges in cultured Chinese hamster ovary cells with and without S9. No increase in chromosomal aberrations was induced by glutaraldehyde in cultured Chinese hamster ovary cells with or without S9 at one laboratory; at another laboratory, chromosomal aberrations were induced in the absence of S9 only. Glutaraldehyde did not induce sex-linked recessive lethal mutations in germ cells of male *D. melanogaster* treated as adults by feeding or injection or treated as larvae by feeding. *In vivo*, glutaraldehyde induced a significant increase in chromosomal aberrations in mouse bone marrow cells 36 hours after a single intraperitoneal injection. In a subset of the 36-hour chromosomal aberrations test, there was a small increase in the number of micronucleated bone marrow polychromatic erythrocytes, which was judged to be equivocal. Additional short-term (3-day) and subchronic (13-week) micronucleus tests in mice, using the intraperitoneal or inhalation routes, respectively, yielded negative results.

CONCLUSIONS

Under the conditions of these 2-year inhalation studies, there was *no evidence of carcinogenic activity** of glutaraldehyde in male or female F344/N rats exposed to 250, 500, or 750 ppb. There was *no evidence of carcinogenic activity* in male or female B6C3F$_1$ mice exposed to 62.5, 125, or 250 ppb.

Incidences of nonneoplastic lesions of the nose were significantly increased in male and female rats and mice.

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* Explanation of Levels of Evidence of Carcinogenic Activity is on page 8. A summary of the Technical Reports Review Subcommittee comments and the public discussion on this Technical Report appears on page 10.

Summary of the 2-Year Carcinogenesis and Genetic Toxicology Studies of Glutaraldehyde

	Male F344/N Rats	Female F344/N Rats	Male $B6C3F_1$ Mice	Female $B6C3F_1$ Mice
Concentrations in air	Chamber control, 250, 500, or 750 ppb	Chamber control, 250, 500, or 750 ppb	Chamber control, 62.5, 125, or 250 ppb	Chamber control, 62.5, 125, or 250 ppb
Body weights	Exposed groups generally less than chamber controls	500 and 750 ppb groups less than chamber controls	Exposed groups similar to chamber controls	250 ppb group less than chamber controls
Survival rates	12/50, 14/50, 9/50, 6/50	26/50, 31/50, 15/50, 14/50	31/50, 27/50, 40/50, 38/50	34/50, 37/50, 35/50, 32/50
Nonneoplastic effects	Nose: squamous epithelium hyperplasia (3/50, 11/50, 39/50, 48/50); squamous epithelium inflammation (6/50, 17/50, 41/50, 49/50); respiratory epithelium hyperplasia (6/50, 5/50, 17/50, 35/50); respiratory epithelium inflammation (17/50, 10/50, 25/50, 43/50); respiratory epithelium squamous metaplasia (1/50, 2/50, 11/50, 24/50); respiratory epithelium goblet cell hyperplasia (1/50, 0/50, 6/50, 6/50); olfactory epithelium hyaline degeneration (4/50, 8/50, 9/50, 14/50)	Nose: squamous epithelium hyperplasia (3/50, 15/50, 29/50, 45/49); squamous epithelium inflammation (6/50, 26/50, 42/50, 48/49); respiratory epithelium hyperplasia (1/50, 6/50, 15/50, 29/49); respiratory epithelium inflammation (5/50, 9/50, 26/50, 42/49); respiratory epithelium squamous metaplasia (1/50, 1/50, 11/50,16/49); respiratory epithelium goblet cell hyperplasia (1/50, 3/50, 5/50, 8/49); olfactory epithelium hyaline degeneration (4/50, 5/50, 12/50, 15/49)	Nose: respiratory epithelium squamous metaplasia (2/48, 5/50, 6/50, 9/50)	Nose: respiratory epithelium squamous metaplasia (7/50, 11/49, 16/50, 21/50); respiratory epithelium hyaline degeneration (16/50, 35/49, 32/50, 30/50); inflammation (6/50, 7/49, 13/50, 14/50)
Neoplastic effects	None	None	None	None
Level of evidence of carcinogenic activity	No evidence	No evidence	No evidence	No evidence
Genetic toxicology				
Salmonella typhimurium gene mutations:	Positive in strains TA100, TA102, and TA104 with and without S9			
Mouse lymphoma gene mutations:	Positive without S9			
Sister chromatid exchanges				
Cultured Chinese hamster ovary cells *in vitro*:	Positive with and without S9			
Chromosomal aberrations				
Cultured Chinese hamster ovary cells *in vitro*:	Weakly positive without S9			
Mouse bone marrow *in vivo*:	Positive			
Sex-linked recessive lethal mutations				
Drosophila melanogaster:	Negative			
Micronucleated erythrocytes				
Mouse bone marrow *in vivo*:	Equivocal (single-injection protocol); negative (three-injection protocol)			
Mouse peripheral blood *in vivo*:	Negative			

EXPLANATION OF LEVELS OF EVIDENCE OF CARCINOGENIC ACTIVITY

The National Toxicology Program describes the results of individual experiments on a chemical agent and notes the strength of the evidence for conclusions regarding each study. Negative results, in which the study animals do not have a greater incidence of neoplasia than control animals, do not necessarily mean that a chemical is not a carcinogen, inasmuch as the experiments are conducted under a limited set of conditions. Positive results demonstrate that a chemical is carcinogenic for laboratory animals under the conditions of the study and indicate that exposure to the chemical has the potential for hazard to humans. Other organizations, such as the International Agency for Research on Cancer, assign a strength of evidence for conclusions based on an examination of all available evidence, including animal studies such as those conducted by the NTP, epidemiologic studies, and estimates of exposure. Thus, the actual determination of risk to humans from chemicals found to be carcinogenic in laboratory animals requires a wider analysis that extends beyond the purview of these studies.

Five categories of evidence of carcinogenic activity are used in the Technical Report series to summarize the strength of the evidence observed in each experiment: two categories for positive results (**clear evidence** and **some evidence**); one category for uncertain findings (**equivocal evidence**); one category for no observable effects (**no evidence**); and one category for experiments that cannot be evaluated because of major flaws (**inadequate study**). These categories of interpretative conclusions were first adopted in June 1983 and then revised in March 1986 for use in the Technical Report series to incorporate more specifically the concept of actual weight of evidence of carcinogenic activity. For each separate experiment (male rats, female rats, male mice, female mice), one of the following five categories is selected to describe the findings. These categories refer to the strength of the experimental evidence and not to potency or mechanism.

- **Clear evidence** of carcinogenic activity is demonstrated by studies that are interpreted as showing a dose-related (i) increase of malignant neoplasms, (ii) increase of a combination of malignant and benign neoplasms, or (iii) marked increase of benign neoplasms if there is an indication from this or other studies of the ability of such tumors to progress to malignancy.
- **Some evidence** of carcinogenic activity is demonstrated by studies that are interpreted as showing a chemical-related increased incidence of neoplasms (malignant, benign, or combined) in which the strength of the response is less than that required for clear evidence.
- **Equivocal evidence** of carcinogenic activity is demonstrated by studies that are interpreted as showing a marginal increase of neoplasms that may be chemical related.
- **No evidence** of carcinogenic activity is demonstrated by studies that are interpreted as showing no chemical-related increases in malignant or benign neoplasms.
- **Inadequate study** of carcinogenic activity is demonstrated by studies that, because of major qualitative or quantitative limitations, cannot be interpreted as valid for showing either the presence or absence of carcinogenic activity.

When a conclusion statement for a particular experiment is selected, consideration must be given to key factors that would extend the actual boundary of an individual category of evidence. Such consideration should allow for incorporation of scientific experience and current understanding of long-term carcinogenesis studies in laboratory animals, especially for those evaluations that may be on the borderline between two adjacent levels. These considerations should include:

- adequacy of the experimental design and conduct;
- occurrence of common versus uncommon neoplasia;
- progression (or lack thereof) from benign to malignant neoplasia as well as from preneoplastic to neoplastic lesions;
- some benign neoplasms have the capacity to regress but others (of the same morphologic type) progress. At present, it is impossible to identify the difference. Therefore, where progression is known to be a possibility, the most prudent course is to assume that benign neoplasms of those types have the potential to become malignant;
- combining benign and malignant tumor incidence known or thought to represent stages of progression in the same organ or tissue;
- latency in tumor induction;
- multiplicity in site-specific neoplasia;
- metastases;
- supporting information from proliferative lesions (hyperplasia) in the same site of neoplasia or in other experiments (same lesion in another sex or species);
- presence or absence of dose relationships;
- statistical significance of the observed tumor increase;
- concurrent control tumor incidence as well as the historical control rate and variability for a specific neoplasm;
- survival-adjusted analyses and false positive or false negative concerns;
- structure-activity correlations; and
- in some cases, genetic toxicology.

NATIONAL TOXICOLOGY PROGRAM BOARD OF SCIENTIFIC COUNSELORS
TECHNICAL REPORTS REVIEW SUBCOMMITTEE

The members of the Technical Reports Review Subcommittee who evaluated the draft NTP Technical Report on glutaraldehyde on 30 October 1998 are listed below. Subcommittee members serve as independent scientists, not as representatives of any institution, company, or governmental agency. In this capacity, subcommittee members have five major responsibilities in reviewing the NTP studies:

- to ascertain that all relevant literature data have been adequately cited and interpreted,
- to determine if the design and conditions of the NTP studies were appropriate,
- to ensure that the Technical Report presents the experimental results and conclusions fully and clearly,
- to judge the significance of the experimental results by scientific criteria, and
- to assess the evaluation of the evidence of carcinogenic activity and other observed toxic responses.

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SUMMARY OF TECHNICAL REPORTS REVIEW SUBCOMMITTEE COMMENTS

On 30 October 1998, the draft Technical Report on the toxicology and carcinogenesis studies of glutaraldehyde received public review by the National Toxicology Program's Board of Scientific Counselors' Technical Reports Review Subcommittee. The review meeting was held at the National Institute of Environmental Health Sciences, Research Triangle Park, NC.

Dr. A.P.J.M. van Birgelen, NIEHS, introduced the toxicology and carcinogenesis studies of glutaraldehyde by discussing the uses of the chemical and the rationale for study, describing the experimental design, reporting on survival and body weight effects, and commenting on compound-related neoplastic and nonneoplastic lesions in rats and mice. The proposed conclusions for the 2-year studies were *no evidence of carcinogenic activity* in male or female F344/N rats or $B6C3F_1$ mice.

Dr. Belinsky, a principal reviewer, agreed with the proposed conclusions. He commented that, given the high reactivity of glutaraldehyde, it was unlikely that any significant amount reached organs other than the nose. If human exposure is truly restricted to that by inhalation, then the studies are probably adequate; however, if dermal exposure is an issue, other routes should be considered. Dr. van Birgelen said it was plausible that glutaraldehyde does not get beyond the nose, but this was not certain without toxicokinetic data. Dr. Belinsky was also concerned about the inadvertant caloric restriction and asked that this and the issue of tissue distribution be incorporated further in the discussion. Dr. van Birgelen said that decreased incidences of mammary gland and pituitary gland neoplasms may be related to mild decreases in body weight gain in female rats.

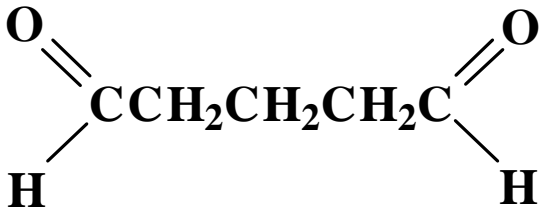
Dr. Bus, the second principal reviewer, agreed with the proposed conclusions. He disagreed with the positive findings reported for *Salmonella typhimurium* and sister chromatid exchanges in cultured Chinese hamster ovary cells *in vitro* and chromosomal aberrations in mouse bone marrow cells *in vivo*. He thought that inconsistencies and lack of a dose response supported an equivocal result. Dr. van Birgelen explained how the genetic toxicology results are determined, noting that the results from different laboratories are not combined for a single finding. She said the results for each of the three assays supported a positive finding but agreed that the finding for chromosomal aberrations in mouse bone marrow should be changed to weakly positive. Dr. Bus commented that the section comparing delivered doses of glutaraldehyde to formaldehyde might not be valid in the absence of comparative tissue distribution data.

Dr. Medinsky, the third principal reviewer, agreed with the proposed conclusions. She noted that structure-activity relationships are important in toxicology research to help explain why similar chemicals have different toxic or carcinogenic endpoints. She said the observation that the more reactive glutaraldehyde is deposited primarily in the anterior portion of the nose, whereas formaldehyde is deposited deeper in the respiratory tract, partly explains the marked differences in carcinogenic activity, and that there should be more discussion of this issue.

Ms. J. Kenepp and Ms. S. Sowers, operating-room nurses from New Holland, PA, spoke on behalf of a chemical injury support group, Workers Against Senseless Toxic Exposure (WASTE). Ms. Kenepp stated that hundreds of healthcare professionals had been exposed to glutaraldehyde used as a cold sterilant while not being warned of its toxic effects or being trained in its proper use and disposal. She described health effects that she attributed to glutaraldehyde, including increased sensitivity to the effects of other chemicals. Ms. Sowers mentioned the lack of regulation or control of glutaraldehyde use in the workplace and the need for more research on toxic and carcinogenic effects in humans.

Dr. Bus moved that the Technical Report on glutaraldehyde be accepted with the revisions discussed and the conclusions as written for male and female rats and mice, *no evidence of carcinogenic activity*. Dr. Medinsky seconded the motion, which was accepted unanimously with five votes (Drs. Bailer, Bus, Cullen, Hecht, and Medinsky).

INTRODUCTION



GLUTARALDEHYDE

CAS No. 111-30-8

Chemical Formula: $C_5H_8O_2$ Molecular Weight: 100.13

Synonyms: 1,3-Diformylpropane; glutaral; glutardialdehyde; glutaric dialdehyde; 1,5-pentanedial; 1,5-pentanedione; potentiated acid glutaraldehyde
Trade names: Cidex; Sonacide

CHEMICAL AND PHYSICAL PROPERTIES

Glutaraldehyde is a colorless, saturated, aliphatic dialdehyde with a pungent odor of rotten apples (Harvey, 1990; Beauchamp *et al.*, 1992). Glutaraldehyde is soluble in water, ethanol, benzene, and ether (Beauchamp *et al.*, 1992). It has a freezing point of –14° C, a boiling point of 60° to 61° C at 1 mm Hg, a vapor pressure of 0.1160 at 25° C, a specific gravity of 1.064 g/ml, and a vapor density of 3.4 (Beauchamp *et al.*, 1992; Ballantyne, 1995). Glutaraldehyde is stable to light but oxidizes in air and polymerizes when heated. Glutaraldehyde is highly reactive and forms mixtures containing hydrates, pyrans, and polymers (Beauchamp *et al.*, 1992). In aqueous solutions, an equilibrium exists between free glutaraldehyde, hemihydrate, dihydrate, and the *cis* and *trans* isomers of the cyclic hemiacetal.

PRODUCTION, USE, AND HUMAN EXPOSURE

Annual production of glutaraldehyde in the United States from 1986 to 1994 was estimated to be greater than 1 million pounds (John Walker, Interagency Testing Committee, personal communication). Glutaraldehyde is mainly produced by the acid hydrolysis of a 2-alkoxy-3,4-dihydro-2H-pyran (Beauchamp *et al.*, 1992). Glutaraldehyde is used as a cold disinfectant in the health care industry; a hardener in X-ray film processing; a cross-linking and tanning agent; a preservative in chemical products such as fabric softeners, industrial oils, and cosmetics; a biocide in water treatment and in sanitary solutions for aircrafts and portable toilets; a tissue fixative in electron and light microscopy and in histochemistry; an embalming agent; a therapeutic agent for various

skin disorders; an intermediate in the production of pharmaceuticals, pesticides, and crop protection agents; a water-resistant agent in the manufacture of wallpaper and paper towels; a stabilizing agent of collagen-based bioimplantable materials; and a disinfectant for animal housing (Beauchamp *et al.*, 1992; NICNAS, 1994; CIRP, 1996; ACGIH, 1997).

The National Occupational Exposure Survey (1981-1983) estimated that at least 318,000 people in the United States are regularly exposed to glutaraldehyde in the workplace each year (NIOSH, 1990). Exposure occurs mainly among those employed in health care, X-ray film processing, tanning, or animal housing. Occupational exposure occurs mainly by inhalation and skin contact. Workplace concentrations ranging from less than 0.005 to 0.57 ppm have been reported (ACGIH, 1997). During disinfection of surgical operating theaters, peak glutaraldehyde concentrations of 0.57 ppm have been reported with a time-weighted average of 0.1 ppm (Binding and Witting, 1990). Concentrations of glutaraldehyde from personal sampling were up to 0.03 ppm for sterilization processes and 0.002 ppm for X-ray development (Leinster *et al.*, 1993). Routine industrial hygiene monitoring from 1977 to 1992 indicated that glutaraldehyde concentrations were generally less than 0.1 ppm in well-ventilated workplaces (NICNAS, 1994; ACGIH, 1997). The odor threshold for glutaraldehyde is 40 ppb (Beauchamp *et al.*, 1992). The threshold limit ceiling value was lowered to 0.05 ppm (0.2 mg/m^3) in 1995 based on glutaraldehyde-induced irritations at or below 0.1 ppm (ACGIH, 1997). In 1989, NIOSH established a recommended exposure level ceiling of 0.2 ppm based on the 1989 Occupational Safety and Health Administration (OSHA) permissible exposure limit for glutaraldehyde; the OSHA permissible exposure limit was vacated in 1992 (ACGIH, 1997).

When used as a solvent in sterilization processes, most of the glutaraldehyde is flushed into sewer systems with water. Like other aldehydes, it is not persistent when released into the environment. Rapid biodegradation has been reported at aqueous concentrations less than 10 mg/L (NICNAS, 1994).

ABSORPTION, DISTRIBUTION, METABOLISM, AND EXCRETION

McKelvey *et al.* (1992) administered radiolabeled glutaraldehyde intravenously or dermally to male and female Fischer 334 rats (0.2 mL) and New Zealand White rabbits (2.5 mL). After intravenous exposure to 0.075% or 0.75% ^{14}C-glutaraldehyde, rats exhaled 65% to 80% of the radiolabel as CO_2, and rabbits exhaled 30% to 70%. Excretion in the urine was about 10% in rats and 20% in rabbits, and excretion in the feces was about 4% in rats and less than 1% in rabbits. The highest concentration of radiolabel was found in blood cells and in well-perfused tissues such as the lung and kidney, and especially the spleen. Dermal application of 0.075%, 0.75%, or 7.5% radiolabeled glutaraldehyde to rats and 0.75% or 7.5% to rabbits resulted in exhalation of 1% to 2% of label by rats and 5% to 15% by rabbits. Percutaneous radiochemical absorption was 0.3% to 2.1% in rats and 2.5% to 24.9% in rabbits. In a pharmacokinetic experiment (Ballantyne, 1995), dermal absorption rate constants were calculated to range from 0.2 to 2 per hour in rats and rabbits. The terminal half-life for elimination after intravenous injection was 10 hours in rats and ranged from 15 to 30 hours in rabbits. After dermal application, terminal half-lives were estimated to be between 40 and 110 hours in rats and between 20 and 100 hours in rabbits. These long half-lives were attributed to the binding of glutaraldehyde to proteins and to the slow excretion of metabolites, in accordance with a proportionally higher tissue retention of radiolabel in comparison to plasma concentration at a higher intravenous dose.

In vitro application to human skin samples yielded no penetration of the thick stratum corneum of the sole, but 3% to 14% of the applied dose penetrated the thin stratum corneum of the chest and the abdomen, and 3% to 4% penetrated the isolated epidermis (Reifenrath *et al.*, 1985). Less than 1.5% of applied glutaraldehyde has been shown to penetrate the skin of humans, rats, rabbits, mice, and guinea pigs (Frantz *et al.*, 1993).

Although metabolites in the pharmacokinetic studies were not identified, the proposed metabolism of

glutaraldehyde involves oxidation to carboxylic acids by aldehyde dehydrogenase and further oxidation to carbon dioxide via an acidic intermediate (Ballantyne, 1995). Beauchamp *et al.* (1992) suggested that the glutaric acid is metabolized by the synthesis of a coenzyme A thioester, yielding glutaryl coenzyme A, which is oxidized by glutaryl coenzyme A dehydrogenase to glutaconyl coenzyme A, which degrades to acetate and carbon dioxide (Figure 1).

TOXICITY

Experimental Animals

Extensive literature overviews on the toxicity of glutaraldehyde have been published (Beauchamp *et al.*, 1992; NICNAS, 1994; Ballantyne, 1995; CIRP, 1996).

Acute toxicity studies of glutaraldehyde have been performed in various species. Four-hour LC_{50} values ranged from 24 to 5,000 ppm for male and female rats in inhalation studies (Sax and Lewis, 1989; Ballantyne, 1995). Effects included labored and audible breathing, wetness and encrustation around the nose, and excess lacrimation and salivation.

Oral LD_{50} values in rats ranged from 66 to 820 mg glutaraldehyde/kg body weight; in general, a higher LD_{50} was observed when higher concentrations were tested (NICNAS, 1994; Ballantyne, 1995; ACGIH, 1997). Sensitivity was similar between males and females. The oral LD_{50} ranged from 15 to 1,300 mg/kg in mice, and an oral LD_{50} of 50 mg/kg was reported in guinea pigs (Ohsumi and Kuroki, 1988; NICNAS, 1994; Ballantyne, 1995). In rabbits, the LD_{50} was 1.59 mL of a 50% aqueous solution/kg body weight and decreased with lower concentrations (Ballantyne, 1995). Necropsy findings included congestion and distension of the stomach and intestines, hemorrhage and congestion of the lung, and congestion of the liver, spleen, kidney, and adrenal glands. Additional effects included wetness and encrustation around the nose and eyes, labored and audible or rapid breathing, diarrhea, piloerection, sluggishness, and a mild thickening of the stomach wall.

Dermal LD_{50} values ranged from 640 to 3,045 mg glutaraldehyde/kg body weight in rabbits (NICNAS, 1994; Ballantyne, 1995); findings included congestion of the liver, lung, kidney, and spleen. Subcutaneous, intraperitoneal, and intravenous glutaraldehyde exposure in rats resulted in LD_{50} values of 2,390, 17.9, and 15.3 mg/kg, respectively; in mice, these values were 1,430, 13.9, and 15.4 mg/kg, respectively (Uemitsu *et al.*, 1976; Sax and Lewis, 1989).

Skin irritation tests with glutaraldehyde in New Zealand White rabbits resulted in erythema, edema, and necrosis (NICNAS, 1994; Ballantyne, 1995). In eye irritation tests in New Zealand White rabbits, corneal opacity, corneal injury, conjunctivitis, and conjunctival irritation and necrosis were reported after exposure to glutaraldehyde at various concentrations (NICNAS, 1994). The no-effect level for acute eye irritation in rabbits was 0.1% glutaraldehyde. Glutaraldehyde was a respiratory irritant in mouse inhalation studies; the concentration that produced a 50% decrease in the respiratory rate was calculated to be 13.8 ppm (NICNAS, 1994). In a 60-minute oronasal exposure study with male Swiss OF1 mice, a 50% decrease in the respiratory rate was reported at 2.6 ppm (Zissu *et al.*, 1994). Following a 7-day recovery period after exposure to glutaraldehyde for 30 minutes, the respiratory rate increased, but not to the preexposure rate (NICNAS, 1994).

Contact hypersensitivity was found in mice and guinea pigs after dermal exposure for 5 to 14 days to 0.3% to 3.3% glutaraldehyde (Stern *et al.*, 1989). Immunologic responses have been reported in rabbits, mice [inhibition of graft versus host reaction and a slight increase in the concentration of serum immunoglobulin E (IgE) antibody], and rats (increase in leukocytes, decrease in lymphocytes, hypertrophy of the white pulp in the thymus, and atrophy of the thymus) (Beauchamp *et al.*, 1992; Potter and Wederbrand, 1995). In a study with Dunkin-Hartley albino guinea pigs, 2% aqueous and 2% alkalinized solutions of glutaraldehyde were skin sensitizers (NICNAS, 1994). Glutaraldehyde was positive in the mouse ear-swelling test, a test proposed for the detection of skin allergens (Descotes, 1988; Gad, 1988). Glutaraldehyde was not found to be a respiratory sensitizer in guinea pigs; however, the concentrations used were irritant, likely masking any hypersensitive response (NICNAS, 1994).

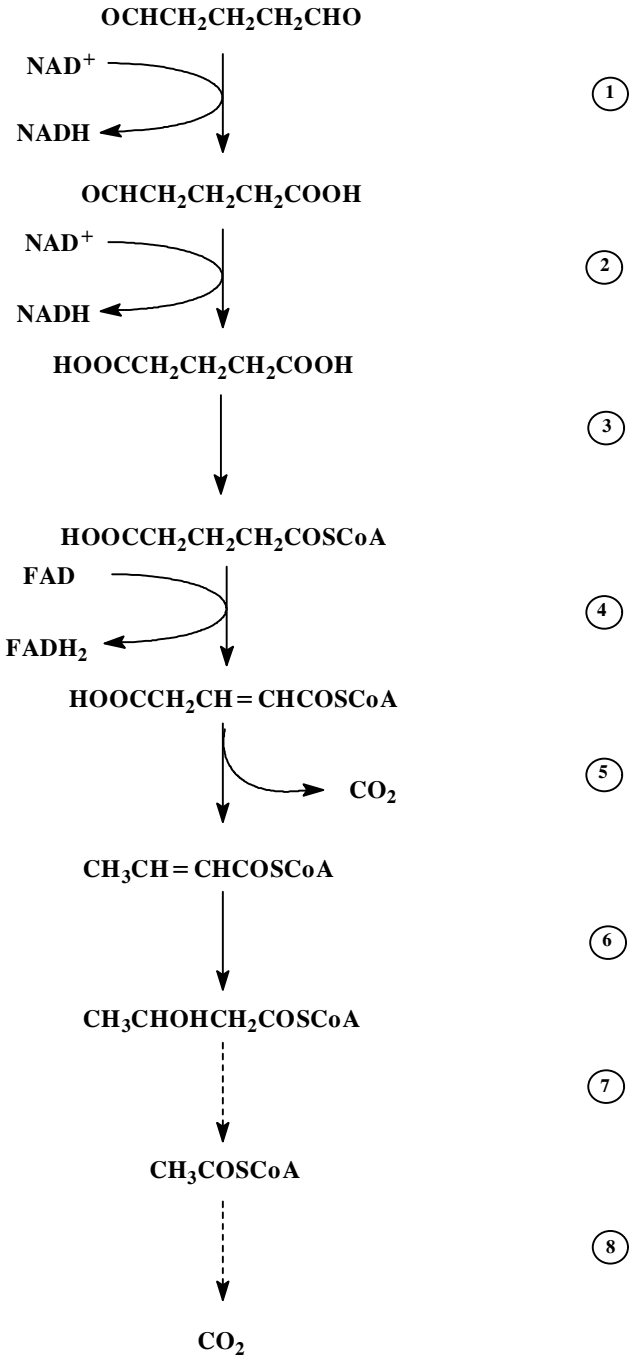


FIGURE 1
Postulated metabolism for glutaraldehyde. 1) Oxidation of glutaraldehyde to glutaric γ-semialdehyde. 2) Oxidation to glutaric acid. 3) Synthesis of glutaryl coenzyme A. 4) Oxidation to glutaconyl coenzyme A. 5) Decarboxylation to give crotonyl coenzyme A. 6) Hydration to ß-hydroxybutyryl coenzyme A. 7) Conversion to acetyl coenzyme A. 8) Oxidation to carbon dioxide (Beauchamp *et al.*, 1992).

Inhalation of glutaraldehyde for 24 hours by NMRI mice resulted in toxic hepatitis, nervous behavior, and excessive grooming and panting at 133 μg/L (33 ppm) (Varpela *et al.*, 1971). The reported effects in rats exposed for up to 9 days included mortality, depressed body weight gain, and decreased liver, lung, kidney, and testis weights. Hepatic atrophy, sensory irritation, rhinitis, squamous metaplasia of the olfactory mucosa, olfactory atrophy, inflammation of the nasal mucosa, excess lacrimation and salivation, audible breathing, and mouth breathing were also observed in rats (Ballantyne, 1995).

In 2-week inhalation studies with male and female F344/N rats and B6C3F$_1$ mice exposed to 0, 0.16, 0.5, 1.6, 5, or 16 ppm glutaraldehyde for 6 hours per day, 5 days per week, a spectrum of necrotic, inflammatory, and regenerative lesions was observed in the upper respiratory tract (NTP, 1993). Mortality was observed at 1.6 ppm and greater. In addition, respiratory irritation and lesions of the trachea, lung, and tongue were observed. The no-observable-adverse-effect level in rats and mice was 0.16 ppm.

Instillation of 20 to 40 mM glutaraldehyde into the nasal cavities of CD/CrlBr rats resulted in inflammation, epithelial degeneration, respiratory epithelial hypertrophy, and squamous metaplasia (St. Clair *et al.*, 1989, 1990). Glutaraldehyde induced these lesions at a concentration about one tenth that at which formaldehyde induced similar effects (St. Clair *et al.*, 1990).

In a 14-day drinking water study in which male and female F344 rats were exposed to glutaraldehyde at concentrations of 10, 100, or 1,000 ppm, reductions in body weight gain, feed consumption, and water consumption and mild gastric mucosal gland hyperplasia were observed (Ballantyne, 1995). Reduced body weight gain, feed consumption, and water consumption were also observed in male and female albino CD-1 mice exposed to glutaraldehyde at concentrations up to 1,000 ppm in drinking water. In male and female beagle dogs exposed to 250 ppm glutaraldehyde in drinking water, water consumption was reduced, and glossitis, esophagitis, and slight atrophy of the mucosa of the gastric fundus were observed.

In a 12-day skin paint study with male C3H/HeJ mice given concentrations up to 25 mg glutaraldehyde/kg body weight per day, deaths, decreased body weights, and skin irritation were observed (Ballantyne, 1995). In a 28-day skin paint study with 50, 100, or 150 mg glutaraldehyde/kg body weight per day administered to F344 rats, decreased body weights and feed consumption, skin irritation manifested as erythema and edema, increased adrenal gland weights, increased platelet and reticulocyte counts, and skin lesions, including acanthosis, hyperkeratosis, parakeratitis, dermatitis, epidermitis, and dermal fibrosis, occurred in a dose-dependent manner (Ballantyne, 1995; Werley *et al.*, 1995).

In a 14-week inhalation study in rats administered glutaraldehyde at concentrations up to 194 ppb, respiratory irritation, decreased body weights, and perinasal wetness were observed. No lesions were observed in the nasal cavity (Greenspan *et al.*, 1985; Ballantyne, 1995).

In 13-week inhalation studies in which male and female F344/N rats and B6C3F$_1$ mice were exposed to 0, 62.5, 125, 250, 500, or 1,000 ppb, all 1,000 ppb mice and 20% of the 500 ppb female mice were killed moribund or died before the end of the studies, and one female rat in the 250 ppb group was killed moribund (NTP, 1993). Mean body weight gain was decreased in 1,000 ppb male and female rats and 500 ppb mice. Clinical findings included encrustation around the nose and eyes, audible and mouth breathing, and dilation of the stomach and intestines in some animals, which was likely due to the ingestion of air as a result of mouth breathing. Lesions in the nasal cavity of rats were observed primarily in the anterior region of the nose and included hyperplasia, squamous metaplasia, and inflammation of the respiratory epithelium; these were primarily in the 1,000 ppb animals, less frequent and less severe in 500 ppb animals, and only occasionally present in the 250 ppb animals. Similarly, squamous exfoliation was diagnosed in the squamous epithelium of the anterior nares. In this region of the nose, squamous epithelium normally keratinizes and eventually sloughs and is removed. In more severely affected animals, the accumulated material probably restricted air flow through the nose, which resulted in mouth breathing as observed clinically. In the mice, inflammation and squamous metaplasia of the respiratory epithelium were observed in many of the 1,000 ppb animals. However, the most significant changes in mice were inflammation and squamous exfoliation which, as in

rats, occurred in the anterior nares. Inflammation occurred in most 500 ppb male mice, in 50% of the 62.5 ppb female mice, and in most female mice in the 125, 250, and 500 ppb groups. Squamous exfoliation occurred in 20% of the 500 ppb male and female mice and in most 1,000 ppb male and female mice and was more severe than in the rats. In the 1,000 ppb groups, inflammation was a component of the squamous exfoliation and was not diagnosed separately. In addition, the unit length labeling index was determined in the squamous and respiratory epithelium of the nose in rats and mice on days 1 and 4 and at 6 and 13 weeks (NTP, 1993; Gross *et al.*, 1994). At 13 weeks, a mild increase in the labeling index was observed in the squamous and respiratory epithelium of female rats exposed to 250 ppb or greater and in the respiratory epithelium of males exposed to 500 or 1,000 ppb. In mice, a mild increase in the labeling index was observed in the squamous epithelium of males at 500 ppb and in all exposed groups of females.

In two drinking water studies in which rats were exposed to glutaraldehyde at concentrations up to 0.5% for 11 to 14 weeks, no histopathologic lesions or neurotoxicity were observed (Spencer *et al.*, 1978). In 13-week drinking water studies with male and female F344 rats and CD-1 mice exposed to concentrations up to 1,000 ppm glutaraldehyde and beagle dogs exposed to concentrations up to 250 ppm, no systemic toxic effects were observed (Ballantyne, 1995).

The cardiotoxic effects of glutaraldehyde were investigated in dogs following a single intravenous dose of 1 to 10 mg/kg. Glutaraldehyde caused prolongation of the Q-T interval, resulting in ventricular fibrillation (James and Bear, 1968).

Humans

Glutaraldehyde is a skin, eye, and respiratory irritant (NICNAS, 1994; Ballantyne, 1995; ACGIH, 1997). The minimum human irritation response level for glutaraldehyde has been reported to be 300 ppb (St. Clair *et al.*, 1990; Ballantyne, 1995).

Skin sensitization, contact dermatitis, and skin discoloration by glutaraldehyde have been well documented (Jordan *et al.*, 1972; Beauchamp *et al.*, 1992; NICNAS, 1994; ACGIH, 1997). Respiratory sensitization such as asthma and rhinitis have been associated with glutaraldehyde in various occupational settings at concentrations as low as 0.032 ppm (NICNAS, 1994; ACGIH, 1997). However, it is unclear if these responses were due to the irritant effect or to allergic hypersensitivity of glutaraldehyde (NICNAS, 1994; ACGIH, 1997). The type of allergic mechanism that would cause asthma after exposure to glutaraldehyde is not known, and no specific antibody has yet been identified (Chan-Yeung *et al.*, 1993; NICNAS, 1994). In some workers with occupational asthma who were exposed to glutaraldehyde, an increase in IgE antibodies to glutaraldehyde-modified proteins was found (Curran *et al.*, 1996).

In patients, the use of endoscopes disinfected with glutaraldehyde has been associated with hemorrhagic proctocolitis and tongue swelling (Lynch *et al.*, 1994; Dolcé *et al.*, 1995). These cases were attributed to residues of glutaraldehyde left on the endoscopes after minimal rinsing with water. Other effects reported after exposure to glutaraldehyde included headache, nausea, light-headedness, fatigue, and palpitations or tachycardia (Connaughton, 1993; NICNAS, 1994; ACGIH, 1997).

REPRODUCTIVE AND DEVELOPMENTAL TOXICITY

Experimental Animals

Exposure of male and female rats to glutaraldehyde concentrations of 0, 50, 250, or 1,000 ppm in drinking water for two generations resulted in a decrease in water consumption and a decrease in body weights of the offspring at 1,000 ppm (Neeper-Bradley *et al.*, 1995). No effects on parental fertility, mating performance, pup viability, or litter size were observed in either generation.

No teratogenic effects were observed in various studies with rats, mice, and rabbits at glutaraldehyde concentrations that were less than those that were maternally toxic (Ballantyne, 1995). In a drinking water study of glutaraldehyde, female Wistar rats were exposed to 0, 25, 50, or 100 mg glutaraldehyde/kg per day from days 6 to 16 of gestation and examined on day 20 of gestation. Fetal body weights were reduced at 100 mg/kg, whereas maternal mortality occurred at 50 and 100 mg/kg (Ema *et al.*, 1992).

Albino rats given up to 50 mg glutaraldehyde/kg by gavage during gestation days 6 to 15 were examined on day 20. Glutaraldehyde caused a slight maternal toxicity at the highest dose and was not teratogenic (NICNAS, 1994; Ballantyne, 1995). Albino mice exposed to Sonacide (2% activated glutaraldehyde solution) by gavage at doses up to 100 mg/kg body weight per day showed maternal mortality and toxicity at 26 mg/kg or greater and fetal malformations at 100 mg/kg (Marks *et al.*, 1980; NICNAS, 1994; Ballantyne, 1995). These malformations included cleft palate, fused sternebrae, missing or fused ribs, and exencephaly.

A dose of 45 mg glutaraldehyde/kg body weight during days 7 through 19 of gestation in pregnant Himalayan rabbits was maternally toxic and embryolethal (NICNAS, 1994; Ballantyne, 1995). Doses of 15 mg/kg or less did not affect the does or the fetuses.

Humans

No increased frequency of spontaneous abortions or fetal malformations was found in Finnish hospital nurses or instrument-sterilizing staff (Hemminki *et al.*, 1982, 1985).

CARCINOGENICITY

Experimental Animals

In a 78-week inhalation study with 30 male and female B6C3F_1 mice exposed to 100 ppb glutaraldehyde, nonneoplastic lesions were observed in the nasal vestibule of female mice (Zissu *et al.*, 1998). These consisted of hyperplasia of the squamous epithelium lining of the dorsal wall and the lateral aspect of atrioturbinate together, with necrosis and exfoliation of epithelial cells and granulocytes in the lumen. No neoplasms were observed. A 2-year drinking water study was conducted in male and female Fischer rats using 50, 250, and 1,000 ppm glutaraldehyde (Ballantyne, 1995; Van Miller *et al.*, 1995). Increased mortality was observed in females. Decreases in mean body weights and body weight gains were observed at 250 and 1,000 ppm in male rats and at 1,000 ppm in female rats. Increased incidences of large granular cell lymphatic leukemia were observed in the spleen of females at all exposure concentrations (0 ppm, 24/100; 50 ppm, 41/100; 250 ppm, 41/100; 1,000 ppm, 53/100). Nonneoplastic lesions included increased incidences of squamous epithelial hyperplasia, keratinized cysts, and edema of the stomach. In addition, labored breathing, decreased mean body weights and body weight gains, and decreased water and feed consumption were observed.

Humans

No increase in the number of cancer deaths was observed in male glutaraldehyde production workers (NICNAS, 1994). However, the length of the observation period was relatively short and the men were relatively young.

In a retrospective study on the cause of deaths among 1,109 embalmers, the number of deaths due to leukemia and cancers in the brain, colon, and prostate were increased when compared to the expected number of deaths based on age-, race-, and calendar year-specific proportions of deaths for each cause among the United States male population (Walrath and Fraumeni, 1984). Deaths due to brain cancer and those that appeared to be due to leukemia were increased among 2,317 men who joined the American Association of Anatomists between 1888 and 1969 (Stroup *et al.*, 1986). Mortality rates in this group were compared to the available mortality rates for Caucasian men in the United States for 1925 to 1979 and to the rates for male members of the American Psychiatric Associates, available for 1900 to 1969. Increases in incidences of leukemia and cancers of the brain and lung were noted in pathologists (Consensus Workshop on Formaldehyde, 1984). Embalmers, anatomists, and pathologists are often exposed to formaldehyde and glutaraldehyde.

GENETIC TOXICITY

Short-term genotoxicity tests with glutaraldehyde have yielded mixed responses, and early assays of the genotoxicity of glutaraldehyde were generally negative (Watts, 1984). However, results from more recent *in vitro* testing generally show the chemical to be genotoxic, with no requirement for S9 metabolic enzymes.

Positive results were reported for glutaraldehyde in a forward mutation assay using a specially constructed *Escherichia coli* WP2 uvrA strain that contained the plasmid pKM101 from *Salmonella typhimurium* (Kosako and Nishioka, 1982); however, negative

results were obtained in a reversion assay using this same strain without the plasmid (Hemminki *et al.*, 1980). In addition, Hemminki *et al.* (1980) detected no alkylation potential for glutaraldehyde *in vitro* using 4-(*p*-nitrobenzyl) pyridine or deoxyguanosine as the target. Results from *S. typhimurium* mutation tests were also mixed. Negative results were reported by laboratories using low doses (less than 52 μg/plate) of glutaraldehyde in strains TA98, TA100, TA1535, and TA1537 (Sasaki and Endo, 1978; Slesinski *et al.*, 1983; Sakagami *et al.*, 1988a), but positive results were obtained when higher doses (up to 1,000 μg/plate) were used with strain TA100 (Haworth *et al.*, 1983; Dillon *et al.*, 1998). These standard tester strains have G:C base pairs at the site of mutation. Clearly positive results were reported for glutaraldehyde in the absence of S9 in *S. typhimurium* strains TA102 and TA104, which have A:T base pairs at the target site and which were reported to be sensitive to carbonyl compounds (Levin *et al.*, 1982; Marnett *et al.*, 1985; Dillon *et al.*, 1998). Positive results were also reported for glutaraldehyde in a collaborative study among three testing laboratories using TA102 with and without S9 (Jung *et al.*, 1992). Positive results were obtained for induction of L-arabinose resistance in *S. typhimurium* strains BA13 and BA9 by glutaraldehyde-induced forward mutations at an A:T base-pairing site, without S9 activation (Ruiz-Rubio *et al.,* 1985). Finally, glutaraldehyde was reported to be positive in the *S. typhimurium* umu test and in the *Bacillus subtilis* recombinant assay (Sakagami *et al.*, 1988a,b).

In other genotoxicity assays, glutaraldehyde was mutagenic in mouse lymphoma cells (McGregor *et al.*, 1988) and cultured human TK6 lymphoblasts (St. Clair *et al.*, 1991). Glutaraldehyde induced sister chromatid exchanges and chromosomal aberrations in Chinese hamster ovary cells in the absence of S9 liver enzymes (Galloway *et al.*, 1985). Studies by Slesinski *et al.* (1983) had negative results in sister chromatid exchange and gene mutation tests in cultured Chinese hamster ovary cells, but these studies used much lower doses than the studies that showed positive results. Assessment of glutaraldehyde-induced unscheduled DNA synthesis in primary hepatocyte cultures revealed a small, dose-related increase in DNA repair activity (St. Clair *et al.*, 1991).

Glutaraldehyde was demonstrated to be a potent DNA-histone crosslinking agent in a comparative investigation of the abilities of several volatile aldehydes to induce covalent crosslinks between calf thymus histones and pUC13 plasmid DNA in a filter-binding assay that used protein precipitation for detection (Kuykendall and Bogdanffy, 1992). The authors suggested that the bifunctional nature of the glutaraldehyde molecule was likely responsible for its increased potency compared to aldehydes of like size and degree of saturation.

In vivo, glutaraldehyde did not induce sex-linked recessive lethal mutations in male *Drosophila melanogaster* treated either as larvae (Zimmering *et al.*, 1989) or as adults (Yoon *et al.*, 1985). Oral administration of glutaraldehyde did not induce unscheduled DNA synthesis in hepatocytes of male rats (Mirsalis *et al.*, 1989) or dominant lethal mutations in mice (Tamada *et al.*, 1978).

STUDY RATIONALE

Glutaraldehyde was nominated by the National Cancer Institute, the Occupational Safety and Health Administration (OSHA), and the National Institute of Environmental Health Sciences for toxicity and carcinogenicity studies because of concerns about occupational exposure. In addition, OSHA nominated glutaraldehyde for study based on increased incidences of leukemia as found in anatomists, embalmers, and pathologists exposed to glutaraldehyde and formaldehyde. Glutaraldehyde is mutagenic in several short-term genotoxicity assays and its structural analogue formaldehyde is a nasal carcinogen in rodents in inhalation studies (Kerns *et al.*, 1983; Monticello *et al.*, 1996). The 2-year, whole-body inhalation studies were performed in male and female F344/N rats and B6C3F$_1$ mice to evaluate the carcinogenicity and toxicity of glutaraldehyde. In addition, chromosomal aberrations, micronuclei in mouse bone marrow cells, and micronuclei in bone marrow erythrocytes were studied in short-term tests in male mice, and micronuclei in peripheral blood erythrocytes were studied in male and female mice in a 13-week inhalation study.

MATERIALS AND METHODS

PROCUREMENT AND CHARACTERIZATION OF GLUTARALDEHYDE

Glutaraldehyde (approximately 25% aqueous solution) was obtained from Union Carbide Corporation (Specialty Chemicals Division, Charleston, WV) in two lots (IS-611699 and IS-678984), which were used during the 2-year studies. A glutaraldehyde reference standard was obtained from Polysciences, Inc. (Warrington, PA). Identity and purity analyses of the bulk chemical were conducted by the study laboratory (Appendix F); the reference standard was analyzed concurrently with each lot. Stability analyses were conducted by the analytical chemistry laboratory, Midwest Research Institute (Kansas City, MO). Reports on analyses performed in support of the glutaraldehyde studies are on file at the National Institute of Environmental Health Sciences.

The chemical, a liquid, and the reference standard were identified as glutaraldehyde by infrared, ultraviolet/visible, and ^{13}C-nuclear magnetic resonance spectroscopy. ^{13}C-nuclear magnetic resonance spectroscopy of samples of lot IS-611699 dissolved in d8-dioxane indicated that glutaraldehyde was present in the following forms and at the following estimated equilibrium composition: free aldehyde (7%), hemihydrate (7%), dihydrate (6%), *cis*-cyclic hemiacetal (36%), and *trans*-cyclic hemiacetal (44%). For lot IS-678984, the free aldehyde (7%), hemihydrate (20%), dihydrate (8%), *cis*-cyclic hemiacetal (37%), and *trans*-cyclic hemiacetal (29%) were also present. The purity of each lot and the reference standard was determined by elemental analyses, Karl Fischer water analyses, pH determination, functional group titration, and gas chromatography. Unsaturated polymer content was measured as the ratio of ultraviolet absorbances at 230 nm and 280 nm.

For lots IS-611699 and IS-678984 and the reference standard, results of elemental analyses for carbon and hydrogen compared well to theoretical values; less than 0.5% nitrogen was detected. Karl Fischer water analysis indicated 70.64% water for lot IS-611699 and 71.46% for the reference standard and 70.71% for lot IS-678984 and 73.33% for the reference standard. The pH ranged from 3.9 to 4.1 for lot IS-611699 and was 3.8 for the reference standard and ranged from 4.2 to 4.3 for lot IS-678984 and was 4.4 for the reference standard, all within the optimum storage range of 3 to 4.5. Functional group titration indicated a glutaraldehyde content of 26.0% $\pm$ 0.4% for lot IS-611699 and 25.0% $\pm$ 0.4% for the reference standard and 25.5% $\pm$ 0.2% for lot IS-678984 and 25.1% $\pm$ 0.1% for the reference standard. Gas chromatography indicated one major peak and one impurity less than 0.6% relative to the major peak area for lot IS-611699 and one impurity in the reference standard with a relative area of less than 0.2%. Major peak comparisons indicated a purity of 91.2% to 92.9% for lot IS-611699 relative to the reference standard. The bulk chemical contained less than 0.6% methanol, and the reference standard contained less than 0.3%. Gas chromatography indicated one major peak and four impurity peaks each, with a total relative area of less than 0.7% for lot IS-678984 and less than 0.8% for the reference standard. Major peak comparisons indicated a purity of 94.6% to 94.8% for lot IS-678984 relative to the reference standard. Gas chromatographic headspace analysis indicated less than 0.3% methanol in lot IS-678984 and less than 0.4% methanol in the reference standard.

Stability studies of lot 95296 (50% aqueous solution, not used in the current studies) were performed by the analytical chemistry laboratory using gas chromatography with flame ionization detection. These studies indicated that glutaraldehyde is stable as a bulk chemical for 2 weeks when stored protected from light at temperatures up to 25° C. To ensure stability, the bulk chemical was stored under nitrogen headspace at approximately 0° C in 1-gallon amber glass bottles.

Stability was monitored during the 2-year studies by gas chromatography with flame ionization detection and by ultraviolet/visible spectroscopy. No degradation of the bulk chemical was detected.

VAPOR GENERATION AND EXPOSURE SYSTEM

Glutaraldehyde vapor was generated with a rotary evaporation system (Büchi Rotavapor, Model EL-1315, Brinkman Instruments, Westberry, NY) with a hot-water bath modified to include a heated stream of nitrogen metered into the flask. The glutaraldehyde and water vapors arising from the flask were carried through the generator by the nitrogen. The generator was maintained at a temperature sufficient to prevent condensation of the vapor as it passed through the generator. Because the evaporation rate of water was faster than that of glutaraldehyde, ultrapure water was pumped into the evaporation flask throughout the generation period to maintain a constant volume in the flask.

Vapor entering the distribution manifold was diluted with heated HEPA- and charcoal-filtered air. All transfer lines were heated to prevent condensation. A three-way valve, mounted between the distribution manifold and each chamber, directed vapor to the exposure chamber exhaust until a stable concentration of glutaraldehyde vapor was built up in the distribution line. Vapor flowed through separate metering valves for each exposure chamber and was further diluted with filtered air to the appropriate concentration. To overcome the adsorption of the vapor once it entered the exposure chambers, recirculation systems were added to increase the air velocity through the exposure chambers; this did not affect the normal air exchange rate in the chambers. The increased chamber air circulation helped maintain uniform exposure concentrations. The study laboratory designed the stainless-steel inhalation exposure chambers (Hazleton H-2000®; Harford Systems Division of Lab Products, Inc., Aberdeen, MD) so that uniform vapor concentrations could be maintained throughout the chambers when catch pans were in place. A small particle detector (Type CN, Gardner Associates, Schenectady, NY) was used with and without animals in the exposure chambers to ensure that glutaraldehyde vapor, and not aerosol, was produced. No particle counts above the minimum resolvable level (approximately 200 particles/cm^3) were detected.

VAPOR CONCENTRATION MONITORING

Chamber concentrations of glutaraldehyde as the free aldehyde were monitored by an online gas chromatograph. The monitor was coupled with the inhalation chambers by a computer-controlled 12-port stream select valve. Calibrations against gravimetrically prepared standards were performed monthly or when excessive calibration drift was detected by shifts in an on-line standard of 2-butoxyethanol vapor in nitrogen that was checked throughout each exposure day. Additionally, the gas chromatograph was calibrated by a comparison of chamber concentration data to data from grab samples, which were analyzed with high-performance liquid chromatography or with an off-line gas chromatograph/mass spectrometer which was calibrated with gravimetrically prepared standards of glutaraldehyde.

CHAMBER ATMOSPHERE CHARACTERIZATION

The time for vapor concentration in the chamber to build up to 90% of its stable final concentration (T_{90}) and to decay to 10% (T_{10}) were measured with animals in the chambers. Based on the results obtained during prestart testing, a T_{90} value of 25 minutes was used for the 2-year studies.

Studies of glutaraldehyde degradation and monitoring for impurities, inhibitors, and stabilizers were conducted throughout the studies with HPLC and gas chromatography. No significant degradation of glutaraldehyde was detected during the studies.

2-YEAR STUDIES

Study Design

The highest exposure concentration in the 2-year study with rats (750 ppb) was chosen based on decreased body weights and significant histopathologic lesions in the anterior part of the nose at 1,000 ppb in the 13-week toxicity study (NTP, 1993), which were expected to become life threatening in a 2-year bioassay. The middle exposure concentration selected, 500 ppb, was based on the slight increase in

the rate of cell replication and mild lesions in the anterior part of the nose. The lowest exposure concentration selected, 250 ppb, was based on the absence of squamous exfoliation. In the 2-year study with mice, the highest exposure concentration of 250 ppb was based on the decrease in body weight, deaths, and absence of significant nasal lesions as observed at 500 and 1,000 ppb. The 125 and 62.5 ppb concentrations were based on the no-effect concentration for squamous exfoliation.

Groups of 50 male and 50 female rats were exposed to glutaraldehyde by whole-body inhalation at concentrations of 0, 250, 500, or 750 ppb for 6 hours plus T_{90} (25 minutes) per day, 5 days per week for 104 weeks. Groups of 50 male and 50 female mice were exposed to glutaraldehyde by whole-body inhalation at concentrations of 0, 62.5, 125, or 250 ppb for 6 hours plus T_{90} (25 minutes) per day, 5 days per week for 104 weeks.

Source and Specification of Animals

Male and female F344/N rats and B6C3F$_1$ mice were obtained from Taconic Farms (Germantown, NY) for use in the 2-year studies. Rats were quarantined for 18 days and mice were quarantined for 14 days before the beginning of the studies. Five male and five female rats and mice were randomly selected for parasite evaluation and gross observation of disease. Rats and mice were approximately 7 weeks old at the beginning of the studies. The health of the animals was monitored during the studies according to the protocols of the NTP Sentinel Animal Program (Appendix H).

Animal Maintenance

Rats and mice were housed individually. Feed and water were available *ad libitum* except during exposure periods. Chambers and cages were rotated once weekly. Further details of animal maintenance are given in Table 1. Information on feed composition and contaminants is provided in Appendix G.

Clinical Examinations and Pathology

All animals were observed twice daily. Body weights were recorded initially, and body weights and clinical observations were recorded every 4 weeks from week 5 through week 89, and every 2 weeks from week 92 (rats) or 93 (mice) until the end of the studies.

A complete necropsy and microscopic examination were performed on all rats and mice. At necropsy, all organs and tissues were examined for grossly visible lesions, and all major tissues were fixed and preserved in 10% neutral buffered formalin, processed and trimmed, embedded in paraffin, sectioned to a thickness of 5 to 6 μm, and stained with hematoxylin and eosin for microscopic examination. For all paired organs (e.g., adrenal gland, kidney, ovary), samples from each organ were examined. Tissues examined microscopically are listed in Table 1.

Microscopic evaluations were completed by the study laboratory pathologist, and the pathology data were entered into the Toxicology Data Management System. The slides, paraffin blocks, and residual wet tissues were sent to the NTP Archives for inventory, slide/block match, and wet tissue audit. The slides, individual animal data records, and pathology tables were evaluated by an independent quality assessment laboratory. The individual animal records and tables were compared for accuracy, the slide and tissue counts were verified, and the histotechnique was evaluated. For the 2-year studies, a quality assessment pathologist evaluated slides from all tumors and all potential target organs, which included the larynx, lung, and nose for rats and mice. In addition to the three nasal sections routinely examined, a fourth section (Level I) from the most rostral portion of the nasal passage was also examined. Additionally, the quality assessment pathologist evaluated all rats for the diagnosis of tooth degeneration. The brain of rats was examined when hydrocephalus or hemorrhage of the brain was diagnosed. In mice, the quality assessment pathologist reviewed kidneys from all males for infarct and nephropathy. Livers of female mice were evaluated for eosinophilic foci. Thyroid glands from male mice were reviewed for hyperplasia by the quality assessment pathologist. The Pathology Working Group pathologist reviewed the thyroid glands of female mice for hyperplasia.

The quality assessment report and the reviewed slides were submitted to the NTP Pathology Working Group (PWG) chairperson, who reviewed the selected tissues and addressed any inconsistencies in the diagnoses made by the laboratory and quality assessment pathologists. Representative histopathology slides containing examples of lesions related to chemical administration, examples of disagreements in diagnoses between the laboratory and quality assessment

pathologists, or lesions of general interest were presented by the chairperson to the PWG for review. The PWG consisted of the quality assessment pathologist and other pathologists experienced in rodent toxicologic pathology. When the PWG consensus differed from the opinion of the laboratory pathologist, the diagnosis was changed. Final diagnoses for reviewed lesions represent a consensus between the laboratory pathologist, reviewing pathologist(s), and the PWG. Details of these review procedures have been described, in part, by Maronpot and Boorman (1982) and Boorman *et al*. (1985). For subsequent analyses of the pathology data, the decision of whether to evaluate the diagnosed lesions for each tissue type separately or combined was generally based on the guidelines of McConnell *et al*. (1986).

TABLE 1
Experimental Design and Materials and Methods in the 2-Year Inhalation Studies of Glutaraldehyde

Study Laboratory
Battelle Pacific Northwest Laboratories
(Richland, WA)

Strain and Species
Rats: F344/N
Mice: $B6C3F_1$

Animal Source
Taconic Farms
(Germantown, NY)

Time Held Before Studies
Rats: 18 days
Mice: 14 days

Average Age When Studies Began
7 weeks

Date of First Exposure
Rats: 27 June 1994
Mice: 7 July 1994

Duration of Exposure
6 hours plus T_{90} (25 minutes) per day, 5 days per week, for 104 weeks

Date of Last Exposure
Rats: 21 June 1996
Mice: 3 July 1996

Necropsy Dates
Rats: 24-26 June 1996
Mice: 8-12 July 1996

Age at Necropsy
111 weeks

Size of Study Groups
50 males and 50 females

Method of Distribution
Animals were distributed randomly into groups of approximately equal initial mean body weights.

Animals per Cage
1

Method of Animal Identification
Tail tattoo

Diet
NIH-07 open formula pellet diet (Zeigler Brothers, Inc., Gardners, PA), available *ad libitum* except during exposure periods, changed weekly

Water Distribution
Softened tap water (Richland municipal supply) via automatic watering system (Edstrom Industries, Waterford, WI), available *ad libitum* except during exposure periods

TABLE 1
Experimental Design and Materials and Methods in the 2-Year Inhalation Studies of Glutaraldehyde

Cages
Stainless-steel wire-bottom (Hazleton System, Inc., Aberdeen, MD), changed weekly

Bedding
Cageboard (Bunzl Cincinnati Paper Co., Cincinnati, OH) (until November 1994) and Techsorb (Shepherd Specialty Papers, Kalamazoo, MI) (thereafter), changed daily, and removed during exposures

Chamber Air Supply Filters
Single HEPA (Flanders Filters, Inc., San Rafael, CA) and charcoal (RSE, Inc., New Baltimore, MI)

Chambers
Stainless-steel with excreta pan suspended below each cage unit (Harford Systems, Division of Lab Products, Inc., Aberdeen, MD), changed weekly

Chamber Environment
Temperature: 75° ± 3° F
Relative humidity: 55% ± 15%
Room fluorescent light: 12 hours/day
Chamber air changes: 15 ± 3 changes/hour

Exposure Concentrations
Rats: 0, 250, 500, or 750 ppb
Mice: 0, 62.5,125, or 250 ppb

Type and Frequency of Observation
Observed twice daily; body weights recorded initially, and body weights and clinical findings recorded every 4 weeks from week 5 through week 89, and every 2 weeks from week 92 (rats) or 93 (mice) until the end of the studies

Method of Sacrifice
CO_2 anesthetization

Necropsy
Necropsy performed on all animals

Histopathology
Complete histopathology was performed on all rats and mice. In addition to gross lesions and tissue masses, the following tissues were examined: adrenal gland, bone with marrow, brain, clitoral gland, esophagus, gallbladder (mice), heart, large intestine (cecum, colon, rectum), small intestine (duodenum, jejunum, ileum), kidney, larynx, liver, lung, lymph nodes (mandibular, mesenteric, bronchial, mediastinal), mammary gland, nose, ovary, pancreas, pancreatic islets, parathyroid gland, pituitary gland, preputial gland, prostate gland, salivary gland, skin, spleen, stomach (forestomach and glandular), testis with epididymis and seminal vesicle, thymus, thyroid gland, trachea, urinary bladder, and uterus.

STATISTICAL METHODS

Survival Analyses

The probability of survival was estimated by the product-limit procedure of Kaplan and Meier (1958) and is presented in the form of graphs. Animals found dead of other than natural causes or missing were censored from the survival analyses; animals dying from natural causes were not censored. Statistical analyses for possible dose-related effects on survival used Cox's (1972) method for testing two groups for equality and Tarone's (1975) life table test to identify dose-related trends. All reported P values for the survival analyses are two sided.

Calculation of Incidence

The incidences of neoplasms or nonneoplastic lesions are presented in Tables A1, A5, B1, B5, C1, C4, D1, and D4 as the numbers of animals bearing such lesions at a specific anatomic site and the numbers of animals with that site examined microscopically. For calculation of statistical significance, the incidences of most neoplasms (Tables A3, B3, C3, and D3) and all nonneoplastic lesions are given as the numbers of animals affected at each site examined microscopically. However, when macroscopic examination was required to detect neoplasms in certain tissues (e.g., harderian gland, intestine, mammary gland, and skin) before microscopic evaluation, or when neoplasms had multiple potential sites of occurrence (e.g., leukemia or lymphoma), the denominators consist of the number of animals on which a necropsy was performed. Tables A3, B3, C3, and D3 also give the survival-adjusted neoplasm rate for each group and each site-specific neoplasm. This survival-adjusted rate (based on the Poly-3 method described below) accounts for differential mortality by assigning a reduced risk of neoplasm, proportional to the third power of the fraction of time on study, to animals that do not reach terminal sacrifice.

Analysis of Neoplasm and Nonneoplastic Lesion Incidences

The Poly-k test (Bailer and Portier, 1988; Portier and Bailer, 1989; Piegorsch and Bailer, 1997) was used to assess neoplasm and nonneoplastic lesion prevalence. This test is a survival-adjusted quantal-response procedure that modifies the Cochran-Armitage linear trend test to take survival differences into account. More specifically, this method modifies the denominator in the quantal estimate of lesion incidence to approximate more closely the total number of animal years at risk. For analysis of a given site, each animal is assigned a risk weight. This value is one if the animal had a lesion at that site or if it survived until terminal sacrifice; if the animal died prior to terminal sacrifice and did not have a lesion at that site, its risk weight is the fraction of the entire study time that it survived, raised to the kth power.

This method yields a lesion prevalence rate that depends only upon the choice of a shape parameter for a Weibull hazard function describing cumulative lesion incidence over time (Bailer and Portier, 1988). Unless otherwise specified, a value of $k=3$ was used in the analysis of site-specific lesions. This value was recommended by Bailer and Portier (1988) following an evaluation of neoplasm onset time distributions for a variety of site-specific neoplasms in control F344 rats and B6C3F$_1$ mice (Portier *et al.*, 1986). Bailer and Portier (1988) showed that the Poly-3 test gave valid results if the true value of k was anywhere in the range from 1 to 5. A further advantage of the Poly-3 method is that it does not require lesion lethality assumptions. Variation introduced by the use of risk weights, which reflect differential mortality, was accommodated by adjusting the variance of the Poly-3 statistic as recommended by Bieler and Williams (1993).

Tests of significance included pairwise comparisons of each exposed group with controls and a test for an overall exposure-related trend. Continuity-corrected tests were used in the analysis of lesion incidence, and reported P values are one sided. Values of P greater than 0.5 are presented as 1–P with the letter N added to indicate a lower incidence or negative trend in neoplasm occurrence relative to the control group (e.g., P=0.99 is presented as P=0.01N).

Analysis of Continuous Variables

Body weight data, which have approximately normal distributions, were analyzed with the parametric multiple comparison procedures of Dunnett (1955) and Williams (1971, 1972). Average severity values were analyzed for significance with the Mann-Whitney U test (Hollander and Wolfe, 1973).

Historical Control Data

Although the concurrent control group is always the first and most appropriate control group used for evaluation, historical control data can be helpful in the overall assessment of neoplasm incidence in certain instances. Consequently, neoplasm incidences from the NTP historical control database, which is updated yearly, are included in the NTP reports for neoplasms appearing to show compound-related effects.

QUALITY ASSURANCE METHODS

The 2-year studies were conducted in compliance with Food and Drug Administration Good Laboratory Practice Regulations (21 CFR, Part 58). In addition, as records from the 2-year studies were submitted to the NTP Archives, these studies were audited retrospectively by an independent quality assurance contractor. Separate audits covered completeness and accuracy of the pathology data, pathology specimens, final pathology tables, and a draft of this NTP Technical Report. Audit procedures and findings are presented in the reports and are on file at NIEHS. The audit findings were reviewed and assessed by NTP staff, and all comments were resolved or otherwise addressed during the preparation of this Technical Report.

GENETIC TOXICOLOGY

The genetic toxicity of glutaraldehyde was assessed by testing the ability of the chemical to induce mutations in various strains of *Salmonella typhimurium*, mutations in L5178Y mouse lymphoma cells, sister chromatid exchanges and chromosomal aberrations in cultured Chinese hamster ovary cells, sex-linked recessive lethal mutations in *Drosophila melanogaster*, and chromosomal aberrations and micronucleated erythrocytes in mouse bone marrow and to increase the frequency of micronucleated erythrocytes in mouse peripheral blood. Protocols for these studies and results are given in Appendix E.

The genetic toxicity studies of glutaraldehyde are part of a larger effort by the NTP to develop a database that would permit the evaluation of carcinogenicity in experimental animals from the molecular structure and the effects of the chemical in short-term *in vitro* and *in vivo* genetic toxicity tests. These genetic toxicity tests were originally developed to study mechanisms of chemical-induced DNA damage and to predict carcinogenicity in animals, based on the electrophilicity theory of chemical mutagenesis and the somatic mutation theory of cancer (Miller and Miller, 1977; Straus, 1981; Crawford, 1985).

There is a strong correlation between a chemical's potential electrophilicity (structural alert to DNA reactivity), mutagenicity in *Salmonella*, and carcinogenicity in rodents. The combination of electrophilicity and *Salmonella* mutagenicity is highly correlated with the induction of carcinogenicity in rats and mice and/or at multiple tissue sites (Ashby and Tennant, 1991). Other *in vitro* genetic toxicity tests correlate less well with rodent carcinogenicity (Tennant *et al.*, 1987; Zeiger *et al.*, 1990), although these other tests can provide information on the types of DNA and chromosome effects that can be induced by the chemical being investigated. Data from NTP studies show that a positive response in *Salmonella* is the most predictive *in vitro* test for rodent carcinogenicity (89% of the *Salmonella* mutagens are rodent carcinogens), and that there is no complementarity among the *in vitro* genetic toxicity tests. That is, no battery of tests that included the *Salmonella* test improved the predictivity of the *Salmonella* test alone.

The predictivity for carcinogenicity of a positive response in bone marrow chromosome aberration or micronucleus tests appears to be less than the *Salmonella* test (Shelby *et al.*, 1993; Shelby and Witt, 1995). Positive responses in long-term peripheral blood micronucleus tests have not been formally evaluated for their predictivity for rodent carcinogenicity. Because of the theoretical and observed associations between induced genetic damage and adverse effects in somatic and germ cells, the determination of *in vivo* genetic effects is important to the overall understanding of the risks associated with exposure to a particular chemical.

RESULTS

RATS

Survival

Estimates of 2-year survival probabilities for males and females are shown in Table 2 and in the Kaplan-Meier survival curves (Figure 2). Survival of 500 and 750 ppb females was decreased compared to that of the chamber controls. Survival of exposed males was similar to that of the chamber controls; however, eight male and five female rats in the 750 ppb groups were removed from the study between weeks 13 and 21. These animals had breathing problems, which were likely related to nasal lesions.

TABLE 2
Survival of Rats in the 2-Year Inhalation Study of Glutaraldehyde

	Chamber Control	250 ppb	500 ppb	750 ppb
Male				
Animals initially in study	50	50	50	50
Moribund	33	30	32	37
Natural deaths	5	6	9	7
Animals surviving to study termination	12[d]	14	9	6
Percent probability of survival at end of study[a]	24	28	18	12
Mean survival (days)[b]	631	660	639	527
Survival analysis[c]	P=0.032	P=0.395N	P=0.788	P=0.094
Female				
Animals initially in study	50	50	50	50
Moribund	22	17	32	34
Natural deaths	2	2	3	2
Animals surviving to study termination	26	31	15	14
Percent probability of survival at end of study	52	62	30	28
Mean survival (days)	675	671	636	573
Survival analysis	P<0.001	P=0.454N	P=0.023	P=0.008

[a] Kaplan-Meier determinations
[b] Mean of all deaths (uncensored, censored, and terminal sacrifice)
[c] The result of the life table trend test (Tarone, 1975) is in the chamber control column, and the results of the life table pairwise comparisons (Cox, 1972) with the chamber controls are in the exposed group columns. A lower mortality in an exposure group is indicated by **N**.
[d] Includes one animal that died during the last week of study

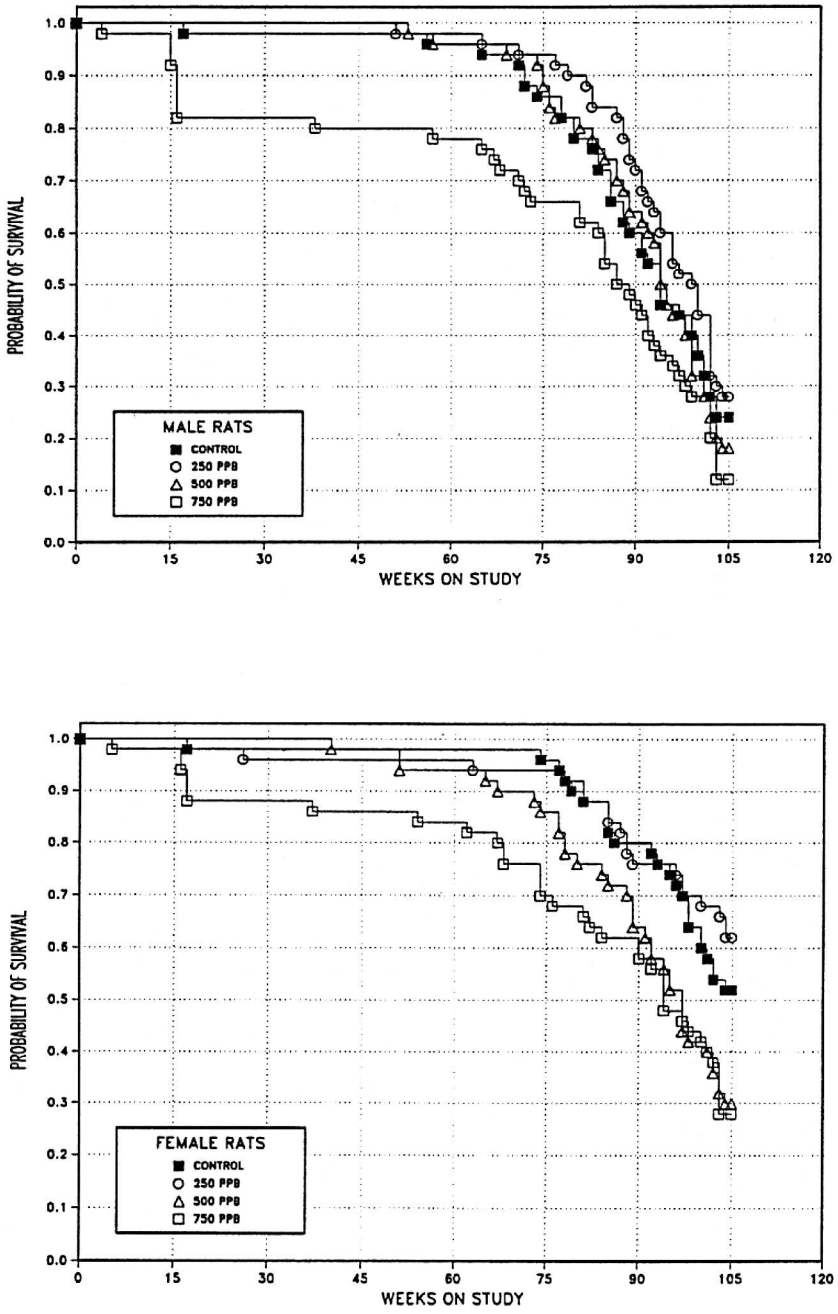


FIGURE 2
Kaplan-Meier Survival Curves for Male and Female Rats Exposed to Glutaraldehyde by Inhalation for 2 Years

Body Weights and Clinical Findings

Mean body weights of all exposed groups of male rats and 500 and 750 ppb female rats were generally less than those of the chamber controls throughout the study; this was a mild effect (Tables 3 and 4; Figure 3). Some female rats exposed to 750 ppb were thin to emaciated at the time they were killed moribund.

TABLE 3
Mean Body Weights and Survival of Male Rats in the 2-Year Inhalation Study of Glutaraldehyde

Weeks on Study	Chamber Control		250 ppb			500 ppb			750 ppb		
	Av. Wt. (g)	No. of Survivors	Av. Wt. (g)	Wt. (% of controls)	No. of Survivors	Av. Wt. (g)	Wt. (% of controls)	No. of Survivors	Av. Wt. (g)	Wt. (% of controls)	No. of Survivors
1	149	50	147	99	50	146	99	50	147	99	50
5	248	50	241	97	50	238	96	50	225	91	49
9	309	50	302	98	50	298	97	50	288	93	49
13	347	50	342	99	50	339	98	50	330	95	49
17	374	50	368	98	50	367	98	50	346	93	41
21	385	49	375	98	50	372	97	50	359	93	41
25	405	49	392	97	50	391	96	50	375	93	41
29	422	49	407	97	50	406	96	50	391	93	41
33	436	49	418	96	50	417	96	50	399	92	41
37	444	49	425	96	50	425	96	50	408	92	41
41	456	49	437	96	50	435	95	50	417	92	40
45	465	49	444	96	50	447	96	50	424	91	40
49	467	49	443	95	50	449	96	50	426	91	40
53	474	49	448	95	49	453	96	50	430	91	40
57	487	48	459	94	49	460	94	49	440	90	40
61	495	48	463	94	49	468	95	48	442	89	39
65	501	48	465	93	49	472	94	48	445	89	39
69	500	47	469	94	48	467	94	48	442	88	36
73	502	44	469	93	47	468	93	47	436	87	35
77	504	43	472	94	47	477	95	42	445	88	33
81	499	39	470	94	45	468	94	41	434	87	33
85	495	36	471	95	42	461	93	38	424	86	29
89	486	31	466	96	39	455	94	34	434	89	25
92	478	28	457	96	34	446	93	31	411	86	22
94	466	27	454	97	32	437	94	29	415	89	19
96	474	23	448	95	30	439	93	23	414	88	18
98	464	22	451	97	26	418	90	22	416	90	16
100	434	20	432	100	25	417	96	16	429	99	14
102	430	16	415	97	22	403	94	14	400	93	13
104	429	12	439	102	15	418	98	10	415	97	6
Mean for weeks											
1-13	263		258	98		255	97		248	94	
14-52	428		412	96		412	96		394	92	
53-104	478		456	95		449	94		428	90	

TABLE 4
Mean Body Weights and Survival of Female Rats in the 2-Year Inhalation Study of Glutaraldehyde

Weeks on Study	Chamber Control		250 ppb			500 ppb			750 ppb		
	Av. Wt. (g)	No. of Survivors	Av. Wt. (g)	Wt. (% of controls)	No. of Survivors	Av. Wt. (g)	Wt. (% of controls)	No. of Survivors	Av. Wt. (g)	Wt. (% of controls)	No. of Survivors
1	112	50	113	101	50	112	100	50	112	100	50
5	151	50	151	100	50	147	98	50	137	90	50
9	173	50	171	99	50	168	98	50	165	95	49
13	188	50	187	100	50	182	97	50	179	95	49
17	200	50	198	99	50	192	96	50	183	92	47
21	204	49	203	100	49	194	95	50	192	94	44
25	214	49	213	99	49	202	94	50	199	93	44
29	223	49	220	99	48	207	93	50	204	92	44
33	234	49	229	98	48	217	93	50	211	90	44
37	245	49	238	97	48	226	92	50	217	89	44
41	254	49	247	97	48	231	91	49	220	87	43
45	268	49	262	97	48	249	93	49	234	87	43
49	278	49	269	97	48	255	92	49	241	87	43
53	287	49	280	97	48	262	91	47	245	85	43
57	301	49	293	97	48	277	92	47	259	86	42
61	313	49	303	97	48	287	92	47	268	86	42
65	319	49	309	97	47	290	91	47	273	86	41
69	327	49	319	98	47	297	91	45	279	85	38
73	332	49	322	97	47	299	90	45	279	84	38
77	337	48	327	97	47	302	89	43	287	85	34
81	340	45	328	96	46	309	91	38	293	86	34
85	342	44	332	97	44	313	91	37	287	84	31
89	354	40	336	95	39	317	90	35	288	81	31
92	353	40	338	96	38	314	89	31	288	82	29
94	350	38	337	96	38	310	89	29	280	80	28
96	346	37	338	98	38	307	89	26	286	83	24
98	346	35	345	100	35	311	90	22	287	83	23
100	351	32	343	98	35	307	87	21	279	80	22
102	353	29	344	97	34	296	84	20	279	79	20
104	349	27	336	96	33	304	87	16	273	78	14
Mean for weeks											
1-13	156		156	100		152	97		148	95	
14-52	236		231	98		219	93		211	89	
53-104	335		325	97		300	90		278	83	

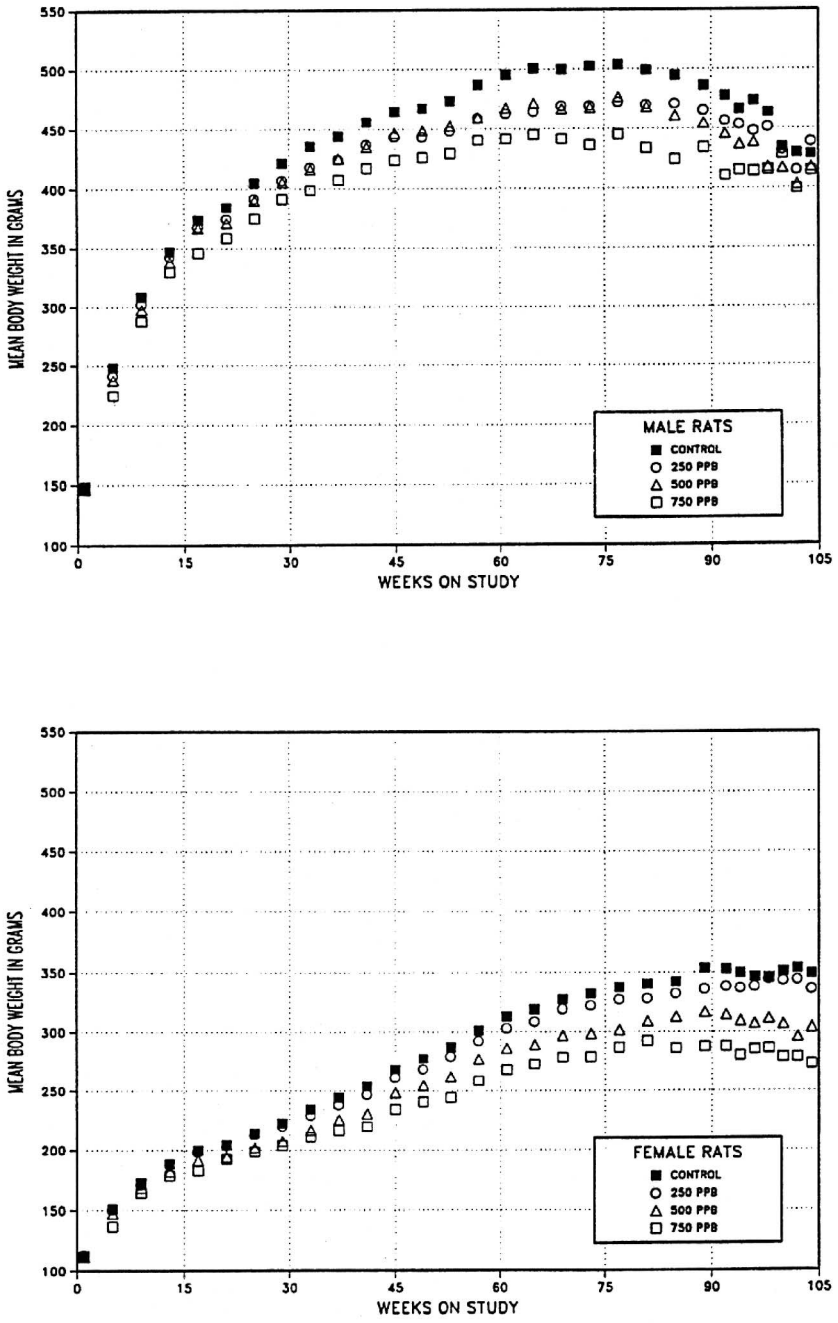


FIGURE 3
Growth Curves for Male and Female Rats
Exposed to Glutaraldehyde by Inhalation for 2 Years

Pathology and Statistical Analyses

This section describes the statistically significant or biologically noteworthy changes in the incidences of neoplasms and/or nonneoplastic lesions of the nose, lung, thyroid gland, mammary gland, pituitary gland, and kidney. Summaries of the incidences of neoplasms and nonneoplastic lesions, individual animal tumor diagnoses, statistical analyses of primary neoplasms that occurred with an incidence of at least 5% in at least one animal group, and historical incidences for the neoplasms mentioned in this section are presented in Appendix A for male rats and Appendix B for female rats.

Nose: In addition to the three nasal sections routinely examined in an NTP 2-year study, a fourth section (Level I) from the most rostral portion of the nasal passage was also examined. This section included the squamous epithelium behind the external nares. The section at Level II included respiratory epithelium while Level III included olfactory epithelium on the dorsal aspect of the nasal passage and respiratory epithelium more ventrally. Level IV was the most caudal level and included the ethmoturbinates, which are covered by olfactory epithelium. Lesions were most common and severe in the squamous epithelium in Level I, less common and severe in the second section, infrequent in the third section, and rarely present in the fourth section.

The changes observed in exposed male and female rats included increased incidences of hyperplasia and inflammation of the squamous epithelium; hyperplasia, goblet cell hyperplasia, inflammation, and squamous metaplasia of the respiratory epithelium; and hyaline degeneration of the olfactory epithelium (Tables 5, A5, and B5). Inflammation was a minimal to marked change consisting of multifocal to locally extensive infiltrates of neutrophils, lymphocytes, plasma cells, and sometimes a few macrophages within the lamina propria and, in severe cases, within the epithelium itself. The number of inflammatory cells and extent of the infiltrates increased with increasing severity. In more severe cases of inflammation, sizable aggregates of neutrophils were present in the nasal passage.

Hyperplasia of the squamous epithelium was a minimal to marked change that occurred in Level I. It was characterized microscopically by variable thickening of the epithelium due to an increase in the number of cell layers, and, especially in more severe cases, varying degrees of accumulation of keratin on the epithelial surface. In severe cases the keratin formed aggregates that partially filled the lumen of the nasal passage. It is possible that the increased keratin represents increased production (hyperkeratosis), but is more likely that the keratin became fixed by the glutaraldehyde and accumulated within the lumen rather than being sloughed and cleared from the nasal passage. In some animals the accumulated keratin produced significant obstruction of the nasal passage, as some animals exhibited dyspnea and mouth breathing. Also, in some animals it was difficult to flush fixative through the nasal passage. At necropsy some rats had air-filled stomachs and intestines (indicating they had swallowed air).

Hyperplasia of the respiratory epithelium was a minimal to moderate change seen primarily in Level II and, in severe cases, in Level III. It was characterized by an increase in the number of epithelial cells resulting in an increased epithelial thickness; increased numbers of goblet cells were sometimes seen, particularly in more severe lesions. Hyperplasia of the transitional epithelium was also observed, especially in more severely affected noses, but was not diagnosed separately. The marginal increase in the incidences of goblet cell hyperplasia of the respiratory epithelium of males and females was a minimal to mild change characterized by aggregates and/or glandular structures of goblet cells and occurred primarily along the nasal septum and ventral meatus of Level II. Increased numbers of goblet cells were sometimes seen as a component of the respiratory epithelial hyperplasia, but goblet cell hyperplasia was diagnosed when the goblet cells formed prominent aggregates and/or glandular formations.

Squamous metaplasia was a minimal to moderate change affecting the respiratory and sometimes the transitional epithelia. Normal cuboidal to columnar epithelium was replaced with three or more layers of squamous epithelial cells. In some of the more severe cases, accumulation of keratin was observed on the epithelial surface.

TABLE 5
Incidences of Nonneoplastic Lesions of the Nose in Rats in the 2-Year Inhalation Study of Glutaraldehyde

	Chamber Control	250 ppb	500 ppb	750 ppb
Male				
Number Examined Microscopically	50	50	50	50
Squamous Epithelium				
Hyperplasia[a]	3 (2.0)[b]	11* (1.6)	39** (2.2)	48** (2.9)
Inflammation	6 (2.0)	17* (1.5)	41** (2.7)	49** (3.6)
Respiratory Epithelium				
Hyperplasia	6 (2.0)	5 (2.0)	17** (1.9)	35** (1.9)
Inflammation	17 (2.1)	10* (1.5)	25 (2.4)	43** (3.2)
Squamous Metaplasia	1 (2.0)	2 (1.5)	11** (2.0)	24** (2.2)
Goblet Cell Hyperplasia	1 (1.0)	0	6 (1.8)	6* (1.2)
Olfactory Epithelium				
Hyaline Degeneration	4 (1.0)	8 (1.3)	9 (1.1)	14** (1.1)
Female				
Number Examined Microscopically	50	50	50	49
Squamous Epithelium				
Hyperplasia	3 (1.3)	15** (1.7)	29** (2.0)	45** (2.7)
Inflammation	6 (2.5)	26** (1.5)	42** (2.1)	48** (3.2)
Respiratory Epithelium				
Hyperplasia	1 (3.0)	6 (1.7)	15** (1.9)	29** (1.9)
Inflammation	5 (2.2)	9 (1.7)	26** (2.1)	42** (2.5)
Squamous Metaplasia	1 (2.0)	1 (3.0)	11** (1.6)	16** (2.3)
Goblet Cell Hyperplasia	1 (2.0)	3 (1.3)	5 (1.4)	8** (1.6)
Olfactory Epithelium				
Hyaline Degeneration	4 (1.0)	5 (1.0)	12* (1.1)	15** (1.1)

* Significantly different ($P \leq 0.05$) from the chamber control group by the Poly-3 test
** $P \leq 0.01$
[a] Number of animals with lesion
[b] Average severity grade of lesions in affected animals: 1=minimal, 2=mild, 3=moderate, 4=marked

Slightly increased incidences of hyaline degeneration of the olfactory epithelium were observed in exposed groups of males and females. The microscopic appearance of this lesion was characteristic of that seen with the spontaneously occurring hyaline degeneration of the olfactory epithelium in F344/N rats; the lesion consisted of an accumulation of homogeneous eosinophilic droplets within the cytoplasm of epithelial cells. The change was of minimal to mild severity and was observed in the olfactory epithelium lining the dorsal meatus of Level III. No neoplasms were observed in the nasal cavity.

Lung: Alveolar/bronchiolar adenomas were present in one male rat each in the 250 and 500 ppb groups, two 750 ppb males, and one 500 ppb female. One male rat in the 750 ppb group with an alveolar/bronchiolar adenoma also had a carcinoma; these incidences were not significantly increased and were within the historical control ranges for inhalation studies (Tables 6, A1, and A4). The neoplasms were typical of those observed in chamber control animals. There was no increase in the incidences of alveolar/bronchiolar hyperplasia in male rats (Tables 6 and A5), and the incidence of alveolar/bronchiolar hyperplasia in 250 ppb males was significantly decreased.

TABLE 6
Incidences of Neoplasms and Nonneoplastic Lesions of the Lung in Rats in the 2-Year Inhalation Study of Glutaraldehyde

	Chamber Control	250 ppb	500 ppb	750 ppb
Male				
Number Examined Microscopically	50	50	50	50
Alveolus, Infiltration Cellular, Histiocyte[a]	23 (1.3)[b]	15 (1.3)	14* (2.1)	11 (1.6)
Interstitium, Fibrosis	8 (1.3)	14 (1.2)	17* (1.8)	7 (1.4)
Alveolar Epithelium, Hyperplasia	9 (2.3)	3* (1.7)	5 (2.2)	4 (2.3)
Alveolar/bronchiolar Adenoma[c]				
Overall rate[d]	0/50 (0%)	1/50 (2%)	1/50 (2%)	2/50 (4%)
Adjusted rate[e]	0.0%	2.6%	2.8%	7.1%
Terminal rate[f]	0/12 (0%)	1/14 (7%)	0/9 (0%)	1/6 (17%)
First incidence (days)	—[h]	729 (T)	533	589
Poly-3 test[g]	P=0.114	P=0.520	P=0.506	P=0.190
Alveolar/bronchiolar Carcinoma[i]	0	0	0	1
Female				
Number Examined Microscopically	50	50	50	49
Alveolus, Infiltration Cellular, Histiocyte	29 (1.5)	24 (1.2)	22 (1.6)	35** (1.6)
Interstitium, Fibrosis	9 (1.6)	13 (1.2)	17* (1.3)	24** (1.4)
Alveolar/bronchiolar Adenoma	0	0	1	0

* Significantly different ($P \leq 0.05$) from the chamber control by the Poly-3 test
** $P \leq 0.01$
(T)Terminal sacrifice
[a] Number of animals with lesion
[b] Average severity grade of lesions in affected animals: 1=minimal, 2=mild, 3=moderate, 4=marked
[c] Historical incidence for 2-year inhalation studies with chamber control groups (mean ± standard deviation): 16/904 (1.8% ± 2.6%); range, 0%-10%
[d] Number of animals with neoplasm per number of animals with lung examined microscopically
[e] Poly-3 estimated neoplasm incidence after adjustment for intercurrent mortality
[f] Observed incidence at terminal kill
[g] Beneath the chamber control incidence is the P value associated with the trend test. Beneath the exposed group incidence are the P values corresponding to the pairwise comparisons between the chamber controls and that exposed group. The Poly-3 test accounts for differential mortality in animals that do not reach terminal sacrifice.
[h] Not applicable; no neoplasms in animal group
[i] Historical incidence: 6/904 (0.7% ± 1.0%); range 0%-2%

The alveolar/bronchiolar adenomas in male and female rats were not considered related to glutaraldehyde exposure.

The incidences of histiocyte infiltration in 750 ppb females and of interstitial fibrosis in 500 and 750 ppb females were increased compared to the chamber controls (Tables 6 and B5). The incidence of histiocyte infiltration was decreased in 500 ppb males, and the incidence of fibrosis was increased only in 500 ppb males. With few exceptions, the fibrosis was present within the areas of histiocytic infiltration. In general, these were minute focal lesions of minimal severity and were qualitatively and quantitatively similar between chamber control and exposed animals. The increased incidences of this common spontaneous lesion in rats were not considered a direct effect of glutaraldehyde. Furthermore, this change was considered to be of little biologic significance.

Thyroid Gland: The incidences of thyroid gland follicular cell adenoma were not significantly increased in rats. However, their occurrence in two 750 ppb female rats (Table B1) exceeded the historical control range for inhalation studies (Table B4a). As many as 3/50 have been observed in control groups from drinking water and corn oil gavage studies (Table B4a). In addition, no supporting hyperplasias of the thyroid gland or other exposure-related effects were observed in the thyroid gland in the current study, suggesting that the two follicular cell adenomas are not related to glutaraldehyde exposure.

Mammary Gland: The incidences of single and multiple fibroadenomas occurred with a negative trend in females (chamber control, 24/50; 250 ppb, 23/50; 500 ppb, 18/50; 750 ppb, 10/50; Tables B1 and B3) and the incidence of fibroadenoma or carcinoma (combined) in 750 ppb female rats was significantly decreased (26/50, 27/50, 21/50, 11/50; Table B3). The incidences of fibroadenoma and fibroadenoma or carcinoma (combined) were below the historical control ranges (Table B4b). Decreased body weights have also been associated with decreased incidences of fibroadenoma of the mammary gland in the F344/N rat (Haseman, 1995; Seilkop, 1995; Haseman and Johnson, 1996). This decrease is considered to be related to the decrease in body weight rather than a direct effect of exposure to glutaraldehyde.

Pituitary Gland (pars distalis): The incidence of adenoma was significantly decreased in 500 ppb females (37/50, 37/50, 27/50, 24/49; Table B3) and occurred with a negative trend. Decreased body weights have also been associated with decreased incidences of this neoplasm in F344/N rats (Seilkop, 1995).

Kidney: There was a slight exposure-related decrease in the severity of nephropathy in male rats (3.5, 3.2, 3.0, 2.9). Nephropathy is a common spontaneous change observed in almost 100% of male rats surviving to 2 years. It has been shown that dietary restrictions that cause decreased body weights will result in decreased incidences and severity of nephropathy (Yu *et al.*, 1982; Roe *et al.*, 1995). Because exposed male rats had some degree of body weight loss throughout most of the study, the decreased severity of nephropathy is most likely a secondary effect.

MICE

Survival

Estimates of 2-year survival probabilities for male and female mice are shown in Table 7 and in the Kaplan-Meier survival curves (Figure 4). Survival of exposed mice was similar to that of the chamber controls.

TABLE 7
Survival of Mice in the 2-Year Inhalation Study of Glutaraldehyde

	Chamber Control	62.5 ppb	125 ppb	250 ppb
Male				
Animals initially in study	50	50	50	50
Moribund	13	15	6	5
Natural deaths	6	8	4	7
Animals surviving to study termination	31	27	40	38
Percent probability of survival at end of study[a]	62	54	80	76
Mean survival (days)[b]	686	666	697	704
Survival analysis[c]	P=0.036N	P=0.464	P=0.091N	P=0.192N
Female				
Animals initially in study	50	50	50	50
Accidental death[d]	0	0	1	0
Moribund	11	10	10	12
Natural deaths	5	3	4	6
Animals surviving to study termination	34	37	35	32
Percent probability of survival at end of study	68	74	72	64
Mean survival (days)	699	708	711	695
Survival analysis	P=0.573	P=0.611N	P=0.771N	P=0.811

[a] Kaplan-Meier determinations
[b] Mean of all deaths (uncensored, censored, and terminal sacrifice)
[c] The result of the life table trend test (Tarone, 1975) is in the chamber control column, and the results of the life table pairwise comparisons (Cox, 1972) with the chamber controls are in the exposed group columns. A negative trend or lower mortality in an exposure group is indicated by **N**.
[d] Censored from survival analyses

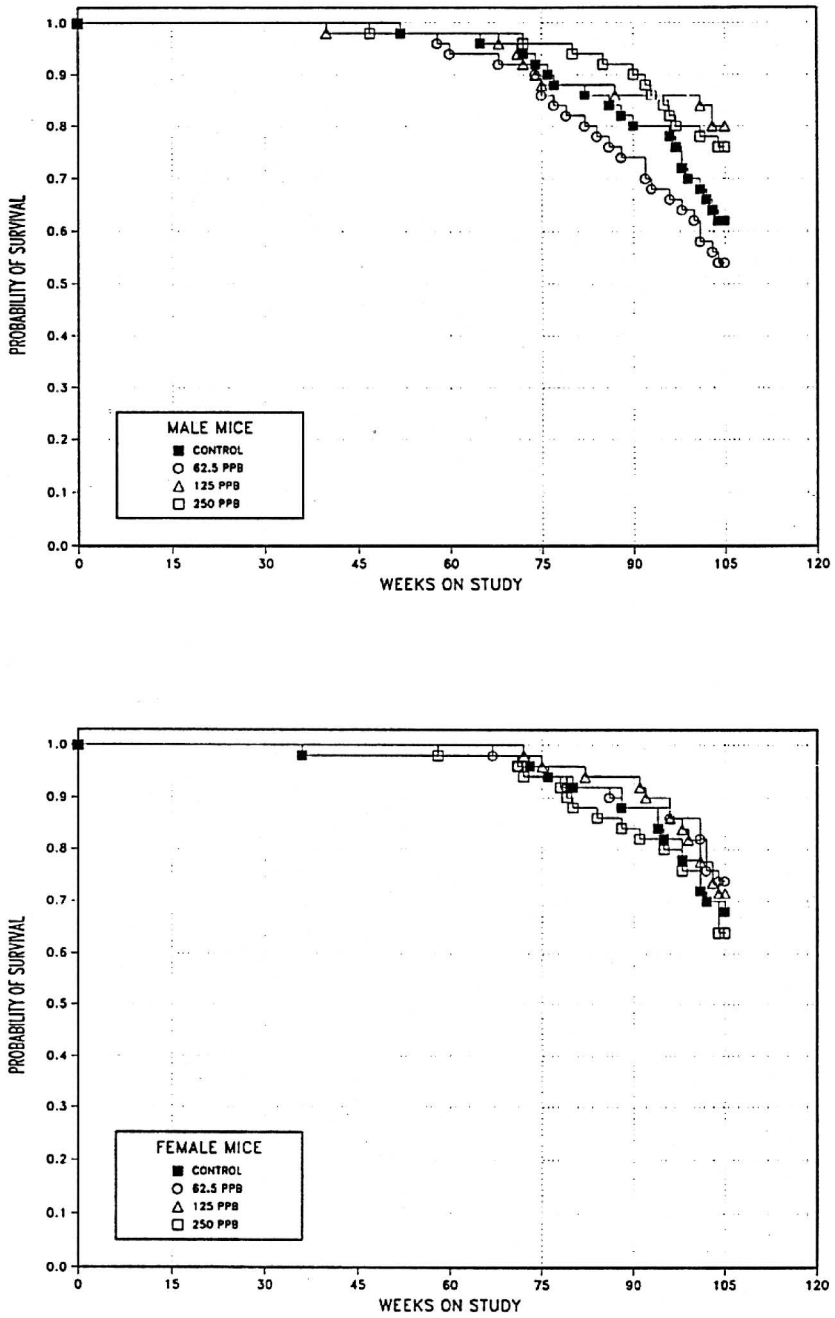


FIGURE 4
Kaplan-Meier Survival Curves for Male and Female Mice Exposed to Glutaraldehyde by Inhalation for 2 Years

Body Weights and Clinical Findings

There were no exposure-related effects on mean body weights of males (Tables 8 and 9; Figure 5). Mean body weights of females exposed to 250 ppb were generally less than those of the chamber controls throughout the study. No clinical findings were attributed to glutaraldehyde exposure.

TABLE 8
Mean Body Weights and Survival of Male Mice in the 2-Year Inhalation Study of Glutaraldehyde

Weeks on Study	Chamber Control		62.5 ppb			125 ppb			250 ppb		
	Av. Wt. (g)	No. of Survivors	Av. Wt. (g)	Wt. (% of controls)	No. of Survivors	Av. Wt. (g)	Wt. (% of controls)	No. of Survivors	Av. Wt. (g)	Wt. (% of controls)	No. of Survivors
1	26.1	50	25.8	99	50	25.9	99	50	26.0	100	50
4	31.0	50	30.6	99	50	30.3	98	50	29.7	96	50
8	33.7	50	33.2	99	50	32.8	97	50	32.3	96	50
12	37.1	50	36.5	98	50	35.8	97	50	35.3	95	50
16	39.6	50	38.8	98	50	37.8	96	50	37.8	96	50
20	41.7	50	41.1	99	50	39.8	95	50	39.5	95	50
24	43.4	50	43.2	100	50	41.5	96	50	41.0	95	50
28	45.6	50	45.3	99	50	43.2	95	50	43.0	94	50
32	45.9	50	46.3	101	50	44.3	97	50	43.8	95	50
36	47.0	50	47.4	101	50	45.9	98	50	45.0	96	50
40	47.8	50	48.8	102	50	47.2	99	49	46.3	97	50
44	49.7	50	50.1	101	50	48.8	98	49	48.3	97	50
48	50.6	50	50.9	101	50	50.0	99	49	48.9	97	49
52	52.2	49	52.2	100	50	51.9	99	49	51.3	98	49
56	52.0	49	51.8	100	49	51.6	99	49	51.3	99	49
60	52.3	49	52.1	100	48	52.2	100	49	51.6	99	49
64	51.7	49	51.7	100	47	51.6	100	49	50.5	98	49
68	52.4	48	51.6	99	47	51.6	99	48	50.6	97	49
72	52.5	47	52.1	99	46	51.4	98	47	51.1	97	49
76	51.4	46	51.9	101	43	51.8	101	44	51.2	100	48
80	51.7	44	51.7	100	41	51.8	100	44	50.8	98	47
84	50.5	43	51.5	102	40	50.9	101	44	50.4	100	47
88	50.4	42	51.4	102	38	51.4	102	43	49.7	99	46
93	49.8	40	51.5	103	35	51.7	104	43	50.4	101	44
94	50.1	40	50.0	100	34	50.5	101	43	49.5	99	43
96	50.2	39	49.8	99	33	50.1	100	43	49.6	99	42
98	50.4	36	49.6	98	32	49.9	99	43	50.8	101	40
100	49.7	35	49.4	99	31	49.5	100	43	50.2	101	40
102	49.9	33	50.0	100	29	48.6	97	42	49.5	99	39
104	50.1	31	49.8	99	27	48.8	97	40	49.7	99	38
Mean for weeks											
1-13	32.0		31.5	98		31.2	98		30.8	96	
14-52	46.4		46.4	100		45.0	97		44.5	96	
53-104	50.9		51.0	100		50.8	100		50.4	99	

TABLE 9
Mean Body Weights and Survival of Female Mice in the 2-Year Inhalation Study of Glutaraldehyde

Weeks on Study	Chamber Control		62.5 ppb			125 ppb			250 ppb		
	Av. Wt. (g)	No. of Survivors	Av. Wt. (g)	Wt. (% of controls)	No. of Survivors	Av. Wt. (g)	Wt. (% of controls)	No. of Survivors	Av. Wt. (g)	Wt. (% of controls)	No. of Survivors
1	20.4	50	20.3	100	50	20.2	99	50	20.2	99	50
4	24.5	50	24.9	102	50	24.7	101	50	24.6	100	50
8	26.7	50	27.2	102	50	27.0	101	50	26.5	99	50
12	29.0	50	29.5	102	50	29.0	100	50	28.1	97	50
16	30.8	50	30.9	100	50	30.7	100	50	29.1	95	50
20	32.6	50	33.2	102	50	32.6	100	50	30.8	95	50
24	34.7	50	34.7	100	50	34.6	100	50	31.6	91	50
28	36.4	50	36.2	100	50	35.7	98	50	32.6	90	50
32	36.9	50	37.8	102	50	36.2	98	50	32.8	89	50
36	38.3	49	38.4	100	50	37.7	98	50	33.4	87	50
40	40.2	49	41.0	102	50	38.2	95	50	36.0	90	50
44	43.1	49	43.7	101	50	41.1	95	50	38.8	90	50
48	43.2	49	44.9	104	50	41.7	97	50	39.5	91	50
52	46.8	49	48.9	105	50	45.3	97	50	44.0	94	50
56	49.2	49	49.6	101	50	46.4	94	50	44.8	91	50
60	50.3	49	51.0	101	50	48.2	96	50	45.4	90	49
64	51.3	49	51.3	100	50	48.0	94	50	45.9	90	49
68	51.7	49	50.7	98	49	47.7	92	50	46.1	89	49
72	52.9	49	52.6	99	48	50.3	95	49	47.6	90	47
76	51.5	48	51.3	100	47	48.9	95	48	47.7	93	47
80	52.5	46	51.2	98	46	49.7	95	48	47.5	91	45
84	51.1	46	50.6	99	46	49.2	96	47	47.8	94	44
88	50.0	45	50.6	101	44	49.4	99	47	46.9	94	43
93	50.8	44	49.9	98	44	49.4	97	45	47.8	94	41
94	50.5	42	48.8	97	44	48.4	96	45	47.0	93	41
96	50.2	41	48.5	97	44	47.3	94	44	46.7	93	40
98	50.0	40	48.5	97	43	48.0	96	42	47.6	95	39
100	50.3	39	48.1	96	43	48.0	95	40	48.2	96	38
102	49.5	35	47.5	96	39	46.8	95	38	47.2	95	35
104	49.6	35	48.3	97	37	47.1	95	35	47.7	96	32
Mean for weeks											
1-13	25.2		25.5	101		25.2	100		24.9	99	
14-52	38.3		39.0	102		37.4	98		34.9	91	
53-104	50.7		49.9	98		48.3	95		47.0	93	

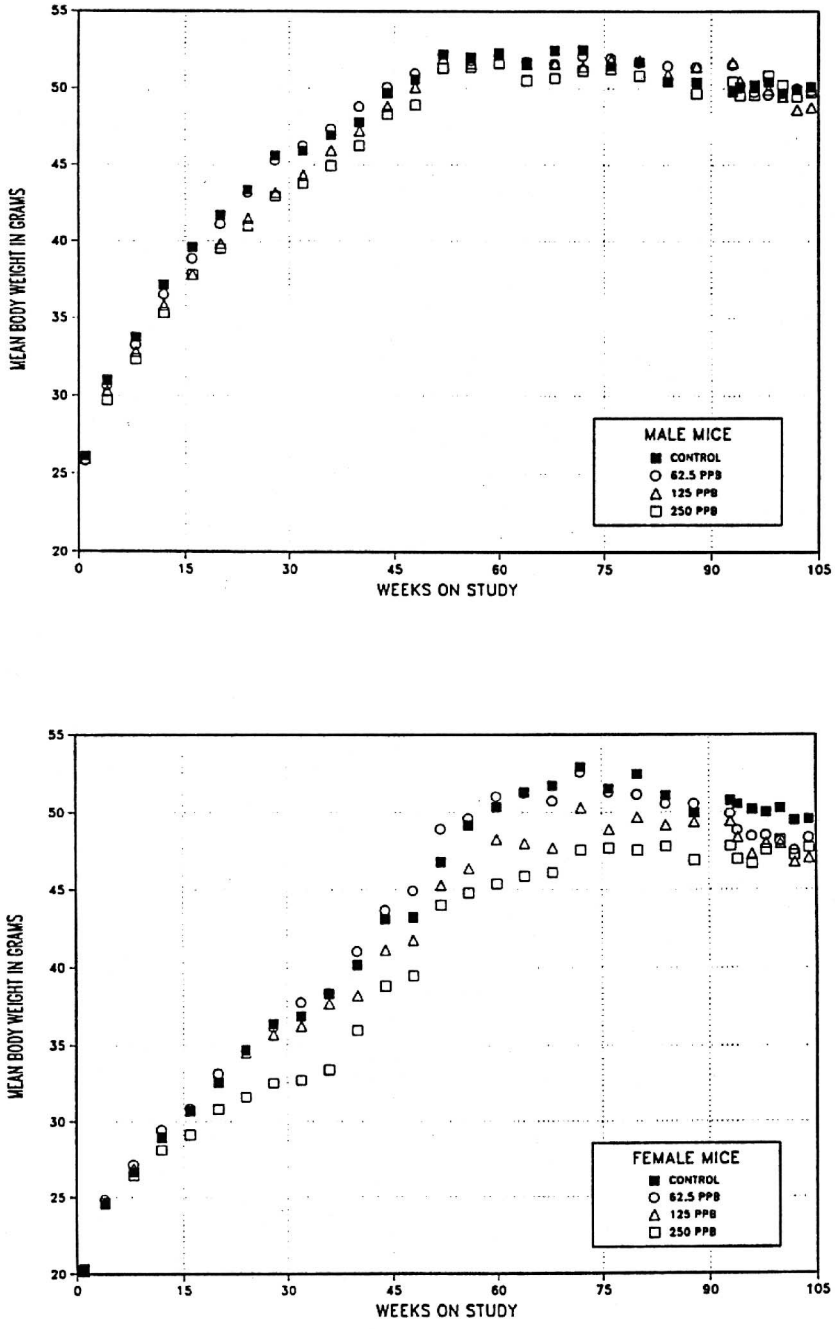


FIGURE 5
Growth Curves for Male and Female Mice Exposed to Glutaraldehyde by Inhalation for 2 Years

Pathology and Statistical Analyses

This section describes the statistically significant or biologically noteworthy changes in the incidences of neoplasms and/or nonneoplastic lesions of the nose, thyroid gland, pituitary gland, and liver. Summaries of the incidences of neoplasms and nonneoplastic lesions, individual animal tumor diagnoses, and statistical analyses of primary neoplasms that occurred with an incidence of at least 5% in at least one animal group are presented in Appendix C for male mice and Appendix D for female mice.

Nose: As in rats, four levels of the nose were examined. There were increased incidences of several lesions within the various sections of the nose. In general, the lesions observed in the noses of mice were qualitatively similar to those which occurred in rats. Female mice were more severely affected than male mice. The incidences of squamous metaplasia of the respiratory epithelium were increased in 250 ppb males and females and 125 ppb females (Tables 10, C4, and D4). The incidences of hyaline degeneration of the respiratory epithelium were increased in all exposed groups of females. The incidence of inflammation of the nose was marginally increased in 250 ppb females. Turbinate necrosis was observed in two 125 ppb males and in all exposed groups of females. While the increase was not statistically significant, this is not a common spontaneous lesion.

Inflammation, squamous metaplasia, and turbinate necrosis were of minimal and, occasionally, mild severity. Lesions were seen on the ventral surfaces of the nasoturbinates, dorsal and medial surfaces of the maxilloturbinates, and sometimes on the septum and lateral walls. Inflammation consisted of one to a few small focal aggregates of neutrophils, sometimes mixed with mononuclear inflammatory cells, within the epithelium and lamina propria, occasionally accompanied by small amounts of cell debris on the surface. Less commonly, the inflammatory infiltrate was present within the nasal lumen adjacent to the epithelium or within the lumens of distended glands within the lamina propria. Squamous metaplasia was a focal to multifocal change generally affecting the tips of the turbinates and was characterized by replacement of the normal cuboidal or columnar epithelium with three or more layers.

Turbinate necrosis was usually a focal change consisting of a small focus of necrosis extending the full thickness of the epithelium into the underlying lamina propria and sometimes affecting the turbinate bone.

The microscopic appearance of the hyaline degeneration of the respiratory epithelium was typical of that seen with the spontaneously occurring hyaline degeneration of the olfactory and respiratory epithelium in $B6C3F_1$ mice and consisted of accumulation of homogeneous eosinophilic material within the cytoplasm of epithelial cells. No neoplasms were observed in the nasal cavity.

TABLE 10
Incidences of Nonneoplastic Lesions of the Nose in Mice in the 2-Year Inhalation Study of Glutaraldehyde

	Chamber Control	62.5 ppb	125 ppb	250 ppb
Male				
Number Examined Microscopically	48	50	50	50
Respiratory Epithelium				
Squamous Metaplasia[a]	2 (1.0)[b]	5 (1.0)	6 (1.2)	9* (1.1)
Turbinate				
Necrosis	0	0	2 (2.0)	0
Female				
Number Examined Microscopically	50	49	50	50
Inflammation	6 (1.2)	7 (1.3)	13 (1.4)	14* (1.4)
Respiratory Epithelium				
Squamous Metaplasia	7 (1.1)	11 (1.0)	16* (1.3)	21** (1.5)
Hyaline Degeneration	16 (1.4)	35** (1.4)	32** (1.3)	30* (1.1)
Turbinate				
Necrosis	0	3 (2.0)	1 (1.0)	4 (1.5)

* Significantly different ($P \leq 0.05$) from the chamber control by the Poly-3 test
** $P \leq 0.01$
[a] Number of animals with lesion
[b] Average severity grade of lesions in affected animals: 1=minimal, 2=mild, 3=moderate, 4=marked

Thyroid Gland: There was an increased incidence of minimal to mild hyperplasia of the thyroid gland follicular cells in 250 ppb female mice (26/50, 24/48, 30/50, 37/50; Table D4). This common spontaneous change in aged mice is variably diagnosed within NTP studies. There were no increases in the incidences of adenoma of the thyroid gland follicular cells in mice (males: 1/48, 3/49, 2/49, 1/49; females: 4/50, 0/48, 2/50, 3/50; Tables C1 and D1), nor were there any other exposure-related effects in the thyroid gland of males. The increased incidence of hyperplasia of the thyroid gland in female mice was considered an incidental finding.

Pituitary Gland (pars distalis): There was an increased incidence of minimal to mild hyperplasia of the pituitary gland pars distalis in 250 ppb female mice (19/49, 24/49, 23/49, 28/50; Table D4). There were no increases in the incidences of adenoma of the pituitary gland in females (20/49, 16/49, 20/49, 16/50; Table D3), nor was there evidence of an exposure-related effect in the pituitary gland of male mice. Since hyperplasia and adenoma are thought to represent a morphologic and biologic continuum in the pituitary gland, this indicates that the increased incidence of hyperplasia of the pituitary gland in female mice was an incidental finding.

Liver: Incidences of hepatocellular adenoma were decreased in 62.5 and 250 ppb male mice and 250 ppb female mice (males: 19/49, 10/50, 20/50, 11/49; females: 11/50, 11/48, 7/50, 3/50; Tables C3 and D3). A decrease in the incidence of hepatocellular adenoma has been associated with a decrease in body weight, which could explain the effect in female mice (Rao *et al.*, 1987, 1990; Haseman, 1995; Seilkop, 1995; Turturro *et al.*, 1995; Haseman and Johnson, 1996). However, in male mice exposed to glutaraldehyde, no decrease in body weight was observed. In male mice, the decrease in the incidences of hepatocellular adenoma was not exposure related. This indicates that the decrease in the incidences of hepatocellular adenoma in male mice was not related to exposure to glutaraldehyde.

GENETIC TOXICOLOGY

Glutaraldehyde was tested for induction of mutations in *Salmonella typhimurium* at three laboratories (Table E1). At the first laboratory, positive results were obtained with strain TA100 with and without liver S9 from Aroclor 1254-induced male Sprague-Dawley rats or Syrian hamsters. At the second laboratory, no increase in mutations was observed in TA100 in the absence of S9 or with 10% induced hamster S9. A small increase in mutations was noted in TA100 in the presence of 10% induced rat S9, and the results were considered equivocal. At both laboratories, negative results were obtained with TA98, TA1535, and TA1537, with and without S9. Complete data sets from these two studies are presented by Haworth *et al*. (1983). The third laboratory tested glutaraldehyde for induction of mutations in *S. typhimurium* strains TA100, TA102, and TA104. Results were clearly positive for all three strains with and without induced hamster or rat liver S9. Glutaraldehyde also induced mutations at the TK locus of L5178Y mouse lymphoma cells at a concentration of 8 μg/mL in each of two trials conducted in the absence of S9 activation (Table E2; McGregor *et al*., 1988).

At one of two test laboratories, glutaraldehyde induced sister chromatid exchanges in cultured Chinese hamster ovary cells with and without Aroclor 1254-induced male Sprague-Dawley rat liver S9; results from the second laboratory were weakly positive in the presence of S9 and negative without S9 (Table E3; Galloway *et al*. 1985). Although the negative trial in the absence of S9 showed a significant increase in sister chromatid exchanges at the highest dose tested, the trial was concluded to be negative on the basis of the trend test, with a P value greater than 0.025 (Galloway *et al*., 1985). Glutaraldehyde was also tested at the same two laboratories for induction of aberrations in cultured Chinese hamster ovary cells (Table E4; Galloway *et al*., 1985). The first laboratory reported negative results with and without S9, while the second laboratory found a weakly positive result in the absence of S9. Higher doses were used in the second study, which may explain the discordant results between laboratories. At the second laboratory, the trial conducted with S9 showed a dose-related increase in aberrations, which met the statistical criteria for a weakly positive response. However, the reviewers concluded that this increase was not of sufficient magnitude to be considered positive (Galloway *et al*., 1985).

Glutaraldehyde was tested for its ability to induce sex-linked recessive lethal mutations in germ cells of male *Drosophila melanogaster* treated as newly emerged adult flies by feeding or injection (Yoon *et al*., 1985) or treated as larvae by feeding (Zimmering *et al*., 1989). Results from all three tests were negative (Table E5).

Glutaraldehyde was tested in several *in vivo* assays for induction of chromosomal damage in mice. Results of an aberrations test showed significant increases in the percentage of aberrant cells in mouse bone marrow 36 hours after intraperitoneal injection of glutaraldehyde (15 to 60 mg/kg) (Table E6); no significant increase in the number of aberrant cells was noted 17 hours after injection. A subset of the mice treated in Trial 2 of the aberrations test was also examined at 36 hours for the presence of micronucleated polychromatic erythrocytes in bone marrow (Table E7). A small increase in the frequency of micronucleated polychromatic erythrocytes was observed in these animals, but the response was concluded to be equivocal, based on the trend test P value of 0.028 ($P \leq 0.025$ required for significance) and the fact that no single dose group was significantly elevated ($P \leq 0.006$) above the control frequency. Additional micronucleus tests were performed with glutaraldehyde. In a three-injection test, no significant increase in micronucleated polychromatic erythrocytes was observed in mouse bone marrow in either of two trials using a dose range of 5 to 20 mg/kg (Table E8). Finally, no significant increases in the frequency of micronucleated normochromatic erythrocytes were observed in peripheral blood samples obtained from male and female mice exposed to glutaraldehyde by whole body inhalation for 13 weeks (Table E9; NTP, 1993). The small but reproducible increase in aberrations noted in bone marrow cells of male mice after a single intraperitoneal injection of glutaraldehyde at doses of 50 and 60 mg/kg was not reflected by significant increases in micronucleated erythrocytes in mice treated under the same protocol or under a multiple-exposure protocol.

In summary, glutaraldehyde was shown to be genotoxic *in vitro*, inducing mutations in bacterial cells and mutations, sister chromatid exchanges, and aberrations in mammalian cells. Its mutagenic activity *in vitro* did not require S9 activation. Results of genotoxicity tests *in vivo* were generally negative. No induction of sex-linked recessive lethal mutations was seen in male *D. melanogaster* treated in a variety of test protocols, and no clear induction of micronuclei was observed in erythrocytes of mice administered glutaraldehyde via short-term inhalation or acute intraperitoneal injection protocols. Results of tests for induction of chromosomal aberrations in mice were positive 36 hours after injection and negative 17 hours after injection.

DISCUSSION AND CONCLUSIONS

Glutaraldehyde was nominated by the National Cancer Institute, the Occupational Safety and Health Administration, and the National Institute of Environmental Health Sciences for toxicity and carcinogenicity testing because of concerns about occupational exposure. Glutaraldehyde was evaluated for carcinogenicity in 2-year inhalation studies (whole body) in male and female F344/N rats and B6C3F$_1$ mice.

In the 16-day and 13-week inhalation studies (NTP, 1993), the nose was the primary target site of nonneoplastic lesions. Lesions in the nasal cavity included hyperplasia, squamous metaplasia, necrosis, and acute inflammation. In addition, exposure-related increases in cell replication of nasal squamous and respiratory epithelia were observed in rats and mice in the 13-week studies (NTP, 1993; Gross *et al.*, 1994). In general, mice were more sensitive than rats to the effects of glutaraldehyde, with mortality and lesions of the nasal cavity occurring at lower exposure concentrations. Exposure concentrations for the 2-year inhalation studies were selected based on the nasal cavity lesions in the 13-week studies, and lower exposure concentrations were selected for mice than for rats.

In the 2-year study, survival of 750 ppb female rats was somewhat less than that of chamber controls. During the first few months in the study, breathing difficulties were observed in some 750 ppb rats, which resulted in their early removal from the study. No effect on survival was observed in mice exposed to glutaraldehyde. Although a number of male and female rats in the 750 ppb groups were removed, subsequent survival was typical for contemporary inhalation studies in rats and/or mice (NTP, 1998, 1999a,b).

The concentration-dependent, nonneoplastic lesions found in the nose in the current studies were similar to those found in the 13-week studies (NTP, 1993) and in a 78-week inhalation study in B6C3F$_1$ mice (Zissu *et al.*, 1998). These lesions included a spectrum of inflammatory, degenerative, and proliferative lesions that were more severe in the anterior portion than in the posterior portion of the nose of rats and mice.

In the squamous epithelium of the nasal cavity, minimal to marked hyperplasia and inflammation in rats and minimal to mild inflammation in mice were observed in the 2-year studies, especially at the highest exposure concentrations (750 ppb for rats and 250 ppb for mice). In severe cases in rats, there was accumulated keratin that partially filled the lumen of the nasal passages (squamous exfoliation). It appeared that accumulated keratin produced significant obstruction of the nasal passage in some animals, resulting in mouth breathing. In general, the nasal lesions were more severe in exposed female rats than in males, and that may explain the increased mortality in females. Squamous exfoliation was observed at 250 ppb and greater in the 13-week rat and mouse studies and was thought to be responsible for the breathing difficulties and subsequent removal of mice from the 13-week studies (NTP, 1993).

In the 2-year rat study, hyperplasia and inflammation as well as squamous metaplasia and goblet cell hyperplasia were observed in the respiratory epithelium. These lesions were slightly less severe than those observed in the squamous epithelium. In the 2-year mouse study, inflammation and squamous metaplasia of the respiratory epithelium were also observed. In rats, degeneration of the olfactory epithelium occurred. Degeneration was less severe in the olfactory epithelium than in the more anterior sections of the nose, but incidences were increased when compared to the 13-week study (NTP, 1993), in which only one 1,000 ppb male rat and two 1,000 ppb female rats had this lesion. This indicated that the nasal lesions appeared to progress in severity with continued exposure to glutaraldehyde. In addition, the incidence of the lesions increased more in the anterior section than in the posterior section of the nose. This selective injury in the anterior portion of the nose has also been observed with other aldehydes and irritant chemicals in inhalation studies (Buckley *et al.*, 1984). Exposure to formaldehyde resulted in both neoplastic and nonneoplastic lesions in the anterior portion of the

nose, but not as anterior as the nonneoplastic lesions produced by glutaraldehyde (Kerns *et al.*, 1983; Monticello *et al.*, 1996). Because glutaraldehyde has two aldehyde groups, it can be expected that glutaraldehyde is more reactive than formaldehyde and does not penetrate as far into the nasal cavity as formaldehyde.

No nasal neoplasms were observed in male or female F344/N rats or $B6C3F_1$ mice in the current 2-year studies or in the $B6C3F_1$ mice exposed to 100 ppb in a 78-week inhalation study (Zissu *et al.*, 1998). In contrast, the structural analogues formaldehyde and acetaldehyde have been shown to produce squamous cell carcinomas in the nasal cavity of rats after long-term exposure by inhalation (Kerns *et al.*, 1983; Woutersen *et al.*, 1986; Monticello *et al.*, 1996).

Glutaraldehyde is a weak *in vitro* mutagen, inducing gene mutations in *S. typhimurium* (Table E1) and mutations (McGregor *et al.*, 1988) and chromosomal effects in mammalian cells (Galloway *et al.*, 1985); S9 activation was not required for the mutagenic activity. The doses that were tested *in vitro* were fairly low due to the toxicity of glutaraldehyde. No induction of sex-linked recessive lethal mutations occurred in *Drosophila melanogaster* treated in a variety of test protocols (Yoon *et al.*, 1985; Zimmering *et al.*, 1989), and no induction of micronuclei was observed in erythrocytes of mice treated via subchronic inhalation or 3-day intraperitoneal injection protocols (Tables E7, E8, and E9). However, positive results were reported in mouse bone marrow chromosomal aberrations assays in which exposure to glutaraldehyde was via a single intraperitoneal injection (Table E4). The inhalation route may not result in significant systemic exposure to glutaraldehyde due to the local reaction in the nasal epithelium and thus, the negative results in the 13-week micronucleus test are not surprising. The conflicting results obtained in the mouse bone marrow studies may be related to differences in the dose concentrations employed. The chromosomal aberrations test, which used a single intraperitoneal injection rather than multiple injections, employed a high dose of 60 mg/kg, which is three times higher than the dose used in the multiple-injection micronucleus tests (20 mg/kg). Also, micronuclei are observed in interphase nuclei, whereas chromosomal aberrations are observed in metaphase nuclei, and this difference in optimal post-treatment observation time may be a consideration in the discordant results obtained for chromosomal aberration (Table E6) and micronucleus induction (Table E7) in a single set of animals analyzed 36 hours postinjection.

Formaldehyde also is an *in vitro* genotoxin, inducing gene mutations in *S. typhimurium* (Haworth *et al.*, 1983), at approximately the same concentrations as glutaraldehyde (100-200 μg/plate), and sister chromatid exchanges and chromosomal aberrations in cultured Chinese hamster ovary cells (Galloway *et al.*, 1985), with and without S9. Positive results were also obtained in *D. melanogaster* for induction of sex-linked recessive lethal mutations and reciprocal translocations (Valencia *et al.*, 1989); doses were comparable to those used in the sex-linked-recessive-lethal test with glutaraldehyde. Formaldehyde has not been tested for chromosomal effects in rodents *in vivo*, but increased frequencies of micronuclei were noted in buccal and nasal mucosal cells of humans occupationally exposed to formaldehyde vapors (Suruda *et al.*, 1993; Titenko-Holland *et al.*, 1996; Ying *et al.*, 1997). Therefore, the genetic toxicity profiles of formaldehyde and glutaraldehyde are similar, but there are insufficient *in vivo* data in mammals to enable a detailed comparison of the genotoxic activity of these two reactive chemicals. In general, the responses noted with formaldehyde were stronger at similar dose concentrations than for glutaraldehyde. This might be due to the higher reactivity of glutaraldehyde which, in turn, may interfere with the chemical's ability to reach the cellular target.

Glutaraldehyde, formaldehyde, and acetaldehyde are low molecular weight, reactive aldehydes that have similar chemical properties, cause similar biologic effects, and have a common metabolic pathway. This metabolic pathway involves aldehyde dehydrogenases, which have been identified in most tissues (Casanova-Schmitz *et al.*, 1984; Heck *et al.*, 1990; Beauchamp *et al.*, 1992). It is generally assumed that aldehydes initially react with amino acids to form Schiff bases with reactive amino groups (Beauchamp *et al.*, 1992). This has also been reported for glutaraldehyde, formaldehyde, and acetaldehyde (Tuma and Sorrell, 1985; Feron *et al.*, 1991; Beauchamp *et al.*, 1992). The reactivity of these aldehydes is due to the electrophilic aldehyde group(s). In addition, the mutagenic potential of glutaraldehyde is strikingly similar to formaldehyde, as previously mentioned.

The biologic effects of these aldehydes as tested by various routes of exposure suggest the involvement of a contact site mechanism. Exposure by inhalation to glutaraldehyde, formaldehyde, or acetaldehyde results in tissue damage that is confined to the upper respiratory tract (Appelman *et al.*, 1982; Woutersen *et al.*, 1987; Heck *et al.*, 1990; NTP, 1993; Gross *et al.*, 1994; Zissu *et al.*, 1994). However, the location of the major nonneoplastic lesions differs for each of these chemicals. Glutaraldehyde had a more profound effect on the most anterior portion of the nasal cavity that is lined by squamous epithelium. Just caudal to this region, respiratory epithelium predominates and was significantly affected by both glutaraldehyde and formaldehyde. However, in that area, changes described as squamous hyperplasia and squamous papillary hyperplasia with foci or cellular atypia in the study of formaldehyde (Kerns *et al.*, 1983; Monticello *et al.*, 1996) were not observed in the current study of glutaraldehyde. These changes were thought to be precursor lesions to squamous cell neoplasia in the formaldehyde study.

Acetaldehyde, an aldehyde with an additional methyl group compared to formaldehyde, caused nasal lesions, including squamous cell carcinomas, that were mainly located in the olfactory epithelium (Woutersen *et al.*, 1986). The noncarcinogenic isobutyraldehyde, which is a larger molecule than acetaldehyde, caused mainly nonneoplastic lesions of the respiratory and olfactory epithelium (Abdo *et al.*, 1998). The extreme anterior location of glutaraldehyde-induced lesions suggests that glutaraldehyde is more reactive and does not penetrate as far into the nasal cavity as do acetaldehyde and isobutyraldehyde.

Oral exposure to glutaraldehyde, formaldehyde, or acetaldehyde results in tissue damage limited to the gastric mucosa (Til *et al.*, 1988; Ballantyne, 1995). Dermal exposure to acetaldehyde in humans resulted in cutaneous erythema (Wilkin and Fortner, 1985). Dermal exposure studies have clearly shown skin irritation and sensitization caused by formaldehyde or glutaraldehyde (IPCS, 1989; Stern *et al.*, 1989; NICNAS, 1994; Ballantyne, 1995).

Based on the exposure concentrations used for glutaraldehyde in the current 2-year inhalation studies, the toxic potency of glutaraldehyde in comparison to formaldehyde in 2-year inhalation studies, and the exposure concentrations at which formaldehyde induced squamous cell carcinomas, glutaraldehyde-induced nasal neoplasms might not have been expected to occur in the current studies. An approach to compare the toxicity of formaldehyde with acetaldehyde and glutaraldehyde in inhalation and oral studies was presented by Morris *et al.* (1996).

Glutaraldehyde was six to eight times more potent than formaldehyde in its ability to produce DNA-protein crosslinks and about 10 times more potent than formaldehyde in producing tissue damage after instillation into the nose (St. Clair *et al.*, 1990; Kuykendall and Bogdanffy, 1992), whereas genotoxicity was generally observed at similar dose concentrations (Galloway *et al.*, 1985; Valencia *et al.*, 1989). This is in agreement with the results of the current 2-year study in male rats using hyperplasia and squamous metaplasia of the respiratory epithelium as an endpoint. The respiratory epithelium was the area in which squamous cell carcinomas were observed after exposure to formaldehyde (Kerns *et al.*, 1983; Monticello *et al.*, 1996). For both hyperplasia and metaplasia of the respiratory epithelium, the no-observable-adverse-effect level (NOAEL) and the lowest-observable-adverse-effect level (LOAEL) after exposure to glutaraldehyde were 250 and 500 ppb, respectively. Exposure to formaldehyde for 2 years resulted in increased incidences of hyperplasia and squamous metaplasia of the respiratory epithelium in rats administered 10 ppm or about 6 ppm, respectively (Table 11).

TABLE 11
Toxicologic Effects (Lowest-Observable-Adverse-Effect Level) of Glutaraldehyde and Formaldehyde in Male F344/N Rats

Parameter	Glutaraldehyde Concentration			Formaldehyde Concentration[a]			
	250 ppb	500 ppb	750 ppb	2 ppm	5.6 or 6 ppm	10 ppm	14.3 or 15 ppm
Concentration (μg/L)	1.02	2.04	3.06	2.4	6.9 or 7.4	12	17.6 or 18.5
Delivered dose (mg/cm^2)[b]	0.012	0.024	0.036	0.03	0.08	0.15	0.21
Responses							
Respiratory epithelium							
Hyperplasia	NOAEL	LOAEL			NOAEL	LOAEL	
Squamous metaplasia (%)	4	22	48		ca. 10[c]		ca. 95[c]
	NOAEL	LOAEL		NOAEL	LOAEL		
Squamous cell carcinoma (%)	0	0	0	0	1[c,d]	22[d]	44[d]-47[c]

NOAEL=no-observable-adverse-effect level; LOAEL=lowest-observable-adverse-effect level

[a] Dose levels used: 2, 5.6 and 14.3 ppm by Kerns *et al.* (1983) and 2, 6, 10, and 15 ppm by Monticello *et al.* (1996)

[b] Based on a ventilation rate of 225 mL/minute, 6 hours per day, a squamous-respiratory nasal surface of 6.7 cm^2, and 100% deposition (Morris *et al.*, 1996)

[c] Kerns *et al.* (1983). Data for squamous metaplasia are based on the nose of male and female Fischer F344 rats. At the 14.3 ppm exposure concentration, squamous metaplasia was observed in all sections, i.e., about 100%, 100%, 95%, 80%, and 75% from the rostral (section I) to the distal (section V) area, respectively.

[d] Monticello *et al.* (1996)

Comparison of the various NOAELs and LOAELs for glutaraldehyde and formaldehyde in 2-year inhalation studies in F344/N rats indicated that glutaraldehyde is three to seven times more potent than formaldehyde (Table 12). This approach has certain drawbacks. It would have been better to compare, for example, the slopes of the dose-response curves instead of the ratios of NOAELs or LOAELs because these ratios depend in part on the experimental design. However, the nonneoplastic lesions in the 2-year inhalation studies with formaldehyde have not been extensively described. In addition, the range of exposure concentrations in the studies with glutaraldehyde and formaldehyde are not well spaced. The highest glutaraldehyde concentration used in the current study was 750 ppb, which was calculated to deliver an estimated dose of 0.036 mg/cm^2 for a 6-hour exposure period. For a three to sevenfold potency ratio of glutaraldehyde to formaldehyde, the estimated delivered dose would be comparable to 0.11 to 0.25 mg formaldehyde/cm^2. The lowest formaldehyde concentration that induced squamous cell carcinomas (22% of male rats; Monticello *et al.*, 1996) was 10 ppm, which was calculated to deliver a dose of 0.15 mg/cm^2 (Table 11). Exposure to formaldehyde resulted in a very steep dose-response curve for squamous cell carcinomas, which has been described as nonlinear, and no data are available for exposures below 10 ppm, which resulted in a significant increase in squamous cell carcinomas (Monticello *et al.*, 1996; Morgan, 1997). Nonetheless, because squamous cell carcinomas are relatively rare, it is anticipated that these would have been detected in the current study if they had occurred. Although survival of female rats was decreased at 750 ppb glutaraldehyde, and some male rats were removed from the study early, sufficient numbers of rats survived to assess the carcinogenic potential because squamous cell carcinomas were detected relatively early (after about 1 year) with formaldehyde (Swenberg *et al.*, 1980; Kerns *et al.*, 1983). The reduced survival indicates that the toxicity of glutaraldehyde precluded the use of greater exposure concentrations.

TABLE 12
Toxic Potency of Glutaraldehyde in Comparison to Formaldehyde in 2-Year Inhalation Studies with Male F344/N Rats

Response in Respiratory Epithelium	Delivered Dose (mg/cm^2)		Potency of Glutaraldehyde versus Formaldehyde
	Glutaraldehyde	Formaldehyde	
Hyperplasia NOAEL	0.012	0.08	7
Hyperplasia LOAEL	0.024	0.15	6
Squamous Metaplasia NOAEL	0.012	0.03	3
Squamous Metaplasia LOAEL	0.024	0.08	3

NOAEL=no-observable-adverse-effect level; LOAEL=lowest-observable-adverse-effect level

The increased incidences of leukemia reported in embalmers, anatomists, and pathologists (Walrath and Fraumeni, 1984; Stroup *et al.*, 1986; Consensus Workshop on Formaldehyde, 1994) suggest that certain aldehydes have the potential to cause leukemia. Although there were no increases in the incidences of mononuclear cell leukemia in the current studies, the exposure concentrations used resulted in doses lower than those that have been shown to cause leukemia in another study; in a drinking water study with glutaraldehyde, increased incidences of large granular cell lymphatic leukemia (mononuclear cell leukemia) were observed in female rats (0 ppm, 24%; 50 ppm, 41%; 250 ppm, 41%; 1,000 ppm, 52%) (Ballantyne, 1995; Van Miller *et al.*, 1995). In a drinking water study with formaldehyde, increased incidences of lymphoblastic leukemia and lymphosarcoma were observed at 50 ppm or greater in female Sprague-Dawley rats and at 100 ppm or greater in male Sprague-Dawley rats (Soffritti *et al.*, 1989). In the drinking water study with glutaraldehyde, average daily consumption for female rats was calculated as 3.6, 17, and 64 mg glutaraldehyde/kg body weight per day in the 50, 250, and 1,000 ppm groups, respectively (Ballantyne, 1995). In the present 2-year inhalation study, the inspired burden was calculated as 0.025, 0.049, and 0.074 mg/kg per day in the 250, 500, and 750 ppb groups, respectively, using a ventilation rate of 225 mL/minute, 6 hours per day, for a 300 g rat (Leong *et al.*, 1964; Lai, 1992; Morris *et al.*, 1996). These were much lower than the doses in the drinking water study.

CONCLUSIONS

Under the conditions of these 2-year inhalation studies, there was *no evidence of carcinogenic activity** of glutaraldehyde in male or female F344/N rats exposed to 250, 500, or 750 ppb. There was *no evidence of carcinogenic activity* in male or female $B6C3F_1$ mice exposed to 62.5, 125, or 250 ppb.

Incidences of nonneoplastic lesions of the nose were significantly increased in male and female rats and mice.

* Explanation of Levels of Evidence of Carcinogenic Activity is on page 8. A summary of the Technical Reports Review Subcommittee comments and the public discussion on this Technical Report appears on page 10.

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APPENDIX A
SUMMARY OF LESIONS IN MALE RATS IN THE 2-YEAR INHALATION STUDY OF GLUTARALDEHYDE

TABLE A1
Summary of the Incidence of Neoplasms in Male Rats in the 2-Year Inhalation Study of Glutaraldehyde[a]

	Chamber Control	250 ppb	500 ppb	750 ppb
Disposition Summary				
Animals initially in study	50	50	50	50
Early deaths				
Moribund	33	30	32	37
Natural deaths	5	6	9	7
Survivors				
Terminal sacrifice	11	14	9	6
Died last week of study	1			
Animals examined microscopically	50	50	50	50
Alimentary System				
Intestine large, colon	(49)	(48)	(48)	(45)
Carcinoma, metastatic, pancreas	1 (2%)			
Intestine large, cecum	(47)	(46)	(48)	(45)
Intestine small, jejunum	(47)	(46)	(43)	(44)
Carcinoma	1 (2%)			
Carcinoma, metastatic, pancreas	1 (2%)			
Liver	(50)	(50)	(50)	(50)
Hepatocellular carcinoma		1 (2%)		
Mesentery	(10)	(7)	(6)	(7)
Carcinoma, metastatic, pancreas	1 (10%)			
Oral mucosa			(1)	(1)
Squamous cell carcinoma			1 (100%)	
Pharyngeal, squamous cell papilloma				1 (100%)
Pancreas	(50)	(49)	(50)	(48)
Carcinoma	1 (2%)			
Stomach, forestomach	(49)	(49)	(50)	(48)
Squamous cell papilloma			1 (2%)	
Tongue	(1)	(2)		(1)
Squamous cell papilloma		1 (50%)		1 (100%)
Cardiovascular System				
Heart	(50)	(50)	(50)	(50)
Endocrine System				
Adrenal cortex	(50)	(50)	(50)	(49)
Adenoma			1 (2%)	
Adrenal medulla	(50)	(50)	(50)	(49)
Pheochromocytoma malignant	1 (2%)	2 (4%)	2 (4%)	1 (2%)
Pheochromocytoma complex	1 (2%)		1 (2%)	
Pheochromocytoma benign	2 (4%)	4 (8%)	6 (12%)	2 (4%)
Bilateral, pheochromocytoma malignant		1 (2%)		
Bilateral, pheochromocytoma benign	2 (4%)	1 (2%)		
Islets, pancreatic	(50)	(49)	(50)	(48)
Adenoma	1 (2%)	3 (6%)	1 (2%)	1 (2%)
Carcinoma	4 (8%)	1 (2%)	1 (2%)	1 (2%)
Pituitary gland	(50)	(49)	(50)	(50)
Pars distalis, adenoma	32 (64%)	26 (53%)	26 (52%)	20 (40%)
Pars intermedia, adenoma				1 (2%)
Thyroid gland	(50)	(50)	(50)	(50)
C-cell, adenoma	1 (2%)	4 (8%)	2 (4%)	2 (4%)
C-cell, carcinoma		1 (2%)		
Follicular cell, adenoma	1 (2%)			
Follicular cell, carcinoma	1 (2%)			

TABLE A1
Summary of the Incidence of Neoplasms in Male Rats in the 2-Year Inhalation Study of Glutaraldehyde

	Chamber Control	250 ppb	500 ppb	750 ppb
General Body System				
Tissue NOS	(1)	(2)		
Organ of Zuckerkandl, paraganglioma malignant		1 (50%)		
Genital System				
Epididymis	(50)	(50)	(50)	(50)
Carcinoma, metastatic, pancreas	1 (2%)			
Preputial gland	(50)	(50)	(50)	(50)
Adenoma	1 (2%)	2 (4%)		
Carcinoma		2 (4%)	1 (2%)	2 (4%)
Seminal vesicle	(50)	(50)	(50)	(49)
Carcinoma, metastatic, pancreas	1 (2%)			
Testes	(50)	(50)	(50)	(50)
Bilateral, interstitial cell, adenoma	26 (52%)	32 (64%)	27 (54%)	25 (50%)
Interstitial cell, adenoma	10 (20%)	12 (24%)	13 (26%)	6 (12%)
Hematopoietic System				
Bone marrow	(50)	(50)	(50)	(50)
Lymph node	(1)	(4)	(1)	(4)
Lymph node, bronchial	(39)	(42)	(40)	(42)
Lymph node, mandibular	(47)	(48)	(49)	(49)
Lymph node, mesenteric	(50)	(49)	(50)	(50)
Carcinoma, metastatic, pancreas	1 (2%)			
Lymph node, mediastinal	(47)	(50)	(50)	(50)
Spleen	(50)	(50)	(50)	(50)
Thymus	(50)	(50)	(50)	(50)
Integumentary System				
Mammary gland	(49)	(50)	(50)	(50)
Adenoma				1 (2%)
Carcinoma	1 (2%)	2 (4%)		
Fibroadenoma	1 (2%)	3 (6%)	2 (4%)	2 (4%)
Skin	(50)	(50)	(50)	(50)
Basal cell adenoma		1 (2%)		
Fibroma		2 (4%)		
Keratoacanthoma	1 (2%)	5 (10%)	2 (4%)	1 (2%)
Squamous cell carcinoma				1 (2%)
Squamous cell papilloma			1 (2%)	
Trichoepithelioma	1 (2%)			
Lip, basal cell adenoma			1 (2%)	
Pinna, squamous cell papilloma				1 (2%)
Sebaceous gland, adenoma	1 (2%)			
Sebaceous gland, carcinoma		1 (2%)		
Subcutaneous tissue, fibroma	4 (8%)	1 (2%)		1 (2%)
Subcutaneous tissue, fibrosarcoma		2 (4%)		
Subcutaneous tissue, lipoma			1 (2%)	
Subcutaneous tissue, sarcoma			1 (2%)	

TABLE A1
Summary of the Incidence of Neoplasms in Male Rats in the 2-Year Inhalation Study of Glutaraldehyde

	Chamber Control	250 ppb	500 ppb	750 ppb
Musculoskeletal System				
Bone	(50)	(50)	(50)	(50)
Mandible, osteosarcoma	1 (2%)			
Nervous System				
None				
Respiratory System				
Lung	(50)	(50)	(50)	(50)
Alveolar/bronchiolar adenoma		1 (2%)		2 (4%)
Alveolar/bronchiolar adenoma, multiple			1 (2%)	
Alveolar/bronchiolar carcinoma				1 (2%)
Carcinoma, metastatic, pancreas	1 (2%)			
Carcinoma, metastatic, skin		1 (2%)		
Fibrosarcoma, metastatic, skin		1 (2%)		
Osteosarcoma, metastatic, bone	1 (2%)			
Sarcoma stromal, metastatic, kidney			1 (2%)	
Special Senses System				
Zymbal's gland	(1)	(3)	(1)	
Adenoma		1 (33%)		
Carcinoma	1 (100%)	2 (67%)	1 (100%)	
Urinary System				
Kidney	(50)	(50)	(50)	(50)
Stromal nephroma			1 (2%)	
Renal tubule, adenoma		3 (6%)		1 (2%)
Renal tubule, carcinoma				1 (2%)
Urinary bladder	(50)	(49)	(50)	(48)
Papilloma			1 (2%)	
Systemic Lesions				
Multiple organs[b]	(50)	(50)	(50)	(50)
Leukemia mononuclear	21 (42%)	24 (48%)	25 (50%)	16 (32%)
Mesothelioma malignant	2 (4%)	1 (2%)		1 (2%)
Neoplasm Summary				
Total animals with primary neoplasms[c]	49	50	50	38
Total primary neoplasms	118	144	120	93
Total animals with benign neoplasms	48	48	50	38
Total benign neoplasms	84	103	86	68
Total animals with malignant neoplasms	28	33	31	19
Total malignant neoplasms	34	41	34	24
Total animals with metastatic neoplasms	3	2	1	1
Total metastatic neoplasms	10	2	1	3

[a] Number of animals examined microscopically at the site and the number of animals with neoplasm
[b] Number of animals with any tissue examined microscopically
[c] Primary neoplasms: all neoplasms except metastatic neoplasms

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Inhalation Study of Glutaraldehyde: Chamber Control

Number of Days on Study	1 1 7	3 9 2	4 5 2	4 9 5	4 9 8	5 0 2	5 1 4	5 4 3	5 4 4	5 5 5	5 5 6	5 8 0	5 8 3	5 8 3	6 0 1	6 0 2	6 0 2	6 1 2	6 1 2	6 1 7	6 3 7	6 3 7	6 3 8	6 5 2	6 5 2
Carcass ID Number	0 0 0 4	0 0 8	0 3 1	0 0 5	0 0 9	0 1 2	0 3 6	0 4 6	0 0 1	0 1 5	0 1 4	0 1 6	0 4 1	0 4 4	0 1 7	0 2 7	0 4 5	0 0 2	0 1 0	0 3 0	0 1 9	0 3 7	0 4 7	0 2 2	0 2 8
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, pancreas																									
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mesothelioma malignant, metastatic, mesentery																									
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma																									
Carcinoma, metastatic, pancreas																									
Intestine small, ileum	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mesentery													+				+								
Carcinoma, metastatic, pancreas																									
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma																									
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tongue																									
Tooth	+																								
Cardiovascular System																									
Blood vessel		+	+		+	+	+	+		+	+	+	+	+	+	+	+		+	+	+	+	+	+	+
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma malignant																									
Pheochromocytoma complex																									
Pheochromocytoma benign																									
Bilateral, pheochromocytoma benign																									
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Carcinoma																			X						
Parathyroid gland	+	+	M	+	+	M	+	M	+	+	M	+	+	+	+	+	+	M	+	+	+	+	+	+	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma		X	X		X	X	X		X		X	X	X		X	X	X	X	X	X			X	X	
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C-cell, adenoma																									
Follicular cell, adenoma																							X		
General Body System																									
Tissue NOS						+																			

+: Tissue examined microscopically
A: Autolysis precludes examination
M: Missing tissue
I: Insufficient tissue
X: Lesion present
Blank: Not examined

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Inhalation Study of Glutaraldehyde: Chamber Control

Number of Days on Study	652	657	676	689	689	694	994	702	002	008	008	117	117	229	229	229	229	229	229	229	229	229	229	229	229	
Carcass ID Number	03 2	05 0	04 2	02 4	02 5	02 9	03 9	01 3	04 0	03 3	00 6	01 8	04 8	04 7	04 1	04 0	04 1	04 2	04 3	04 6	03 3	03 4	03 5	03 8	04 3	04 4	Total Tissues/ Tumors
Alimentary System																											
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, colon	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Carcinoma, metastatic, pancreas						X																					1
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, cecum	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	47
Mesothelioma malignant, metastatic, mesentery			X																								1
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	49
Intestine small, jejunum	+	+	A	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Carcinoma																				X							1
Carcinoma, metastatic, pancreas						X																					1
Intestine small, ileum	+	+	A	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	46
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Mesentery		+	+			+		+			+			+	+					+							10
Carcinoma, metastatic, pancreas						X																					1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma						X																					1
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Tongue															+												1
Tooth																											1
Cardiovascular System																											
Blood vessel	+	+	+	+	+	+	+	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																											
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma malignant				X																							1
Pheochromocytoma complex																						X					1
Pheochromocytoma benign																			X		X						2
Bilateral, pheochromocytoma benign								X		X																	2
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma										X																	1
Carcinoma								X				X						X									4
Parathyroid gland	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	M	42
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pars distalis, adenoma	X	X	X				X		X	X			X	X		X	X	X		X			X	X	X		32
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
C-cell, adenoma																										X	1
Follicular cell, adenoma																											1
General Body System																											
Tissue NOS																											1

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Inhalation Study of Glutaraldehyde: Chamber Control

Number of Days on Study	1 1 7	3 9 2	4 5 2	4 9 5	4 9 8	5 0 2	5 1 4	5 4 3	5 4 4	5 5 5	5 5 6	5 8 0	5 8 3	5 8 3	6 0 1	6 0 2	6 0 2	6 1 2	6 1 2	6 1 7	6 3 7	6 3 7	6 3 8	6 5 2	6 5 2
Carcass ID Number	0 0 0 4	0 0 8	0 3 1	0 0 5	0 0 9	0 1 2	0 3 6	0 4 6	0 0 1	0 1 5	0 1 4	0 1 6	0 4 1	0 4 4	0 1 7	0 2 7	0 4 5	0 0 2	0 1 0	0 3 0	0 1 9	0 3 7	0 4 7	0 2 2	0 2 8
Genital System																									
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, pancreas																									
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, pancreas																									
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Bilateral, interstitial cell, adenoma				X				X				X		X								X	X		X
Interstitial cell, adenoma									X	X								X						X	
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node																				+					
Lymph node, bronchial	+	+	+	+	+	+	M	+	M	+	M	M	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	M	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, pancreas																									
Lymph node, mediastinal	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mesothelioma malignant, metastatic, mesentery																									
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	I	+	+	+	+	+	+	+
Carcinoma																									
Fibroadenoma																									
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Keratoacanthoma																									
Trichoepithelioma																									
Sebaceous gland, adenoma																				X					
Subcutaneous tissue, fibroma																							X		
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mandible, osteosarcoma														X											
Skeletal muscle							+																		
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Respiratory System																									
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, pancreas																									
Osteosarcoma, metastatic, bone														X											
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pleura		+																+							
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Inhalation Study of Glutaraldehyde: Chamber Control

Number of Days on Study	652	655	676	689	689	694	699	702	702	708	708	711	717	729	729	729	729	729	729	729	729	729	729	729	729	
Carcass ID Number	00332	00550	00442	00224	00225	00229	00339	00113	00140	00033	00066	00188	00448	00407	00111	00120	00121	00123	00126	00133	00134	00135	00138	00143	00149	Total Tissues/ Tumors
Genital System																										
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma, metastatic, pancreas						X																				1
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma																								X		1
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma, metastatic, pancreas						X																				1
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Bilateral, interstitial cell, adenoma			X	X	X	X	X	X	X				X	X	X		X	X	X	X	X	X	X	X	X	26
Interstitial cell, adenoma	X	X								X	X	X				X										10
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node																										1
Lymph node, bronchial	+	+	M	+	M	+	+	+	+	I	+	M	+	+	+	M	M	+	M	+	+	+	+	+	+	39
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma, metastatic, pancreas						X																				1
Lymph node, mediastinal	+	+	+	+	+	+	+	+	+	+	+	+	+	I	+	+	+	+	+	+	+	+	+	+	+	47
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Mesothelioma malignant, metastatic, mesentery			X																							1
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Carcinoma							X																			1
Fibroadenoma		X																								1
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Keratoacanthoma	X																									1
Trichoepithelioma	X																									1
Sebaceous gland, adenoma																										1
Subcutaneous tissue, fibroma				X		X												X								4
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Mandible, osteosarcoma																										1
Skeletal muscle																										1
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Respiratory System																										
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma, metastatic, pancreas						X																				1
Osteosarcoma, metastatic, bone																										1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pleura																										2
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Inhalation Study of Glutaraldehyde: Chamber Control

Number of Days on Study	1	3	4	4	4	5	5	5	5	5	5	5	5	5	6	6	6	6	6	6	6	6	6	6	6
	1	9	5	9	9	0	1	4	4	5	5	8	8	8	0	0	0	1	1	1	3	3	3	5	5
	7	2	2	5	8	2	4	3	4	5	6	0	3	3	1	2	2	2	2	7	7	7	8	2	2
Carcass ID Number	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	0	0	3	0	0	1	3	4	0	1	1	1	4	4	1	2	4	0	1	3	1	3	4	2	2
	4	8	1	5	9	2	6	6	1	5	4	6	1	4	7	7	5	2	0	0	9	7	7	2	8
Special Senses System																									
Eye																									
Zymbal's gland																								+	
Carcinoma																								X	
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear				X			X	X	X						X				X	X	X	X	X		X
Mesothelioma malignant																							X		

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Inhalation Study of Glutaraldehyde: Chamber Control

Number of Days on Study	652	655	676	689	689	694	699	702	702	708	708	711	717	729	729	729	729	729	729	729	729	729	729	729	729	
Carcass ID Number	00332	00550	00442	00224	00225	00229	00239	00313	00140	00403	00003	00006	00118	00448	00107	00111	00120	00121	00126	00133	00134	00135	00138	00143	00149	Total Tissues/ Tumors
Special Senses System																										
Eye						+																				1
Zymbal's gland																										1
Carcinoma																										1
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear	X			X			X		X	X							X	X		X			X	X		21
Mesothelioma malignant			X																							2

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Inhalation Study of Glutaraldehyde: 250 ppb

Number of Days on Study	3 5 6	4 4 9	4 9 5	5 3 3	5 5 0	5 6 9	5 7 7	5 7 9	6 0 7	6 1 3	6 1 5	6 1 7	6 2 1	6 2 5	6 3 2	6 3 4	6 3 8	6 4 7	6 5 2	6 5 4	6 6 6	6 6 6	6 7 1	6 7 5	6 8 9
Carcass ID Number	2 2 9	2 3 1	2 4 7	2 1 0	2 0 9	2 4 9	2 3 0	2 2 4	2 3 7	2 1 1	2 3 5	2 5 0	2 0 6	2 0 2	2 1 9	2 3 3	2 4 0	2 0 3	2 3 9	2 0 8	2 1 6	2 4 3	2 4 1	2 3 2	2 2 5
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	A	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	A	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	A	+	+	+	+	+	A	+	A	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	A	+	+	+	+	+	A	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	A	+	+	+	+	+	A	+	A	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	A	+	+	+	+	+	A	+	A	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular carcinoma																									
Mesentery					+						+														+
Pancreas	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tongue																							+		
Squamous cell papilloma																							X		
Cardiovascular System																									
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma malignant																									
Pheochromocytoma benign															X				X						
Bilateral, pheochromocytoma malignant								X																	
Bilateral, pheochromocytoma benign																									
Islets, pancreatic	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Carcinoma																									
Parathyroid gland	+	+	+	+	+	+	+	+	M	M	+	+	+	+	+	+	+	M	+	M	M	+	M	+	+
Pituitary gland	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma					X					X	X		X	X				X			X	X			X
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C-cell, adenoma											X														X
C-cell, carcinoma																									
Follicular cell, carcinoma																							X		
General Body System																									
Tissue NOS										+															
Organ of Zuckerkandl, paraganglioma, malignant																									

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Inhalation Study of Glutaraldehyde: 250 ppb

Number of Days on Study	6 9 4	6 9 4	6 9 4	7 0 8	7 0 8	7 0 8	7 1 2	7 1 2	7 1 2	7 1 6	7 2 4	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	
Carcass ID Number	2 1 8	2 3 8	2 4 5	2 0 7	2 2 8	2 4 2	2 1 4	2 2 0	2 4 8	2 1 7	2 0 1	2 0 4	2 0 5	2 1 2	2 1 3	2 1 5	2 2 1	2 2 2	2 2 3	2 2 6	2 2 7	2 3 4	2 3 6	2 4 4	2 4 6	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular carcinoma		X																								1
Mesentery								+		+								+			+					7
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Tongue																						+				2
Squamous cell papilloma																										1
Cardiovascular System																										
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma malignant								X							X											2
Pheochromocytoma benign										X					X											4
Bilateral, pheochromocytoma malignant																										1
Bilateral, pheochromocytoma benign																						X				1
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenoma												X								X					X	3
Carcinoma						X																				1
Parathyroid gland	+	+	M	M	+	M	+	+	+	+	+	+	M	M	+	+	+	+	+	+	+	+	M	+	+	38
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pars distalis, adenoma			X	X	X	X			X	X	X	X	X	X			X		X		X	X	X	X	X	26
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
C-cell, adenoma						X		X																		4
C-cell, carcinoma																				X						1
Follicular cell, carcinoma																										1
General Body System																										
Tissue NOS																+										2
Organ of Zuckerkandl, paraganglioma, malignant																X										1

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Inhalation Study of Glutaraldehyde: 250 ppb

Number of Days on Study	3 5 6	4 4 9	4 9 5	5 3 3	5 5 0	5 6 9	5 7 7	5 7 9	6 0 7	6 1 3	6 1 5	6 1 7	6 2 1	6 2 5	6 3 2	6 3 4	6 3 8	6 4 7	6 5 2	6 5 4	6 6 6	6 6 6	6 7 1	6 7 5	6 8 9
Carcass ID Number	2 2 9	2 3 1	2 4 7	2 1 0	2 0 9	2 4 9	2 3 0	2 2 4	2 3 7	2 1 1	2 3 5	2 5 0	2 0 6	2 0 2	2 1 9	2 3 3	2 4 0	2 0 3	2 3 9	2 0 8	2 1 6	2 4 3	2 4 1	2 3 2	2 2 5
Genital System																									
Coagulating gland																									
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma			X																						
Carcinoma												X													
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Bilateral, interstitial cell, adenoma					X		X	X	X			X			X	X	X		X	X		X	X	X	X
Interstitial cell, adenoma	X	X									X		X	X				X			X				
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node				+												+				+					
Lymph node, bronchial	+	+	+	+	+	+	+	+	M	+	+	M	+	M	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mediastinal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma																									
Fibroadenoma																									
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Basal cell adenoma																		X							
Fibroma					X																				
Keratoacanthoma																	X			X					
Sebaceous gland, carcinoma																									
Subcutaneous tissue, fibroma																							X		
Subcutaneous tissue, fibrosarcoma				X																					
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Respiratory System																									
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																									
Carcinoma, metastatic, skin																									
Fibrosarcoma, metastatic, skin																									
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Inhalation Study of Glutaraldehyde: 250 ppb

Number of Days on Study	6 9 4	6 9 4	6 9 4	7 0 8	7 0 8	7 0 8	7 1 2	7 1 2	7 1 2	7 1 6	7 2 4	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	
Carcass ID Number	2 1 8	2 3 8	2 4 5	2 0 7	2 2 8	2 4 2	2 1 4	2 2 0	2 4 8	2 1 7	2 0 1	2 0 4	2 0 5	2 1 2	2 1 3	2 1 5	2 2 1	2 2 2	2 2 3	2 2 6	2 2 7	2 3 4	2 3 6	2 4 4	2 4 6	Total Tissues/ Tumors
Genital System																										
Coagulating gland									+									+								2
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma																		X								2
Carcinoma									X																	2
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Bilateral, interstitial cell, adenoma	X	X			X				X		X	X		X	X	X	X	X	X	X	X	X	X	X	X	32
Interstitial cell, adenoma			X	X		X	X			X																12
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node						+																				4
Lymph node, bronchial	M	+	+	M	+	+	+	+	+	+	M	+	+	+	+	+	+	+	M	+	+	M	+	+	+	42
Lymph node, mandibular	+	+	+	M	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymph node, mediastinal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma				X																		X				2
Fibroadenoma								X										X						X		3
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Basal cell adenoma																										1
Fibroma													X													2
Keratoacanthoma						X							X							X						5
Sebaceous gland, carcinoma															X											1
Subcutaneous tissue, fibroma																										1
Subcutaneous tissue, fibrosarcoma																				X						2
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Respiratory System																										
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma																			X							1
Carcinoma, metastatic, skin															X											1
Fibrosarcoma, metastatic, skin																				X						1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Inhalation Study of Glutaraldehyde: 250 ppb

Number of Days on Study	3 5 6	4 4 9	4 9 5	5 3 3	5 5 0	5 6 9	5 7 7	5 7 9	6 0 7	6 1 3	6 1 5	6 1 7	6 2 1	6 2 5	6 3 2	6 3 4	6 3 8	6 4 7	6 5 2	6 5 4	6 6 6	6 6 6	6 6 1	6 7 5	6 7 9
Carcass ID Number	2 2 9	2 3 1	2 4 7	2 1 0	2 0 9	2 4 9	2 3 0	2 2 4	2 3 7	2 1 1	2 3 5	2 5 0	2 0 6	2 0 2	2 1 9	2 3 3	2 4 0	2 0 3	2 3 9	2 0 8	2 1 6	2 4 3	2 4 1	2 3 2	2 2 5
Special Senses System																									
Eye																									
Lacrimal gland						+																			
Zymbal's gland																			+					+	
Adenoma																								X	
Carcinoma																			X						
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Renal tubule, adenoma																								X	
Urinary bladder	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear		X	X	X		X	X		X			X		X	X	X	X			X			X		
Mesothelioma malignant																									

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Inhalation Study of Glutaraldehyde: 250 ppb

Number of Days on Study	6 9 4	6 9 4	6 9 4	7 0 8	7 0 8	7 0 8	7 1 2	7 1 2	7 1 2	7 1 6	7 2 4	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	
Carcass ID Number	2 1 8	2 3 8	2 4 5	2 0 7	2 2 8	2 4 2	2 1 4	2 2 0	2 4 8	2 1 7	2 0 1	2 0 4	2 0 5	2 1 2	2 1 3	2 1 5	2 2 1	2 2 2	2 2 3	2 2 6	2 2 7	2 3 4	2 3 6	2 4 4	2 4 6	Total Tissues/ Tumors
Special Senses System																										
Eye			+							+						+										3
Lacrimal gland																										1
Zymbal's gland																									+	3
Adenoma																										1
Carcinoma																									X	2
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Renal tubule, adenoma										X	X															3
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear	X		X		X	X	X	X		X									X			X	X	X		24
Mesothelioma malignant																				X						1

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Inhalation Study of Glutaraldehyde: 500 ppb

Number of Days on Study	3 6 5	3 9 3	4 8 1	5 1 2	5 2 4	5 2 5	5 2 6	5 2 6	5 3 3	5 6 1	5 8 1	5 8 7	5 9 3	6 0 8	6 0 9	6 1 2	6 1 7	6 1 7	6 3 2	6 3 8	6 4 5	6 5 2	6 5 2	6 5 4	6 5 6
Carcass ID Number	4 1 7	4 4 5	4 0 5	4 1 5	4 4 2	4 3 5	4 0 7	4 2 3	4 2 7	4 0 1	4 4 8	4 0 3	4 2 1	4 0 9	4 4 6	4 2 6	4 0 2	4 2 2	4 5 0	4 0 6	4 4 9	4 0 4	4 3 8	4 3 4	4 1 3
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	A	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	A	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	A	A	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	A
Intestine small, ileum	+	+	+	+	A	A	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	A
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mesentery									+				+						+						
Oral mucosa																									
Squamous cell carcinoma																									
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell papilloma						X																			
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cardiovascular System																									
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma malignant													X												
Pheochromocytoma complex																							X		
Pheochromocytoma benign																		X							
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Carcinoma																									
Parathyroid gland	+	+	+	+	+	M	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma		X	X	X		X	X			X		X		X	X	X	X	X			X	X	X		X
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C-cell, adenoma																				X					X
General Body System																									
None																									
Genital System																									
Coagulating gland																									
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma																									
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Bilateral, interstitial cell, adenoma	X				X			X	X		X	X	X							X	X	X	X	X	
Interstitial cell, adenoma						X				X					X	X			X						

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Inhalation Study of Glutaraldehyde: 500 ppb

Number of Days on Study	661	664	666	682	886	888	888	889	899	902	905	908	911	916	921	926	929	929	929	929	929	929	929	929	929	
Carcass ID Number	44414	44416	44419	44418	44420	44411	44417	44433	44433	44431	44514	44508	44530	44510	44528	44620	44612	44624	44625	44629	44632	44636	44637	44639	44641	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine small, jejunum	+	A	+	+	A	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	43
Intestine small, ileum	+	+	+	+	A	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	44
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Mesentery		+														+			+							6
Oral mucosa						+																				1
Squamous cell carcinoma						X																				1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Squamous cell papilloma																										1
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cardiovascular System																										
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma									X																	1
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma malignant						X																				2
Pheochromocytoma complex																										1
Pheochromocytoma benign							X			X	X		X								X					6
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma																X										1
Carcinoma										X																1
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	M	+	M	45
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pars distalis, adenoma	X				X	X		X	X	X		X								X		X		X		26
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
C-cell, adenoma																										2
General Body System																										
None																										
Genital System																										
Coagulating gland																					+					1
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma								X																		1
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Bilateral, interstitial cell, adenoma		X	X	X		X		X				X	X	X		X	X	X	X	X	X				X	27
Interstitial cell, adenoma					X		X		X	X	X											X	X	X		13

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Inhalation Study of Glutaraldehyde: 500 ppb

Number of Days on Study	3 6 5	3 9 3	4 8 1	5 1 2	5 2 4	5 2 5	5 2 6	5 2 6	5 3 3	5 6 1	5 8 1	5 8 7	5 9 3	6 0 8	6 0 9	6 1 2	6 1 7	6 1 7	6 3 2	6 3 8	6 4 5	6 5 2	6 5 2	6 5 4	6 5 6
Carcass ID Number	4 1 7	4 4 5	4 0 5	4 1 5	4 4 2	4 3 5	4 0 7	4 2 3	4 2 7	4 0 1	4 4 8	4 0 3	4 2 1	4 0 9	4 4 6	4 2 6	4 0 2	4 2 2	4 5 0	4 0 6	4 4 9	4 0 4	4 3 8	4 3 4	4 1 3
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node																								+	
Lymph node, bronchial	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	M	+
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mediastinal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibroadenoma																									
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Keratoacanthoma																									
Squamous cell papilloma																	X								
Lip, basal cell adenoma																									
Subcutaneous tissue, lipoma																									
Subcutaneous tissue, sarcoma																									
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Respiratory System																									
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma, multiple									X																
Sarcoma stromal, metastatic, kidney							X																		
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Eye			+																						
Zymbal's gland											+														
Carcinoma											X														
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stromal nephroma							X																		
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Papilloma																									
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear			X					X	X	X		X	X	X		X	X	X		X	X	X		X	

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Inhalation Study of Glutaraldehyde: 500 ppb

Number of Days on Study	6 6 1	6 6 4	6 6 6	6 8 2	6 8 6	6 8 8	6 8 8	6 8 9	6 8 9	7 0 2	7 0 5	7 0 8	7 1 1	7 1 6	7 2 1	7 2 6	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	
Carcass ID Number	4 4 4	4 1 6	4 1 9	4 1 8	4 4 0	4 1 1	4 4 7	4 3 3	4 4 3	4 3 1	4 1 4	4 0 8	4 3 0	4 1 0	4 2 8	4 2 0	4 1 2	4 2 4	4 2 5	4 2 9	4 3 2	4 3 6	4 3 7	4 3 9	4 4 1	Total Tissues/ Tumors
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node																										1
Lymph node, bronchial	+	+	+	M	+	M	+	M	+	+	+	+	+	+	M	+	M	+	M	+	+	+	M	+	+	40
Lymph node, mandibular	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node, mediastinal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Fibroadenoma															X			X								2
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Keratoacanthoma			X												X											2
Squamous cell papilloma																										1
Lip, basal cell adenoma																							X			1
Subcutaneous tissue, lipoma																							X			1
Subcutaneous tissue, sarcoma			X																							1
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Respiratory System																										
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma, multiple																										1
Sarcoma stromal, metastatic, kidney																										1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
Eye			+																						+	3
Zymbal's gland																										1
Carcinoma																										1
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stromal nephroma																										1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Papilloma																			X							1
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear		X		X			X	X			X			X	X	X	X			X			X			25

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Inhalation Study of Glutaraldehyde: 750 ppb

Number of Days on Study	0 2 3	0 9 9	1 0 0	1 0 5	1 0 6	1 0 6	1 0 6	1 0 7	1 1 1	1 6 2	2 9 3	3 4 9	4 6 8	4 7 4	4 9 2	5 0 2	5 0 8	5 6 1	5 6 4	5 8 6	5 8 9	5 8 9	5 9 3	6 0 3	6 0 8
Carcass ID Number	6 1 0	6 1 6	6 1 7	6 0 5	6 0 4	6 4 0	6 4 7	6 4 6	6 0 7	6 0 1	6 2 9	6 3 9	6 0 2	6 3 3	6 0 8	6 4 2	6 2 6	6 4 3	6 2 0	6 3 7	6 2 3	6 2 8	6 3 5	6 2 7	6 3 1
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	A	+	+	+	+	A	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	A	+	+	+	+	A	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	A	+	+	+	+	A	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	A	+	+	+	+	A	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	A	+	+	+	+	A	+	+	+	+	+	A	+	+	+	+	+	+	A	+	+	+
Mesothelioma malignant, metastatic, mesentery																									
Intestine small, ileum	+	+	+	A	+	+	+	+	A	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mesentery												+		+		+				+					
Oral mucosa																									
Pharyngeal, squamous cell papilloma																									
Pancreas	+	+	+	+	+	+	+	+	A	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+
Mesothelioma malignant, metastatic, mesentery																									
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	A	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	A	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tongue																									
Squamous cell papilloma																									
Tooth		+	+	+	+	+		+	+	+															
Cardiovascular System																									
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma malignant																									
Pheochromocytoma benign																									
Islets, pancreatic	+	+	+	+	+	+	+	+	A	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Carcinoma																									
Parathyroid gland	M	+	M	M	+	+	M	+	+	M	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma																X	X			X	X		X	X	
Pars intermedia, adenoma					X																				
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C-cell, adenoma																			X						
General Body System																									
None																									
Genital System																									
Coagulating gland									+																
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma																									
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Bilateral, interstitial cell, adenoma																	X	X	X			X	X		X
Interstitial cell, adenoma												X		X		X									

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Inhalation Study of Glutaraldehyde: 750 ppb

Number of Days on Study	620	625	634	638	638	646	652	666	673	683	689	708	708	708	712	716	718	720	721	729	729	729	729	729	729	
Carcass ID Number	649	614	634	615	625	621	632	641	613	630	609	603	638	645	606	624	650	644	622	611	612	618	619	636	648	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, colon	+	+	+	+	+	A	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Intestine large, rectum	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Intestine large, cecum	+	+	+	+	+	A	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Intestine small, duodenum	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Intestine small, jejunum	+	+	+	+	+	A	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
Mesothelioma malignant, metastatic, mesentery								X																		1
Intestine small, ileum	+	+	+	+	+	A	A	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Mesentery	+						+	+																		7
Oral mucosa																								+		1
Pharyngeal, squamous cell papilloma																								X		1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Mesothelioma malignant, metastatic, mesentery								X																		1
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Tongue																		+								1
Squamous cell papilloma																		X								1
Tooth																										8
Cardiovascular System																										
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pheochromocytoma malignant						X																				1
Pheochromocytoma benign									X								X									2
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Adenoma																				X						1
Carcinoma											X															1
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	M	+	+	+	M	+	+	+	+	+	41
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pars distalis, adenoma		X	X	X	X		X			X		X			X	X		X			X	X	X		X	20
Pars intermedia, adenoma																										1
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
C-cell, adenoma									X																	2
General Body System																										
None																										
Genital System																										
Coagulating gland																										1
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma	X											X														2
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Bilateral, interstitial cell, adenoma				X	X		X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	25
Interstitial cell, adenoma	X	X								X																6

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Inhalation Study of Glutaraldehyde: 750 ppb

Number of Days on Study	0 2 3	0 9 9	1 0 0	1 0 5	1 0 6	1 0 6	1 0 6	1 0 7	1 1 1	1 6 2	3 9 3	4 4 9	4 6 8	4 7 4	4 9 2	5 0 2	5 0 8	5 6 1	5 6 4	5 8 6	5 8 9	5 8 9	5 9 3	6 0 3	6 0 8
Carcass ID Number	6 1 0	6 1 6	6 1 7	6 0 5	6 0 4	6 4 0	6 4 7	6 4 6	6 0 7	6 0 1	6 2 9	6 3 9	6 0 2	6 3 3	6 0 8	6 4 2	6 2 6	6 4 3	6 2 0	6 3 7	6 2 3	6 2 8	6 3 5	6 2 7	6 3 1
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node																			+						+
Lymph node, bronchial	+	+	+	M	M	+	+	+	M	M	+	+	+	+	+	M	M	+	+	M	+	+	+	+	+
Lymph node, mandibular	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mediastinal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mesothelioma malignant, metastatic, mesentery																									
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Fibroadenoma																	X								
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Keratoacanthoma																X									
Squamous cell carcinoma																									
Pinna, squamous cell papilloma																									
Subcutaneous tissue, fibroma																									
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Respiratory System																									
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																						X			
Alveolar/bronchiolar carcinoma																									
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Ear									+																
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Renal tubule, adenoma																									
Renal tubule, carcinoma																									
Urinary bladder	+	+	+	+	+	+	+	+	A	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear												X							X			X			X
Mesothelioma malignant																									

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Inhalation Study of Glutaraldehyde: 750 ppb

Number of Days on Study	6 2 0	6 2 5	6 3 4	6 3 8	6 3 8	6 4 6	6 5 2	6 6 6	6 7 3	6 8 3	6 8 9	7 0 8	7 0 8	7 0 8	7 1 2	7 1 6	7 1 8	7 2 0	7 2 1	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	
Carcass ID Number	6 4 9	6 1 4	6 3 4	6 1 5	6 2 5	6 2 1	6 3 2	6 4 1	6 1 3	6 3 0	6 0 9	6 0 3	6 3 8	6 4 5	6 0 6	6 2 4	6 5 0	6 4 4	6 2 2	6 1 1	6 1 2	6 1 8	6 1 9	6 3 6	6 4 8	Total Tissues/ Tumors
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node	+																+									4
Lymph node, bronchial	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	42
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node, mediastinal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Mesothelioma malignant, metastatic, mesentery								X																		1
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma					X																					1
Fibroadenoma																					X					2
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Keratoacanthoma																										1
Squamous cell carcinoma						X																				1
Pinna, squamous cell papilloma																					X					1
Subcutaneous tissue, fibroma																							X			1
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Respiratory System																										
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma																					X					2
Alveolar/bronchiolar carcinoma																					X					1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
Ear																										1
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Renal tubule, adenoma																		X								1
Renal tubule, carcinoma							X																			1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear	X	X		X			X				X	X	X	X	X	X	X							X		16
Mesothelioma malignant								X																		1

TABLE A3
Statistical Analysis of Primary Neoplasms in Male Rats in the 2-Year Inhalation Study of Glutaraldehyde

	Chamber Control	250 ppb	500 ppb	750 ppb
Adrenal Medulla: Benign Pheochromocytoma				
Overall rate[a]	4/50 (8%)	5/50 (10%)	6/50 (12%)	2/49 (4%)
Adjusted rate[b]	11.4%	12.7%	16.5%	7.3%
Terminal rate[c]	2/12 (17%)	2/14 (14%)	1/9 (11%)	0/6 (0%)
First incidence (days)	702	632	617	673
Poly-3 test[d]	P=0.514N	P=0.571	P=0.386	P=0.456N
Adrenal Medulla: Malignant Pheochromocytoma				
Overall rate	1/50 (2%)	3/50 (6%)	2/50 (4%)	1/49 (2%)
Adjusted rate	2.8%	7.6%	5.5%	3.6%
Terminal rate	0/12 (0%)	1/14 (7%)	0/9 (0%)	0/6 (0%)
First incidence (days)	689	579	593	646
Poly-3 test	P=0.541	P=0.344	P=0.509	P=0.704
Adrenal Medulla: Benign, Complex, or Malignant Pheochromocytoma				
Overall rate	6/50 (12%)	7/50 (14%)	9/50 (18%)	3/49 (6%)
Adjusted rate	17.0%	17.5%	24.2%	10.8%
Terminal rate	3/12 (25%)	2/14 (14%)	1/9 (11%)	0/6 (0%)
First incidence (days)	689	579	593	646
Poly-3 test	P=0.503N	P=0.595	P=0.317	P=0.370N
Kidney (Renal Tubule): Adenoma				
Overall rate	0/50 (0%)	3/50 (6%)	0/50 (0%)	1/50 (2%)
Adjusted rate	0.0%	7.7%	0.0%	3.6%
Terminal rate	0/12 (0%)	0/14 (0%)	0/9 (0%)	0/6 (0%)
First incidence (days)	—[e]	675	—	720
Poly-3 test	P=0.559	P=0.137	—[f]	P=0.453
Kidney (Renal Tubule): Adenoma or Carcinoma				
Overall rate	0/50 (0%)	3/50 (6%)	0/50 (0%)	2/50 (4%)
Adjusted rate	0.0%	7.7%	0.0%	7.2%
Terminal rate	0/12 (0%)	0/14 (0%)	0/9 (0%)	0/6 (0%)
First incidence (days)	—	675	—	652
Poly-3 test	P=0.322	P=0.137	—	P=0.189
Mammary Gland: Fibroadenoma				
Overall rate	1/50 (2%)	3/50 (6%)	2/50 (4%)	2/50 (4%)
Adjusted rate	2.8%	7.7%	5.6%	7.1%
Terminal rate	0/12 (0%)	2/14 (14%)	1/9 (11%)	1/6 (17%)
First incidence (days)	657	712	721	508
Poly-3 test	P=0.354	P=0.338	P=0.502	P=0.422
Mammary Gland: Fibroadenoma or Adenoma				
Overall rate	1/50 (2%)	3/50 (6%)	2/50 (4%)	3/50 (6%)
Adjusted rate	2.8%	7.7%	5.6%	10.5%
Terminal rate	0/12 (0%)	2/14 (14%)	1/9 (11%)	1/6 (17%)
First incidence (days)	657	712	721	508
Poly-3 test	P=0.212	P=0.338	P=0.502	P=0.231

TABLE A3
Statistical Analysis of Primary Neoplasms in Male Rats in the 2-Year Inhalation Study of Glutaraldehyde

	Chamber Control	250 ppb	500 ppb	750 ppb
Mammary Gland: Fibroadenoma, Adenoma, or Carcinoma				
Overall rate	2/50 (4%)	5/50 (10%)	2/50 (4%)	3/50 (6%)
Adjusted rate	5.6%	12.9%	5.6%	10.5%
Terminal rate	0/12 (0%)	3/14 (21%)	1/9 (11%)	1/6 (17%)
First incidence (days)	657	708	721	508
Poly-3 test	P=0.464	P=0.252	P=0.695N	P=0.401
Pancreatic Islets: Adenoma				
Overall rate	1/50 (2%)	3/49 (6%)	1/50 (2%)	1/48 (2%)
Adjusted rate	2.8%	7.8%	2.8%	3.7%
Terminal rate	0/12 (0%)	3/14 (21%)	0/9 (0%)	1/6 (17%)
First incidence (days)	708	729 (T)	726	729 (T)
Poly-3 test	P=0.519N	P=0.338	P=0.759N	P=0.702
Pancreatic Islets: Carcinoma				
Overall rate	4/50 (8%)	1/49 (2%)	1/50 (2%)	1/48 (2%)
Adjusted rate	11.2%	2.6%	2.8%	3.7%
Terminal rate	1/12 (8%)	0/14 (0%)	0/9 (0%)	0/6 (0%)
First incidence (days)	612	708	702	689
Poly-3 test	P=0.116N	P=0.152N	P=0.175N	P=0.265N
Pancreatic Islets: Adenoma or Carcinoma				
Overall rate	5/50 (10%)	4/49 (8%)	2/50 (4%)	2/48 (4%)
Adjusted rate	14.0%	10.3%	5.6%	7.3%
Terminal rate	1/12 (8%)	3/14 (21%)	0/9 (0%)	1/6 (17%)
First incidence (days)	612	708	702	689
Poly-3 test	P=0.158N	P=0.449N	P=0.212N	P=0.333N
Pituitary Gland (Pars Distalis): Adenoma				
Overall rate	32/50 (64%)	26/49 (53%)	26/50 (52%)	20/50 (40%)
Adjusted rate	71.0%	62.2%	58.8%	61.0%
Terminal rate	8/12 (67%)	10/14 (71%)	3/9 (33%)	4/6 (67%)
First incidence (days)	392	550	393	502
Poly-3 test	P=0.136N	P=0.246N	P=0.149N	P=0.237N
Preputial Gland: Adenoma or Carcinoma				
Overall rate	1/50 (2%)	4/50 (8%)	1/50 (2%)	2/50 (4%)
Adjusted rate	2.9%	10.0%	2.8%	7.1%
Terminal rate	1/12 (8%)	1/14 (7%)	0/9 (0%)	0/6 (0%)
First incidence (days)	729 (T)	495	689	620
Poly-3 test	P=0.502	P=0.218	P=0.758N	P=0.422
Skin: Keratoacanthoma				
Overall rate	1/50 (2%)	5/50 (10%)	2/50 (4%)	1/50 (2%)
Adjusted rate	2.8%	12.7%	5.6%	3.5%
Terminal rate	0/12 (0%)	2/14 (14%)	0/9 (0%)	0/6 (0%)
First incidence (days)	652	638	666	502
Poly-3 test	P=0.502N	P=0.126	P=0.505	P=0.709

TABLE A3
Statistical Analysis of Primary Neoplasms in Male Rats in the 2-Year Inhalation Study of Glutaraldehyde

	Chamber Control	250 ppb	500 ppb	750 ppb
Skin: Squamous Cell Papilloma or Keratoacanthoma				
Overall rate	1/50 (2%)	5/50 (10%)	3/50 (6%)	2/50 (4%)
Adjusted rate	2.8%	12.7%	8.3%	7.1%
Terminal rate	0/12 (0%)	2/14 (14%)	0/9 (0%)	1/6 (17%)
First incidence (days)	652	638	617	502
Poly-3 test	P=0.384	P=0.126	P=0.312	P=0.422
Skin: Squamous Cell Papilloma, Keratoacanthoma, or Squamous Cell Carcinoma				
Overall rate	1/50 (2%)	5/50 (10%)	3/50 (6%)	3/50 (6%)
Adjusted rate	2.8%	12.7%	8.3%	10.5%
Terminal rate	0/12 (0%)	2/14 (14%)	0/9 (0%)	1/6 (17%)
First incidence (days)	652	638	617	502
Poly-3 test	P=0.252	P=0.126	P=0.312	P=0.231
Skin: Squamous Cell Papilloma, Keratoacanthoma, Trichoepithelioma, Basal Cell Adenoma, or Squamous Cell Carcinoma				
Overall rate	1/50 (2%)	6/50 (12%)	4/50 (8%)	3/50 (6%)
Adjusted rate	2.8%	15.1%	11.1%	10.5%
Terminal rate	0/12 (0%)	2/14 (14%)	1/9 (11%)	1/6 (17%)
First incidence (days)	652	638	617	502
Poly-3 test	P=0.240	P=0.074	P=0.183	P=0.231
Skin (Subcutaneous Tissue): Fibroma				
Overall rate	4/50 (8%)	3/50 (6%)	0/50 (0%)	1/50 (2%)
Adjusted rate	11.2%	7.6%	0.0%	3.6%
Terminal rate	1/12 (8%)	1/14 (7%)	0/9 (0%)	1/6 (17%)
First incidence (days)	638	550	—	729 (T)
Poly-3 test	P=0.051N	P=0.444N	P=0.059N	P=0.264N
Skin (Subcutaneous Tissue): Fibroma, Fibrosarcoma, or Sarcoma				
Overall rate	4/50 (8%)	5/50 (10%)	1/50 (2%)	1/50 (2%)
Adjusted rate	11.2%	12.5%	2.8%	3.6%
Terminal rate	1/12 (8%)	2/14 (14%)	0/9 (0%)	1/6 (17%)
First incidence (days)	638	533	666	729 (T)
Poly-3 test	P=0.079N	P=0.574	P=0.174N	P=0.264N
Testes: Adenoma				
Overall rate	36/50 (72%)	44/50 (88%)	40/50 (80%)	31/50 (62%)
Adjusted rate	85.9%	92.2%	88.1%	87.4%
Terminal rate	12/12 (100%)	13/14 (93%)	9/9 (100%)	6/6 (100%)
First incidence (days)	495	356	365	449
Poly-3 test	P=0.553	P=0.219	P=0.507	P=0.571
Thyroid Gland (C-Cell): Adenoma				
Overall rate	1/50 (2%)	4/50 (8%)	2/50 (4%)	2/50 (4%)
Adjusted rate	2.9%	10.2%	5.5%	7.1%
Terminal rate	1/12 (8%)	0/14 (0%)	0/9 (0%)	0/6 (0%)
First incidence (days)	729 (T)	615	638	564
Poly-3 test	P=0.419	P=0.214	P=0.511	P=0.426

TABLE A3
Statistical Analysis of Primary Neoplasms in Male Rats in the 2-Year Inhalation Study of Glutaraldehyde

	Chamber Control	250 ppb	500 ppb	750 ppb
Thyroid Gland (C-Cell): Adenoma or Carcinoma				
Overall rate	1/50 (2%)	5/50 (10%)	2/50 (4%)	2/50 (4%)
Adjusted rate	2.9%	12.7%	5.5%	7.1%
Terminal rate	1/12 (8%)	1/14 (7%)	0/9 (0%)	0/6 (0%)
First incidence (days)	729 (T)	615	638	564
Poly-3 test	P=0.471	P=0.128	P=0.511	P=0.426
Zymbal's Gland: Adenoma or Carcinoma				
Overall rate	1/50 (2%)	3/50 (6%)	1/50 (2%)	0/50 (0%)
Adjusted rate	2.8%	7.7%	2.8%	0.0%
Terminal rate	0/12 (0%)	1/14 (7%)	0/9 (0%)	0/6 (0%)
First incidence (days)	652	652	581	—
Poly-3 test	P=0.296N	P=0.342	P=0.757N	P=0.549N
All Organs: Mononuclear Cell Leukemia				
Overall rate	21/50 (42%)	24/50 (48%)	25/50 (50%)	16/50 (32%)
Adjusted rate	51.4%	53.2%	58.6%	50.5%
Terminal rate	5/12 (42%)	4/14 (29%)	3/9 (33%)	1/6 (17%)
First incidence (days)	495	449	481	449
Poly-3 test	P=0.439	P=0.522	P=0.324	P=0.566N
All Organs: Benign Neoplasms				
Overall rate	48/50 (96%)	48/50 (96%)	50/50 (100%)	38/50 (76%)
Adjusted rate	98.6%	98.2%	100.0%	97.9%
Terminal rate	12/12 (100%)	14/14 (100%)	9/9 (100%)	6/6 (100%)
First incidence (days)	392	356	365	106
Poly-3 test	P=0.625	P=0.811N	P=0.684	P=0.809N
All Organs: Malignant Neoplasms				
Overall rate	28/50 (56%)	33/50 (66%)	31/50 (62%)	19/50 (38%)
Adjusted rate	66.5%	71.1%	69.5%	59.0%
Terminal rate	6/12 (50%)	7/14 (50%)	3/9 (33%)	2/6 (33%)
First incidence (days)	495	449	481	449
Poly-3 test	P=0.338N	P=0.401	P=0.471	P=0.328N
All Organs: Benign or Malignant Neoplasms				
Overall rate	49/50 (98%)	50/50 (100%)	50/50 (100%)	38/50 (76%)
Adjusted rate	100.0%	100.0%	100.0%	97.9%
Terminal rate	12/12 (100%)	14/14 (100%)	9/9 (100%)	6/6 (100%)
First incidence (days)	392	356	365	106
Poly-3 test	P=0.115N	P=1.000	P=1.000	P=0.603N

(T)Terminal sacrifice
[a] Number of neoplasm-bearing animals/number of animals examined. Denominator is number of animals examined microscopically for adrenal gland, kidney, pancreatic islets, pituitary gland, preputial gland, testis, and thyroid gland; for other tissues, denominator is number of animals necropsied.
[b] Poly-3 estimated neoplasm incidence after adjustment for intercurrent mortality
[c] Observed incidence at terminal kill
[d] Beneath the chamber control incidence are the P values associated with the trend test. Beneath the exposed group incidence are the P values corresponding to pairwise comparisons between the chamber controls and that exposed group. The Poly-3 test accounts for differential mortality in animals that do not reach terminal sacrifice. A negative trend or a lower incidence in an exposure group is indicated by **N**.
[e] Not applicable; no neoplasms in animal group
[f] Value of statistic cannot be computed.

TABLE A4
Historical Incidence of Alveolar/bronchiolar Neoplasms in Chamber Control Male F344/N Rats[a]

Study	Incidence in Controls	
	Adenoma	Carcinoma
Historical Incidence at Battelle Pacific Northwest Laboratories		
Acetonitrile	1/48	1/48
Chloroprene	2/50	0/50
Cobalt sulfate heptahydrate	1/50	0/50
Furfuryl alcohol	0/50	0/50
Hexachlorocyclopentadiene	5/50	0/50
Isobutene	2/50	0/50
Isobutyraldehyde	1/50	0/50
Isoprene	0/49	1/49
Molybdenum trioxide	0/50	0/50
Nitromethane	1/50	0/50
Ozone	1/50	1/50
Tetrafluoroethylene	0/50	0/50
Tetrahydrofuran	0/50	0/50
Overall Historical Incidence		
Total (%)	16/904 (1.8%)	6/904 (0.7%)
Mean ± standard deviation	1.8% ± 2.6%	0.7% ± 1.0%
Range	0%-10%	0%-2%

[a] Data as of 12 November 1997

TABLE A5
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 2-Year Inhalation Study of Glutaraldehyde[a]

	Chamber Control	250 ppb	500 ppb	750 ppb
Disposition Summary				
Animals initially in study	50	50	50	50
Early deaths				
Moribund	33	30	32	37
Natural deaths	5	6	9	7
Survivors				
Terminal sacrifice	11	14	9	6
Died last week of study	1			
Animals examined microscopically	50	50	50	50
Alimentary System				
Esophagus	(50)	(50)	(50)	(50)
Foreign body	1 (2%)			
Ulcer	1 (2%)			
Intestine large, colon	(49)	(48)	(48)	(45)
Mineralization			1 (2%)	
Parasite metazoan	2 (4%)	3 (6%)		
Muscularis, mineralization	1 (2%)			
Intestine large, rectum	(50)	(48)	(49)	(46)
Diverticulum				1 (2%)
Parasite metazoan		4 (8%)	2 (4%)	3 (7%)
Intestine large, cecum	(47)	(46)	(48)	(45)
Parasite metazoan	3 (6%)	1 (2%)	9 (19%)	2 (4%)
Intestine small, jejunum	(47)	(46)	(43)	(44)
Necrosis				1 (2%)
Intestine small, ileum	(46)	(46)	(44)	(44)
Inflammation, focal, suppurative	1 (2%)			
Liver	(50)	(50)	(50)	(50)
Angiectasis	2 (4%)	2 (4%)	1 (2%)	3 (6%)
Basophilic focus	1 (2%)	1 (2%)		
Clear cell focus		4 (8%)	1 (2%)	1 (2%)
Clear cell focus, multiple			2 (4%)	
Hepatodiaphragmatic nodule	1 (2%)	2 (4%)		
Inflammation, suppurative	1 (2%)			
Necrosis	1 (2%)	2 (4%)	1 (2%)	
Thrombosis	1 (2%)			
Vacuolization cytoplasmic	7 (14%)	1 (2%)	2 (4%)	1 (2%)
Bile duct, hyperplasia	3 (6%)			2 (4%)
Hepatocyte, degeneration, focal	3 (6%)			1 (2%)
Hepatocyte, hyperplasia	1 (2%)			
Mesentery	(10)	(7)	(6)	(7)
Hemorrhage			1 (17%)	
Thrombosis			1 (17%)	
Fat, necrosis	8 (80%)	6 (86%)	5 (83%)	6 (86%)
Pancreas	(50)	(49)	(50)	(48)
Angiectasis	1 (2%)			
Hemorrhage	1 (2%)			
Acinus, atrophy	9 (18%)	3 (6%)	2 (4%)	5 (10%)
Stomach, forestomach	(49)	(49)	(50)	(48)
Hemorrhage				1 (2%)
Inflammation, suppurative	8 (16%)	3 (6%)	3 (6%)	5 (10%)
Mineralization	4 (8%)	1 (2%)	1 (2%)	
Ulcer	5 (10%)	7 (14%)	4 (8%)	2 (4%)
Epithelium, hyperplasia	11 (22%)	2 (4%)	2 (4%)	4 (8%)

[a] Number of animals examined microscopically at the site and the number of animals with lesion

TABLE A5
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 2-Year Inhalation Study of Glutaraldehyde

	Chamber Control	250 ppb	500 ppb	750 ppb
Alimentary System (continued)				
Stomach, glandular	(49)	(49)	(50)	(48)
Erosion	1 (2%)		1 (2%)	2 (4%)
Inflammation, suppurative		1 (2%)	1 (2%)	
Ulcer		2 (4%)		
Epithelium, mineralization	9 (18%)	5 (10%)	3 (6%)	4 (8%)
Epithelium, necrosis			1 (2%)	
Tongue	(1)	(2)		(1)
Hyperkeratosis		1 (50%)		
Tooth	(1)			(8)
Degeneration	1 (100%)			8 (100%)
Inflammation				1 (13%)
Cardiovascular System				
Blood vessel	(45)	(50)	(50)	(50)
Inflammation	1 (2%)	2 (4%)		
Mineralization	7 (16%)	3 (6%)	1 (2%)	4 (8%)
Heart	(50)	(50)	(50)	(50)
Mineralization	6 (12%)	2 (4%)	1 (2%)	4 (8%)
Atrium, thrombosis	3 (6%)	2 (4%)	1 (2%)	
Myocardium, fibrosis	12 (24%)	10 (20%)	8 (16%)	7 (14%)
Myocardium, ventricle, hypertrophy			1 (2%)	
Valve, thrombosis	1 (2%)			
Endocrine System				
Adrenal cortex	(50)	(50)	(50)	(49)
Accessory adrenal cortical nodule			1 (2%)	
Hemorrhage	1 (2%)			1 (2%)
Hyperplasia				1 (2%)
Vacuolization cytoplasmic	9 (18%)	6 (12%)	8 (16%)	2 (4%)
Adrenal medulla	(50)	(50)	(50)	(49)
Hyperplasia	12 (24%)	9 (18%)	6 (12%)	2 (4%)
Bilateral, hyperplasia	1 (2%)			
Islets, pancreatic	(50)	(49)	(50)	(48)
Hyperplasia	1 (2%)		1 (2%)	
Parathyroid gland	(42)	(38)	(45)	(41)
Hyperplasia	7 (17%)	7 (18%)	1 (2%)	3 (7%)
Pituitary gland	(50)	(49)	(50)	(50)
Cyst	2 (4%)	2 (4%)	1 (2%)	1 (2%)
Hemorrhage	1 (2%)		3 (6%)	3 (6%)
Pars distalis, hyperplasia	6 (12%)	5 (10%)	4 (8%)	1 (2%)
Thyroid gland	(50)	(50)	(50)	(50)
C-cell, hyperplasia	6 (12%)	2 (4%)	8 (16%)	5 (10%)
Follicular cell, hyperplasia			1 (2%)	
General Body System				
None				
Genital System				
Epididymis	(50)	(50)	(50)	(50)
Inflammation		1 (2%)		
Spermatocele	1 (2%)			

TABLE A5
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 2-Year Inhalation Study of Glutaraldehyde

	Chamber Control	250 ppb	500 ppb	750 ppb
Genital System (continued)				
Preputial gland	(50)	(50)	(50)	(50)
Cyst			1 (2%)	
Hyperplasia		1 (2%)	2 (4%)	
Inflammation, suppurative	5 (10%)	2 (4%)	3 (6%)	1 (2%)
Prostate	(50)	(50)	(50)	(50)
Hyperplasia		1 (2%)	2 (4%)	
Inflammation	9 (18%)	4 (8%)	5 (10%)	3 (6%)
Seminal vesicle	(50)	(50)	(50)	(49)
Inflammation, chronic				1 (2%)
Inflammation, suppurative	3 (6%)	1 (2%)		
Testes	(50)	(50)	(50)	(50)
Arteriole, inflammation	1 (2%)			
Bilateral, interstitial cell, hyperplasia	4 (8%)		1 (2%)	4 (8%)
Germinal epithelium, atrophy	12 (24%)	9 (18%)	13 (26%)	6 (12%)
Hematopoietic System				
Bone marrow	(50)	(50)	(50)	(50)
Fibrosis	7 (14%)	5 (10%)	2 (4%)	3 (6%)
Lymph node, bronchial	(39)	(42)	(40)	(42)
Fibrosis	1 (3%)	1 (2%)		
Lymph node, mandibular	(47)	(48)	(49)	(49)
Hyperplasia			1 (2%)	
Lymph node, mediastinal	(47)	(50)	(50)	(50)
Hemorrhage	1 (2%)			
Spleen	(50)	(50)	(50)	(50)
Accessory spleen				1 (2%)
Fibrosis	15 (30%)	15 (30%)	16 (32%)	9 (18%)
Hematopoietic cell proliferation		1 (2%)		
Hemorrhage		1 (2%)	1 (2%)	
Infarct		3 (6%)		
Integumentary System				
Mammary gland	(49)	(50)	(50)	(50)
Galactocele	2 (4%)	1 (2%)	5 (10%)	
Skin	(50)	(50)	(50)	(50)
Cyst epithelial inclusion	2 (4%)	2 (4%)		
Hyperkeratosis				1 (2%)
Hyperplasia	1 (2%)			1 (2%)
Ulcer		1 (2%)		1 (2%)
Musculoskeletal System				
Bone	(50)	(50)	(50)	(50)
Tibia, fracture	1 (2%)			
Nervous System				
Brain	(50)	(50)	(50)	(50)
Hemorrhage	3 (6%)	4 (8%)	10 (20%)	1 (2%)
Hydrocephalus	5 (10%)	7 (14%)	10 (20%)	5 (10%)
Mineralization			1 (2%)	

TABLE A5
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 2-Year Inhalation Study of Glutaraldehyde

	Chamber Control	250 ppb	500 ppb	750 ppb
Respiratory System				
Larynx	(50)	(50)	(50)	(50)
Foreign body	1 (2%)	2 (4%)	3 (6%)	2 (4%)
Epiglottis, inflammation, suppurative	1 (2%)			1 (2%)
Glands, inflammation	28 (56%)	18 (36%)	18 (36%)	26 (52%)
Squamous epithelium, hyperplasia	1 (2%)		1 (2%)	1 (2%)
Lung	(50)	(50)	(50)	(50)
Inflammation				1 (2%)
Mineralization			1 (2%)	
Alveolar epithelium, hyperplasia	9 (18%)	3 (6%)	5 (10%)	4 (8%)
Alveolus, emphysema	1 (2%)			
Alveolus, hemorrhage	3 (6%)	2 (4%)	1 (2%)	1 (2%)
Alveolus, infiltration cellular, histiocyte	23 (46%)	15 (30%)	14 (28%)	11 (22%)
Alveolus, inflammation, suppurative		2 (4%)		2 (4%)
Alveolus, metaplasia, osseous		1 (2%)	1 (2%)	
Alveolus, mineralization	4 (8%)	3 (6%)	1 (2%)	4 (8%)
Bronchiole, foreign body				1 (2%)
Bronchiole, hyperplasia			1 (2%)	
Bronchiole, inflammation, suppurative			1 (2%)	
Interstitium, fibrosis	8 (16%)	14 (28%)	17 (34%)	7 (14%)
Nose	(50)	(50)	(50)	(50)
Foreign body	2 (4%)	2 (4%)	1 (2%)	
Goblet cell, respiratory epithelium, hyperplasia	1 (2%)		6 (12%)	6 (12%)
Nasolacrimal duct, inflammation		3 (6%)		
Olfactory epithelium, atrophy				4 (8%)
Olfactory epithelium, degeneration, hyaline	4 (8%)	8 (16%)	9 (18%)	14 (28%)
Olfactory epithelium, foreign body	1 (2%)		1 (2%)	
Olfactory epithelium, hyperplasia		1 (2%)		
Olfactory epithelium, inflammation	1 (2%)	1 (2%)	1 (2%)	
Respiratory epithelium, hyperplasia	6 (12%)	5 (10%)	17 (34%)	35 (70%)
Respiratory epithelium, inflammation	17 (34%)	10 (20%)	25 (50%)	43 (86%)
Respiratory epithelium, metaplasia, squamous	1 (2%)	2 (4%)	11 (22%)	24 (48%)
Squamous epithelium, foreign body	1 (2%)			
Squamous epithelium, hyperplasia	3 (6%)	11 (22%)	39 (78%)	48 (96%)
Squamous epithelium, inflammation	6 (12%)	17 (34%)	41 (82%)	49 (98%)
Pleura	(2)			
Inflammation, suppurative	1 (50%)			
Trachea	(50)	(50)	(50)	(50)
Mineralization		1 (2%)		
Special Senses System				
Eye	(1)	(3)	(3)	
Cataract	1 (100%)	3 (100%)	2 (67%)	
Inflammation, suppurative			1 (33%)	

TABLE A5
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 2-Year Inhalation Study of Glutaraldehyde

	Chamber Control	250 ppb	500 ppb	750 ppb
Urinary System				
Kidney	(50)	(50)	(50)	(50)
Cyst		2 (4%)	1 (2%)	2 (4%)
Infarct		1 (2%)		
Mineralization	3 (6%)	1 (2%)		
Nephropathy, chronic	43 (86%)	48 (96%)	48 (96%)	38 (76%)
Papilla, transitional epithelium, hyperplasia	1 (2%)	1 (2%)		
Pelvis, dilatation	1 (2%)			
Pelvis, inflammation, suppurative	1 (2%)			
Renal tubule, atrophy	1 (2%)			
Renal tubule, atypia cellular	1 (2%)			
Renal tubule, regeneration	1 (2%)			
Urinary bladder	(50)	(49)	(50)	(48)
Inflammation, suppurative	1 (2%)			
Transitional epithelium, hyperplasia	2 (4%)		1 (2%)	

APPENDIX B
SUMMARY OF LESIONS IN FEMALE RATS IN THE 2-YEAR INHALATION STUDY OF GLUTARALDEHYDE

TABLE B1
Summary of the Incidence of Neoplasms in Female Rats in the 2-Year Inhalation Study of Glutaraldehyde[a]

	Chamber Control	250 ppb	500 ppb	750 ppb
Disposition Summary				
Animals initially in study	50	50	50	50
Early deaths				
Moribund	22	17	32	34
Natural deaths	2	2	3	2
Survivors				
Terminal sacrifice	26	31	15	14
Animals examined microscopically	50	50	50	50
Alimentary System				
Esophagus	(50)	(50)	(50)	(49)
Liver	(50)	(50)	(50)	(50)
Rhabdomyosarcoma, metastatic, skeletal muscle			1 (2%)	
Mesentery	(10)	(9)	(7)	(3)
Sarcoma	2 (20%)			
Oral mucosa	(1)			(1)
Gingival, squamous cell carcinoma	1 (100%)			
Lingual, squamous cell carcinoma				1 (100%)
Pancreas	(50)	(50)	(50)	(50)
Stomach, glandular	(49)	(49)	(50)	(50)
Tongue	(1)	(1)		
Squamous cell papilloma	1 (100%)			
Cardiovascular System				
Heart	(50)	(50)	(50)	(50)
Endocrine System				
Adrenal cortex	(50)	(50)	(50)	(49)
Adrenal medulla	(50)	(50)	(50)	(49)
Pheochromocytoma malignant		1 (2%)		1 (2%)
Pheochromocytoma benign			1 (2%)	
Islets, pancreatic	(49)	(50)	(50)	(50)
Adenoma		1 (2%)		
Carcinoma			1 (2%)	
Pituitary gland	(50)	(50)	(50)	(49)
Pars distalis, adenoma	37 (74%)	37 (74%)	27 (54%)	24 (49%)
Thyroid gland	(50)	(50)	(49)	(49)
C-cell, adenoma	2 (4%)	1 (2%)	2 (4%)	
C-cell, carcinoma		2 (4%)		
Follicular cell, adenoma				2 (4%)
General Body System				
None				

TABLE B1
Summary of the Incidence of Neoplasms in Female Rats in the 2-Year Inhalation Study of Glutaraldehyde

	Chamber Control	250 ppb	500 ppb	750 ppb
Genital System				
Clitoral gland	(49)	(50)	(50)	(50)
Adenoma	3 (6%)	3 (6%)	1 (2%)	
Carcinoma	3 (6%)	2 (4%)	1 (2%)	1 (2%)
Ovary	(50)	(50)	(50)	(49)
Granulosa cell tumor malignant				1 (2%)
Granulosa-theca tumor malignant	1 (2%)		1 (2%)	
Uterus	(50)	(50)	(50)	(50)
Deciduoma benign			1 (2%)	
Polyp stromal	8 (16%)	10 (20%)	8 (16%)	3 (6%)
Sarcoma stromal			1 (2%)	
Serosa, leiomyoma				1 (2%)
Hematopoietic System				
Bone marrow	(50)	(50)	(50)	(50)
Lymph node	(2)	(3)	(3)	(2)
Iliac, sarcoma, metastatic, skin	1 (50%)			
Lymph node, bronchial	(46)	(46)	(48)	(42)
Sarcoma, metastatic, skin	1 (2%)			
Lymph node, mandibular	(48)	(49)	(48)	(46)
Lymph node, mesenteric	(50)	(50)	(50)	(50)
Lymph node, mediastinal	(50)	(50)	(50)	(49)
Sarcoma, metastatic, skin	1 (2%)			
Spleen	(50)	(50)	(50)	(50)
Thymus	(50)	(50)	(50)	(49)
Integumentary System				
Mammary gland	(50)	(50)	(50)	(50)
Carcinoma	5 (10%)	8 (16%)	3 (6%)	1 (2%)
Fibroadenoma	15 (30%)	18 (36%)	15 (30%)	9 (18%)
Fibroadenoma, multiple	9 (18%)	5 (10%)	3 (6%)	1 (2%)
Skin	(50)	(50)	(50)	(50)
Fibroma			1 (2%)	
Fibrosarcoma	1 (2%)			
Keratoacanthoma	2 (4%)			
Schwannoma benign		1 (2%)		
Squamous cell papilloma		1 (2%)	1 (2%)	
Lip, squamous cell carcinoma	1 (2%)			
Subcutaneous tissue, fibrosarcoma		1 (2%)		
Subcutaneous tissue, sarcoma	1 (2%)			
Musculoskeletal System				
Bone	(50)	(50)	(50)	(50)
Squamous cell carcinoma, metastatic, oral mucosa				1 (2%)
Mandible, squamous cell carcinoma, metastatic, skin	1 (2%)			
Mandible, squamous cell carcinoma, metastatic, oral mucosa	1 (2%)			
Skeletal muscle	(1)		(1)	
Rhabdomyosarcoma			1 (100%)	
Squamous cell carcinoma, metastatic, oral mucosa	1 (100%)			

TABLE B1
Summary of the Incidence of Neoplasms in Female Rats in the 2-Year Inhalation Study of Glutaraldehyde

	Chamber Control	250 ppb	500 ppb	750 ppb
Nervous System				
None				
Respiratory System				
Lung	(50)	(50)	(50)	(49)
Alveolar/bronchiolar adenoma			1 (2%)	
Sarcoma, metastatic, mesentery	1 (2%)			
Sarcoma, metastatic, skin	1 (2%)			
Squamous cell carcinoma, metastatic, oral mucosa	1 (2%)			
Special Senses System				
Zymbal's gland			(1)	
Carcinoma			1 (100%)	
Urinary System				
Kidney	(49)	(50)	(50)	(50)
Systemic Lesions				
Multiple organs[b]	(50)	(50)	(50)	(50)
Leukemia mononuclear	18 (36%)	20 (40%)	25 (50%)	12 (24%)
Neoplasm Summary				
Total animals with primary neoplasms[c]	49	46	49	36
Total primary neoplasms	110	111	95	57
Total animals with benign neoplasms	42	43	40	31
Total benign neoplasms	77	77	61	40
Total animals with malignant neoplasms	27	26	29	16
Total malignant neoplasms	33	34	34	17
Total animals with metastatic neoplasms	4		1	1
Total metastatic neoplasms	9		1	1

[a] Number of animals examined microscopically at the site and the number of animals with neoplasm
[b] Number of animals with any tissue examined microscopically
[c] Primary neoplasms: all neoplasms except metastatic neoplasms

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Inhalation Study of Glutaraldehyde: Chamber Control

Number of Days on Study	1 1 9	5 1 8	5 3 3	5 4 2	5 5 0	5 6 6	5 8 9	5 8 9	5 8 9	5 9 8	6 3 8	6 5 1	6 6 0	6 6 6	6 7 4	6 8 0	6 8 0	6 8 2	6 9 4	6 9 8	7 0 3	7 0 8	7 1 2	7 2 2	7 3 0
Carcass ID Number	1 2 4	1 1 8	1 1 6	1 4 9	1 3 7	1 2 1	1 1 4	1 2 0	1 3 8	1 1 1	1 4 7	1 3 0	1 2 6	1 3 6	1 4 4	1 2 8	1 4 6	1 2 7	1 1 0	1 1 2	1 0 4	1 0 3	1 4 3	1 3 4	1 0 6
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	A	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	A	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	A	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	A	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	+	A	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	+	+	+	A	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mesentery		+										+				+							+	+	
Sarcoma		X																						X	
Oral mucosa														+											
Gingival, squamous cell carcinoma														X											
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+
Tongue																				+					
Squamous cell papilloma																				X					
Tooth	+																								
Cardiovascular System																									
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+
Parathyroid gland	+	+	M	+	M	+	+	+	+	+	M	+	+	M	+	+	M	+	+	+	+	+	+	+	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma				X		X	X		X		X	X		X	X			X	X	X	X	X	X	X	
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C-cell, adenoma																									
General Body System																									
Tissue NOS																									
Genital System																									
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+
Adenoma																			X						
Carcinoma													X												
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Granulosa-theca tumor malignant																								X	
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Polyp stromal						X		X											X		X		X		
Vagina																	+								

+: Tissue examined microscopically
A: Autolysis precludes examination
M: Missing tissue
I: Insufficient tissue
X: Lesion present
Blank: Not examined

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Inhalation Study of Glutaraldehyde: Chamber Control

Number of Days on Study	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	
Carcass ID Number	1 1 3	1 1 7	1 1 9	1 3 9	1 4 0	1 4 1	1 5 0	1 0 1	1 0 0 2	1 0 0 5	1 0 0 7	1 0 0 8	1 0 0 9	1 1 5	1 2 2	1 2 3	1 2 5	1 2 9	1 3 1	1 3 2	1 3 3	1 3 5	1 4 2	1 4 5	1 4 8	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Mesentery		+		+	+				+		+															10
Sarcoma																										2
Oral mucosa																										1
Gingival, squamous cell carcinoma																										1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Tongue																										1
Squamous cell papilloma																										1
Tooth																										1
Cardiovascular System																										
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Parathyroid gland	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	M	+	42
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pars distalis, adenoma	X		X	X	X	X	X	X	X	X	X	X	X	X			X	X	X	X	X	X	X	X	X	37
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
C-cell, adenoma	X																			X						2
General Body System																										
Tissue NOS																								+		1
Genital System																										
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenoma					X									X												3
Carcinoma													X								X					3
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Granulosa-theca tumor malignant																										1
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Polyp stromal			X			X																			X	8
Vagina																										1

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Inhalation Study of Glutaraldehyde: Chamber Control

Number of Days on Study	1 1 9	5 1 8	5 3 3	5 4 2	5 5 0	5 6 6	5 8 9	5 8 9	5 8 9	5 9 8	6 3 8	6 5 1	6 6 0	6 6 6	6 7 4	6 8 0	6 8 0	6 8 2	6 9 4	6 9 8	7 0 3	7 0 8	7 1 2	7 2 2	7 3 0
Carcass ID Number	1 2 4	1 1 8	1 1 6	1 4 9	1 3 7	1 2 1	1 1 4	1 2 0	1 3 8	1 1 1	1 4 7	1 3 0	1 2 6	1 3 6	1 4 4	1 2 8	1 4 6	1 2 7	1 1 0	1 1 2	1 0 4	1 0 3	1 4 3	1 3 4	1 0 6
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node					+								+												
Iliac, sarcoma, metastatic, skin													X												
Lymph node, bronchial	+	+	+	M	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma, metastatic, skin													X												
Lymph node, mandibular	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mediastinal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma, metastatic, skin													X												
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma									X									X							
Fibroadenoma											X	X		X			X			X		X	X		
Fibroadenoma, multiple						X									X			X							
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrosarcoma			X																						
Keratoacanthoma																		X							X
Lip, squamous cell carcinoma																X									
Subcutaneous tissue, sarcoma													X												
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mandible, squamous cell carcinoma, metastatic, skin																X									
Mandible, squamous cell carcinoma, metastatic, oral mucosa														X											
Skeletal muscle														+											
Squamous cell carcinoma, metastatic, oral mucosa														X											
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+
Spinal cord	+																								
Respiratory System																									
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma, metastatic, mesentery		X																							
Sarcoma, metastatic, skin													X												
Squamous cell carcinoma, metastatic, oral mucosa														X											
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Inhalation Study of Glutaraldehyde: Chamber Control

Number of Days on Study	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	
Carcass ID Number	1 1 3	1 1 7	1 1 9	1 3 9	1 4 0	1 4 1	1 5 0	1 0 1	1 0 2	1 0 5	1 0 7	1 0 8	1 0 9	1 1 5	1 2 2	1 2 3	1 2 5	1 2 9	1 3 1	1 3 2	1 3 3	1 3 5	1 4 2	1 4 5	1 4 8	Total Tissues/ Tumors
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node																										2
Iliac, sarcoma, metastatic, skin																										1
Lymph node, bronchial	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	46
Sarcoma, metastatic, skin																										1
Lymph node, mandibular	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node, mediastinal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Sarcoma, metastatic, skin																										1
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma	X																	X							X	5
Fibroadenoma						X		X		X	X					X		X				X			X	15
Fibroadenoma, multiple					X		X								X				X		X		X			9
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Fibrosarcoma																										1
Keratoacanthoma																										2
Lip, squamous cell carcinoma																										1
Subcutaneous tissue, sarcoma																										1
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Mandible, squamous cell carcinoma, metastatic, skin																										1
Mandible, squamous cell carcinoma, metastatic, oral mucosa																										1
Skeletal muscle																										1
Squamous cell carcinoma, metastatic, oral mucosa																										1
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Spinal cord																										1
Respiratory System																										
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Sarcoma, metastatic, mesentery																										1
Sarcoma, metastatic, skin																										1
Squamous cell carcinoma, metastatic, oral mucosa																										1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Inhalation Study of Glutaraldehyde: Chamber Control

Number of Days on Study	1 1 9	5 1 8	5 3 3	5 4 2	5 5 0	5 6 6	5 8 9	5 8 9	5 8 9	5 9 8	6 3 8	6 5 1	6 6 0	6 6 6	6 7 4	6 8 0	6 8 0	6 8 2	6 9 4	6 9 8	7 0 3	7 0 8	7 1 2	7 2 2	7 3 0
Carcass ID Number	1 2 4	1 1 8	1 1 6	1 4 9	1 3 7	1 2 1	1 1 4	1 2 0	1 3 8	1 1 1	1 4 7	1 3 0	1 2 6	1 3 6	1 4 4	1 2 8	1 4 6	1 2 7	1 1 0	1 1 2	1 0 4	1 0 3	1 4 3	1 3 4	1 0 6
Special Senses System																									
Eye								+																	
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear			X		X			X	X	X	X				X		X	X				X	X		

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Inhalation Study of Glutaraldehyde: Chamber Control

Number of Days on Study	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	
Carcass ID Number	1 1 3	1 1 7	1 1 9	1 3 9	1 4 0	1 4 1	1 5 0	1 0 1	1 0 2	1 0 5	1 0 7	1 0 8	1 0 9	1 1 5	1 2 2	1 2 3	1 2 5	1 2 9	1 3 1	1 3 2	1 3 3	1 3 5	1 4 2	1 4 5	1 4 8	Total Tissues/ Tumors
Special Senses System																											
Eye																	+										2
Urinary System																											
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Systemic Lesions																											
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear	X	X		X	X		X												X				X				18

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Inhalation Study of Glutaraldehyde: 250 ppb

Number of Days on Study	1 1 4 5 5 5 5 5 6 6 6 6 6 6 6 7 7 7 7 7 7 7 7 7
	1 7 3 4 6 6 8 9 0 1 1 1 6 6 7 7 9 2 2 2 3 3 3 3 3 3
	7 8 7 2 1 1 9 3 6 2 5 7 6 4 5 4 0 4 6 0 0 0 0 0 0
Carcass ID Number	3 3 3 3 3 3 3 3 3 3 3 3 3 3 3 3 3 3 3 3 3 3 3 3 3
	4 1 1 1 0 1 1 1 4 2 0 2 2 4 4 1 2 2 2 0 0 0 1 2 2
	0 5 7 0 1 4 1 6 2 9 7 2 1 8 9 3 8 4 5 2 6 8 9 0 6
Alimentary System	
Esophagus	+ +
Intestine large, colon	+ + A +
Intestine large, rectum	+ +
Intestine large, cecum	+ + A + + + + + A + + + + + + + + + + + + + + + +
Intestine small, duodenum	+ + A +
Intestine small, jejunum	+ + A + + + + + A + + + + + + + + + + + + + + + +
Intestine small, ileum	+ + A + + + + + A + + + + + + + + + + + + + + + +
Liver	+ +
Mesentery	+ + + +
Pancreas	+ +
Salivary glands	+ +
Stomach, forestomach	+ +
Stomach, glandular	+ + A +
Tongue	
Tooth	+ +
Cardiovascular System	
Blood vessel	+ +
Heart	+ +
Endocrine System	
Adrenal cortex	+ +
Adrenal medulla	+ +
Pheochromocytoma malignant	X
Islets, pancreatic	+ +
Adenoma	
Parathyroid gland	+ M + + + M + M + + + + + + M + + M + + M + + M + +
Pituitary gland	+ +
Pars distalis, adenoma	X X X X X X X X X X X X X
Thyroid gland	+ +
C-cell, adenoma	
C-cell, carcinoma	
General Body System	
Tissue NOS	+
Genital System	
Clitoral gland	+ +
Adenoma	X X
Carcinoma	
Ovary	+ +
Uterus	+ +
Polyp stromal	X X X X X
Hematopoietic System	
Bone marrow	+ +
Lymph node	+ +
Lymph node, bronchial	+ M + + + + +
Lymph node, mandibular	+ +
Lymph node, mesenteric	+ +
Lymph node, mediastinal	+ +
Spleen	+ +
Thymus	+ +

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Inhalation Study of Glutaraldehyde: 250 ppb

Number of Days on Study	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	
Carcass ID Number	3 2 7	3 3 2	3 3 4	3 3 6	3 4 1	3 4 5	3 5 0	3 0 3	3 0 0 4	3 0 0 5	3 0 0 9	3 1 1 2	3 1 1 8	3 2 3 3	3 3 0	3 3 1	3 3 3	3 3 5	3 3 7	3 3 8	3 3 9	3 4 4 3	3 4 4 4	3 4 4 6	3 4 7	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Mesentery					+				+	+	+			+										+		9
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Tongue							+																			1
Tooth																										2
Cardiovascular System																										
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma malignant																										1
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma				X																						1
Parathyroid gland	+	+	+	+	M	+	+	+	+	+	+	+	+	M	+	+	+	M	+	+	M	+	+	+	+	39
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pars distalis, adenoma	X	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X		X		X		X		37
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
C-cell, adenoma		X																								1
C-cell, carcinoma										X					X											2
General Body System																										
Tissue NOS																										1
Genital System																										
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma	X																									3
Carcinoma		X			X																					2
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Polyp stromal					X		X				X		X	X												10
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node					+																					3
Lymph node, bronchial	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	M	46
Lymph node, mandibular	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node, mediastinal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Inhalation Study of Glutaraldehyde: 250 ppb

Number of Days on Study	1 1 4 5 5 5 5 5 6 6 6 6 6 6 6 7 7 7 7 7 7 7 7 7 1 7 3 4 6 6 8 9 0 1 1 1 6 7 7 9 2 2 2 3 3 3 3 3 3 7 8 7 2 1 1 9 3 6 2 5 7 6 4 5 4 0 4 6 0 0 0 0 0 0
Carcass ID Number	3 3 3 3 3 3 3 3 3 3 3 3 3 3 3 3 3 3 3 3 3 3 3 3 3 4 1 1 1 0 1 1 1 4 2 0 2 2 1 4 4 1 2 2 2 0 0 0 1 2 2 0 5 7 0 1 4 1 6 2 9 7 2 1 8 9 3 8 4 5 2 6 8 9 0 6
Integumentary System	
Mammary gland	+ +
Carcinoma	X X X X X X
Fibroadenoma	X X X X X X X
Fibroadenoma, multiple	X
Skin	+ +
Schwannoma benign	
Squamous cell papilloma	
Subcutaneous tissue, fibrosarcoma	X
Musculoskeletal System	
Bone	+ +
Nervous System	
Brain	+ +
Spinal cord	+ +
Respiratory System	
Larynx	+ +
Lung	+ +
Nose	+ +
Pleura	
Trachea	+ +
Special Senses System	
Eye	+ + +
Urinary System	
Kidney	+ +
Urinary bladder	+ +
Systemic Lesions	
Multiple organs	+ +
Leukemia mononuclear	X X X X X X X X

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Inhalation Study of Glutaraldehyde: 250 ppb

Number of Days on Study	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	
Carcass ID Number	3 2 7	3 3 2	3 3 4	3 3 6	3 4 1	3 4 5	3 5 0	3 0 3	3 0 4	3 0 5	3 0 9	3 1 2	3 1 8	3 2 3	3 3 0	3 3 1	3 3 3	3 3 5	3 3 7	3 3 8	3 3 9	3 4 3	3 4 4	3 4 6	3 4 7	Total Tissues/ Tumors
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma		X								X																8
Fibroadenoma		X	X	X	X		X	X					X	X		X		X		X						18
Fibroadenoma, multiple										X	X	X					X									5
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Schwannoma benign					X																					1
Squamous cell papilloma								X																		1
Subcutaneous tissue, fibrosarcoma																										1
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spinal cord																										2
Respiratory System																										
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pleura															+					+						2
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
Eye																										2
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear		X			X					X				X	X	X		X		X	X				X	20

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Inhalation Study of Glutaraldehyde: 500 ppb

Number of Days on Study	2 7 6	3 5 5	3 5 7	4 5 5	4 6 9	5 0 8	5 1 3	5 3 3	5 3 3	5 4 3	5 4 4	5 4 4	5 5 8	5 8 3	5 8 9	6 1 4	6 1 7	6 1 7	6 1 9	6 3 4	6 3 8	6 3 8	6 5 4	6 6 0	6 6 2	6 7 4
Carcass ID Number	5 4 9	5 1 0	5 1 1	5 0 3	5 3 1	5 2 5	5 0 4	5 3 2	5 4 4	5 4 3	5 4 3	5 0 9	5 3 6	5 0 8	5 1 5	5 0 2	5 2 4	5 3 9	5 2 3	5 3 4	5 3 0 5	5 4 3 8	5 3 7	5 1 3	5 4 0	5 0 1
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Rhabdomyosarcoma, metastatic, skeletal muscle	X																									
Mesentery																				+					+	
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cardiovascular System																										
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma benign																										
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma																		X								
Parathyroid gland	+	+	+	M	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	M	+	+	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma					X	X	X		X		X			X	X	X						X			X	X
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C-cell, adenoma																										
General Body System																										
Tissue NOS																										
Genital System																										
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																										
Carcinoma																				X						
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Granulosa-theca tumor malignant																										
Oviduct																								+		
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Deciduoma benign																										
Polyp stromal				X					X			X														
Sarcoma stromal				X																						

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Inhalation Study of Glutaraldehyde: 500 ppb

Number of Days on Study	6 7 4	6 7 6	6 7 6	6 8 0	7 0 3	7 0 9	7 1 1	7 1 5	7 1 6	7 2 4	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 1	7 3 1	7 3 1	7 3 1	
Carcass ID Number	5 2 6	5 1 4	5 1 7	5 1 9	5 1 8	5 2 7	5 2 9	5 4 6	5 2 0	5 2 6	5 0 6	5 0 7	5 1 2	5 1 6	5 2 1	5 2 2	5 2 8	5 3 0	5 3 3	5 3 8	5 4 5	5 4 7	5 3 5	5 4 1	5 4 2	5 5 0	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Rhabdomyosarcoma, metastatic, skeletal muscle																										1
Mesentery		+					+							+					+						+	7
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cardiovascular System																										
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma benign																									X	1
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma																										1
Parathyroid gland	M	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	M	+	44
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pars distalis, adenoma	X			X	X	X	X	X	X			X	X	X	X	X			X	X	X			X		27
Thyroid gland	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
C-cell, adenoma													X			X										2
General Body System																										
Tissue NOS																									+	1
Genital System																										
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma											X															1
Carcinoma																										1
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Granulosa-theca tumor malignant														X												1
Oviduct																										1
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Deciduoma benign																									X	1
Polyp stromal		X							X	X						X							X			8
Sarcoma stromal																										1

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Inhalation Study of Glutaraldehyde: 500 ppb

Number of Days on Study	2 7 6	3 5 5	3 5 7	4 5 5	4 6 9	5 0 8	5 1 3	5 3 3	5 3 3	5 4 3	5 4 4	5 0 9	5 3 6	5 0 8	5 1 5	6 0 2	6 1 4	6 1 7	6 1 7	6 1 9	6 3 4	6 3 8	6 3 8	6 5 4	6 6 0	6 6 2	6 7 4
Carcass ID Number	5 4 9	5 1 0	5 1 1	5 0 1	5 3 1	5 2 5	5 0 4	5 3 2	5 4 4	5 4 3	5 4 3	5 0 9	5 3 6	5 0 8	5 1 5	5 0 2	5 2 4	5 3 9	5 2 3	5 3 4	5 3 5	5 4 8	5 3 7	5 1 3	5 4 0	5 0 1
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node													+													
Lymph node, bronchial	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	M	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mediastinal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma																							X			X
Fibroadenoma								X	X							X	X	X				X		X	X	
Fibroadenoma, multiple																										
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibroma																			X							
Squamous cell papilloma																										
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skeletal muscle	+																									
Rhabdomyosarcoma	X																									
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Respiratory System																										
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																										
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																										
Eye			+																				+			
Zymbal's gland																										
Carcinoma																										
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear		X	X				X	X	X	X		X	X							X	X	X			X	X

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Inhalation Study of Glutaraldehyde: 500 ppb

Number of Days on Study	6 7 4	6 7 6	6 7 6	6 8 0	7 0 3	7 0 9	7 1 1	7 1 5	7 1 6	7 2 4	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 1	7 3 1	7 3 1	7 3 1	
Carcass ID Number	5 2 6	5 1 4	5 1 7	5 1 9	5 1 8	5 2 7	5 2 9	5 4 6	5 2 0	5 0 6	5 0 7	5 1 2	5 1 6	5 2 1	5 2 2	5 2 8	5 3 0	5 3 3	5 3 8	5 4 5	5 4 7	5 3 5	5 4 1	5 4 2	5 5 0	Total Tissues/ Tumors
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node							+		+																	3
Lymph node, bronchial	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node, mediastinal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma			X																							3
Fibroadenoma	X				X			X							X	X		X					X			15
Fibroadenoma, multiple				X					X					X												3
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Fibroma																										1
Squamous cell papilloma															X											1
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Skeletal muscle																										1
Rhabdomyosarcoma																										1
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Respiratory System																										
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma																		X								1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
Eye																+										3
Zymbal's gland																		+								1
Carcinoma																		X								1
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear		X	X	X	X	X	X	X	X					X	X	X		X								25

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Inhalation Study of Glutaraldehyde: 750 ppb

Number of Days on Study	0 3 2	1 0 6	1 0 8	1 1 3	1 1 3	1 1 7	2 5 3	3 7 5	4 3 2	4 6 3	4 7 4	4 7 4	5 1 2	5 1 4	5 1 6	5 2 8	5 6 7	5 6 9	5 8 3	6 2 8	6 3 0	6 4 1	6 5 2	6 5 4	6 5 4
Carcass ID Number	7 2 5	7 3 6	7 3 4	7 0 9	7 2 8	7 1 6	7 4 2	7 1 3	7 0 6	7 4 1	7 0 8	7 3 2	7 2 1	7 0 5	7 2 4	7 4 5	7 1 9	7 0 7	7 3 8	7 2 7	7 0 1	7 3 9	7 5 0	7 3 7	7 4 0
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	A	A	+	+	+
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	A	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mesentery																									
Oral mucosa													+												
Lingual, squamous cell carcinoma													X												
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tooth		+			+	+																			
Cardiovascular System																									
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+	+	+	+	+	+	+	+	+	+
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal medulla	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma malignant																									
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid gland	+	M	M	+	+	+	+	M	M	M	+	+	+	+	+	+	+	+	M	+	+	+	+	M	+
Pituitary gland	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma											X	X		X							X	X	X	X	X
Thyroid gland	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell, adenoma																								X	
General Body System																									
Tissue NOS																									
Genital System																									
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma																									
Ovary	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Granulosa cell tumor malignant																									
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Polyp stromal																						X			
Serosa, leiomyoma																			X						
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node																									
Lymph node, bronchial	+	+	M	+	+	+	M	+	+	M	+	+	+	+	+	+	M	+	+	+	+	+	+	M	+
Lymph node, mandibular	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mediastinal	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Inhalation Study of Glutaraldehyde: 750 ppb

Number of Days on Study	654	677	683	698	702	708	716	716	717	718	721	730	730	730	730	730	730	730	730	730	730	731	731	731	
Carcass ID Number	74 46	74 47	73 43	74 48	71 47	71 44	70 43	73 41	74 43	71 45	74 44	70 42	70 44	71 42	71 48	72 20	72 22	72 23	72 26	73 45	74 49	71 40	71 41	72 19	73 30	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Mesentery											+	+		+												3
Oral mucosa																										1
Lingual, squamous cell carcinoma																										1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Tooth																										3
Cardiovascular System																										
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pheochromocytoma malignant																									X	1
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Parathyroid gland	+	+	M	+	M	M	+	+	+	+	+	+	+	+	+	+	M	+	M	M	+	M	+	+	+	36
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pars distalis, adenoma	X				X	X	X	X	X		X	X	X	X			X		X	X			X	X	X	24
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Follicular cell, adenoma		X																								2
General Body System																										
Tissue NOS													+													1
Genital System																										
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma															X											1
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Granulosa cell tumor malignant																								X		1
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Polyp stromal									X												X					3
Serosa, leiomyoma																										1
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node		+																			+					2
Lymph node, bronchial	+	+	M	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	M	42
Lymph node, mandibular	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	M	+	+	+	46
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node, mediastinal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Inhalation Study of Glutaraldehyde: 750 ppb

Number of Days on Study	0 3 2	1 0 6	1 0 8	1 1 3	1 1 3	1 1 7	2 5 3	3 7 5	4 3 2	4 6 3	4 7 4	4 7 4	5 1 2	5 1 4	5 1 6	5 2 8	5 6 7	5 6 9	5 8 3	6 2 8	6 3 0	6 4 1	6 5 2	6 5 4	6 5 4
Carcass ID Number	7 2 5	7 3 6	7 3 4	7 0 9	7 2 8	7 1 6	7 4 2	7 1 3	7 0 6	7 4 1	7 0 8	7 3 2	7 2 1	7 0 5	7 2 4	7 4 5	7 1 9	7 0 7	7 3 8	7 2 7	7 0 1	7 3 9	7 5 0	7 3 7	7 4 0
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma										X															
Fibroadenoma														X		X					X		X		
Fibroadenoma, multiple																		X							
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell carcinoma, metastatic, oral mucosa													X												
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spinal cord		+	+	+	+																				
Respiratory System																									
Larynx	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lung	+	+	+	+	+	+	+	+	+	I	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nose	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
None																									
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urethra																									
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear														X				X	X	X	X				X

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Inhalation Study of Glutaraldehyde: 750 ppb

Number of Days on Study	6 5 4	6 7 7	6 8 0	6 9 8	7 0 2	7 0 8	7 1 6	7 1 6	7 1 7	7 1 8	7 2 1	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 1	7 3 1	7 3 1	
Carcass ID Number	7 4 6	7 4 7	7 3 3	7 4 8	7 1 7	7 1 4	7 0 3	7 3 1	7 4 3	7 1 5	7 4 4	7 0 2	7 0 4	7 1 2	7 1 8	7 2 0	7 2 2	7 2 3	7 2 6	7 3 5	7 4 9	7 1 0	7 1 1	7 2 9	7 3 0	Total Tissues/ Tumors
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma																										1
Fibroadenoma			X							X	X			X											X	9
Fibroadenoma, multiple																										1
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Squamous cell carcinoma, metastatic, oral mucosa																										1
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spinal cord																										4
Respiratory System																										
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
None																										
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urethra																		+								1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear		X							X		X		X									X			X	12

TABLE B3
Statistical Analysis of Primary Neoplasms in Female Rats in the 2-Year Inhalation Study of Glutaraldehyde

	Chamber Control	250 ppb	500 ppb	750 ppb
Clitoral Gland: Adenoma				
Overall rate[a]	3/49 (6%)	3/50 (6%)	1/50 (2%)	0/50 (0%)
Adjusted rate[b]	7.3%	7.1%	2.8%	0.0%
Terminal rate[c]	2/26 (8%)	2/31 (7%)	1/15 (7%)	0/14 (0%)
First incidence (days)	694	694	730 (T)	—[e]
Poly-3 test[d]	P=0.080N	P=0.650N	P=0.356N	P=0.170N
Clitoral Gland: Carcinoma				
Overall rate	3/49 (6%)	2/50 (4%)	1/50 (2%)	1/50 (2%)
Adjusted rate	7.3%	4.8%	2.8%	3.1%
Terminal rate	2/26 (8%)	2/31 (7%)	0/15 (0%)	1/14 (7%)
First incidence (days)	660	730 (T)	634	730 (T)
Poly-3 test	P=0.220N	P=0.490N	P=0.354N	P=0.401N
Clitoral Gland: Adenoma or Carcinoma				
Overall rate	6/49 (12%)	5/50 (10%)	2/50 (4%)	1/50 (2%)
Adjusted rate	14.5%	11.8%	5.5%	3.1%
Terminal rate	4/26 (15%)	4/31 (13%)	1/15 (7%)	1/14 (7%)
First incidence (days)	660	694	634	730 (T)
Poly-3 test	P=0.042N	P=0.485N	P=0.179N	P=0.109N
Mammary Gland: Fibroadenoma				
Overall rate	24/50 (48%)	23/50 (46%)	18/50 (36%)	10/50 (20%)
Adjusted rate	54.6%	52.2%	45.4%	28.9%
Terminal rate	14/26 (54%)	16/31 (52%)	5/15 (33%)	2/14 (14%)
First incidence (days)	566	561	533	514
Poly-3 test	P=0.014N	P=0.496N	P=0.263N	P=0.017N
Mammary Gland: Carcinoma				
Overall rate	5/50 (10%)	8/50 (16%)	3/50 (6%)	1/50 (2%)
Adjusted rate	11.8%	18.5%	8.2%	3.1%
Terminal rate	3/26 (12%)	5/31 (16%)	0/15 (0%)	0/14 (0%)
First incidence (days)	589	593	654	463
Poly-3 test	P=0.097N	P=0.289	P=0.441N	P=0.173N
Mammary Gland: Fibroadenoma or Carcinoma				
Overall rate	26/50 (52%)	27/50 (54%)	21/50 (42%)	11/50 (22%)
Adjusted rate	58.5%	60.1%	52.1%	31.1%
Terminal rate	15/26 (58%)	18/31 (58%)	5/15 (33%)	2/14 (14%)
First incidence (days)	566	561	533	463
Poly-3 test	P=0.010N	P=0.524	P=0.349N	P=0.011N
Pituitary Gland (Pars Distalis): Adenoma				
Overall rate	37/50 (74%)	37/50 (74%)	27/50 (54%)	24/49 (49%)
Adjusted rate	81.1%	80.2%	64.5%	66.7%
Terminal rate	22/26 (85%)	26/31 (84%)	9/15 (60%)	9/14 (64%)
First incidence (days)	542	561	469	474
Poly-3 test	P=0.022N	P=0.562N	P=0.050N	P=0.092N

TABLE B3
Statistical Analysis of Primary Neoplasms in Female Rats in the 2-Year Inhalation Study of Glutaraldehyde

	Chamber Control	250 ppb	500 ppb	750 ppb
Skin: Squamous Cell Papilloma, Keratoacanthoma, or Squamous Cell Carcinoma				
Overall rate	3/50 (6%)	1/50 (2%)	1/50 (2%)	0/50 (0%)
Adjusted rate	7.1%	2.4%	2.8%	0.0%
Terminal rate	1/26 (4%)	1/31 (3%)	1/15 (7%)	0/14 (0%)
First incidence (days)	680	730 (T)	730 (T)	—
Poly-3 test	P=0.085N	P=0.305N	P=0.366N	P=0.176N
Thyroid Gland (C-Cell): Adenoma or Carcinoma				
Overall rate	2/50 (4%)	3/50 (6%)	2/49 (4%)	0/49 (0%)
Adjusted rate	4.8%	7.1%	5.7%	0.0%
Terminal rate	2/26 (8%)	3/31 (10%)	2/15 (13%)	0/14 (0%)
First incidence (days)	730 (T)	730 (T)	730 (T)	—
Poly-3 test	P=0.264N	P=0.504	P=0.629	P=0.303N
Thyroid Gland (Follicular Cell): Adenoma				
Overall rate	0/50 (0%)	0/50 (0%)	0/49 (0%)	2/49 (4%)
Adjusted rate	0.0%	0.0%	0.0%	6.2%
Terminal rate	0/26 (0%)	0/31 (0%)	0/15 (0%)	0/14 (0%)
First incidence (days)	—	—[f]	—	654
Poly-3 test	P=0.055		—	P=0.184
Uterus: Stromal Polyp or Stromal Sarcoma				
Overall rate	8/50 (16%)	10/50 (20%)	8/50 (16%)	3/50 (6%)
Adjusted rate	18.6%	23.1%	21.1%	9.3%
Terminal rate	3/26 (12%)	6/31 (19%)	2/15 (13%)	1/14 (7%)
First incidence (days)	566	612	455	641
Poly-3 test	P=0.239N	P=0.400	P=0.499	P=0.215N
All Organs: Mononuclear Cell Leukemia				
Overall rate	18/50 (36%)	20/50 (40%)	25/50 (50%)	12/50 (24%)
Adjusted rate	39.7%	45.2%	57.5%	34.4%
Terminal rate	7/26 (27%)	11/31 (36%)	4/15 (27%)	3/14 (21%)
First incidence (days)	533	542	355	514
Poly-3 test	P=0.410	P=0.375	P=0.065	P=0.401N
All Organs: Benign Neoplasms				
Overall rate	42/50 (84%)	43/50 (86%)	40/50 (80%)	31/50 (62%)
Adjusted rate	90.8%	92.2%	88.8%	80.9%
Terminal rate	25/26 (96%)	29/31 (94%)	14/15 (93%)	10/14 (71%)
First incidence (days)	542	561	455	474
Poly-3 test	P=0.079N	P=0.552	P=0.517N	P=0.132N
All Organs: Malignant Neoplasms				
Overall rate	27/50 (54%)	26/50 (52%)	29/50 (58%)	16/50 (32%)
Adjusted rate	57.8%	56.7%	63.2%	44.1%
Terminal rate	11/26 (42%)	14/31 (45%)	4/15 (27%)	5/14 (36%)
First incidence (days)	518	437	276	463
Poly-3 test	P=0.259N	P=0.541N	P=0.369	P=0.152N

TABLE B3
Statistical Analysis of Primary Neoplasms in Female Rats in the 2-Year Inhalation Study of Glutaraldehyde

	Chamber Control	250 ppb	500 ppb	750 ppb
All Organs: Benign or Malignant Neoplasms				
Overall rate	49/50 (98%)	46/50 (92%)	49/50 (98%)	36/50(72%)
Adjusted rate	100.0%	95.8%	98.0%	89.8%
Terminal rate	26/26 (100%)	29/31 (94%)	14/15 (93%)	12/14 (86%)
First incidence (days)	518	437	276	463
Poly-3 test	P=0.026N	P=0.230N	P=0.506N	P=0.021N

(T)Terminal sacrifice
[a] Number of neoplasm-bearing animals/number of animals examined. Denominator is number of animals examined microscopically for clitoral gland, pituitary gland, thyroid gland, and uterus; for other tissues, denominator is number of animals necropsied.
[b] Poly-3 estimated neoplasm incidence after adjustment for intercurrent mortality
[c] Observed incidence at terminal kill
[d] Beneath the chamber control incidence are the P values associated with the trend test. Beneath the exposed group incidence are the P values corresponding to pairwise comparisons between the chamber controls and that exposed group. The Poly-3 test accounts for differential mortality in animals that do not reach terminal sacrifice. A negative trend or a lower incidence in an exposure group is indicated by **N**.
[e] Not applicable; no neoplasms in animal group
[f] Value of statistic cannot be computed.

TABLE B4a
Historical Incidence of Thyroid Gland Follicular Cell Adenoma in Chamber Control Female F344/N Rats[a]

Study	Incidence in Controls
Historical Incidence at Battelle Pacific Northwest Laboratories	
Acetonitrile	0/48
Chloroprene	1/49
Cobalt sulfate heptahydrate	0/49
Furfuryl alcohol	0/49
Hexachlorocyclopentadiene	1/50
Isobutene	0/50
Isobutyraldehyde	0/49
Isoprene	0/48
Molybdenum trioxide	1/49
Nitromethane	0/50
Ozone	0/50
Tetrafluoroethylene	0/50
Tetrahydrofuran	0/48
Overall Historical Incidence: Inhalation Studies	
Total (%)	3/888 (0.3%)
Mean ± standard deviation	0.3% ± 0.8%
Range	0%-2%
Overall Historical Incidence: Gavage (Corn Oil) Studies	
Total (%)	6/398 (1.5%)
Mean ± standard deviation	1.5% ± 2.3%
Range	0%-6%
Overall Historical Incidence: Drinking Water Studies	
Total (%)	5/329 (1.5%)
Mean ± standard deviation	1.7% ± 2.3%
Range	0%-6%

[a] Data as of 12 November 1997

TABLE B4b
Historical Incidence of Mammary Gland Neoplasms in Chamber Control Female F344/N Rats[a]

Study	Incidence in Controls		
	Fibroadenoma	Carcinoma	Fibroadenoma or Carcinoma
Historical Incidence at Battelle Pacific Northwest Laboratories			
Acetonitrile	16/48	2/48	17/48
Chloroprene	24/49	4/49	28/49
Cobalt sulfate heptahydrate	22/50	3/50	25/50
Furfuryl alcohol	19/50	9/50	25/50
Hexachlorocyclopentadiene	12/50	3/50	14/50
Isobutene	22/50	2/50	23/50
Isobutyraldehyde	27/50	1/50	27/50
Isoprene	19/50	4/50	20/50
Molybdenum trioxide	22/50	1/50	23/50
Nitromethane	19/50	2/50	21/50
Ozone	20/50	4/50	23/50
Tetrafluoroethylene	22/50	3/50	24/50
Tetrahydrofuran	23/50	5/50	27/50
Overall Historical Incidence			
Total (%)	348/902 (38.6%)	55/902 (6.1%)	382/902 (42.4%)
Mean ± standard deviation	38.6% ± 8.7%	6.1% ± 3.9%	42.4% ± 9.2%
Range	23%-54%	2%-18%	23%-57%

[a] Data as of 12 November 1997

TABLE B5
Summary of the Incidence of Nonneoplastic Lesions in Female Rats in the 2-Year Inhalation Study of Glutaraldehyde[a]

	Chamber Control	250 ppb	500 ppb	750 ppb
Disposition Summary				
Animals initially in study	50	50	50	50
Early deaths				
Moribund	22	17	32	34
Natural deaths	2	2	3	2
Survivors				
Terminal sacrifice	26	31	15	14
Animals examined microscopically	50	50	50	50
Alimentary System				
Intestine large, colon	(48)	(49)	(49)	(49)
Diverticulum				1 (2%)
Parasite metazoan	2 (4%)	4 (8%)	1 (2%)	1 (2%)
Intestine large, rectum	(48)	(50)	(49)	(49)
Parasite metazoan	3 (6%)	4 (8%)	4 (8%)	
Intestine large, cecum	(48)	(48)	(49)	(49)
Parasite metazoan	5 (10%)	4 (8%)	3 (6%)	3 (6%)
Liver	(50)	(50)	(50)	(50)
Angiectasis	1 (2%)		2 (4%)	
Basophilic focus	1 (2%)	2 (4%)	1 (2%)	1 (2%)
Basophilic focus, multiple	1 (2%)		2 (4%)	2 (4%)
Clear cell focus	6 (12%)	4 (8%)	4 (8%)	3 (6%)
Clear cell focus, multiple		3 (6%)	2 (4%)	1 (2%)
Hematopoietic cell proliferation	1 (2%)		1 (2%)	
Hepatodiaphragmatic nodule	3 (6%)	6 (12%)	3 (6%)	3 (6%)
Inflammation, granulomatous		1 (2%)		
Necrosis	2 (4%)			
Vacuolization cytoplasmic	5 (10%)	1 (2%)		3 (6%)
Mesentery	(10)	(9)	(7)	(3)
Inflammation, granulomatous			1 (14%)	
Fat, necrosis	9 (90%)	9 (100%)	7 (100%)	3 (100%)
Pancreas	(50)	(50)	(50)	(50)
Acinus, atrophy	3 (6%)	3 (6%)	3 (6%)	4 (8%)
Salivary glands	(50)	(50)	(50)	(50)
Atrophy	1 (2%)			
Stomach, forestomach	(49)	(50)	(50)	(50)
Erosion				1 (2%)
Hyperkeratosis			1 (2%)	
Inflammation, suppurative	3 (6%)	4 (8%)	2 (4%)	4 (8%)
Ulcer	3 (6%)	2 (4%)	2 (4%)	2 (4%)
Epithelium, hyperplasia	3 (6%)	4 (8%)	3 (6%)	5 (10%)
Stomach, glandular	(49)	(49)	(50)	(50)
Erosion		1 (2%)	1 (2%)	
Inflammation, suppurative		1 (2%)	2 (4%)	
Tongue	(1)	(1)		
Hyperkeratosis		1 (100%)		
Hyperplasia		1 (100%)		
Tooth	(1)	(2)		(3)
Degeneration	1 (100%)	2 (100%)		2 (67%)
Inflammation, suppurative		1 (50%)		

[a] Number of animals examined microscopically at the site and the number of animals with lesion

TABLE B5
Summary of the Incidence of Nonneoplastic Lesions in Female Rats in the 2-Year Inhalation Study of Glutaraldehyde

	Chamber Control	250 ppb	500 ppb	750 ppb
Cardiovascular System				
Blood vessel	(50)	(50)	(50)	(49)
Inflammation	1 (2%)	1 (2%)		1 (2%)
Mineralization			1 (2%)	
Thrombosis		1 (2%)		
Heart	(50)	(50)	(50)	(50)
Atrium, thrombosis	1 (2%)	1 (2%)		
Myocardium, fibrosis	3 (6%)	1 (2%)	4 (8%)	1 (2%)
Endocrine System				
Adrenal cortex	(50)	(50)	(50)	(49)
Atrophy		1 (2%)		
Fibrosis	1 (2%)			
Hematopoietic cell proliferation	1 (2%)		1 (2%)	
Hemorrhage			1 (2%)	1 (2%)
Vacuolization cytoplasmic	7 (14%)	6 (12%)	11 (22%)	9 (18%)
Adrenal medulla	(50)	(50)	(50)	(49)
Hyperplasia	2 (4%)	1 (2%)	2 (4%)	1 (2%)
Islets, pancreatic	(49)	(50)	(50)	(50)
Hyperplasia	1 (2%)			
Parathyroid gland	(42)	(39)	(44)	(36)
Hyperplasia			2 (5%)	
Pituitary gland	(50)	(50)	(50)	(49)
Cyst	3 (6%)	1 (2%)	3 (6%)	2 (4%)
Hemorrhage	1 (2%)		1 (2%)	1 (2%)
Pars distalis, hyperplasia	3 (6%)	4 (8%)	4 (8%)	7 (14%)
Thyroid gland	(50)	(50)	(49)	(49)
C-cell, hyperplasia	3 (6%)	4 (8%)	4 (8%)	4 (8%)
General Body System				
None				
Genital System				
Clitoral gland	(49)	(50)	(50)	(50)
Cyst	1 (2%)			
Hyperplasia	4 (8%)	7 (14%)		2 (4%)
Inflammation, suppurative	1 (2%)	1 (2%)		1 (2%)
Ovary	(50)	(50)	(50)	(49)
Cyst	2 (4%)	3 (6%)	7 (14%)	3 (6%)
Cyst, multiple				1 (2%)
Bilateral, cyst	1 (2%)			
Oviduct			(1)	
Cyst			1 (100%)	
Uterus	(50)	(50)	(50)	(50)
Cyst				1 (2%)
Hemorrhage	1 (2%)		1 (2%)	
Hydrometra			1 (2%)	
Cervix, myometrium, hypertrophy		1 (2%)		
Vagina	(1)			
Inflammation	1 (100%)			

TABLE B5
Summary of the Incidence of Nonneoplastic Lesions in Female Rats in the 2-Year Inhalation Study of Glutaraldehyde

	Chamber Control	250 ppb	500 ppb	750 ppb
Hematopoietic System				
Bone marrow	(50)	(50)	(50)	(50)
Fibrosis			2 (4%)	
Lymph node, bronchial	(46)	(46)	(48)	(42)
Fibrosis			1 (2%)	
Lymph node, mesenteric	(50)	(50)	(50)	(50)
Fibrosis				1 (2%)
Infiltration cellular, histiocyte	1 (2%)			
Spleen	(50)	(50)	(50)	(50)
Accessory spleen			1 (2%)	1 (2%)
Fibrosis	5 (10%)	7 (14%)	8 (16%)	4 (8%)
Hematopoietic cell proliferation	2 (4%)	1 (2%)	1 (2%)	
Hemorrhage	1 (2%)		2 (4%)	1 (2%)
Thymus	(50)	(50)	(50)	(49)
Cyst			1 (2%)	
Integumentary System				
Mammary gland	(50)	(50)	(50)	(50)
Galactocele	2 (4%)	2 (4%)		
Hyperplasia				1 (2%)
Metaplasia, squamous	1 (2%)			
Epithelium, hyperplasia			2 (4%)	
Skin	(50)	(50)	(50)	(50)
Cyst epithelial inclusion	1 (2%)	3 (6%)		
Hyperkeratosis	2 (4%)			
Inflammation, suppurative				1 (2%)
Ulcer			1 (2%)	
Hair follicle, inflammation, chronic			1 (2%)	
Subcutaneous tissue, inflammation	1 (2%)			
Musculoskeletal System				
Bone	(50)	(50)	(50)	(50)
Osteopetrosis			1 (2%)	
Sternum, cyst				1 (2%)
Nervous System				
Brain	(49)	(50)	(50)	(50)
Hemorrhage	3 (6%)	1 (2%)	7 (14%)	3 (6%)
Hydrocephalus	10 (20%)	10 (20%)	7 (14%)	2 (4%)
Spinal cord	(1)	(2)		(4)
Demyelination		2 (100%)		2 (50%)
Neuron, degeneration	1 (100%)			
Respiratory System				
Larynx	(49)	(50)	(50)	(49)
Foreign body	4 (8%)	3 (6%)	2 (4%)	6 (12%)
Epiglottis, inflammation, suppurative	1 (2%)		2 (4%)	5 (10%)
Epiglottis, metaplasia, squamous				1 (2%)
Glands, inflammation	20 (41%)	16 (32%)	18 (36%)	19 (39%)
Squamous epithelium, hyperplasia	5 (10%)	1 (2%)	1 (2%)	

TABLE B5
Summary of the Incidence of Nonneoplastic Lesions in Female Rats in the 2-Year Inhalation Study of Glutaraldehyde

	Chamber Control	250 ppb	500 ppb	750 ppb
Respiratory System (continued)				
Lung	(50)	(50)	(50)	(49)
Hemorrhage	1 (2%)			
Inflammation, chronic	1 (2%)			1 (2%)
Necrosis	1 (2%)			
Alveolar epithelium, hyperplasia	7 (14%)	4 (8%)	2 (4%)	4 (8%)
Alveolus, emphysema				2 (4%)
Alveolus, hemorrhage	1 (2%)		1 (2%)	
Alveolus, infiltration cellular, histiocyte	29 (58%)	24 (48%)	22 (44%)	35 (71%)
Alveolus, inflammation, suppurative	2 (4%)	1 (2%)		1 (2%)
Interstitium, fibrosis	9 (18%)	13 (26%)	17 (34%)	24 (49%)
Venule, thrombosis		1 (2%)		
Nose	(50)	(50)	(50)	(49)
Concretion	2 (4%)			
Foreign body	5 (10%)	3 (6%)	2 (4%)	
Goblet cell, respiratory epithelium, hyperplasia	1 (2%)	3 (6%)	5 (10%)	8 (16%)
Nasolacrimal duct, inflammation	4 (8%)	2 (4%)	2 (4%)	1 (2%)
Olfactory epithelium, atrophy				2 (4%)
Olfactory epithelium, degeneration, hyaline	4 (8%)	5 (10%)	12 (24%)	15 (31%)
Olfactory epithelium, inflammation			1 (2%)	
Respiratory epithelium, hyperplasia	1 (2%)	6 (12%)	15 (30%)	29 (59%)
Respiratory epithelium, inflammation	5 (10%)	9 (18%)	26 (52%)	42 (86%)
Respiratory epithelium, metaplasia, squamous	1 (2%)	1 (2%)	11 (22%)	16 (33%)
Septum, respiratory epithelium, ulcer			1 (2%)	
Squamous epithelium, hyperplasia	3 (6%)	15 (30%)	29 (58%)	45 (92%)
Squamous epithelium, inflammation	6 (12%)	26 (52%)	42 (84%)	48 (98%)
Pleura		(2)		
Hyperplasia, focal		1 (50%)		
Inflammation, chronic		1 (50%)		
Trachea	(49)	(50)	(50)	(50)
Inflammation, suppurative				1 (2%)
Special Senses System				
Eye	(2)	(2)	(3)	
Atrophy		1 (50%)		
Cataract	1 (50%)	1 (50%)	3 (100%)	
Degeneration	1 (50%)			
Urinary System				
Kidney	(49)	(50)	(50)	(50)
Cyst				1 (2%)
Mineralization	1 (2%)			
Nephropathy, chronic	38 (78%)	42 (84%)	37 (74%)	33 (66%)
Pelvis, dilatation	1 (2%)			

APPENDIX C
SUMMARY OF LESIONS IN MALE MICE IN THE 2-YEAR INHALATION STUDY OF GLUTARALDEHYDE

TABLE C1
Summary of the Incidence of Neoplasms in Male Mice in the 2-Year Inhalation Study of Glutaraldehyde[a]

	Chamber Control	62.5 ppb	125 ppb	250 ppb
Disposition Summary				
Animals initially in study	50	50	50	50
Early deaths				
Moribund	13	15	6	5
Natural deaths	6	8	4	7
Survivors				
Terminal sacrifice	31	27	40	38
Animals examined microscopically	50	50	50	50
Alimentary System				
Gallbladder	(42)	(36)	(41)	(46)
Sarcoma, metastatic, mesentery			1 (2%)	
Intestine large, cecum	(45)	(44)	(48)	(47)
Intestine small, duodenum	(43)	(43)	(47)	(46)
Carcinoma			1 (2%)	
Intestine small, jejunum	(43)	(44)	(47)	(46)
Intestine small, ileum	(44)	(46)	(48)	(47)
Liver	(49)	(50)	(50)	(49)
Hemangiosarcoma	2 (4%)		3 (6%)	2 (4%)
Hepatocellular carcinoma	15 (31%)	9 (18%)	10 (20%)	10 (20%)
Hepatocellular carcinoma, multiple		6 (12%)	2 (4%)	2 (4%)
Hepatocellular adenoma	15 (31%)	7 (14%)	16 (32%)	9 (18%)
Hepatocellular adenoma, multiple	4 (8%)	3 (6%)	4 (8%)	2 (4%)
Hepatocholangiocarcinoma		1 (2%)		1 (2%)
Histiocytic sarcoma	3 (6%)			
Mesentery	(2)	(2)	(3)	(5)
Sarcoma			1 (33%)	
Pancreas	(47)	(49)	(50)	(48)
Sarcoma, metastatic, mesentery			1 (2%)	
Stomach, forestomach	(48)	(49)	(50)	(48)
Sarcoma, metastatic, mesentery			1 (2%)	
Squamous cell carcinoma		1 (2%)		
Squamous cell papilloma		1 (2%)		
Stomach, glandular	(46)	(47)	(50)	(48)
Tooth	(13)	(17)	(10)	(19)
Odontoma	1 (8%)			
Cardiovascular System				
Heart	(49)	(50)	(50)	(49)
Hemangiosarcoma				1 (2%)
Hepatocholangiocarcinoma, metastatic, liver		1 (2%)		
Sarcoma, metastatic, mesentery			1 (2%)	
Endocrine System				
Adrenal cortex	(47)	(49)	(50)	(49)
Capsule, adenoma	2 (4%)		3 (6%)	1 (2%)
Pituitary gland	(46)	(47)	(48)	(47)
Pars distalis, adenoma	1 (2%)			
Pars intermedia, adenoma	1 (2%)			
Thyroid gland	(48)	(49)	(49)	(49)
Bilateral, follicular cell, adenoma	1 (2%)			
Follicular cell, adenoma		3 (6%)	2 (4%)	1 (2%)
Follicular cell, carcinoma	1 (2%)			

TABLE C1
Summary of the Incidence of Neoplasms in Male Mice in the 2-Year Inhalation Study of Glutaraldehyde

	Chamber Control	62.5 ppb	125 ppb	250 ppb
General Body System				
None				
Genital System				
Epididymis	(48)	(50)	(50)	(49)
Histiocytic sarcoma	1 (2%)	1 (2%)		
Preputial gland	(48)	(49)	(50)	(47)
Squamous cell carcinoma		1 (2%)		
Prostate	(49)	(48)	(50)	(47)
Seminal vesicle	(47)	(49)	(50)	(49)
Granular cell tumor benign			1 (2%)	
Testes	(48)	(50)	(50)	(50)
Interstitial cell, adenoma		1 (2%)	2 (4%)	2 (4%)
Hematopoietic System				
Bone marrow	(48)	(47)	(50)	(49)
Hemangiosarcoma	1 (2%)	1 (2%)		1 (2%)
Mast cell tumor malignant			1 (2%)	
Lymph node	(1)	(2)	(1)	(1)
Lymph node, bronchial	(34)	(28)	(35)	(37)
Alveolar/bronchiolar carcinoma, metastatic, lung			1 (3%)	
Histiocytic sarcoma	1 (3%)			
Lymph node, mandibular	(36)	(22)	(30)	(33)
Lymph node, mesenteric	(46)	(44)	(47)	(47)
Sarcoma, metastatic, mesentery			1 (2%)	
Lymph node, mediastinal	(29)	(27)	(33)	(30)
Histiocytic sarcoma	1 (3%)			
Spleen	(48)	(48)	(50)	(48)
Hemangiosarcoma	1 (2%)	1 (2%)	1 (2%)	1 (2%)
Histiocytic sarcoma		1 (2%)		
Thymus	(39)	(34)	(43)	(44)
Integumentary System				
Skin	(48)	(50)	(50)	(48)
Subcutaneous tissue, fibrosarcoma	1 (2%)	1 (2%)		
Subcutaneous tissue, sarcoma		1 (2%)		
Musculoskeletal System				
Skeletal muscle		(1)		
Hepatocholangiocarcinoma, metastatic, liver		1 (100%)		
Nervous System				
None				

TABLE C1
Summary of the Incidence of Neoplasms in Male Mice in the 2-Year Inhalation Study of Glutaraldehyde

	Chamber Control	62.5 ppb	125 ppb	250 ppb
Respiratory System				
Lung	(48)	(50)	(50)	(50)
Alveolar/bronchiolar adenoma	8 (17%)	10 (20%)	9 (18%)	6 (12%)
Alveolar/bronchiolar adenoma, multiple				1 (2%)
Alveolar/bronchiolar carcinoma	9 (19%)	6 (12%)	7 (14%)	6 (12%)
Alveolar/bronchiolar carcinoma, multiple	1 (2%)			1 (2%)
Hepatocellular carcinoma, metastatic, liver	6 (13%)	2 (4%)	6 (12%)	4 (8%)
Hepatocholangiocarcinoma, metastatic, liver		1 (2%)		
Histiocytic sarcoma	2 (4%)			
Mediastinum, alveolar/bronchiolar carcinoma, metastatic, lung				1 (2%)
Pleura		(1)		(2)
Alveolar/bronchiolar carcinoma, metastatic, lung		1 (100%)		1 (50%)
Special Senses System				
Harderian gland	(4)	(5)	(2)	(2)
Adenoma	3 (75%)	3 (60%)	2 (100%)	1 (50%)
Carcinoma	1 (25%)	2 (40%)		1 (50%)
Urinary System				
Kidney	(48)	(49)	(50)	(49)
Alveolar/bronchiolar carcinoma, metastatic, lung			1 (2%)	
Hepatocholangiocarcinoma, metastatic, liver		1 (2%)		
Histiocytic sarcoma	1 (2%)			
Mast cell tumor malignant, metastatic, bone marrow			1 (2%)	
Systemic Lesions				
Multiple organs[b]	(50)	(50)	(50)	(50)
Histiocytic sarcoma	3 (6%)	1 (2%)		
Lymphoma malignant	4 (8%)	5 (10%)	1 (2%)	5 (10%)
Neoplasm Summary				
Total animals with primary neoplasms[c]	44	42	39	33
Total primary neoplasms	75	64	66	54
Total animals with benign neoplasms	27	24	29	19
Total benign neoplasms	36	28	39	23
Total animals with malignant neoplasms	33	28	23	22
Total malignant neoplasms	39	36	27	31
Total animals with metastatic neoplasms	6	4	8	5
Total metastatic neoplasms	6	7	14	6

[a] Number of animals examined microscopically at the site and the number of animals with neoplasm
[b] Number of animals with any tissue examined microscopically
[c] Primary neoplasms: all neoplasms except metastatic neoplasms

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Inhalation Study of Glutaraldehyde: Chamber Control

Number of Days on Study	3 5 9	4 5 4	4 9 8	5 1 6	5 3 2	5 3 4	5 7 3	6 0 2	6 1 6	6 2 6	6 7 0	6 7 5	6 8 4	6 8 4	6 8 8	7 0 2	7 1 2	7 1 6	7 2 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3
Carcass ID Number	0 3 2	0 0 5	0 0 8	0 1 7	0 2 3	0 1 5	0 1 3	0 1 9	0 1 6	0 1 1	0 1 7	0 3 4	0 2 4	0 3 1	0 4 3	0 1 4	0 2 2	0 3 5	0 3 8	0 2 0	0 2 0	0 1 0	0 1 2	0 2 5	0 2 6	0 2 8
Alimentary System																										
Esophagus	+	+	A	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder	+	+	A	+	+	+	M	+	+	A	A	A	+	A	A	+	A	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	A	+	+	+	+	+	+	A	A	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	A	+	+	+	I	+	+	A	A	A	+	A	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	A	+	+	+	+	+	+	A	+	A	+	A	+	+	A	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	A	+	+	+	+	+	+	A	A	A	+	A	A	+	A	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	A	+	+	+	+	+	+	A	A	A	+	A	A	+	A	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	A	+	+	+	+	+	+	A	A	A	+	A	A	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																			X							
Hepatocellular carcinoma			X		X	X	X		X	X		X		X	X	X	X			X						
Hepatocellular adenoma				X					X						X							X	X	X	X	
Hepatocellular adenoma, multiple																										
Histiocytic sarcoma							X						X									X				
Mesentery														+												
Oral mucosa						+																				
Pancreas	+	+	M	+	+	+	+	+	+	+	A	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	A	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	A	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	A	+	+	+	+	+	+	A	A	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+
Tooth								+										+	+	+					+	
Odontoma																										
Cardiovascular System																										
Blood vessel														+												
Heart	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																										
Adrenal cortex	+	+	A	+	+	+	+	+	+	+	A	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+
Capsule, adenoma																										
Adrenal medulla	+	+	A	+	+	+	+	+	+	+	A	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+
Islets, pancreatic	+	+	M	+	+	+	+	+	+	+	A	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid gland	+	+	A	M	+	M	M	+	+	+	A	M	M	M	M	+	M	+	M	M	M	M	M	M	M	M
Pituitary gland	+	+	I	+	+	+	+	+	+	+	A	+	+	+	+	+	+	I	+	+	+	+	+	+	+	+
Pars distalis, adenoma																										
Pars intermedia, adenoma																										
Thyroid gland	+	+	A	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Bilateral, follicular cell, adenoma																						X				
Follicular cell, carcinoma																		X								
General Body System																										
None																										
Genital System																										
Coagulating gland													+													
Epididymis	+	+	A	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma							X																			
Preputial gland	+	+	A	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Prostate	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Seminal vesicle	+	+	A	+	+	+	+	+	+	+	A	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+
Testes	+	+	A	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	

+: Tissue examined microscopically
A: Autolysis precludes examination
M: Missing tissue
I: Insufficient tissue
X: Lesion present
Blank: Not examined

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Inhalation Study of Glutaraldehyde: Chamber Control

Number of Days on Study	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	
Carcass ID Number	0 2 9	0 3 0	0 3 3	0 3 4	0 3 9	0 4 1	0 4 4	0 4 6	0 4 7	0 4 8	0 4 9	0 0 3	0 0 4	0 2 1	0 2 7	0 3 6	0 4 5	0 5 0	0 0 1	0 0 6	0 0 7	0 0 9	0 1 8	0 4 0	0 4 2	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	42
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Intestine large, rectum	+	+	+	+	+	+	+	+	+	I	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	43
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	43
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	43
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Hemangiosarcoma																X										2
Hepatocellular carcinoma		X									X			X												15
Hepatocellular adenoma			X					X								X		X		X		X		X	X	15
Hepatocellular adenoma, multiple													X		X						X		X			4
Histiocytic sarcoma																										3
Mesentery																							+			2
Oral mucosa																										1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Tooth				+	+							+		+		+			+	+				+		13
Odontoma												X														1
Cardiovascular System																										
Blood vessel																										1
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Capsule, adenoma					X							X														2
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Parathyroid gland	M	M	M	M	+	M	+	+	+	M	+	+	+	+	M	+	M	+	M	M	+	+	+	M	M	21
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	I	+	+	+	+	+	+	+	+	+	46
Pars distalis, adenoma																							X			1
Pars intermedia, adenoma																				X						1
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Bilateral, follicular cell, adenoma																										1
Follicular cell, carcinoma																										1
General Body System																										
None																										
Genital System																										
Coagulating gland																										1
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Histiocytic sarcoma																										1
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Inhalation Study of Glutaraldehyde: Chamber Control

Number of Days on Study	3 5 9	4 5 4	4 9 8	5 1 6	5 3 2	5 3 4	5 7 3	6 0 2	6 1 6	6 2 6	6 7 0	6 7 5	6 8 4	6 8 4	6 8 8	7 0 2	7 1 2	7 1 6	7 2 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3
Carcass ID Number	0 3 2	0 0 5	0 0 8	0 1 7	0 2 3	0 1 5	0 1 3	0 1 9	0 1 6	0 1 1	0 3 7	0 2 4	0 3 1	0 4 3	0 1 4	0 2 2	0 3 5	0 3 8	0 2 0	0 1 0	0 1 2	0 2 5	0 2 6	0 2 8
Hematopoietic System																								
Bone marrow	+	+	A	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma				X																				
Lymph node											+													
Lymph node, bronchial	+	M	A	+	+	M	+	M	+	M	+	M	+	+	+	+	M	M	M	+	+	+	+	M
Histiocytic sarcoma													X											
Lymph node, mandibular	+	+	A	+	+	+	+	M	M	+	+	+	M	+	+	+	M	M	M	+	+	M	+	+
Lymph node, mesenteric	+	+	A	+	+	+	+	+	+	+	A	+	+	M	+	+	M	+	+	+	+	+	+	+
Lymph node, mediastinal	+	M	A	+	+	+	+	M	+	M	+	+	+	M	M	+	+	M	M	M	M	M	+	+
Histiocytic sarcoma													X											
Spleen	+	+	M	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma				X																				
Thymus	+	+	A	+	M	+	+	M	+	+	A	M	M	A	+	+	+	+	+	+	+	+	+	+
Integumentary System																								
Mammary gland	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M
Skin	+	+	A	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+
Subcutaneous tissue, fibrosarcoma																	X							
Musculoskeletal System																								
Bone	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+
Nervous System																								
Brain	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+
Respiratory System																								
Larynx	+	+	A	+	+	+	+	+	+	+	A	+	+	A	+	+	+	+	+	+	+	+	+	+
Lung	+	+	A	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma							X															X		X
Alveolar/bronchiolar carcinoma		X						X											X	X			X	
Alveolar/bronchiolar carcinoma, multiple																								
Hepatocellular carcinoma, metastatic, liver					X					X		X			X	X	X							
Histiocytic sarcoma							X						X											
Nose	+	+	A	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	A	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																								
Ear														+										
Harderian gland													+				+							
Adenoma													X				X							
Carcinoma																								
Urinary System																								
Kidney	+	+	A	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma							X																	
Urinary bladder	+	+	A	+	+	+	+	+	+	+	A	+	+	A	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																								
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma							X						X							X				
Lymphoma malignant											X											X		X

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Inhalation Study of Glutaraldehyde: Chamber Control

Number of Days on Study	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	
Carcass ID Number	0 2 9	0 3 0	0 3 3	0 3 4	0 3 9	0 4 1	0 4 4	0 4 6	0 4 7	0 4 8	0 4 9	0 0 3	0 0 4	0 2 1	0 2 7	0 3 6	0 4 5	0 5 0	0 0 1	0 0 6	0 0 7	0 0 9	0 1 8	0 4 0	0 4 2	Total Tissues/ Tumors
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Hemangiosarcoma																										1
Lymph node																										1
Lymph node, bronchial	+	+	M	M	+	+	+	M	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	M	34
Histiocytic sarcoma																										1
Lymph node, mandibular	+	+	+	M	+	+	+	+	+	+	M	+	+	M	M	+	+	+	+	+	+	+	M	M	+	36
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Lymph node, mediastinal	M	+	M	M	+	M	+	M	+	M	+	+	+	+	M	M	M	+	+	+	+	+	+	+	M	29
Histiocytic sarcoma																										1
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Hemangiosarcoma																										1
Thymus	+	+	+	+	M	M	+	+	+	+	+	M	+	M	+	+	+	+	+	+	+	+	+	+	+	39
Integumentary System																										
Mammary gland	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Subcutaneous tissue, fibrosarcoma																										1
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Respiratory System																										
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Alveolar/bronchiolar adenoma										X		X			X	X		X								8
Alveolar/bronchiolar carcinoma		X							X				X								X					9
Alveolar/bronchiolar carcinoma, multiple																								X		1
Hepatocellular carcinoma, metastatic, liver																										6
Histiocytic sarcoma																										2
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Special Senses System																										
Ear																										1
Harderian gland		+																		+						4
Adenoma		X																								3
Carcinoma																				X						1
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Histiocytic sarcoma																										1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																										3
Lymphoma malignant							X																			4

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Inhalation Study of Glutaraldehyde: 62.5 ppb

Number of Days on Study	3 6 4	4 0 2	4 2 0	4 7 6	5 1 7	5 2 4	5 2 4	5 3 9	5 5 1	5 7 3	5 8 8	5 9 8	6 1 6	6 4 0	6 4 0	6 4 7	6 6 6	6 8 5	6 9 8	7 0 6	7 0 7	7 1 8	7 2 3	7 3 3	7 3 3
Carcass ID Number	2 1 7	2 0 5	2 4 4	2 4 8	2 4 3	2 3 1	2 3 3	2 2 0	2 2 7	2 0 7	2 1 6	2 4 9	2 2 6	2 2 1	2 2 2	2 2 3	2 0 6	2 0 2	2 1 0	2 0 3	2 1 4	2 0 4	2 5 0	2 1 1	2 1 2
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder	+	+	+	+	+	+	M	A	+	+	A	+	+	A	A	A	+	+	A	+	M	A	+	+	M
Intestine large, colon	+	+	+	+	+	+	+	A	+	+	A	+	+	+	A	+	+	+	A	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	A	+	+	A	+	+	+	A	+	+	+	A	+	+	A	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	A	+	+	A	+	+	+	A	A	+	+	A	+	+	A	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	A	+	+	A	+	+	A	A	A	+	+	A	+	+	A	+	+	+
Intestine small, jejunum	+	+	+	+	+	+	+	A	+	+	A	+	+	A	A	A	+	+	+	+	+	A	+	+	+
Intestine small, ileum	+	+	+	+	+	+	+	A	+	+	A	+	+	+	A	A	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular carcinoma						X				X		X	X		X				X				X		
Hepatocellular carcinoma, multiple					X		X	X													X				
Hepatocellular adenoma										X	X						X								
Hepatocellular adenoma, multiple																									
Hepatocholangiocarcinoma									X																
Mesentery																		+							
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+
Squamous cell carcinoma																						X			
Squamous cell papilloma																									
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	A	+	+	+	A	+	+	+	A	+	+	+	+	+	+
Tooth																	+			+		+		+	
Cardiovascular System																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocholangiocarcinoma, metastatic, liver									X																
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	A	+	+	+
Parathyroid gland	+	+	M	+	+	M	+	+	M	M	M	M	+	M	+	+	+	M	M	M	+	+	+	+	M
Pituitary gland	+	+	+	+	+	M	+	+	+	+	+	+	+	+	A	+	+	+	A	+	+	+	+	+	+
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+
Follicular cell, adenoma																									
General Body System																									
None																									
Genital System																									
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma													X												
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+
Squamous cell carcinoma																									
Prostate	+	+	+	M	+	+	+	+	+	I	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Interstitial cell, adenoma														X											

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Inhalation Study of Glutaraldehyde: 62.5 ppb

Number of Days on Study	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 5	7 3 5	7 3 5	7 3 5	
Carcass ID Number	2 1 3	2 1 8	2 1 9	2 3 0	2 3 5	2 4 0	2 4 5	2 0 1	2 0 8	2 2 4	2 2 5	2 2 8	2 2 9	2 3 4	2 3 6	2 3 7	2 3 8	2 4 1	2 4 2	2 4 6	2 4 7	2 0 9	2 1 5	2 3 2	2 3 9	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder	M	M	M	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	36
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	43
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular carcinoma		X					X																			9
Hepatocellular carcinoma, multiple														X			X									6
Hepatocellular adenoma				X															X			X			X	7
Hepatocellular adenoma, multiple										X	X					X										3
Hepatocholangiocarcinoma																										1
Mesentery																						+				2
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Squamous cell carcinoma																										1
Squamous cell papilloma													X													1
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Tooth	+		+	+	+	+	+		+				+		+		+		+				+		+	17
Cardiovascular System																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocholangiocarcinoma, metastatic, liver																										1
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Parathyroid gland	M	+	M	+	M	M	+	+	+	+	M	+	M	+	+	+	+	+	M	M	M	+	M	M	M	27
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Follicular cell, adenoma			X						X									X								3
General Body System																										
None																										
Genital System																										
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																										1
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Squamous cell carcinoma														X												1
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Interstitial cell, adenoma																										1

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Inhalation Study of Glutaraldehyde: 62.5 ppb

Number of Days on Study	3 6 4	4 0 2	4 2 0	4 7 6	5 1 7	5 2 4	5 2 4	5 3 9	5 5 1	5 7 3	5 8 8	5 9 8	6 1 6	6 4 0	6 4 0	6 4 7	6 6 6	6 8 5	6 9 8	7 0 6	7 0 7	7 1 8	7 2 3	7 3 3	7 3 3
Carcass ID Number	2 1 7	2 0 5	2 4 4	2 4 8	2 4 3	2 3 1	2 3 3	2 2 0	2 2 7	2 0 7	2 1 6	2 4 9	2 2 6	2 2 1	2 2 2	2 2 3	2 0 6	2 0 2	2 1 0	2 0 3	2 1 4	2 0 4	2 5 0	2 1 1	2 1 2
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	A	+	+	A	+	+	+	+	+	+
Hemangiosarcoma																		X							
Lymph node														+								+			
Lymph node, bronchial	+	+	M	M	+	M	+	+	+	+	M	+	M	+	+	+	M	M	M	M	M	M	M	M	M
Lymph node, mandibular	+	M	M	M	M	+	+	+	+	+	M	+	M	M	A	+	+	+	+	M	+	A	M	M	M
Lymph node, mesenteric	+	M	+	+	+	+	+	+	+	+	A	+	+	+	A	+	+	+	+	+	M	+	+	M	+
Lymph node, mediastinal	+	M	M	+	+	M	M	+	M	+	+	+	+	+	M	+	M	+	M	M	M	M	I	M	+
Spleen	+	+	+	+	+	+	+	A	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																		X							
Histiocytic sarcoma													X												
Thymus	+	+	+	M	+	+	M	+	+	+	+	+	M	M	A	+	+	M	M	M	M	A	M	M	+
Integumentary System																									
Mammary gland	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Subcutaneous tissue, fibrosarcoma				X																					
Subcutaneous tissue, sarcoma																X									
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skeletal muscle									+																
Hepatocholangiocarcinoma, metastatic, liver									X																
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Respiratory System																									
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma					X								X								X				
Alveolar/bronchiolar carcinoma	X					X					X													X	
Hepatocellular carcinoma, metastatic, liver					X																				
Hepatocholangiocarcinoma, metastatic, liver									X																
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pleura	+																								
Alveolar/bronchiolar carcinoma, metastatic, lung	X																								
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Harderian gland																				+					
Adenoma																									
Carcinoma																				X					
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+
Hepatocholangiocarcinoma, metastatic, liver									X																
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	A	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma													X												
Lymphoma malignant														X					X			X			

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Inhalation Study of Glutaraldehyde: 62.5 ppb

Number of Days on Study	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 5	7 3 5	7 3 5	7 3 5	
Carcass ID Number	2 1 3	2 1 8	2 1 9	2 3 0	2 3 5	2 4 0	2 4 5	2 0 1	2 0 8	2 2 4	2 2 5	2 2 8	2 2 9	2 3 4	2 3 6	2 3 7	2 3 8	2 4 1	2 4 2	2 4 6	2 4 7	2 0 9	2 1 5	2 3 2	2 3 9	Total Tissues/ Tumors
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Hemangiosarcoma																										1
Lymph node																										2
Lymph node, bronchial	M	+	+	M	+	+	M	+	M	+	+	M	+	+	+	+	M	+	M	+	+	M	+	+	+	28
Lymph node, mandibular	M	+	M	M	M	+	M	M	+	I	M	+	M	M	M	M	M	M	+	+	M	+	+	+	+	22
Lymph node, mesenteric	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
Lymph node, mediastinal	+	M	M	M	+	+	M	+	+	+	+	+	M	M	+	M	+	M	+	+	+	M	+	M	+	27
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Hemangiosarcoma																										1
Histiocytic sarcoma																										1
Thymus	M	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	M	+	+	34
Integumentary System																										
Mammary gland	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Subcutaneous tissue, fibrosarcoma																										1
Subcutaneous tissue, sarcoma																										1
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Skeletal muscle																										1
Hepatocholangiocarcinoma, metastatic, liver																										1
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Respiratory System																										
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma				X			X										X		X	X			X	X		10
Alveolar/bronchiolar carcinoma													X				X									6
Hepatocellular carcinoma, metastatic, liver																	X									2
Hepatocholangiocarcinoma, metastatic, liver																										1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pleura																										1
Alveolar/bronchiolar carcinoma, metastatic, lung																										1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Special Senses System																										
Harderian gland										+	+	+				+										5
Adenoma											X	X				X										3
Carcinoma										X																2
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Hepatocholangiocarcinoma, metastatic, liver																										1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																										1
Lymphoma malignant					X					X																5

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Inhalation Study of Glutaraldehyde: 125 ppb

Number of Days on Study	2 7 9	4 7 0	4 9 2	5 0 4	5 1 6	5 1 9	6 0 5	7 0 2	7 1 5	7 1 9	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3
Carcass ID Number	4 1 2	4 0 9	4 2 7	4 1 4	4 0 7	4 3 8	4 2 0	4 4 5	4 4 1	4 4 6	4 0 2	4 0 4	4 1 0	4 1 8	4 1 9	4 2 6	4 2 8	4 3 0	4 3 2	4 3 4	4 3 5	4 3 9	4 4 3	4 4 7	4 5 0
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder	+	A	A	+	M	M	A	+	A	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma, metastatic, mesentery				X																					
Intestine large, colon	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	A	+	+	+	+	I	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma																									
Intestine small, jejunum	+	A	+	+	+	+	A	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	A	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma															X			X	X						
Hepatocellular carcinoma			X		X				X						X	X								X	
Hepatocellular carcinoma, multiple						X																			
Hepatocellular adenoma			X						X	X			X		X		X	X						X	
Hepatocellular adenoma, multiple																				X			X		
Mesentery				+						+															+
Sarcoma				X																					
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma, metastatic, mesentery				X																					
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma, metastatic, mesentery				X																					
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tooth				+										+			+								
Cardiovascular System																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma, metastatic, mesentery				X																					
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Capsule, adenoma																					X				
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid gland	M	+	+	+	+	+	M	M	M	+	+	+	+	+	I	+	+	+	M	M	M	M	M	M	I
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	I	+	+	+	+	+	+	+
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+
Follicular cell, adenoma																			X						
General Body System																									
None																									
Genital System																									
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Penis										+															
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Granular cell tumor benign																									
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Interstitial cell, adenoma																							X		

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Inhalation Study of Glutaraldehyde: 125 ppb

Number of Days on Study	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	
Carcass ID Number	4 0 1	4 0 3	4 0 5	4 0 6	4 0 8	4 1 1	4 1 3	4 1 7	4 2 1	4 2 2	4 2 3	4 2 4	4 2 9	4 3 1	4 3 6	4 3 7	4 4 0	4 4 2	4 4 4	4 4 9	4 1 5	4 1 6	4 2 5	4 3 3	4 4 8	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	M	+	+	+	41
Sarcoma, metastatic, mesentery																										1
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	I	+	+	+	48
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Carcinoma																						X				1
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma																										3
Hepatocellular carcinoma	X	X				X					X															10
Hepatocellular carcinoma, multiple										X																2
Hepatocellular adenoma				X	X	X			X		X						X					X		X		16
Hepatocellular adenoma, multiple																		X	X							4
Mesentery																										3
Sarcoma																										1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Sarcoma, metastatic, mesentery																										1
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Sarcoma, metastatic, mesentery																										1
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Tooth			+		+	+						+				+	+						+		10
Cardiovascular System																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Sarcoma, metastatic, mesentery																										1
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Capsule, adenoma							X									X										3
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Parathyroid gland	M	+	M	+	+	+	+	M	M	M	+	M	+	+	+	+	M	M	+	+	M	+	M	+	M	27
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	48
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Follicular cell, adenoma																				X						2
General Body System																										
None																										
Genital System																										
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Penis																										1
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Granular cell tumor benign											X															1
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Interstitial cell, adenoma				X																						2

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Inhalation Study of Glutaraldehyde: 125 ppb

Number of Days on Study	2 7 9	4 7 0	4 9 2	5 0 4	5 1 6	5 1 9	6 0 5	7 0 2	7 1 5	7 1 9	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3
Carcass ID Number	4 1 2	4 0 9	4 2 7	4 1 4	4 0 4	4 3 8	4 2 0	4 4 5	4 4 1	4 4 6	4 0 2	4 0 4	4 1 0	4 1 8	4 1 9	4 2 6	4 2 8	4 3 0	4 3 2	4 3 4	4 3 5	4 3 9	4 4 3	4 4 7	4 5 0
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mast cell tumor malignant																									
Lymph node																									
Lymph node, bronchial	M	+	+	+	+	M	M	M	+	M	+	+	+	+	+	+	+	+	M	M	+	+	+	+	+
Alveolar/bronchiolar carcinoma, metastatic, lung				X																					
Lymph node, mandibular	+	M	M	M	+	+	+	M	M	+	+	+	+	+	M	M	+	+	M	M	M	M	M	+	M
Lymph node, mesenteric	+	+	+	+	M	+	+	+	+	+	+	M	+	M	+	+	+	+	+	+	+	+	+	+	+
Sarcoma, metastatic, mesentery				X																					
Lymph node, mediastinal	+	+	M	+	+	+	M	M	+	M	+	M	+	+	+	+	M	+	M	+	M	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																						X			
Thymus	+	+	+	+	+	M	M	+	+	+	+	+	+	+	M	+	+	+	M	+	+	+	+	+	+
Integumentary System																									
Mammary gland	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	+
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Respiratory System																									
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma					X				X	X					X										
Alveolar/bronchiolar carcinoma		X		X							X				X										
Hepatocellular carcinoma, metastatic, liver																X								X	
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Eye					+																				
Harderian gland																+									
Adenoma																X									
Lacrimal gland			+																						
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar carcinoma, metastatic, lung				X																					
Mast cell tumor malignant, metastatic, bone marrow																									
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant																									

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Inhalation Study of Glutaraldehyde: 125 ppb

Number of Days on Study	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	
Carcass ID Number	4 0 1	4 0 3	4 0 5	4 0 6	4 0 8	4 1 1	4 1 3	4 1 7	4 2 1	4 2 2	4 2 3	4 2 4	4 2 9	4 3 1	4 3 6	4 3 7	4 4 0	4 4 2	4 4 4	4 4 9	4 1 5	4 1 6	4 2 5	4 3 3	4 4 8	Total Tissues/ Tumors
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Mast cell tumor malignant																			X							1
Lymph node												+														1
Lymph node, bronchial	+	+	+	M	+	+	M	M	+	M	+	M	M	+	+	+	+	+	+	M	+	M	+	+	+	35
Alveolar/bronchiolar carcinoma, metastatic, lung																										1
Lymph node, mandibular	M	+	+	M	+	+	+	M	+	+	+	+	+	M	M	+	+	M	+	+	+	+	+	M	+	30
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Sarcoma, metastatic, mesentery																										1
Lymph node, mediastinal	M	M	M	M	+	+	M	M	+	+	+	+	M	+	+	+	+	+	+	+	+	M	M	+	+	33
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma																										1
Thymus	+	M	+	+	+	+	+	+	M	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	43
Integumentary System																										
Mammary gland	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	1
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Respiratory System																										
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma				X				X					X				X							X		9
Alveolar/bronchiolar carcinoma						X			X																X	7
Hepatocellular carcinoma, metastatic, liver	X	X								X	X															6
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Special Senses System																										
Eye																										1
Harderian gland													+													2
Adenoma													X													2
Lacrimal gland																										1
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar carcinoma, metastatic, lung																										1
Mast cell tumor malignant, metastatic, bone marrow																			X							1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymphoma malignant												X														1

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Inhalation Study of Glutaraldehyde: 250 ppb

Number of Days on Study	3 2 7	5 0 4	5 5 8	5 8 9	6 2 8	6 4 1	6 5 1	6 6 3	6 7 2	6 7 3	7 0 4	7 2 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3
Carcass ID Number	6 2 4	6 3 9	6 1 4	6 3 2	6 3 0	6 2 9	6 0 5	6 2 5	6 4 1	6 1 0	6 2 7	6 1 5	6 0 1	6 0 7	6 0 8	6 0 9	6 1 1	6 1 2	6 1 3	6 1 6	6 1 9	6 2 0	6 2 2	6 3 1	6 3 5
Alimentary System																									
Esophagus	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder	A	+	+	A	A	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	A	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	A	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	A	+	+	+	A	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	A	+	+	+	A	A	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	A	+	+	+	A	A	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	A	+	+	+	A	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma								X																	
Hepatocellular carcinoma			X				X	X	X											X					
Hepatocellular carcinoma, multiple				X							X														
Hepatocellular adenoma										X			X	X			X			X					
Hepatocellular adenoma, multiple																									
Hepatocholangiocarcinoma									X																
Mesentery									+	+															+
Pancreas	A	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	A	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	A	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tooth			+									+			+	+	+		+	+	+		+		+
Cardiovascular System																									
Heart	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma								X																	
Endocrine System																									
Adrenal cortex	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Capsule, adenoma																									
Adrenal medulla	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islets, pancreatic	A	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid gland	+	+	+	+	A	M	M	+	M	+	+	M	M	+	+	M	+	+	M	M	+	M	+	M	M
Pituitary gland	A	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thyroid gland	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell, adenoma																									
General Body System																									
None																									
Genital System																									
Epididymis	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Preputial gland	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Prostate	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	I	+	+	+	+	+	+
Seminal vesicle	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Interstitial cell, adenoma							X													X					

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Inhalation Study of Glutaraldehyde: 250 ppb

Number of Days on Study	7 3 3	7 3 3	7 3 3	7 3 3	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 5	7 3 5	7 3 5	
Carcass ID Number	6 3 7	6 3 8	6 4 3	6 4 7	6 0 2	6 0 3	6 0 4	6 0 6	6 1 8	6 2 1	6 2 3	6 2 6	6 2 8	6 3 3	6 3 4	6 3 6	6 4 2	6 4 4	6 4 5	6 4 6	6 4 8	6 5 0	6 1 7	6 4 0	6 4 9	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Hemangiosarcoma																							X			2
Hepatocellular carcinoma			X			X											X			X			X			10
Hepatocellular carcinoma, multiple																										2
Hepatocellular adenoma											X		X		X								X			9
Hepatocellular adenoma, multiple																X									X	2
Hepatocholangiocarcinoma																										1
Mesentery	+						+																			5
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Tooth	+								+		+	+	+	+		+		+					+			19
Cardiovascular System																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Hemangiosarcoma																										1
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Capsule, adenoma																							X			1
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Parathyroid gland	M	M	M	M	+	+	+	M	+	+	+	+	M	+	+	+	+	M	M	M	+	+	M	+	M	27
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	I	+	+	+	+	+	+	+	+	+	+	+	47
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Follicular cell, adenoma						X																				1
General Body System																										
None																										
Genital System																										
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	M	+	+	+	+	47
Prostate	+	+	+	+	+	I	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Interstitial cell, adenoma																										2

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Inhalation Study of Glutaraldehyde: 250 ppb

Number of Days on Study	3 2 7	5 0 4	5 5 8	5 8 9	6 2 8	6 4 1	6 5 1	6 6 3	6 7 2	6 7 3	7 0 4	7 2 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3
Carcass ID Number	6 2 4	6 3 9	6 1 4	6 3 2	6 3 0	6 2 9	6 0 5	6 2 5	6 4 1	6 1 0	6 2 7	6 1 5	6 0 1	6 0 7	6 0 8	6 0 9	6 1 1	6 1 2	6 1 3	6 1 6	6 1 9	6 2 0	6 2 2	6 3 1	6 3 5
Hematopoietic System																									
Bone marrow	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma								X																	
Lymph node																									
Lymph node, bronchial	+	+	+	M	M	+	M	M	+	M	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mandibular	+	M	M	+	A	+	+	M	M	+	+	+	M	+	+	+	M	+	+	+	M	+	M	M	M
Lymph node, mesenteric	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+
Lymph node, mediastinal	+	M	M	+	A	M	M	+	+	+	+	M	M	M	+	+	+	M	M	M	M	+	+	+	+
Spleen	A	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma								X																	
Thymus	+	+	+	+	A	M	M	M	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	M	+
Integumentary System																									
Mammary gland	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M
Skin	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Respiratory System																									
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma					X						X					X									
Alveolar/bronchiolar adenoma, multiple																	X								
Alveolar/bronchiolar carcinoma										X		X	X									X			X
Alveolar/bronchiolar carcinoma, multiple																									
Hepatocellular carcinoma, metastatic, liver							X	X																	
Mediastinum, alveolar/bronchiolar carcinoma, metastatic, lung										X															
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pleura	+									+															
Alveolar/bronchiolar carcinoma, metastatic, lung										X															
Trachea	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Harderian gland																									
Adenoma																									
Carcinoma																									
Urinary System																									
Kidney	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	A	+	+	A	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant																									

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Inhalation Study of Glutaraldehyde: 250 ppb

Number of Days on Study	7 3 3	7 3 3	7 3 3	7 3 3	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 5	7 3 5	7 3 5	
Carcass ID Number	6 3 7	6 3 8	6 4 3	6 4 7	6 0 2	6 0 3	6 0 4	6 0 6	6 1 8	6 2 1	6 2 3	6 2 6	6 2 8	6 3 3	6 3 4	6 3 6	6 4 2	6 4 4	6 4 5	6 4 6	6 4 8	6 5 0	6 1 7	6 4 0	6 4 9	Total Tissues/ Tumors
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Hemangiosarcoma																										1
Lymph node																			+							1
Lymph node, bronchial	+	+	+	M	M	M	+	+	M	+	+	+	+	+	+	+	+	M	+	+	M	+	M	+	+	37
Lymph node, mandibular	+	M	+	+	+	+	+	M	M	+	+	+	+	M	+	M	+	+	+	+	M	+	+	+	+	33
Lymph node, mesenteric	+	+	+	I	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Lymph node, mediastinal	+	+	+	+	M	M	M	+	+	+	+	+	+	M	+	+	M	M	+	M	+	+	M	+	+	30
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Hemangiosarcoma																										1
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
Integumentary System																										
Mammary gland	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	
Skin	+	+	+	+	+	+	I	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Respiratory System																										
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma									X						X			X								6
Alveolar/bronchiolar adenoma, multiple																										1
Alveolar/bronchiolar carcinoma																			X							6
Alveolar/bronchiolar carcinoma, multiple																							X			1
Hepatocellular carcinoma, metastatic, liver																	X			X						4
Mediastinum, alveolar/bronchiolar carcinoma, metastatic, lung																										1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pleura																										2
Alveolar/bronchiolar carcinoma, metastatic, lung																										1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Special Senses System																										
Harderian gland								+																+		2
Adenoma								X																		1
Carcinoma																								X		1
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymphoma malignant	X														X				X	X	X					5

TABLE C3
Statistical Analysis of Primary Neoplasms in Male Mice in the 2-Year Inhalation Study of Glutaraldehyde

	Chamber Control	62.5 ppb	125 ppb	250 ppb
Adrenal Cortex: Adenoma				
Overall rate[a]	2/47 (4%)	0/49 (0%)	3/50 (6%)	1/49 (2%)
Adjusted rate[b]	4.9%	0.0%	6.7%	2.2%
Terminal rate[c]	2/31 (7%)	0/27 (0%)	3/40 (8%)	1/38 (3%)
First incidence (days)	733 (T)	—[e]	733 (T)	733 (T)
Poly-3 test[d]	P=0.500N	P=0.246N	P=0.544	P=0.467N
Harderian Gland: Adenoma				
Overall rate	3/50 (6%)	3/50 (6%)	2/50 (4%)	1/50 (2%)
Adjusted rate	7.0%	7.5%	4.4%	2.2%
Terminal rate	1/31 (3%)	3/27 (11%)	2/40 (5%)	1/38 (3%)
First incidence (days)	684	733 (T)	733 (T)	733 (T)
Poly-3 test	P=0.171N	P=0.628	P=0.480N	P=0.285N
Harderian Gland: Adenoma or Carcinoma				
Overall rate	4/50 (8%)	5/50 (10%)	2/50 (4%)	2/50 (4%)
Adjusted rate	9.3%	12.5%	4.4%	4.4%
Terminal rate	2/31 (7%)	4/27 (15%)	2/40 (5%)	2/38 (5%)
First incidence (days)	684	706	733 (T)	733 (T)
Poly-3 test	P=0.154N	P=0.455	P=0.316N	P=0.311N
Liver: Hemangiosarcoma				
Overall rate	2/49 (4%)	0/50 (0%)	3/50 (6%)	2/49 (4%)
Adjusted rate	4.8%	0.0%	6.7%	4.4%
Terminal rate	1/31 (3%)	0/27 (0%)	3/40 (8%)	1/38 (3%)
First incidence (days)	716	—	733 (T)	663
Poly-3 test	P=0.477	P=0.248N	P=0.531	P=0.668N
Liver: Hepatocellular Adenoma				
Overall rate	19/49 (39%)	10/50 (20%)	20/50 (40%)	11/49 (22%)
Adjusted rate	44.0%	24.3%	43.7%	24.4%
Terminal rate	16/31 (52%)	7/27 (26%)	17/40 (43%)	10/38 (26%)
First incidence (days)	516	573	492	673
Poly-3 test	P=0.083N	P=0.042N	P=0.573N	P=0.039N
Liver: Hepatocellular Carcinoma				
Overall rate	15/49 (31%)	15/50 (30%)	12/50 (24%)	12/49 (24%)
Adjusted rate	32.6%	33.8%	25.5%	25.6%
Terminal rate	3/31 (10%)	4/27 (15%)	8/40 (20%)	6/38 (16%)
First incidence (days)	498	517	492	558
Poly-3 test	P=0.209N	P=0.543	P=0.300N	P=0.305N
Liver: Hepatocellular Adenoma or Carcinoma				
Overall rate	32/49 (65%)	24/50 (48%)	26/50 (52%)	21/49 (43%)
Adjusted rate	68.6%	53.1%	55.2%	44.6%
Terminal rate	19/31 (61%)	11/27 (41%)	21/40 (53%)	14/38 (37%)
First incidence (days)	498	517	492	558
Poly-3 test	P=0.018N	P=0.091N	P=0.128N	P=0.014N

TABLE C3
Statistical Analysis of Primary Neoplasms in Male Mice in the 2-Year Inhalation Study of Glutaraldehyde

	Chamber Control	62.5 ppb	125 ppb	250 ppb
Lung: Alveolar/bronchiolar Adenoma				
Overall rate	8/48 (17%)	10/50 (20%)	9/50 (18%)	7/50 (14%)
Adjusted rate	19.0%	24.3%	19.7%	15.2%
Terminal rate	7/31 (23%)	7/27 (26%)	6/40 (15%)	5/38 (13%)
First incidence (days)	573	517	516	628
Poly-3 test	P=0.283N	P=0.371	P=0.574	P=0.427N
Lung: Alveolar/bronchiolar Carcinoma				
Overall rate	10/48 (21%)	6/50 (12%)	7/50 (14%)	7/50 (14%)
Adjusted rate	23.3%	14.3%	15.1%	15.3%
Terminal rate	7/31 (23%)	3/27 (11%)	5/40 (13%)	5/38 (13%)
First incidence (days)	454	364	470	673
Poly-3 test	P=0.253N	P=0.216N	P=0.236N	P=0.245N
Lung: Alveolar/bronchiolar Adenoma or Carcinoma				
Overall rate	18/48 (38%)	15/50 (30%)	15/50 (30%)	14/50 (28%)
Adjusted rate	41.5%	34.8%	31.8%	30.3%
Terminal rate	14/31 (45%)	9/27 (33%)	10/40 (25%)	10/38 (26%)
First incidence (days)	454	364	470	628
Poly-3 test	P=0.165N	P=0.338N	P=0.230N	P=0.186N
Thyroid Gland (Follicular Cell): Adenoma				
Overall rate	1/48 (2%)	3/49 (6%)	2/49 (4%)	1/49 (2%)
Adjusted rate	2.4%	7.6%	4.5%	2.2%
Terminal rate	1/31 (3%)	3/27 (11%)	2/39 (5%)	1/38 (3%)
First incidence (days)	733 (T)	733 (T)	733 (T)	733 (T)
Poly-3 test	P=0.439N	P=0.284	P=0.519	P=0.744N
Thyroid Gland (Follicular Cell): Adenoma or Carcinoma				
Overall rate	2/48 (4%)	3/49 (6%)	2/49 (4%)	1/49 (2%)
Adjusted rate	4.8%	7.6%	4.5%	2.2%
Terminal rate	1/31 (3%)	3/27 (11%)	2/39 (5%)	1/38 (3%)
First incidence (days)	716	733 (T)	733 (T)	733 (T)
Poly-3 test	P=0.280N	P=0.472	P=0.675N	P=0.475N
All Organs: Hemangiosarcoma				
Overall rate	3/50 (6%)	1/50 (2%)	4/50 (8%)	2/50 (4%)
Adjusted rate	6.9%	2.5%	8.9%	4.4%
Terminal rate	1/31 (3%)	0/27 (0%)	4/40 (10%)	1/38 (3%)
First incidence (days)	516	685	733 (T)	663
Poly-3 test	P=0.495N	P=0.334N	P=0.519	P=0.476N
All Organs: Histiocytic Sarcoma				
Overall rate	3/50 (6%)	1/50 (2%)	0/50 (0%)	0/50 (0%)
Adjusted rate	6.9%	2.5%	0.0%	0.0%
Terminal rate	1/31 (3%)	0/27 (0%)	0/40 (0%)	0/38 (0%)
First incidence (days)	573	616	—	—
Poly-3 test	P=0.039N	P=0.332N	P=0.112N	P=0.110N

TABLE C3
Statistical Analysis of Primary Neoplasms in Male Mice in the 2-Year Inhalation Study of Glutaraldehyde

	Chamber Control	62.5 ppb	125 ppb	250 ppb
All Organs: Malignant Lymphoma				
Overall rate	4/50 (8%)	5/50 (10%)	1/50 (2%)	5/50 (10%)
Adjusted rate	9.3%	12.4%	2.2%	11.0%
Terminal rate	3/31 (10%)	2/27 (7%)	1/40 (3%)	5/38 (13%)
First incidence (days)	670	640	733 (T)	733 (T)
Poly-3 test	P=0.558	P=0.462	P=0.165N	P=0.536
All Organs: Benign Neoplasms				
Overall rate	27/50 (54%)	24/50 (48%)	29/50 (58%)	19/50 (38%)
Adjusted rate	60.3%	56.2%	62.4%	40.8%
Terminal rate	21/31 (68%)	17/27 (63%)	25/40 (63%)	15/38 (40%)
First incidence (days)	516	517	492	628
Poly-3 test	P=0.033N	P=0.430N	P=0.504	P=0.045N
All Organs: Malignant Neoplasms				
Overall rate	33/50 (66%)	28/50 (56%)	23/50 (46%)	22/50 (44%)
Adjusted rate	67.2%	58.2%	47.5%	46.1%
Terminal rate	15/31 (48%)	8/27 (30%)	17/40 (43%)	14/38 (37%)
First incidence (days)	454	364	470	558
Poly-3 test	P=0.018N	P=0.240N	P=0.037N	P=0.027N
All Organs: Benign or Malignant Neoplasms				
Overall rate	44/50 (88%)	42/50 (84%)	39/50 (78%)	33/50 (66%)
Adjusted rate	89.6%	86.9%	80.4%	68.6%
Terminal rate	26/31 (84%)	21/27 (78%)	32/40 (80%)	24/38 (63%)
First incidence (days)	454	364	470	558
Poly-3 test	P=0.002N	P=0.459N	P=0.159N	P=0.009N

(T)Terminal sacrifice
[a] Number of neoplasm-bearing animals/number of animals examined. Denominator is number of animals examined microscopically for adrenal gland, liver, lung, and thyroid gland; for other tissues, denominator is number of animals necropsied.
[b] Poly-3 estimated neoplasm incidence after adjustment for intercurrent mortality
[c] Observed incidence at terminal kill
[d] Beneath the chamber control incidence are the P values associated with the trend test. Beneath the exposed group incidence are the P values corresponding to pairwise comparisons between the chamber controls and that exposed group. The Poly-3 test accounts for differential mortality in animals that do not reach terminal sacrifice. A negative trend or a lower incidence in an exposure group is indicated by **N**.
[e] Not applicable; no neoplasms in animal group

TABLE C4
Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the 2-Year Inhalation Study of Glutaraldehyde[a]

	Chamber Control	62.5 ppb	125 ppb	250 ppb
Disposition Summary				
Animals initially in study	50	50	50	50
Early deaths				
Moribund	13	15	6	5
Natural deaths	6	8	4	7
Survivors				
Terminal sacrifice	31	27	40	38
Animals examined microscopically	50	50	50	50
Alimentary System				
Liver	(49)	(50)	(50)	(49)
Atypia cellular, diffuse	1 (2%)			
Basophilic focus	5 (10%)	8 (16%)	4 (8%)	6 (12%)
Clear cell focus	9 (18%)	6 (12%)	9 (18%)	7 (14%)
Eosinophilic focus	7 (14%)	6 (12%)	5 (10%)	3 (6%)
Fatty change				2 (4%)
Inflammation, granulomatous			1 (2%)	
Mixed cell focus	2 (4%)	2 (4%)		
Necrosis	1 (2%)	1 (2%)		2 (4%)
Tension lipidosis		1 (2%)		
Centrilobular, necrosis		2 (4%)		1 (2%)
Mesentery (2)	(2)	(3)	(5)	
Artery, mineralization	1 (50%)			
Fat, necrosis	1 (50%)	2 (100%)	2 (67%)	5 (100%)
Pancreas	(47)	(49)	(50)	(48)
Atrophy			1 (2%)	1 (2%)
Basophilic focus				1 (2%)
Metaplasia, hepatocyte			1 (2%)	1 (2%)
Duct, cyst			1 (2%)	
Stomach, forestomach	(48)	(49)	(50)	(48)
Diverticulum	1 (2%)			
Hyperplasia, squamous	2 (4%)	1 (2%)	1 (2%)	
Inflammation, acute	2 (4%)	1 (2%)		
Necrosis			1 (2%)	
Stomach, glandular	(46)	(47)	(50)	(48)
Infiltration cellular, mixed cell		2 (4%)		
Metaplasia, hepatocyte			1 (2%)	
Necrosis		1 (2%)		1 (2%)
Tooth	(13)	(17)	(10)	(19)
Developmental malformation	12 (92%)	17 (100%)	10 (100%)	19 (100%)
Inflammation, chronic active	2 (15%)			1 (5%)
Cardiovascular System				
Blood vessel	(1)			
Aorta, mineralization	1 (100%)			
Heart	(49)	(50)	(50)	(49)
Angiectasis			1 (2%)	
Inflammation, chronic active	1 (2%)	1 (2%)		
Artery, inflammation	1 (2%)	1 (2%)	1 (2%)	
Artery, mineralization	1 (2%)			

[a] Number of animals examined microscopically at the site and the number of animals with lesion

TABLE C4
Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the 2-Year Inhalation Study of Glutaraldehyde

	Chamber Control	62.5 ppb	125 ppb	250 ppb
Endocrine System				
Adrenal cortex	(47)	(49)	(50)	(49)
Hyperplasia	10 (21%)	9 (18%)	18 (36%)	12 (24%)
Hypertrophy	32 (68%)	26 (53%)	31 (62%)	34 (69%)
Necrosis	1 (2%)			
Adrenal medulla	(47)	(49)	(50)	(49)
Hyperplasia	2 (4%)	2 (4%)	2 (4%)	2 (4%)
Necrosis	1 (2%)			
Islets, pancreatic	(47)	(48)	(50)	(48)
Hyperplasia	3 (6%)	2 (4%)	1 (2%)	6 (13%)
Pituitary gland	(46)	(47)	(48)	(47)
Pars distalis, hyperplasia	2 (4%)	1 (2%)	2 (4%)	4 (9%)
Thyroid gland	(48)	(49)	(49)	(49)
Bilateral, follicular cell, hyperplasia				1 (2%)
Follicular cell, hyperplasia	14 (29%)	9 (18%)	11 (22%)	18 (37%)
General Body System				
None				
Genital System				
Epididymis	(48)	(50)	(50)	(49)
Granuloma sperm	2 (4%)			1 (2%)
Penis			(1)	
Inflammation, acute			1 (100%)	
Preputial gland	(48)	(49)	(50)	(47)
Cyst		1 (2%)		
Inflammation, chronic active	2 (4%)	2 (4%)	2 (4%)	
Prostate	(49)	(48)	(50)	(47)
Hyperplasia			1 (2%)	
Inflammation, chronic active	1 (2%)		1 (2%)	1 (2%)
Testes	(48)	(50)	(50)	(50)
Atrophy	1 (2%)	1 (2%)		
Hematopoietic System				
Lymph node, mandibular	(36)	(22)	(30)	(33)
Hyperplasia, lymphoid	1 (3%)			
Lymph node, mesenteric	(46)	(44)	(47)	(47)
Infiltration cellular, plasma cell	1 (2%)		1 (2%)	
Lymph node, mediastinal	(29)	(27)	(33)	(30)
Hyperplasia, lymphoid			1 (3%)	
Spleen	(48)	(48)	(50)	(48)
Hematopoietic cell proliferation	12 (25%)	14 (29%)	12 (24%)	7 (15%)
Hyperplasia, lymphoid		2 (4%)		
Thymus	(39)	(34)	(43)	(44)
Hyperplasia, tubular				1 (2%)
Integumentary System				
Skin	(48)	(50)	(50)	(48)
Prepuce, inflammation, chronic active	7 (15%)	7 (14%)	4 (8%)	5 (10%)

TABLE C4
Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the 2-Year Inhalation Study of Glutaraldehyde

	Chamber Control	62.5 ppb	125 ppb	250 ppb
Musculoskeletal System				
None				
Nervous System				
Brain	(49)	(50)	(50)	(50)
Demyelination, focal		1 (2%)		
Meninges, infiltration cellular, mononuclear cell	1 (2%)			
Respiratory System				
Larynx	(47)	(49)	(50)	(50)
Glands, inflammation	5 (11%)	3 (6%)	3 (6%)	3 (6%)
Lung	(48)	(50)	(50)	(50)
Inflammation, chronic active			1 (2%)	
Alveolar epithelium, hyperplasia	3 (6%)	3 (6%)	5 (10%)	2 (4%)
Alveolus, infiltration cellular, histiocyte		1 (2%)	1 (2%)	
Artery, mediastinum, mineralization	1 (2%)			
Nose	(48)	(50)	(50)	(50)
Inflammation	6 (13%)	4 (8%)	3 (6%)	5 (10%)
Polyp, inflammatory	1 (2%)			
Nasolacrimal duct, inflammation				1 (2%)
Olfactory epithelium, atrophy	1 (2%)	1 (2%)		2 (4%)
Olfactory epithelium, degeneration, hyaline	1 (2%)	1 (2%)	5 (10%)	2 (4%)
Olfactory epithelium, metaplasia	1 (2%)			1 (2%)
Respiratory epithelium, degeneration, hyaline	5 (10%)	3 (6%)	6 (12%)	10 (20%)
Respiratory epithelium, metaplasia, squamous	2 (4%)	5 (10%)	6 (12%)	9 (18%)
Turbinate, necrosis			2 (4%)	
Special Senses System				
Eye			(1)	
Cornea, inflammation, acute			1 (100%)	
Urinary System				
Kidney	(48)	(49)	(50)	(49)
Cyst		4 (8%)	2 (4%)	
Hydronephrosis	2 (4%)	3 (6%)	2 (4%)	1 (2%)
Inflammation	1 (2%)			
Metaplasia, osseous		1 (2%)	2 (4%)	
Mineralization	1 (2%)			
Nephropathy	44 (92%)	43 (88%)	46 (92%)	47 (96%)
Thrombosis			1 (2%)	
Glomerulus, inflammation, suppurative	1 (2%)	1 (2%)		
Papilla, inflammation, suppurative				2 (4%)
Renal tubule, necrosis		1 (2%)	1 (2%)	
Urinary bladder	(47)	(48)	(50)	(47)
Infiltration cellular, polymorphonuclear			1 (2%)	
Inflammation, chronic active	3 (6%)	1 (2%)	1 (2%)	1 (2%)

APPENDIX D
SUMMARY OF LESIONS IN FEMALE MICE IN THE 2-YEAR INHALATION STUDY OF GLUTARALDEHYDE

TABLE D1
Summary of the Incidence of Neoplasms in Female Mice in the 2-Year Inhalation Study of Glutaraldehyde[a]

	Chamber Control	62.5 ppb	125 ppb	250 ppb
Disposition Summary				
Animals initially in study	50	50	50	50
Early deaths				
Accidental death			1	
Moribund	11	10	10	12
Natural deaths	5	3	4	6
Survivors				
Terminal sacrifice	34	37	35	32
Animals examined microscopically	50	50	50	50
Alimentary System				
Gallbladder	(45)	(41)	(43)	(41)
Adenoma				1 (2%)
Hepatocholangiocarcinoma, metastatic, liver			1 (2%)	
Histiocytic sarcoma	1 (2%)			
Intestine large, rectum	(47)	(47)	(48)	(45)
Intestine large, cecum	(47)	(47)	(47)	(46)
Leiomyosarcoma				1 (2%)
Intestine small, duodenum	(45)	(47)	(48)	(48)
Polyp adenomatous				1 (2%)
Intestine small, jejunum	(46)	(47)	(47)	(45)
Carcinoma, metastatic, uterus			1 (2%)	
Intestine small, ileum	(46)	(48)	(47)	(46)
Polyp adenomatous				1 (2%)
Liver	(50)	(48)	(50)	(50)
Hemangiosarcoma		2 (4%)	1 (2%)	1 (2%)
Hepatocellular carcinoma	3 (6%)	6 (13%)	5 (10%)	3 (6%)
Hepatocellular carcinoma, multiple	1 (2%)	1 (2%)		1 (2%)
Hepatocellular adenoma	6 (12%)	11 (23%)	7 (14%)	3 (6%)
Hepatocellular adenoma, multiple	5 (10%)			
Hepatocholangiocarcinoma			1 (2%)	
Histiocytic sarcoma			1 (2%)	
Ito cell tumor malignant				1 (2%)
Mesentery	(12)	(6)	(5)	(6)
Carcinoma, metastatic, uterus			1 (20%)	
Histiocytic sarcoma			1 (20%)	
Pancreas	(50)	(48)	(49)	(49)
Carcinoma, metastatic, uterus			1 (2%)	
Histiocytic sarcoma			1 (2%)	
Salivary glands	(50)	(49)	(50)	(50)
Stomach, forestomach	(50)	(49)	(48)	(48)
Squamous cell carcinoma			1 (2%)	
Squamous cell papilloma	1 (2%)	1 (2%)	1 (2%)	
Stomach, glandular	(50)	(48)	(48)	(48)
Cardiovascular System				
Heart	(50)	(49)	(50)	(50)

TABLE D1
Summary of the Incidence of Neoplasms in Female Mice in the 2-Year Inhalation Study of Glutaraldehyde

	Chamber Control	62.5 ppb	125 ppb	250 ppb
Endocrine System				
Adrenal cortex	(50)	(49)	(49)	(50)
Carcinoma, metastatic, uterus			1 (2%)	
Capsule, adenoma		1 (2%)		
Capsule, carcinoma		1 (2%)	1 (2%)	
Adrenal medulla	(50)	(49)	(48)	(49)
Pheochromocytoma malignant		1 (2%)		
Pheochromocytoma benign	4 (8%)	1 (2%)	1 (2%)	2 (4%)
Islets, pancreatic	(50)	(48)	(49)	(49)
Adenoma			1 (2%)	
Pituitary gland	(49)	(49)	(49)	(50)
Pars distalis, adenoma	20 (41%)	16 (33%)	20 (41%)	16 (32%)
Pars distalis, carcinoma	1 (2%)			
Pars intermedia, adenoma		1 (2%)	1 (2%)	
Thyroid gland	(50)	(48)	(50)	(50)
Follicular cell, adenoma	4 (8%)		2 (4%)	3 (6%)
Follicular cell, carcinoma				1 (2%)
General Body System				
Peritoneum			(2)	
Carcinoma, metastatic, uterus			1 (50%)	
Histiocytic sarcoma			1 (50%)	
Genital System				
Ovary	(49)	(47)	(49)	(50)
Carcinoma, metastatic, uterus			1 (2%)	
Cystadenoma	1 (2%)	1 (2%)	1 (2%)	2 (4%)
Hemangiosarcoma			1 (2%)	
Histiocytic sarcoma			1 (2%)	
Luteoma	2 (4%)			
Bilateral, tubulostromal adenoma			1 (2%)	
Uterus	(50)	(48)	(49)	(49)
Adenoma		1 (2%)		
Carcinoma		1 (2%)	2 (4%)	2 (4%)
Granular cell tumor benign	1 (2%)			
Hemangioma		1 (2%)		
Leiomyoma			2 (4%)	1 (2%)
Polyp stromal	3 (6%)	4 (8%)	3 (6%)	
Hematopoietic System				
Bone marrow	(50)	(48)	(50)	(49)
Hemangiosarcoma	1 (2%)	3 (6%)	1 (2%)	
Lymph node	(7)	(4)	(3)	(1)
Pancreatic, histiocytic sarcoma	1 (14%)			
Lymph node, bronchial	(29)	(32)	(37)	(36)
Histiocytic sarcoma	1 (3%)		1 (3%)	
Lymph node, mandibular	(43)	(40)	(39)	(38)
Hemangiosarcoma		1 (3%)		
Lymph node, mesenteric	(47)	(48)	(46)	(46)
Histiocytic sarcoma	1 (2%)			1 (2%)
Lymph node, mediastinal	(31)	(23)	(34)	(37)
Alveolar/bronchiolar carcinoma, metastatic, lung		1 (4%)		
Carcinoma, metastatic, uncertain primary site	1 (3%)			
Histiocytic sarcoma			1 (3%)	

TABLE D1
Summary of the Incidence of Neoplasms in Female Mice in the 2-Year Inhalation Study of Glutaraldehyde

	Chamber Control	62.5 ppb	125 ppb	250 ppb
Hematopoietic System (continued)				
Spleen	(50)	(48)	(48)	(49)
Hemangiosarcoma	1 (2%)	3 (6%)	1 (2%)	1 (2%)
Histiocytic sarcoma			1 (2%)	
Thymus	(45)	(44)	(39)	(47)
Carcinoma, metastatic, uncertain primary site	1 (2%)			
Integumentary System				
Mammary gland	(49)	(49)	(50)	(49)
Carcinoma	3 (6%)		3 (6%)	
Skin	(50)	(50)	(50)	(50)
Subcutaneous tissue, fibrosarcoma	1 (2%)	1 (2%)	3 (6%)	
Subcutaneous tissue, hemangiosarcoma	1 (2%)	1 (2%)	1 (2%)	
Subcutaneous tissue, sarcoma				3 (6%)
Subcutaneous tissue, sarcoma, multiple	2 (4%)			
Musculoskeletal System				
Bone	(50)	(49)	(50)	(50)
Hemangiosarcoma		1 (2%)		
Skeletal muscle	(2)	(1)		
Hemangiosarcoma		1 (100%)		
Nervous System				
Brain	(50)	(49)	(50)	(50)
Carcinoma, metastatic, pituitary gland	1 (2%)			
Respiratory System				
Larynx	(50)	(49)	(50)	(48)
Lung	(50)	(49)	(50)	(50)
Alveolar/bronchiolar adenoma	2 (4%)	3 (6%)	2 (4%)	2 (4%)
Alveolar/bronchiolar adenoma, multiple		1 (2%)		
Alveolar/bronchiolar carcinoma	1 (2%)	4 (8%)	5 (10%)	2 (4%)
Carcinoma, metastatic, uncertain primary site	1 (2%)			
Carcinoma, metastatic, uterus			1 (2%)	
Hepatocellular carcinoma, metastatic, liver	2 (4%)	5 (10%)	1 (2%)	2 (4%)
Hepatocholangiocarcinoma, metastatic, liver			1 (2%)	
Histiocytic sarcoma			1 (2%)	
Leiomyosarcoma, metastatic, intestine large, cecum				1 (2%)
Osteosarcoma, metastatic, uncertain primary site		1 (2%)		
Nose	(50)	(49)	(50)	(50)
Pleura	(1)	(1)	(1)	
Alveolar/bronchiolar carcinoma, metastatic, lung		1 (100%)	1 (100%)	
Carcinoma, metastatic, uncertain primary site	1 (100%)			
Special Senses System				
Harderian gland	(3)		(1)	(2)
Adenoma	1 (33%)			
Carcinoma	2 (67%)			1 (50%)

TABLE D1
Summary of the Incidence of Neoplasms in Female Mice in the 2-Year Inhalation Study of Glutaraldehyde

	Chamber Control	62.5 ppb	125 ppb	250 ppb
Urinary System				
Kidney	(50)	(49)	(49)	(49)
Hepatocholangiocarcinoma, metastatic, liver			1 (2%)	
Histiocytic sarcoma			1 (2%)	
Capsule, sarcoma	1 (2%)			
Urinary bladder	(48)	(48)	(48)	(47)
Carcinoma, metastatic, uterus			1 (2%)	
Histiocytic sarcoma			1 (2%)	
Systemic Lesions				
Multiple organs[b]	(50)	(50)	(50)	(50)
Histiocytic sarcoma	1 (2%)		1 (2%)	1 (2%)
Lymphoma malignant	12 (24%)	12 (24%)	8 (16%)	12 (24%)
Neoplasm Summary				
Total animals with primary neoplasms[c]	41	44	41	40
Total primary neoplasms	81	81	77	62
Total animals with benign neoplasms	32	32	30	26
Total benign neoplasms	50	42	42	32
Total animals with malignant neoplasms	24	26	24	25
Total malignant neoplasms	31	39	35	30
Total animals with metastatic neoplasms	3	6	4	3
Total metastatic neoplasms	7	8	13	3
Total animals with malignant neoplasms of uncertain primary site	1	1		

[a] Number of animals examined microscopically at the site and the number of animals with neoplasm
[b] Number of animals with any tissue examined microscopically
[c] Primary neoplasms: all neoplasms except metastatic neoplasms

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Inhalation Study of Glutaraldehyde: Chamber Control

Number of Days on Study	2 4 8	5 0 7	5 3 2	5 5 8	6 1 4	6 1 6	6 5 5	6 5 7	6 6 4	6 8 1	6 8 6	7 0 1	7 0 2	7 0 4	7 0 8	7 3 4	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5
Carcass ID Number	1 4 5	1 3 4	1 1 9	1 2 3	1 1 4	1 3 5	1 2 1	1 1 3	1 3 6	1 0 6	1 2 5	1 3 0	1 0 1	1 3 1	1 2 0	1 4 1	1 0 3	1 0 9	1 1 0	1 1 2	1 1 7	1 2 4	1 2 7	1 3 8	1 4 8
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder	A	+	+	+	A	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+
Histiocytic sarcoma				X																					
Intestine large, colon	A	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	A	+	+	+	A	+	+	+	+	+	+	+	+	I	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	A	+	+	+	A	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	A	+	+	+	A	+	+	A	+	+	+	+	+	A	+	A	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	A	+	+	+	A	+	+	A	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+
Intestine small, ileum	A	+	+	+	A	+	+	A	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular carcinoma								X			X														
Hepatocellular carcinoma, multiple																									
Hepatocellular adenoma												X													
Hepatocellular adenoma, multiple																X				X					
Mesentery		+	+		+		+	+						+											
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell papilloma																									
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cardiovascular System																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma benign																				X					
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid gland	M	+	+	+	M	+	+	M	+	+	+	M	+	M	+	M	+	+	+	M	M	M	+	+	+
Pituitary gland	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma						X							X			X		X	X		X		X	X	
Pars distalis, carcinoma									X																
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell, adenoma																			X		X				
General Body System																									
None																									
Genital System																									
Clitoral gland	+	+	M	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	M	+	M	+	+	+
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	I	+	+	+	+	+	+	+	+	+	+
Cystadenoma																									
Luteoma													X						X						
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Granular cell tumor benign															X										
Polyp stromal																									

+: Tissue examined microscopically
A: Autolysis precludes examination
M: Missing tissue
I: Insufficient tissue
X: Lesion present
Blank: Not examined

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Inhalation Study of Glutaraldehyde: Chamber Control

Number of Days on Study	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	
Carcass ID Number	1 0 2	1 0 8	1 1 5	1 1 6	1 1 8	1 2 2	1 2 8	1 2 9	1 3 7	1 4 0	1 4 3	1 4 4	1 4 6	1 4 7	1 5 0	1 0 4	1 0 5	1 0 7	1 1 1	1 2 6	1 3 2	1 3 3	1 3 9	1 4 2	1 4 9	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	45
Histiocytic sarcoma																										1
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular carcinoma			X																							3
Hepatocellular carcinoma, multiple																		X								1
Hepatocellular adenoma					X			X							X			X		X						6
Hepatocellular adenoma, multiple						X							X						X							5
Mesentery		+			+			+				+											+		+	12
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Squamous cell papilloma																						X				1
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cardiovascular System																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma benign							X											X			X					4
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Parathyroid gland	+	I	M	+	+	+	M	M	M	+	+	+	M	M	+	M	+	M	M	+	M	M	M	M	+	27
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pars distalis, adenoma			X	X	X	X					X	X				X	X			X	X	X	X			20
Pars distalis, carcinoma																										1
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Follicular cell, adenoma				X							X															4
General Body System																										
None																										
Genital System																										
Clitoral gland	M	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	I	+	+	+	+	+	+	43
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Cystadenoma											X															1
Luteoma																										2
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Granular cell tumor benign																										1
Polyp stromal	X																X							X	3

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Inhalation Study of Glutaraldehyde: Chamber Control

Number of Days on Study	2 4 8	5 0 7	5 3 2	5 5 8	6 1 4	6 1 6	6 5 5	6 5 7	6 6 4	6 8 1	6 8 6	7 0 1	7 0 2	7 0 4	7 0 8	7 3 4	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5
Carcass ID Number	1 1 4 5	1 3 4	1 1 9	1 2 3	1 1 4	1 3 5	1 2 1	1 1 3	1 3 6	1 0 6	1 2 5	1 3 0	1 0 1	1 3 1	1 2 0	1 4 1	1 0 3	1 0 9	1 1 0	1 1 2	1 1 7	1 2 4	2 2 7	3 3 8	4 4 8
Hematopoietic System																								
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																								
Lymph node	+			+							+					+			+		+			+	
Pancreatic, histiocytic sarcoma				X																				
Lymph node, bronchial	+	+	M	+	M	M	+	M	M	+	+	+	+	+	M	+	+	+	+	M	M	+	+	M	M
Histiocytic sarcoma				X																					
Lymph node, mandibular	+	+	M	+	+	+	+	+	+	M	+	M	M	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	M	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma				X																					
Lymph node, mediastinal	+	+	+	+	M	M	+	+	+	+	+	+	+	+	+	+	M	+	+	M	M	M	M	+	M
Carcinoma, metastatic, uncertain primary site								X																	
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																									
Thymus	M	M	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, uncertain primary site								X																	
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+
Carcinoma									X												X				
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Subcutaneous tissue, fibrosarcoma																									
Subcutaneous tissue, hemangiosarcoma												X													
Subcutaneous tissue, sarcoma, multiple										X			X												
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skeletal muscle												+													
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, pituitary gland									X																
Respiratory System																									
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																						X			
Alveolar/bronchiolar carcinoma																									
Carcinoma, metastatic, uncertain primary site								X																	
Hepatocellular carcinoma, metastatic, liver								X			X														
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pleura								+																	
Carcinoma, metastatic, uncertain primary site								X																	
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Inhalation Study of Glutaraldehyde: Chamber Control

Number of Days on Study	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	
Carcass ID Number	1 0 2	1 0 8	1 1 5	1 1 6	1 1 8	1 2 2	1 2 8	1 2 9	1 3 7	1 4 0	1 4 3	1 4 4	1 4 6	1 4 7	1 5 0	1 0 4	1 0 5	1 0 7	1 1 1	1 2 6	1 3 2	1 3 3	1 3 9	1 4 2	1 4 9	Total Tissues/ Tumors
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma													X													1
Lymph node																										7
Pancreatic, histiocytic sarcoma																										1
Lymph node, bronchial	+	+	+	M	+	M	+	+	M	+	M	M	M	M	+	+	+	+	M	+	+	M	M	M	+	29
Histiocytic sarcoma																										1
Lymph node, mandibular	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	M	+	43
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	I	+	+	+	+	+	+	+	+	+	+	+	47
Histiocytic sarcoma																										1
Lymph node, mediastinal	M	+	M	M	+	+	+	+	M	+	M	M	+	M	M	+	+	M	+	+	M	+	M	+	+	31
Carcinoma, metastatic, uncertain primary site																										1
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma						X																				1
Thymus	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+		45
Carcinoma, metastatic, uncertain primary site																										1
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Carcinoma										X																3
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Subcutaneous tissue, fibrosarcoma										X																1
Subcutaneous tissue, hemangiosarcoma																										1
Subcutaneous tissue, sarcoma, multiple																										2
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Skeletal muscle																								+		2
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma, metastatic, pituitary gland																										1
Respiratory System																										
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma																							X			2
Alveolar/bronchiolar carcinoma														X												1
Carcinoma, metastatic, uncertain primary site																										1
Hepatocellular carcinoma, metastatic, liver																										2
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pleura																										1
Carcinoma, metastatic, uncertain primary site																										1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Inhalation Study of Glutaraldehyde: Chamber Control

Number of Days on Study	2 4 8	5 0 7	5 3 2	5 5 8	6 1 4	6 1 6	6 5 5	6 5 7	6 6 4	6 8 1	6 8 6	7 0 1	7 0 2	7 0 4	7 0 8	7 3 4	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5
Carcass ID Number	1 4 5	1 3 4	1 1 9	1 2 3	1 1 4	1 3 5	1 2 1	1 1 3	1 3 6	1 0 6	1 2 5	1 3 0	1 0 1	1 3 1	1 2 0	1 4 1	1 0 3	1 0 9	1 1 0	1 1 2	1 1 7	1 2 4	1 2 7	1 3 8	1 4 8
Special Senses System																									
Harderian gland															+										
Adenoma																									
Carcinoma															X										
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Capsule, sarcoma																									
Urinary bladder	+	+	+	M	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma				X																					
Lymphoma malignant											X				X	X			X		X			X	X

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Inhalation Study of Glutaraldehyde: Chamber Control

Number of Days on Study	736	736	736	736	736	736	736	736	736	736	736	736	736	736	736	736	737	737	737	737	737	737	737	737	737	737	
Carcass ID Number	10202	10208	10215	10216	10218	10222	10228	10229	10237	10240	10243	10244	10246	10247	10250	10404	10405	10407	10411	10426	10432	10433	10439	10442	10449	Total Tissues/ Tumors
Special Senses System																											
Harderian gland																+				+						3
Adenoma																X										1
Carcinoma																				X						2
Urinary System																											
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Capsule, sarcoma																							X				1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Systemic Lesions																											
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																											1
Lymphoma malignant																			X	X			X	X	X		12

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Inhalation Study of Glutaraldehyde: 62.5 ppb

Number of Days on Study	4 6 3	4 9 2	5 2 7	5 5 1	5 9 8	6 1 0	6 7 2	7 0 6	7 0 7	7 0 8	7 0 8	7 1 4	7 2 8	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5
Carcass ID Number	3 4 5	3 0 7	3 4 1	3 0 6	3 1 7	3 4 9	3 4 2	3 3 1	3 2 9	3 1 2	3 1 5	3 1 9	3 2 1	3 0 1	3 1 0	3 1 1	3 1 4	3 1 8	3 1 9	3 2 2	3 2 5	3 3 2	3 3 4	3 4 0	3 4 7
Alimentary System																									
Esophagus	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder	A	+	+	+	A	+	+	M	+	+	M	+	A	+	+	+	+	+	+	+	+	+	+	+	I
Intestine large, colon	A	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	A	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	A	+	+	+	A	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	A	+	+	+	A	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	A	+	+	+	A	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	A	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	A	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																			X						
Hepatocellular carcinoma				X				X			X		X												
Hepatocellular carcinoma, multiple																									
Hepatocellular adenoma											X						X			X		X			
Mesentery						+				+				+				+	+						
Pancreas	A	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell papilloma																									
Stomach, glandular	A	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tooth																									
Cardiovascular System																									
Heart	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal cortex	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Capsule, adenoma																			X						
Capsule, carcinoma																									
Adrenal medulla	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma malignant																									
Pheochromocytoma benign																					X				
Islets, pancreatic	A	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid gland	M	+	+	+	A	M	M	M	M	+	M	M	M	M	M	M	M	+	M	M	+	M	+	M	+
Pituitary gland	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma												X			X	X	X			X	X	X		X	
Pars intermedia, adenoma																									
Thyroid gland	A	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
General Body System																									
None																									
Genital System																									
Clitoral gland	+	+	+	M	A	+	+	+	+	M	+	+	M	+	+	+	+	+	+	+	+	M	M	+	+
Ovary	A	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	I	+	+	+	+	+	+
Cystadenoma																							X		
Uterus	A	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Carcinoma												X													
Hemangioma																									
Polyp stromal			X																						

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Inhalation Study of Glutaraldehyde: 62.5 ppb

Number of Days on Study	735	736	736	736	736	736	736	736	736	736	736	736	736	736	737	737	737	737	737	737	737	737	737	737	
Carcass ID Number	34 8	34 0	34 0	34 0	34 1	34 2	34 2	34 2	34 3	34 3	34 3	34 3	34 4	34 5	34 0	34 0	34 1	34 2	34 2	34 2	34 3	34 3	34 3	34 4	34 4	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Gallbladder	+	+	+	+	+	+	+	+	+	M	M	+	+	+	+	+	+	+	+	+	+	+	+	M	+	41
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	I	+	+	+	+	+	+	+	+	47
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Hemangiosarcoma																					X					2
Hepatocellular carcinoma				X	X																					6
Hepatocellular carcinoma, multiple										X																1
Hepatocellular adenoma			X			X			X				X	X	X								X			11
Mesentery																	+									6
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Squamous cell papilloma															X											1
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Tooth														+												1
Cardiovascular System																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Capsule, adenoma																										1
Capsule, carcinoma															X											1
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pheochromocytoma malignant				X																						1
Pheochromocytoma benign																										1
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Parathyroid gland	M	M	M	M	M	M	+	M	M	M	+	M	+	M	+	M	M	M	+	M	+	M	M	M	+	15
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pars distalis, adenoma		X	X						X		X					X		X		X		X				16
Pars intermedia, adenoma									X																	1
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
General Body System																										
None																										
Genital System																										
Clitoral gland	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	M	+	+	+	+	+	42
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Cystadenoma																										1
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Adenoma																				X						1
Carcinoma																										1
Hemangioma																			X							1
Polyp stromal			X					X																	X	4

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Inhalation Study of Glutaraldehyde: 62.5 ppb

Number of Days on Study	4 6 3	4 9 2	5 2 7	5 5 1	5 9 8	6 1 0	6 7 2	7 0 6	7 0 7	7 0 8	7 0 8	7 1 4	7 2 8	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5
Carcass ID Number	3 4 5	3 0 7	3 4 1	3 0 6	3 1 7	3 4 9	3 4 2	3 3 1	3 2 9	3 1 2	3 1 5	3 0 9	3 2 1	3 0 1	3 1 0	3 1 1	3 1 4	3 1 8	3 1 9	3 2 2	3 2 5	3 3 2	3 3 4	3 4 0	4 4 7
Hematopoietic System																									
Bone marrow	A	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma							X													X		X			
Lymph node									+	+		+													
Lymph node, bronchial	+	M	M	+	A	+	M	+	M	+	+	M	+	M	+	+	+	+	+	M	+	+	+	+	+
Lymph node, mandibular	+	M	+	+	A	M	+	+	+	+	+	+	M	+	M	+	+	+	+	+	+	+	M	+	M
Hemangiosarcoma							X																		
Lymph node, mesenteric	A	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mediastinal	A	+	M	+	A	+	M	+	+	+	+	+	+	M	+	+	+	M	+	+	M	+	M	+	M
Alveolar/bronchiolar carcinoma, metastatic, lung													X												
Spleen	A	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma							X													X					
Thymus	A	+	+	+	A	M	+	+	+	+	+	+	M	+	+	M	+	+	+	+	+	+	+	+	+
Integumentary System																									
Mammary gland	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Subcutaneous tissue, fibrosarcoma																									
Subcutaneous tissue, hemangiosarcoma																									
Musculoskeletal System																									
Bone	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma							X																		
Skeletal muscle							+																		
Hemangiosarcoma							X																		
Nervous System																									
Brain	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spinal cord							+																		
Respiratory System																									
Larynx	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lung	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma	X													X											X
Alveolar/bronchiolar adenoma, multiple																									
Alveolar/bronchiolar carcinoma													X										X		
Hepatocellular carcinoma, metastatic, liver								X			X		X												
Osteosarcoma, metastatic, uncertain primary site		X																							
Nose	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pleura													+												
Alveolar/bronchiolar carcinoma, metastatic, lung													X												
Trachea	A	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Inhalation Study of Glutaraldehyde: 62.5 ppb

Number of Days on Study	735	736	736	736	736	736	736	736	736	736	736	736	736	736	737	737	737	737	737	737	737	737	737	737	
Carcass ID Number	34808	34003	34005	34008	34013	34023	34027	34028	34030	34035	34037	34039	34043	34050	34062	34064	34116	34120	34124	34126	34133	34136	34138	34146	Total Tissues/ Tumors
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Hemangiosarcoma																									3
Lymph node																					+				4
Lymph node, bronchial	M	M	+	+	+	M	+	M	+	M	+	+	+	+	M	+	M	M	M	+	+	+	+	+	M	32
Lymph node, mandibular	+	+	+	M	+	+	+	+	+	+	M	+	+	+	+	M	+	+	+	+	+	+	+	+	+	40
Hemangiosarcoma																									1
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Lymph node, mediastinal	+	M	+	+	M	M	+	M	M	M	M	M	+	M	M	+	M	M	+	M	M	M	M	M	M	23
Alveolar/bronchiolar carcinoma, metastatic, lung																									1
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Hemangiosarcoma																					X				3
Thymus	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Subcutaneous tissue, fibrosarcoma			X																						1
Subcutaneous tissue, hemangiosarcoma														X											1
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Hemangiosarcoma																									1
Skeletal muscle																									1
Hemangiosarcoma																									1
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Spinal cord																									1
Respiratory System																									
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Alveolar/bronchiolar adenoma																									3
Alveolar/bronchiolar adenoma, multiple	X																								1
Alveolar/bronchiolar carcinoma																				X		X			4
Hepatocellular carcinoma, metastatic, liver					X					X															5
Osteosarcoma, metastatic, uncertain primary site																									1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pleura																									1
Alveolar/bronchiolar carcinoma, metastatic, lung																									1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Inhalation Study of Glutaraldehyde: 62.5 ppb

Number of Days on Study	4	4	5	5	5	6	6	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7
	6	9	2	5	9	1	7	0	0	0	0	1	2	3	3	3	3	3	3	3	3	3	3	3	3	3
	3	2	7	1	8	0	2	6	7	8	8	4	8	5	5	5	5	5	5	5	5	5	5	5	5	5
Carcass ID Number	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3
	4	0	4	0	1	4	4	3	2	1	1	0	2	0	1	1	1	1	1	2	2	3	3	4	4	
	5	7	1	6	7	9	2	1	9	2	5	9	1	1	0	1	4	8	9	2	5	2	4	0	7	
Special Senses System																										
None																										
Urinary System																										
Kidney	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Urinary bladder	A	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Lymphoma malignant									X	X							X		X				X			

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Inhalation Study of Glutaraldehyde: 62.5 ppb

Number of Days on Study	7 3 5	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	
Carcass ID Number	3 4 8	3 0 3	3 0 5	3 0 8	3 1 3	3 2 3	3 2 7	3 2 8	3 3 0	3 3 5	3 3 7	3 3 9	3 4 3	3 5 0	3 0 2	3 0 4	3 1 6	3 2 0	3 2 4	3 2 6	3 3 3	3 3 6	3 3 8	3 4 4	3 4 6	Total Tissues/ Tumors
Special Senses System																										
None																										
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymphoma malignant								X				X	X		X					X		X		X		12

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Inhalation Study of Glutaraldehyde: 125 ppb

Number of Days on Study	5	5	5	6	6	6	6	6	6	6	7	7	7	7	7	7	7	7	7	7	7	7	7	7
	0	2	7	3	4	6	7	7	8	8	0	0	1	1	2	3	3	3	3	3	3	3	3	3
	2	4	0	5	0	6	2	2	6	7	2	4	5	9	3	5	5	5	5	5	5	5	5	5
Carcass ID Number	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
	4	3	0	2	0	2	1	3	4	3	3	1	4	0	0	0	1	1	1	1	2	2	2	2
	8	3	8	2	7	0	9	6	9	0	1	8	3	5	4	3	1	2	3	4	6	1	3	4	9
Alimentary System																								
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder	+	+	A	A	+	A	+	+	+	+	+	+	A	M	+	+	+	+	+	+	+	+	+	+
Hepatocholangiocarcinoma, metastatic, liver												X												
Intestine large, colon	+	A	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	I	+	+	+	+
Intestine large, cecum	+	+	A	A	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	A	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	A	+	A	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, uterus			X																					
Intestine small, ileum	+	A	+	A	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma										X														
Hepatocellular carcinoma							X												X		X			
Hepatocellular adenoma		X														X			X			X		
Hepatocholangiocarcinoma												X												
Histiocytic sarcoma												X												
Mesentery			+									+								+	+			
Carcinoma, metastatic, uterus			X																					
Histiocytic sarcoma												X												
Pancreas	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, uterus			X																					
Histiocytic sarcoma												X												
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	A	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell carcinoma																								
Squamous cell papilloma																								X
Stomach, glandular	+	+	+	A	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cardiovascular System																								
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																								
Adrenal cortex	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, uterus			X																					
Capsule, carcinoma																								
Adrenal medulla	+	+	+	+	+	A	+	+	+	+	+	+	+	I	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma benign				X																				
Islets, pancreatic	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma	X																							
Parathyroid gland	M	M	+	M	+	M	+	M	M	+	+	+	+	M	+	+	+	+	+	+	M	+	M	M	M
Pituitary gland	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma	X					X		X				X										X	X	X	X
Pars intermedia, adenoma											X														
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell, adenoma																								

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Inhalation Study of Glutaraldehyde: 125 ppb

Number of Days on Study	735	736	736	736	736	736	736	736	736	736	736	736	736	736	736	736	737	737	737	737	737	737	737	737	737	
Carcass ID Number	50232	50101	50202	50006	50009	50110	51017	53505	53707	53808	53909	54004	54402	54505	54707	55010	55105	55225	55626	55727	56028	56434	56441	56446	Total Tissues/ Tumors	
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50	
Gallbladder	+	+	+	+	+	+	M	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	43	
Hepatocholangiocarcinoma, metastatic, liver																									1	
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48	
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48	
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47	
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48	
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47	
Carcinoma, metastatic, uterus																									1	
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47	
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50	
Hemangiosarcoma																									1	
Hepatocellular carcinoma															X			X							5	
Hepatocellular adenoma								X			X									X					7	
Hepatocholangiocarcinoma																									1	
Histiocytic sarcoma																									1	
Mesentery												+													5	
Carcinoma, metastatic, uterus																									1	
Histiocytic sarcoma																									1	
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49	
Carcinoma, metastatic, uterus																									1	
Histiocytic sarcoma																									1	
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50	
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48	
Squamous cell carcinoma																								X	1	
Squamous cell papilloma																									1	
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48	
Cardiovascular System																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50	
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49	
Carcinoma, metastatic, uterus																									1	
Capsule, carcinoma		X																							1	
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48	
Pheochromocytoma benign																									1	
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49	
Adenoma																									1	
Parathyroid gland	+	M	M	M	+	+	+	+	M	+	+	M	+	+	M	M	M	+	M	+	+	+	M	+	+	29
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pars distalis, adenoma		X	X		X	X	X		X	X	X				X						X		X	X		20
Pars intermedia, adenoma																									1	
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50	
Follicular cell, adenoma								X								X									2	

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Inhalation Study of Glutaraldehyde: 125 ppb

Number of Days on Study	5 0 2	5 2 4	5 7 0	6 3 5	6 4 0	6 6 6	6 7 2	6 7 2	6 8 6	6 8 7	7 0 2	7 0 4	7 1 5	7 1 9	7 2 3	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5
Carcass ID Number	5 4 8	5 3 3	5 0 8	5 2 2	5 0 7	5 2 0	5 1 9	5 3 6	5 4 9	5 3 0	5 3 1	5 1 8	5 4 3	5 0 5	5 0 4	5 0 3	5 1 1	5 1 2	5 1 3	5 1 4	5 1 6	5 2 1	5 2 3	5 2 9
General Body System																								
Peritoneum			+									+												
Carcinoma, metastatic, uterus			X																					
Histiocytic sarcoma												X												
Genital System																								
Clitoral gland	+	+	+	+	+	M	+	+	+	+	+	M	+	+	M	+	+	+	+	+	+	+	M	+
Ovary	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, uterus			X																					
Cystadenoma																								
Hemangiosarcoma										X														
Histiocytic sarcoma												X												
Bilateral, tubulostromal adenoma																								
Uterus	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma			X																					
Leiomyoma																X								
Polyp stromal																								X
Hematopoietic System																								
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma													X											
Lymph node							+		+					+										
Lymph node, bronchial	+	+	+	A	+	+	+	M	+	+	+	+	+	+	M	+	M	+	+	+	+	+	+	+
Histiocytic sarcoma												X												
Lymph node, mandibular	+	+	M	+	M	+	+	M	+	+	+	+	+	+	M	+	+	+	+	+	+	+	M	+ M
Lymph node, mesenteric	+	+	+	A	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mediastinal	M	M	+	M	M	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	M	+	+
Histiocytic sarcoma												X												
Spleen	+	+	+	A	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma													X											
Histiocytic sarcoma												X												
Thymus	M	+	M	+	M	M	+	M	+	+	+	+	M	+	+	+	+	+	+	+	M	+	+	+
Integumentary System																								
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma												X			X	X								
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Subcutaneous tissue, fibrosarcoma													X									X		X
Subcutaneous tissue, hemangiosarcoma													X											
Musculoskeletal System																								
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nervous System																								
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Inhalation Study of Glutaraldehyde: 125 ppb

Number of Days on Study	7 3 5	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	
Carcass ID Number	5 3 2	5 0 1	5 0 2	5 0 6	5 0 9	5 1 0	5 1 7	5 3 5	5 3 7	5 3 8	5 3 9	5 4 0	5 4 2	5 4 5	5 4 7	5 5 0	5 1 5	5 2 5	5 2 6	5 2 7	5 2 8	5 3 4	5 4 1	5 4 4	5 4 6	Total Tissues/ Tumors
General Body System																										
Peritoneum																										2
Carcinoma, metastatic, uterus																										1
Histiocytic sarcoma																										1
Genital System																										
Clitoral gland	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Carcinoma, metastatic, uterus																										1
Cystadenoma																									X	1
Hemangiosarcoma																										1
Histiocytic sarcoma																										1
Bilateral, tubulostromal adenoma																				X						1
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Carcinoma																						X				2
Leiomyoma															X											2
Polyp stromal											X			X												3
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma																										1
Lymph node																										3
Lymph node, bronchial	+	+	+	+	+	+	+	M	+	M	M	+	+	+	M	+	+	M	M	+	M	M	M	+	+	37
Histiocytic sarcoma																										1
Lymph node, mandibular	+	+	+	+	+	M	+	+	M	+	+	M	+	+	M	+	+	+	+	+	M	+	+	+	+	39
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	M	+	+	+	+	+	+	46
Lymph node, mediastinal	+	+	M	+	+	+	+	M	M	M	M	M	+	+	M	+	+	M	M	+	+	M	+	+	+	34
Histiocytic sarcoma																										1
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Hemangiosarcoma																										1
Histiocytic sarcoma																										1
Thymus	+	+	+	+	+	M	+	+	+	+	M	+	+	+	+	+	+	M	+	+	+	M	+	+	+	39
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma																										3
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Subcutaneous tissue, fibrosarcoma																										3
Subcutaneous tissue, hemangiosarcoma																										1
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Inhalation Study of Glutaraldehyde: 125 ppb

Number of Days on Study	502	524	570	635	640	666	672	772	786	787	802	804	815	919	923	935	955	955	955	955	955	955	955	955	955
Carcass ID Number	54 8	53 3	50 8	52 2	50 7	52 0	51 9	53 6	54 9	53 0	53 1	51 8	54 3	40 5	00 4	00 3	01 1	11 2	11 3	11 4	11 6	22 1	22 3	22 4	22 9
Respiratory System																									
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma											X	X													
Alveolar/bronchiolar carcinoma				X																					X
Carcinoma, metastatic, uterus			X																						
Hepatocellular carcinoma, metastatic, liver																									
Hepatocholangiocarcinoma, metastatic, liver												X													
Histiocytic sarcoma												X													
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pleura				+																					
Alveolar/bronchiolar carcinoma, metastatic, lung				X																					
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Harderian gland													+												
Lacrimal gland																									
Urinary System																									
Kidney	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocholangiocarcinoma, metastatic, liver												X													
Histiocytic sarcoma												X													
Urinary bladder	+	+	+	A	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, uterus			X																						
Histiocytic sarcoma												X													
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma												X													
Lymphoma malignant							X		X					X				X	X				X		

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Inhalation Study of Glutaraldehyde: 125 ppb

Number of Days on Study	735	736	736	736	736	736	736	736	736	736	736	736	736	736	736	736	736	737	737	737	737	737	737	737	737	737	
Carcass ID Number	50332	50401	50002	50006	50009	50110	51107	51135	53357	53387	53398	54040	54402	54455	54477	55010	55155	55225	55266	55277	55288	55334	55411	55444	55446	Total Tissues/ Tumors
Respiratory System																											
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma																										2
Alveolar/bronchiolar carcinoma								X							X						X					5
Carcinoma, metastatic, uterus																										1
Hepatocellular carcinoma, metastatic, liver																			X							1
Hepatocholangiocarcinoma, metastatic, liver																										1
Histiocytic sarcoma																										1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pleura																										1
Alveolar/bronchiolar carcinoma, metastatic, lung																										1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																											
Harderian gland										+																1
Lacrimal gland																										1
Urinary System																											
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Hepatocholangiocarcinoma, metastatic, liver																										1
Histiocytic sarcoma																										1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Carcinoma, metastatic, uterus																										1
Histiocytic sarcoma																										1
Systemic Lesions																											
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																										1
Lymphoma malignant																							X		X	8

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Inhalation Study of Glutaraldehyde: 250 ppb

Number of Days on Study	4 0 1	4 9 2	5 0 2	5 4 2	5 5 2	5 6 0	5 8 8	6 1 6	6 3 1	6 6 0	6 8 5	6 8 6	7 0 1	7 0 7	7 1 2	7 2 3	7 2 3	7 3 3	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 6
Carcass ID Number	7 2 3	7 3 8	7 2 7	7 4 2	7 2 9	7 0 8	7 2 5	7 0 6	7 3 5	7 2 2	7 3 2	7 3 9	7 1 6	7 4 6	7 3 1	7 2 0	7 2 8	7 3 3	7 0 9	7 1 2	7 1 7	7 2 6	7 3 6	7 4 0	7 0 1
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder	A	+	+	+	+	+	+	I	A	M	A	+	+	+	A	+	+	M	+	+	+	+	+	+	+
Adenoma																					X				
Intestine large, colon	A	+	+	+	+	+	+	+	A	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	A	+	+	+	+	+	+	+	A	+	A	+	A	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	A	+	+	+	+	+	+	+	A	+	A	+	+	+	A	+	+	+	+	+	+	+	+	+	+
Leiomyosarcoma																									
Intestine small, duodenum	A	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Polyp adenomatous																						X			
Intestine small, jejunum	A	+	+	+	+	+	+	+	A	+	A	+	+	A	A	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	A	+	+	+	+	+	+	+	A	+	A	+	+	+	A	+	+	+	+	+	+	+	+	+	+
Polyp adenomatous																									
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																				X					
Hepatocellular carcinoma																	X	X							
Hepatocellular carcinoma, multiple	X																								
Hepatocellular adenoma								X																	
Ito cell tumor malignant																									
Mesentery													+	+		+		+						+	
Pancreas	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	A	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	A	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tooth																									
Cardiovascular System																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma benign																									
Islets, pancreatic	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid gland	+	+	M	+	+	+	M	+	M	M	M	+	+	M	+	M	M	+	M	+	M	+	+	M	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma					X	X			X			X	X								X			X	
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell, adenoma																						X			
Follicular cell, carcinoma																									
General Body System																									
None																									
Genital System																									
Clitoral gland	M	M	+	+	+	M	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cystadenoma																									
Uterus	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma																									
Leiomyoma																									

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Inhalation Study of Glutaraldehyde: 250 ppb

Number of Days on Study	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	
Carcass ID Number	7 0 2	7 0 3	7 0 5	7 0 7	7 1 0	7 1 1	7 1 3	7 1 5	7 1 8	7 2 1	7 3 0	7 3 7	7 4 1	7 4 8	7 4 9	7 0 4	7 1 4	7 1 9	7 2 4	7 3 4	7 4 3	7 4 4	7 4 5	7 4 7	7 5 0	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	M	+	+	+	+	+	+	41
Adenoma																										1
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	I	+	+	+	+	+	45
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Leiomyosarcoma													X													1
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Polyp adenomatous																										1
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Polyp adenomatous								X																		1
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma																										1
Hepatocellular carcinoma																									X	3
Hepatocellular carcinoma, multiple																										1
Hepatocellular adenoma	X						X																			3
Ito cell tumor malignant											X															1
Mesentery																									+	6
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Tooth															+											1
Cardiovascular System																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal medulla	+	+	+	+	+	+	+	+	+	I	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pheochromocytoma benign							X									X										2
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Parathyroid gland	+	+	M	M	M	+	M	+	M	+	+	M	+	+	M	+	+	M	M	M	+	+	M	+	+	28
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pars distalis, adenoma			X	X					X	X					X	X					X			X	X	16
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Follicular cell, adenoma				X															X							3
Follicular cell, carcinoma											X															1
General Body System																										
None																										
Genital System																										
Clitoral gland	+	M	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cystadenoma									X				X													2
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Carcinoma																X				X						2
Leiomyoma																							X			1

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Inhalation Study of Glutaraldehyde: 250 ppb

Number of Days on Study	4 0 1	4 9 2	5 0 2	5 4 2	5 5 2	5 6 0	5 8 8	6 1 6	6 3 1	6 6 0	6 8 5	6 8 6	7 0 1	7 0 7	7 1 2	7 2 3	7 2 3	7 3 3	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 6
Carcass ID Number	7 2 3	7 3 8	7 2 7	7 4 2	7 2 9	7 0 8	7 2 5	7 0 6	7 3 5	7 2 2	7 3 2	7 3 9	7 1 6	7 4 6	7 3 1	7 2 0	7 2 8	7 3 3	7 0 9	7 1 2	7 1 7	7 2 6	7 3 6	7 4 0	7 0 1
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node													+												
Lymph node, bronchial	+	M	+	+	+	+	+	+	A	M	+	+	M	+	M	+	+	+	+	+	+	M	+	+	+
Lymph node, mandibular	+	+	+	+	+	M	+	+	+	M	M	+	+	+	+	+	+	+	+	M	+	+	+	M	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																									
Lymph node, mediastinal	M	M	+	+	+	+	+	+	M	+	+	+	+	M	M	+	+	+	+	M	+	M	+	+	+
Spleen	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																				X					
Thymus	+	+	+	M	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Integumentary System																									
Mammary gland	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Subcutaneous tissue, sarcoma										X															X
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Respiratory System																									
Larynx	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																									
Alveolar/bronchiolar carcinoma																									
Hepatocellular carcinoma, metastatic, liver	X																X								
Leiomyosarcoma, metastatic, intestine large, cecum																									
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Harderian gland														+						+					
Carcinoma																				X					
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	A	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																									
Lymphoma malignant				X			X	X						X								X	X	X	X

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Inhalation Study of Glutaraldehyde: 250 ppb

Number of Days on Study	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	
Carcass ID Number	7 0 2	7 0 3	7 0 5	7 0 7	7 1 0	7 1 1	7 1 3	7 1 5	7 1 8	7 2 1	7 3 0	7 3 7	7 4 1	7 4 8	7 4 9	7 0 4	7 1 4	7 1 9	7 2 4	7 3 4	7 4 3	7 4 4	7 4 5	7 4 7	7 5 0	Total Tissues/ Tumors
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymph node																										1
Lymph node, bronchial	+	+	+	+	+	+	M	+	+	+	M	M	+	+	M	+	M	+	+	+	+	+	M	M	M	36
Lymph node, mandibular	+	+	+	+	+	+	M	+	+	I	M	M	+	M	+	+	+	+	+	+	+	M	+	+	M	38
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	I	+	46
Histiocytic sarcoma					X																					1
Lymph node, mediastinal	+	M	+	+	+	+	M	+	+	+	+	M	+	M	+	+	+	+	+	+	M	M	+	+	+	37
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Hemangiosarcoma																										1
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	47
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Subcutaneous tissue, sarcoma						X																				3
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Respiratory System																										
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	I	48
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma														X			X									2
Alveolar/bronchiolar carcinoma								X							X											2
Hepatocellular carcinoma, metastatic, liver																										2
Leiomyosarcoma, metastatic, intestine large, cecum													X													1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Special Senses System																										
Harderian gland																										2
Carcinoma																										1
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Urinary bladder	+	+	+	I	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma					X																					1
Lymphoma malignant				X									X		X				X							12

TABLE D3
Statistical Analysis of Primary Neoplasms in Female Mice in the 2-Year Inhalation Study of Glutaraldehyde

	Chamber Control	62.5 ppb	125 ppb	250 ppb
Adrenal Medulla: Benign Pheochromocytoma				
Overall rate[a]	4/50 (8%)	1/49 (2%)	1/48 (2%)	2/49 (4%)
Adjusted rate[b]	9.0%	2.2%	2.2%	4.7%
Terminal rate[c]	4/34 (12%)	1/37 (3%)	0/35 (0%)	2/31 (7%)
First incidence (days)	735 (T)	735 (T)	635	735 (T)
Poly-3 test[d]	P=0.328N	P=0.175N	P=0.179N	P=0.358N
Adrenal Medulla: Benign or Malignant Pheochromocytoma				
Overall rate	4/50 (8%)	2/49 (4%)	1/48 (2%)	2/49 (4%)
Adjusted rate	9.0%	4.4%	2.2%	4.7%
Terminal rate	4/34 (12%)	2/37 (5%)	0/35 (0%)	2/31 (7%)
First incidence (days)	735 (T)	735 (T)	635	735 (T)
Poly-3 test	P=0.278N	P=0.332N	P=0.179N	P=0.358N
Bone Marrow: Hemangiosarcoma				
Overall rate	1/50 (2%)	3/48 (6%)	1/50 (2%)	0/49 (0%)
Adjusted rate	2.2%	6.6%	2.2%	0.0%
Terminal rate	1/34 (3%)	2/37 (5%)	0/35 (0%)	0/32 (0%)
First incidence (days)	735 (T)	672	715	—[e]
Poly-3 test	P=0.203N	P=0.309	P=0.754N	P=0.507N
Harderian Gland: Adenoma or Carcinoma				
Overall rate	3/50 (6%)	0/50 (0%)	0/50 (0%)	1/50 (2%)
Adjusted rate	6.7%	0.0%	0.0%	2.3%
Terminal rate	2/34 (6%)	0/37 (0%)	0/35 (0%)	1/32 (3%)
First incidence (days)	708	—	—	735 (T)
Poly-3 test	P=0.247N	P=0.115N	P=0.114N	P=0.314N
Liver: Hepatocellular Adenoma				
Overall rate	11/50 (22%)	11/48 (23%)	7/50 (14%)	3/50 (6%)
Adjusted rate	24.6%	24.5%	15.0%	6.8%
Terminal rate	9/34 (27%)	10/37 (27%)	6/35 (17%)	2/32 (6%)
First incidence (days)	701	708	524	616
Poly-3 test	P=0.009N	P=0.592N	P=0.188N	P=0.020N
Liver: Hepatocellular Carcinoma				
Overall rate	4/50 (8%)	7/48 (15%)	5/50 (10%)	4/50 (8%)
Adjusted rate	8.9%	15.3%	10.8%	9.0%
Terminal rate	2/34 (6%)	3/37 (8%)	4/35 (11%)	1/32 (3%)
First incidence (days)	657	551	672	401
Poly-3 test	P=0.441N	P=0.268	P=0.514	P=0.637
Liver: Hepatocellular Adenoma or Carcinoma				
Overall rate	14/50 (28%)	17/48 (35%)	11/50 (22%)	7/50 (14%)
Adjusted rate	30.9%	37.2%	23.5%	15.6%
Terminal rate	10/34 (29%)	13/37 (35%)	9/35 (26%)	3/32 (9%)
First incidence (days)	657	551	524	401
Poly-3 test	P=0.021N	P=0.342	P=0.285N	P=0.067N

TABLE D3
Statistical Analysis of Primary Neoplasms in Female Mice in the 2-Year Inhalation Study of Glutaraldehyde

	Chamber Control	62.5 ppb	125 ppb	250 ppb
Lung: Alveolar/bronchiolar Adenoma				
Overall rate	2/50 (4%)	4/49 (8%)	2/50 (4%)	2/50 (4%)
Adjusted rate	4.5%	8.7%	4.3%	4.6%
Terminal rate	2/34 (6%)	3/37 (8%)	0/35 (0%)	2/32 (6%)
First incidence (days)	735 (T)	463	702	735 (T)
Poly-3 test	P=0.464N	P=0.350	P=0.682N	P=0.686
Lung: Alveolar/bronchiolar Carcinoma				
Overall rate	1/50 (2%)	4/49 (8%)	5/50 (10%)	2/50 (4%)
Adjusted rate	2.2%	8.9%	10.8%	4.6%
Terminal rate	1/34 (3%)	3/37 (8%)	4/35 (11%)	2/32 (6%)
First incidence (days)	735 (T)	728	635	735 (T)
Poly-3 test	P=0.482	P=0.182	P=0.110	P=0.492
Lung: Alveolar/bronchiolar Adenoma or Carcinoma				
Overall rate	3/50 (6%)	8/49 (16%)	7/50 (14%)	4/50 (8%)
Adjusted rate	6.7%	17.4%	15.0%	9.2%
Terminal rate	3/34 (9%)	6/37 (16%)	4/35 (11%)	4/32 (13%)
First incidence (days)	735 (T)	463	635	735 (T)
Poly-3 test	P=0.549N	P=0.107	P=0.174	P=0.488
Mammary Gland: Carcinoma				
Overall rate	3/50 (6%)	0/50 (0%)	3/50 (6%)	0/50 (0%)
Adjusted rate	6.7%	0.0%	6.5%	0.0%
Terminal rate	2/34 (6%)	0/37 (0%)	1/35 (3%)	0/32 (0%)
First incidence (days)	664	—	704	—
Poly-3 test	P=0.171N	P=0.116N	P=0.650N	P=0.124N
Pituitary Gland (Pars Distalis): Adenoma				
Overall rate	20/49 (41%)	16/49 (33%)	20/49 (41%)	16/50 (32%)
Adjusted rate	44.9%	35.4%	43.0%	35.2%
Terminal rate	17/34 (50%)	15/37 (41%)	16/35 (46%)	11/32 (34%)
First incidence (days)	616	714	502	552
Poly-3 test	P=0.277N	P=0.240N	P=0.511N	P=0.233N
Pituitary Gland (Pars Distalis): Adenoma or Carcinoma				
Overall rate	21/49 (43%)	16/49 (33%)	20/49 (41%)	16/50 (32%)
Adjusted rate	46.8%	35.4%	43.0%	35.2%
Terminal rate	17/34 (50%)	15/37 (41%)	16/35 (46%)	11/32 (34%)
First incidence (days)	616	714	502	552
Poly-3 test	P=0.225N	P=0.185N	P=0.436N	P=0.179N
Skin (Subcutaneous Tissue): Fibrosarcoma				
Overall rate	1/50 (2%)	1/50 (2%)	3/50 (6%)	0/50 (0%)
Adjusted rate	2.2%	2.2%	6.5%	0.0%
Terminal rate	1/34 (3%)	1/37 (3%)	2/35 (6%)	0/32 (0%)
First incidence (days)	735 (T)	735 (T)	715	—
Poly-3 test	P=0.423N	P=0.756N	P=0.316	P=0.504N

TABLE D3
Statistical Analysis of Primary Neoplasms in Female Mice in the 2-Year Inhalation Study of Glutaraldehyde

	Chamber Control	62.5 ppb	125 ppb	250 ppb
Skin (Subcutaneous Tissue): Sarcoma				
Overall rate	2/50 (4%)	0/50 (0%)	0/50 (0%)	3/50 (6%)
Adjusted rate	4.4%	0.0%	0.0%	6.8%
Terminal rate	0/34 (0%)	0/37 (0%)	0/35 (0%)	2/32 (6%)
First incidence (days)	681	—	—	660
Poly-3 test	P=0.240	P=0.234N	P=0.232N	P=0.489
Skin (Subcutaneous Tissue): Fibrosarcoma or Sarcoma				
Overall rate	3/50 (6%)	1/50 (2%)	3/50 (6%)	3/50 (6%)
Adjusted rate	6.7%	2.2%	6.5%	6.8%
Terminal rate	1/34 (3%)	1/37 (3%)	2/35 (6%)	2/32 (6%)
First incidence (days)	681	735 (T)	715	660
Poly-3 test	P=0.442	P=0.300N	P=0.652N	P=0.652
Spleen: Hemangiosarcoma				
Overall rate	1/50 (2%)	3/48 (6%)	1/48 (2%)	1/49 (2%)
Adjusted rate	2.2%	6.6%	2.2%	2.3%
Terminal rate	1/34 (3%)	2/37 (5%)	0/35 (0%)	1/32 (3%)
First incidence (days)	735 (T)	672	715	735 (T)
Poly-3 test	P=0.452N	P=0.309	P=0.760	P=0.753
Thyroid Gland (Follicular Cell): Adenoma				
Overall rate	4/50 (8%)	0/48 (0%)	2/50 (4%)	3/50 (6%)
Adjusted rate	9.0%	0.0%	4.4%	6.9%
Terminal rate	4/34 (12%)	0/37 (0%)	2/35 (6%)	3/32 (9%)
First incidence (days)	735 (T)	—	735 (T)	735 (T)
Poly-3 test	P=0.554	P=0.059N	P=0.324N	P=0.512N
Thyroid Gland (Follicular Cell): Adenoma or Carcinoma				
Overall rate	4/50 (8%)	0/48 (0%)	2/50 (4%)	4/50 (8%)
Adjusted rate	9.0%	0.0%	4.4%	9.2%
Terminal rate	4/34 (12%)	0/37 (0%)	2/35 (6%)	4/32 (13%)
First incidence (days)	735 (T)	—	735 (T)	735 (T)
Poly-3 test	P=0.357	P=0.059N	P=0.324N	P=0.631
Uterus: Stromal Polyp				
Overall rate	3/50 (6%)	4/50 (8%)	3/50 (6%)	0/50 (0%)
Adjusted rate	6.7%	8.6%	6.5%	0.0%
Terminal rate	3/34 (9%)	3/37 (8%)	3/35 (9%)	0/32 (0%)
First incidence (days)	735 (T)	527	735 (T)	—
Poly-3 test	P=0.082N	P=0.520	P=0.649N	P=0.122N
All Organs: Hemangiosarcoma				
Overall rate	3/50 (6%)	6/50 (12%)	2/50 (4%)	1/50 (2%)
Adjusted rate	6.7%	13.1%	4.3%	2.3%
Terminal rate	2/34 (6%)	5/37 (14%)	0/35 (0%)	1/32 (3%)
First incidence (days)	701	672	687	735 (T)
Poly-3 test	P=0.117N	P=0.254	P=0.486N	P=0.314N

TABLE D3
Statistical Analysis of Primary Neoplasms in Female Mice in the 2-Year Inhalation Study of Glutaraldehyde

	Chamber Control	62.5 ppb	125 ppb	250 ppb
All Organs: Hemangioma or Hemangiosarcoma				
Overall rate	3/50 (6%)	7/50 (14%)	2/50 (4%)	1/50 (2%)
Adjusted rate	6.7%	15.2%	4.3%	2.3%
Terminal rate	2/34 (6%)	6/37 (16%)	0/35 (0%)	1/32 (3%)
First incidence (days)	701	672	687	735 (T)
Poly-3 test	P=0.097N	P=0.167	P=0.486N	P=0.314N
All Organs: Malignant Lymphoma				
Overall rate	12/50 (24%)	12/50 (24%)	8/50 (16%)	12/50 (24%)
Adjusted rate	26.7%	26.2%	17.2%	26.5%
Terminal rate	9/34 (27%)	10/37 (27%)	5/35 (14%)	8/32 (25%)
First incidence (days)	686	707	672	542
Poly-3 test	P=0.495N	P=0.570N	P=0.200N	P=0.586N
All Organs: Benign Neoplasms				
Overall rate	32/50 (64%)	32/50 (64%)	30/50 (60%)	26/50 (52%)
Adjusted rate	70.5%	67.7%	62.1%	56.7%
Terminal rate	27/34 (79%)	28/37 (76%)	23/35 (66%)	20/32 (63%)
First incidence (days)	616	463	502	552
Poly-3 test	P=0.079N	P=0.476N	P=0.256N	P=0.116N
All Organs: Malignant Neoplasms				
Overall rate	24/50 (48%)	27/50 (54%)	24/50 (48%)	25/50 (50%)
Adjusted rate	51.6%	56.6%	50.3%	53.8%
Terminal rate	15/34 (44%)	18/37 (49%)	15/35 (43%)	17/32 (53%)
First incidence (days)	558	492	570	401
Poly-3 test	P=0.526	P=0.391	P=0.531N	P=0.498
All Organs: Benign or Malignant Neoplasms				
Overall rate	41/50 (82%)	45/50 (90%)	41/50 (82%)	40/50 (80%)
Adjusted rate	87.4%	91.6%	82.6%	82.8%
Terminal rate	31/34 (91%)	34/37 (92%)	27/35 (77%)	27/32 (84%)
First incidence (days)	558	463	502	401
Poly-3 test	P=0.185N	P=0.356	P=0.348N	P=0.362N

(T)Terminal sacrifice
[a] Number of neoplasm-bearing animals/number of animals examined. Denominator is number of animals examined microscopically for adrenal gland, bone marrow, liver, lung, pituitary gland, spleen, and thyroid gland; for other tissues, denominator is number of animals necropsied.
[b] Poly-3 estimated neoplasm incidence after adjustment for intercurrent mortality
[c] Observed incidence at terminal kill
[d] Beneath the chamber control incidence are the P values associated with the trend test. Beneath the exposed group incidence are the P values corresponding to pairwise comparisons between the chamber controls and that exposed group. The Poly-3 test accounts for differential mortality in animals that do not reach terminal sacrifice. A negative trend or a lower incidence in an exposure group is indicated by **N**.
[e] Not applicable; no neoplasms in animal group

TABLE D4
Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 2-Year Inhalation Study of Glutaraldehyde[a]

	Chamber Control	62.5 ppb	125 ppb	250 ppb
Disposition Summary				
Animals initially in study	50	50	50	50
Early deaths				
Accidental death			1	
Moribund	11	10	10	12
Natural deaths	5	3	4	6
Survivors				
Terminal sacrifice	34	37	35	32
Animals examined microscopically	50	50	50	50
Alimentary System				
Gallbladder	(45)	(41)	(43)	(41)
Hyperplasia				1 (2%)
Intestine small, duodenum	(45)	(47)	(48)	(48)
Necrosis	1 (2%)	1 (2%)		
Liver	(50)	(48)	(50)	(50)
Amyloid deposition				1 (2%)
Basophilic focus	2 (4%)	4 (8%)	5 (10%)	2 (4%)
Clear cell focus	2 (4%)	1 (2%)		
Eosinophilic focus	6 (12%)	6 (13%)	4 (8%)	
Fatty change			3 (6%)	
Hematopoietic cell proliferation	1 (2%)			
Hyperplasia, lymphoid			1 (2%)	
Necrosis	1 (2%)	1 (2%)	1 (2%)	2 (4%)
Tension lipidosis	1 (2%)	1 (2%)	1 (2%)	1 (2%)
Vacuolization cytoplasmic, focal		1 (2%)		
Bile duct, hyperplasia	1 (2%)			
Centrilobular, necrosis	1 (2%)		2 (4%)	1 (2%)
Mesentery	(12)	(6)	(5)	(6)
Inflammation, suppurative	1 (8%)			1 (17%)
Thrombosis	1 (8%)	1 (17%)		1 (17%)
Artery, inflammation, chronic active	2 (17%)			
Fat, necrosis	9 (75%)	5 (83%)	3 (60%)	4 (67%)
Pancreas	(50)	(48)	(49)	(49)
Atrophy		1 (2%)		
Basophilic focus	1 (2%)	1 (2%)		
Hypertrophy			1 (2%)	
Inflammation, suppurative	1 (2%)			
Duct, cyst	1 (2%)		2 (4%)	
Stomach, forestomach	(50)	(49)	(48)	(48)
Hyperplasia, squamous	1 (2%)		1 (2%)	1 (2%)
Infiltration cellular, mast cell		1 (2%)		
Inflammation, acute		1 (2%)	2 (4%)	
Stomach, glandular	(50)	(48)	(48)	(48)
Infiltration cellular, mixed cell			1 (2%)	
Mineralization	1 (2%)	1 (2%)		1 (2%)
Necrosis			1 (2%)	
Tooth		(1)		(1)
Developmental malformation		1 (100%)		1 (100%)
Cardiovascular System				
Heart	(50)	(49)	(50)	(50)
Artery, inflammation	1 (2%)			
Atrium, thrombosis	2 (4%)			

[a] Number of animals examined microscopically at the site and the number of animals with lesion

TABLE D4
Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 2-Year Inhalation Study of Glutaraldehyde

	Chamber Control	62.5 ppb	125 ppb	250 ppb
Endocrine System				
Adrenal cortex	(50)	(49)	(49)	(50)
Atrophy	1 (2%)			
Hyperplasia	2 (4%)	2 (4%)	7 (14%)	1 (2%)
Hypertrophy	2 (4%)	2 (4%)	1 (2%)	2 (4%)
Capsule, inflammation, chronic active	1 (2%)			
Adrenal medulla	(50)	(49)	(48)	(49)
Hyperplasia	3 (6%)	1 (2%)	5 (10%)	1 (2%)
Islets, pancreatic	(50)	(48)	(49)	(49)
Hyperplasia	1 (2%)		2 (4%)	1 (2%)
Pituitary gland	(49)	(49)	(49)	(50)
Pars distalis, hyperplasia	19 (39%)	24 (49%)	23 (47%)	28 (56%)
Pars intermedia, hypertrophy			1 (2%)	
Thyroid gland	(50)	(48)	(50)	(50)
Follicular cell, hyperplasia	26 (52%)	24 (50%)	30 (60%)	37 (74%)
General Body System				
None				
Genital System				
Ovary	(49)	(47)	(49)	(50)
Angiectasis		1 (2%)		1 (2%)
Cyst	16 (33%)	12 (26%)	18 (37%)	18 (36%)
Inflammation, suppurative	1 (2%)			1 (2%)
Thrombosis				1 (2%)
Uterus	(50)	(48)	(49)	(49)
Angiectasis	2 (4%)	1 (2%)	1 (2%)	
Cyst	1 (2%)			
Hemorrhage			1 (2%)	
Hydrometra	3 (6%)	7 (15%)	3 (6%)	5 (10%)
Infiltration cellular, mast cell		1 (2%)		
Infiltration cellular, polymorphonuclear	3 (6%)	1 (2%)		1 (2%)
Inflammation, chronic			1 (2%)	
Necrosis		1 (2%)		
Thrombosis		1 (2%)		
Myometrium, hyperplasia			1 (2%)	
Hematopoietic System				
Bone marrow	(50)	(48)	(50)	(49)
Infiltration cellular, mast cell		1 (2%)		
Necrosis			1 (2%)	
Lymph node	(7)	(4)	(3)	(1)
Iliac, infiltration cellular, plasma cell	1 (14%)			
Lumbar, hyperplasia, lymphoid		1 (25%)		
Lumbar, inflammation, suppurative				1 (100%)
Renal, infiltration cellular, plasma cell	1 (14%)			
Lymph node, bronchial	(29)	(32)	(37)	(36)
Hyperplasia, lymphoid			1 (3%)	
Infiltration cellular, plasma cell	2 (7%)			
Lymph node, mandibular	(43)	(40)	(39)	(38)
Hyperplasia, lymphoid	1 (2%)			
Lymph node, mesenteric	(47)	(48)	(46)	(46)
Ectasia	1 (2%)		1 (2%)	
Hemorrhage			1 (2%)	1 (2%)
Hyperplasia, lymphoid	4 (9%)		1 (2%)	

TABLE D4
Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 2-Year Inhalation Study of Glutaraldehyde

	Chamber Control	62.5 ppb	125 ppb	250 ppb
Hematopoietic System (continued)				
Lymph node, mediastinal	(31)	(23)	(34)	(37)
Hemorrhage			1 (3%)	
Hyperplasia, lymphoid	1 (3%)			
Infiltration cellular, plasma cell	1 (3%)			
Inflammation, suppurative				1 (3%)
Spleen	(50)	(48)	(48)	(49)
Amyloid deposition				1 (2%)
Hematopoietic cell proliferation	11 (22%)	8 (17%)	8 (17%)	12 (24%)
Hyperplasia, lymphoid	4 (8%)	2 (4%)	1 (2%)	
Integumentary System				
Skin	(50)	(50)	(50)	(50)
Cyst epithelial inclusion	1 (2%)			
Hyperplasia		1 (2%)		
Inflammation, chronic active		1 (2%)		
Inflammation, suppurative				1 (2%)
Musculoskeletal System				
Skeletal muscle	(2)	(1)		
Hemorrhage	1 (50%)			
Nervous System				
Brain	(50)	(49)	(50)	(50)
Degeneration	1 (2%)			
Necrosis	1 (2%)			
Artery, inflammation	1 (2%)			
Respiratory System				
Larynx	(50)	(49)	(50)	(48)
Inflammation			1 (2%)	
Epiglottis, hyperplasia			1 (2%)	
Epiglottis, metaplasia, squamous		1 (2%)	1 (2%)	
Lung	(50)	(49)	(50)	(50)
Hemorrhage		1 (2%)		
Inflammation, chronic active				1 (2%)
Thrombosis	1 (2%)		2 (4%)	
Alveolar epithelium, hyperplasia	4 (8%)	4 (8%)		
Alveolus, infiltration cellular, histiocyte	1 (2%)			1 (2%)
Mediastinum, inflammation, suppurative	1 (2%)			
Nose	(50)	(49)	(50)	(50)
Inflammation	5 (10%)	7 (14%)	13 (26%)	14 (28%)
Inflammation, suppurative	1 (2%)			
Thrombosis				1 (2%)
Olfactory epithelium, atrophy		1 (2%)	3 (6%)	3 (6%)
Olfactory epithelium, degeneration, hyaline	11 (22%)	10 (20%)	15 (30%)	10 (20%)
Respiratory epithelium, degeneration, hyaline	16 (32%)	35 (71%)	32 (64%)	30 (60%)
Respiratory epithelium, metaplasia, squamous	7 (14%)	11 (22%)	16 (32%)	21 (42%)
Turbinate, necrosis		3 (6%)	1 (2%)	4 (8%)
Special Senses System				
None				

TABLE D4
Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 2-Year Inhalation Study of Glutaraldehyde

	Chamber Control	62.5 ppb	125 ppb	250 ppb
Urinary System				
Kidney	(50)	(49)	(49)	(49)
Amyloid deposition				1 (2%)
Hydronephrosis			1 (2%)	
Infarct	1 (2%)	2 (4%)	3 (6%)	2 (4%)
Metaplasia, osseous	1 (2%)			2 (4%)
Nephropathy	20 (40%)	14 (29%)	19 (39%)	16 (33%)
Artery, inflammation, chronic active	1 (2%)			
Renal tubule, necrosis	1 (2%)			
Urinary bladder	(48)	(48)	(48)	(47)
Infiltration cellular, mast cell		1 (2%)		
Inflammation, suppurative	1 (2%)			

APPENDIX E
GENETIC TOXICOLOGY

GENETIC TOXICOLOGY

SALMONELLA TYPHIMURIUM MUTAGENICITY TEST PROTOCOL

Testing was performed as reported by Haworth *et al.* (1983) and Zeiger *et al.* (1992). Glutaraldehyde was sent to the laboratories as a coded aliquot from Radian Corporation (Austin, TX). It was incubated with the *Salmonella typhimurium* tester strains TA98, TA100, TA102, TA104, TA1535, and TA1537 either in buffer or S9 mix (metabolic activation enzymes and cofactors from Aroclor 1254-induced male Sprague-Dawley rat, Syrian hamster, or B6C3F_1 mouse liver) for 20 minutes at 37° C. Top agar supplemented with L-histidine and d-biotin was added, and the contents of the tubes were mixed and poured onto the surfaces of minimal glucose agar plates. Histidine-independent mutant colonies arising on these plates were counted following incubation for 2 days at 37° C.

Each trial consisted of triplicate plates of concurrent positive and negative controls and five doses of glutaraldehyde. The high dose was limited by toxicity. All trials were repeated.

In this assay, a positive response is defined as a reproducible, dose-related increase in histidine-independent (revertant) colonies in any one strain/activation combination. An equivocal response is defined as an increase in revertants that is not dose related, is not reproducible, or is not of sufficient magnitude to support a determination of mutagenicity. A negative response is obtained when no increase in revertant colonies is observed following chemical treatment. There is no minimum percentage or fold increase required for a chemical to be judged positive or weakly positive.

MOUSE LYMPHOMA MUTAGENICITY TEST PROTOCOL

The experimental protocol is presented in detail by McGregor *et al.* (1988). Glutaraldehyde was supplied as a coded aliquot by Radian Corporation. The high dose of 8 μg/mL was determined by toxicity. L5178Y mouse lymphoma cells were maintained at 37° C as suspension cultures in supplemented Fischer's medium; normal cycling time was approximately 10 hours. To reduce the number of spontaneously occurring cells resistant to trifluorothymidine (TFT), subcultures were exposed to medium containing thymidine, hypoxanthine, methotrexate, and glycine for 1 day; to medium containing thymidine, hypoxanthine, and glycine for 1 day; and to normal medium for 3 to 5 days. For cloning, the horse serum content was increased and Noble agar was added.

All treatment levels within an experiment, including concurrent positive and solvent controls, were replicated. Treated cultures contained 6×10^6 cells in 10 mL medium. This volume included the S9 fraction in those experiments performed with metabolic activation. Incubation with glutaraldehyde continued for 4 hours, at which time the medium plus glutaraldehyde was removed, and the cells were resuspended in fresh medium and incubated for an additional 2 days to express the mutant phenotype. Cell density was monitored so that log phase growth was maintained. After the 48-hour expression period, cells were plated in medium and soft agar supplemented with TFT for selection of TFT-resistant cells, and cells were plated in nonselective medium and soft agar to determine cloning efficiency. Plates were incubated at 37° C in 5% CO_2 for 10 to 12 days.

Minimum criteria for accepting an experiment as valid and a detailed description of the statistical analysis and data evaluation are presented by Caspary *et al.* (1988). All data were evaluated statistically for trend and peak responses. Both responses had to be significant ($P \leq 0.05$) for glutaraldehyde to be considered positive, i.e., capable of inducing TFT resistance. A single significant response led to a call of "questionable," and the absence of both a trend and peak response resulted in a "negative" call.

CHINESE HAMSTER OVARY CELL CYTOGENETICS PROTOCOLS

Testing was performed as reported by Galloway *et al.* (1985). Glutaraldehyde was sent to the laboratories as a coded aliquot by Radian Corporation. It was tested in cultured Chinese hamster ovary (CHO) cells for induction of sister chromatid exchanges (SCEs) and chromosomal aberrations (Abs), both in the presence and absence of Aroclor 1254-induced male Sprague-Dawley rat liver S9 and cofactor mix. Cultures were handled under gold lights to prevent photolysis of bromodeoxyuridine-substituted DNA. Each test consisted of concurrent solvent and positive controls and of at least three doses of glutaraldehyde; the high dose was limited by toxicity. A single flask per dose was used.

***Sister Chromatid Exchange Test*:** In the SCE test without S9, CHO cells were incubated for 25.5 or 26 hours with glutaraldehyde in supplemented McCoy's 5A medium. Bromodeoxyuridine (BrdU) was added 2 hours after culture initiation. After 25.5 or 26 hours, the medium containing glutaraldehyde was removed and replaced with fresh medium plus BrdU and Colcemid, and incubation was continued for 2 hours. Cells were then harvested by mitotic shake-off, fixed, and stained with Hoechst 33258 and Giemsa. In the SCE test with S9, cells were incubated with glutaraldehyde, serum-free medium, and S9 for 2 hours. The medium was then removed and replaced with medium containing serum and BrdU and no glutaraldehyde. Incubation proceeded for an additional 25.5 or 26 hours, with Colcemid present for the final 2 hours. Harvesting and staining were the same as for cells treated without S9. All slides were scored blind and those from a single test were read by the same person. Fifty second-division metaphase cells were scored for frequency of SCEs/cell from each dose level.

Statistical analyses were conducted on the slopes of the dose-response curves and the individual dose points (Galloway *et al.*, 1985). An SCE frequency 20% above the concurrent solvent control value was chosen as a statistically conservative positive response. The probability of this level of difference occurring by chance at one dose point is less than 0.01; the probability for such a chance occurrence at two dose points is less than 0.001. An increase of 20% or greater at any single dose (and a trend P value of less than 0.025) was considered weak evidence of activity; increases at two or more doses resulted in a determination that the trial was positive. A statistically significant trend ($P < 0.005$) in the absence of any responses reaching 20% above background led to a call of equivocal.

Chromosomal Aberrations Test: In the Abs test without S9, cells were incubated in McCoy's 5A medium with glutaraldehyde for 8.5 to 12 hours; Colcemid was added and incubation continued for 2 hours. The cells were then harvested by mitotic shake-off, fixed, and stained with Giemsa. For the Abs test with S9, cells were treated with glutaraldehyde and S9 for 2 hours, after which the treatment medium was removed and the cells were incubated for 8.5 to 12 hours in fresh medium, with Colcemid present for the final 2 hours. Cells were harvested in the same manner as for the treatment without S9. The harvest time for the Abs test was based on the cell cycle information obtained in the SCE test.

Cells were selected for scoring on the basis of good morphology and completeness of karyotype (21 ± 2 chromosomes). All slides were scored blind and those from a single test were read by the same person. One hundred first-division metaphase cells were scored at each dose level. Classes of aberrations included simple (breaks and terminal deletions), complex (rearrangements and translocations), and other (pulverized cells, despiralized chromosomes, and cells containing 10 or more aberrations).

Chromosomal aberration data are presented as percentage of cells with aberrations. To arrive at a statistical call for a trial, analyses were conducted on both the dose response curve and individual dose points. For a single trial, a statistically significant ($P \leq 0.01$) difference for one dose point and a significant trend ($P \leq 0.005$) were considered weak evidence for a response; significant differences for two or more doses indicated the trial was positive. A positive trend test in the absence of a statistically significant increase at any one dose resulted in an equivocal call (Galloway *et al.*, 1985). Ultimately, the trial calls were based on a consideration of the statistical analyses as well as the biological information available to the reviewers.

DROSOPHILA MELANOGASTER TEST PROTOCOL

The assays for induction of sex-linked recessive lethal (SLRL) mutations were performed with adult flies as described by Yoon *et al.* (1985) and with larvae as described by Zimmering *et al.* (1989). Glutaraldehyde was supplied as a coded aliquot by Radian Corporation. Glutaraldehyde was assayed in the SLRL test by feeding for 3 days to adult Canton-S wild-type males no more than 24 hours old at the beginning of treatment. Because no response was obtained, glutaraldehyde was retested by injection into adult males.

To administer glutaraldehyde by injection, a glass Pasteur pipette was drawn out in a flame to a microfine filament, and the tip was broken off to allow delivery of the test solution. Injection was performed either manually, by attaching a rubber bulb to the other end of the pipette and forcing through sufficient solution (0.2 to 0.3 μL) to slightly distend the abdomen of the fly, or by attaching the pipette to a microinjector that automatically delivered a calibrated volume. Flies were anesthetized with ether and immobilized on a strip of tape. Injection into the thorax, under the wing, was performed with the aid of a dissecting microscope.

Toxicity tests were performed to set concentrations of glutaraldehyde at a level that would induce 30% mortality after 72 hours of feeding or 24 hours after injection, while keeping induced sterility at an acceptable level. Canton-S males were allowed to feed for 72 hours on an aqueous solution of glutaraldehyde in 5% sucrose. In the injection experiments, 24- to 72-hour old Canton-S males were treated with an aqueous solution of glutaraldehyde diluted in saline and allowed to recover for 24 hours. A concurrent saline control group was also included. In the adult exposures, treated males were mated to three *Basc* females for 3 days and were given fresh females at 2-day intervals to produce three matings of 3, 2, and 2 days (in each case, sample sperm from successive matings was treated at successively earlier postmeiotic stages). For the larval feeding experiment, Canton-S males and females were mated and eggs were exposed in vials with standard cornmeal feed containing glutaraldehyde in solvent (distilled water) or solvent alone (Valencia *et al.*, 1989). Adult emergent males were mated at approximately 24 hours of age with two successive harems of three to five *Basc* females to establish two single-day broods. For both the adult and larval exposure experiments, F_1 heterozygous females were mated with their siblings and then placed in individual vials. F_1 daughters from the same parental male were kept together to identify clusters. (A cluster occurs when a number of mutants from a given male result from a single spontaneous premeiotic mutation event and is identified when the number of mutants from that male exceeds the number predicted by a Poisson distribution.) If a cluster was identified, all data from the male in question were discarded. Presumptive lethal mutations were identified as vials containing fewer than 5% of the expected number of wild-type males after 17 days; these were retested to confirm the response.

SLRL data were analyzed by simultaneous comparison with the concurrent and historical controls (Mason *et al.,* 1992) using a normal approximation to the binomial test (Margolin *et al.*, 1983). A test result was considered positive if the P value was less than or equal to 0.01 and the mutation frequency in the tested group was greater than 0.10% or if the P value was less than or equal to 0.05 and the frequency in the treatment group was greater than 0.15%. A test was considered to be inconclusive if the P value was between 0.05 and 0.01 but the frequency in the treatment group was between 0.10% and 0.15% or if the P value was between 0.10 and 0.05 but the frequency in the treatment group was greater than 0.10%. A test was considered negative if the P value was greater than or equal to 0.10 or if the frequency in the treatment group was less than 0.10%.

MOUSE BONE MARROW CYTOGENETICS AND MICRONUCLEUS TEST PROTOCOLS

Chromosomal Aberrations Test: A dose range-finding study was performed. The highest dose was limited by toxicity. Glutaraldehyde was tested for induction of Abs in mouse bone marrow by two different protocols. The first protocol used a standard harvest time of 17 hours (Shelby *et al.*, 1989), and the second protocol used a delayed harvest time of 36 hours (McFee *et al.*, 1992).

Male B6C3F_1 mice (10 animals per dose group) were injected intraperitoneally with glutaraldehyde dissolved in phosphate-buffered saline (injection volume = 0.4 mL). Solvent control animals received equivalent injections of phosphate-buffered saline only. The positive control was mitomycin-C. The animals were subcutaneously implanted with a BrdU tablet (McFee *et al.*, 1983) 18 hours before the scheduled harvest. (For the standard protocol, this required BrdU implantation to precede injection with glutaraldehyde by 1 hour.) The use of BrdU allowed selection of the appropriate cell population for scoring. (Abs induced by chemical administration are present in maximum number at the first metaphase following treatment; they decline in number during subsequent nuclear divisions due to cell death.) Two hours before sacrifice, the animals received an intraperitoneal injection of colchicine in saline. The animals were killed 17 or 36 hours after glutaraldehyde injection (18 hours after BrdU dosing). One or both femurs were removed, and the marrow was flushed out with phosphate-buffered saline (pH 7.0). Cells were treated with a hypotonic salt solution, fixed, and dropped onto chilled slides. After a 24-hour drying period, the slides were stained (with a modified fluorescence-plus-Giemsa technique) and scored.

Fifty first-division metaphase cells were scored from each of eight animals per treatment. Responses were evaluated as the percentage of aberrant metaphase cells, excluding gaps. The data were analyzed by a trend test (Margolin *et al.*, 1986). The trend test P value must be less than or equal to 0.025 for a test to be significant; pairwise comparisons of each treatment group to the corresponding solvent control group are significant when P is less than or equal to 0.025 divided by the number of glutaraldehyde-treated groups.

Micronucleus Test: The standard three-exposure protocol is described in detail by Shelby *et al.* (1993). For the micronucleus analysis that was performed in conjunction with the 36-hour Abs test (Trial 2), animal treatment is described under that test protocol, and slide preparation, staining, and scoring were performed as per Shelby *et al.* (1993). In the multiple-treatment protocol, male mice were injected intraperitoneally three times at 24-hour intervals with glutaraldehyde dissolved in phosphate-buffered saline. The total dosing volume, regardless of injection number, was 0.4 mL. Solvent control animals were injected with 0.4 mL of phosphate-buffered saline only. The positive control animals received injections of mitomycin-C. The animals were killed 24 hours after the third injection (36 hours in the single-injection protocol), and blood smears were prepared from bone marrow cells obtained from the femurs. Air-dried smears were fixed and stained; 2,000 polychromatic erythrocytes (PCEs) were scored for the frequency of micronucleated cells in four or five animals per dose group.

The results were tabulated as the mean of the pooled results from all animals within a treatment group plus or minus the standard error of the mean. The frequency of micronucleated cells among PCEs was analyzed by a statistical software package that tested for increasing trend over dose groups with a one-tailed Cochran-Armitage trend test, followed by pairwise comparisons between each dosed group and the control group (ILS, 1990). In the presence of excess binomial variation, as detected by a binomial dispersion test, the binomial variance of the Cochran-Armitage test was adjusted upward in proportion to the excess variation. In the micronucleus test, an individual trial is considered positive if the trend test P value is less than or equal to 0.025 or if the P value for any single dose group is less than or equal to 0.025 divided by the number of dose groups. A final call of positive for micronucleus induction is preferably based on reproducibly positive trials (as noted above). Ultimately, the final call is determined by the scientific staff after considering the results of statistical analyses, the reproducibility of any effects observed, and the magnitudes of those effects.

MOUSE PERIPHERAL BLOOD MICRONUCLEUS TEST PROTOCOL

A detailed discussion of this assay is presented by MacGregor *et al.* (1990). At the end of a 13-week toxicity study (NTP, 1993), peripheral blood samples were obtained from male and female mice. Smears were immediately prepared and fixed in absolute methanol. The methanol-fixed slides were stained with a chromatin-specific fluorescent dye mixture of Hoechst 33258/pyronin Y (MacGregor *et al.*, 1983) and coded. Slides were scanned to determine the frequency of micronuclei in 10,000 normochromatic erythrocytes (NCEs) in each of ten animals per dose group. The criteria of Schmid (1976) were used in defining micronuclei, with the additional requirement that micronuclei exhibit the characteristic fluorescent emissions of DNA (blue with 360 nm and orange with 540 nm utlraviolet illumination); the minimum size limit was approximately 1/20 the diameter of the NCE.

The results were tabulated as the mean of the pooled results from all animals within a treatment group plus or minus the standard error of the mean. The frequency of micronucleated NCEs was analyzed by a statistical software package that tested for increasing trend over exposure groups with a one-tailed Cochran-Armitage trend test, followed by pairwise comparisons between each exposure group and the control group (ILS, 1990). In the presence of excess binomial variation, as detected by a binomial dispersion test, the binomial variance of the Cochran-Armitage test was adjusted upward in proportion to the excess variation. In the micronucleus test, an individual trial is considered positive if the trend test P value is less than or equal to 0.025 or if the P value for any single exposure group is less than or equal to 0.025 divided by the number of exposure groups. A final call of positive for micronucleus induction is preferably based on reproducibly positive trials (as noted above). Ultimately, the final call is determined by the scientific staff after considering the results of statistical analyses, the reproducibility of any effects observed, and the magnitudes of those effects.

EVALUATION PROTOCOL

These are the basic guidelines for arriving at an overall assay result for assays performed by the National Toxicology Program. Statistical as well as biological factors are considered. For an individual assay, the statistical procedures for data analysis have been described in the preceding protocols. There have been instances, however, in which multiple aliquots of a chemical were tested in the same assay, and differing results were obtained among aliquots and/or among laboratories. Results from more than one aliquot or from more than one laboratory are not simply combined into an overall result. Rather, all the data are critically evaluated, particularly with regard to pertinent protocol variations, in determining the weight of evidence for an overall conclusion of chemical activity in an assay. In addition to multiple aliquots, the *in vitro* assays have another variable that must be considered in arriving at an overall test result. *In vitro* assays are conducted with and without exogenous metabolic activation. Results obtained in the absence of activation are not combined with results obtained in the presence of activation; each testing condition is evaluated separately. The summary table in the Abstract of this Technical Report presents a result that represents a scientific judgement of the overall evidence for activity of the chemical in an assay.

RESULTS

Glutaraldehyde was tested for induction of mutations in *S. typhimurium* at three laboratories (Table E1). At the first laboratory, positive results were obtained with strain TA100 with and without liver S9 from Aroclor 1254-induced male Sprague-Dawley rats or Syrian hamsters. At the second laboratory, no increase in mutations was observed in TA100 in the absence of S9 or with 10% induced hamster S9. A small increase in mutations was noted in TA100 in the presence of 10% induced rat S9, and the results were considered equivocal. At both laboratories, negative results were obtained with TA98, TA1535, and TA1537, with and without S9. Complete data sets from these two studies are presented by Haworth *et al.* (1983). The third laboratory tested glutaraldehyde for induction of mutations in *S. typhimurium*

strains TA100, TA102, and TA104. Results were clearly positive for all three strains with and without induced hamster or rat liver S9. Glutaraldehyde also induced mutations at the TK locus of L5178Y mouse lymphoma cells at a concentration of 8 μg/mL in each of two trials conducted in the absence of S9 activation (Table E2; McGregor *et al.*, 1988).

At one of two test laboratories, glutaraldehyde induced SCEs in cultured CHO cells with and without Aroclor 1254-induced male Sprague-Dawley rat liver S9; results from the second laboratory were weakly positive in the presence of S9 and negative without S9 (Table E3; Galloway *et al.*, 1985). Although the negative trial in the absence of S9 showed a significant increase in SCEs at the highest dose tested, the trial was concluded to be negative on the basis of the trend test, with a P value greater than 0.025 (Galloway *et al.*, 1985). Glutaraldehyde was also tested at the same two laboratories for induction of Abs in CHO cells (Table E4; Galloway *et al.*, 1985). The first laboratory reported negative results with and without S9, while the second laboratory found a weakly positive result in the absence of S9. Higher doses were used in the second study, which may explain the discordant results between laboratories. At the second laboratory, the trial conducted with S9 showed a dose-related increase in Abs which met the statistical criteria for a weakly positive response. However, the reviewers concluded that this increase was not of sufficient magnitude to be considered positive (Galloway *et al.*, 1985).

Glutaraldehyde was tested for its ability to induce sex-linked recessive lethal mutations in germ cells of male *Drosophila melanogaster* treated as newly emerged adult flies by feeding or injection (Yoon *et al.*, 1985) or treated as larvae by feeding (Zimmering *et al.*, 1989). Results from all three tests were negative (Table E5).

Glutaraldehyde was tested in several *in vivo* assays for induction of chromosomal damage in mice. Results of an Abs test showed significant increases in the percentage of aberrant cells in mouse bone marrow 36 hours after intraperitoneal injection of glutaraldehyde (15 to 60 mg/kg) (Table E6); no significant increase in the number of aberrant cells was noted 17 hours after injection. A subset of the mice treated in Trial 2 of the Abs test was also examined at 36 hours for the presence of micronucleated PCEs in bone marrow (Table E7). A small increase in the frequency of micronucleated PCEs was observed in these animals, but the response was concluded to be equivocal, based on the trend test P value of 0.028 ($P \leq 0.025$ required for significance) and the fact that no single dose group was significantly elevated ($P \leq 0.006$) above the control frequency. Additional micronucleus tests were performed with glutaraldehyde. In a three-injection test, no significant increase in micronucleated PCEs was observed in mouse bone marrow in either of two trials using a dose range of 5 to 20 mg/kg (Table E8). Finally, no significant increases in the frequency of micronucleated NCEs were observed in peripheral blood samples obtained from male and female mice exposed to glutaraldehyde by whole body inhalation for 13 weeks (Table E9; NTP, 1993). The small but reproducible increase in Abs noted in bone marrow cells of male mice after a single intraperitoneal injection of glutaraldehyde at doses of 50 to 60 mg/kg was not reflected by significant increases in micronucleated erythrocytes in mice treated under the same protocol or under a multiple-exposure protocol.

In summary, glutaraldehyde was shown to be genotoxic *in vitro*, inducing mutations in bacterial cells and mutations, SCEs, and Abs in mammalian cells. Its mutagenic activity *in vitro* did not require S9 activation. Results of genotoxicity tests *in vivo* were generally negative. No induction of sex-linked recessive lethal mutations was seen in male *D. melanogaster* treated in a variety of test protocols, and no clear induction of micronuclei was observed in erythrocytes of mice administered glutaraldehyde via short-term inhalation or acute intraperitoneal injection protocols. Results of tests for induction of chromosomal aberrations in mice were positive 36 hours after injection and negative 17 hours after injection.

TABLE E1
Mutagenicity of Glutaraldehyde in *Salmonella typhimurium*[a]

Strain	Dose (μg/plate)	Revertants/Plate[b] -S9 Trial 1	-S9 Trial 2	+10% hamster S9 Trial 1	+10% hamster S9 Trial 2	+10% rat S9 Trial 1	+10% rat S9 Trial 2
Study performed at EG&G Mason Research Institute							
TA100	0	120 ± 6.9	116 ± 8.6	124 ± 10.4	76 ± 0.9	148 ± 4.4	122 ± 1.2
	3.3	133 ± 1.7	134 ± 3.8	126 ± 10.1		134 ± 2.4	
	10	140 ± 9.8	130 ± 10.1	132 ± 4.4	81 ± 4.7	135 ± 8.7	135 ± 2.9
	20		159 ± 7.2				
	33	192 ± 11.7	229 ± 8.4	124 ± 7.8	88 ± 8.5	178 ± 8.2	178 ± 13.3
	50		227 ± 23.6[c]				218 ± 13.6
	75						219 ± 1.8
	100	70 ± 8.6[c]		179 ± 5.5	146 ± 9.8	182 ± 12.8[c]	147 ± 11.3[c]
	150				163 ± 4.9[c]		
	200				75 ± 2.9[c]		
	333	Toxic		Toxic		75 ± 7.5[c]	
Trial summary		Equivocal	Positive	Equivocal	Positive	Equivocal	Positive
Positive control[d]		1,496 ± 14.6	1,949 ± 20.1	1,326 ± 58.7	1,337 ± 47.2	972 ± 24.8	1,262 ± 69.9
TA1535	0	19 ± 2.5	19 ± 4.6	12 ± 1.5	10 ± 0.3	11 ± 3.9	11 ± 2.2
	3.3	29 ± 1.9	19 ± 1.5	10 ± 2.4		10 ± 0.7	
	10	27 ± 2.3	17 ± 0.6	10 ± 1.5	10 ± 0.9	9 ± 1.2	12 ± 1.3
	20		23 ± 1.5				
	33	22 ± 2.3	19 ± 1.3	9 ± 2.0	13 ± 2.0	9 ± 1.5	11 ± 1.8
	50		19 ± 3.0[c]				11 ± 1.5
	75						13 ± 1.3
	100	Toxic		14 ± 1.9	11 ± 0.9	9 ± 0.7[c]	13 ± 1.3
	150				10 ± 2.1		
	200				9 ± 1.7[c]		
	333	Toxic		Toxic		Toxic	
Trial summary		Negative	Negative	Negative	Negative	Negative	Negative
Positive control		1,521 ± 10.7	1,467 ± 30.2	170 ± 40.8	123 ± 17.7	38 ± 6.1	71 ± 6.4
TA1537	0	9 ± 0.9	9 ± 2.0	8 ± 1.2	11 ± 0.3	7 ± 1.0	10 ± 1.9
	3.3	8 ± 1.2	6 ± 0.0	8 ± 1.9		7 ± 0.3	
	10	11 ± 2.5	7 ± 1.2	9 ± 2.3	10 ± 1.2	8 ± 1.3	8 ± 2.3
	20		11 ± 0.7				
	33	10 ± 1.2	11 ± 0.9	8 ± 1.5	9 ± 1.7	11 ± 1.9	11 ± 0.9
	50		9 ± 2.0				9 ± 1.5
	75						8 ± 1.8
	100	Toxic		9 ± 1.0	11 ± 1.7	8 ± 1.2	15 ± 3.2
	150				15 ± 3.3		
	200				9 ± 0.9[c]		
	333	Toxic		Toxic		Toxic	
Trial summary		Negative	Negative	Negative	Negative	Negative	Negative
Positive control		509 ± 84.3	447 ± 21.4	71 ± 6.1	129 ± 1.5	34 ± 8.1	125 ± 9.8

TABLE E1
Mutagenicity of Glutaraldehyde in *Salmonella typhimurium*

Strain	Dose (μg/plate)	Revertants/Plate -S9 Trial 1	-S9 Trial 2	+10% hamster S9 Trial 1	+10% hamster S9 Trial 2	+10% rat S9 Trial 1	+10% rat S9 Trial 2
Study performed at EG&G Mason Research Institute (continued)							
TA98	0	25 ± 5.7	27 ± 5.6	28 ± 2.5	32 ± 2.8	27 ± 1.9	32 ± 3.2
	3.3	22 ± 0.7	28 ± 2.7	19 ± 2.1		23 ± 1.5	
	10	25 ± 1.5	32 ± 2.1	23 ± 4.3	30 ± 4.6	24 ± 1.2	28 ± 2.5
	20		30 ± 3.6				
	33	32 ± 3.3[c]	37 ± 7.4	26 ± 2.8	28 ± 3.2	34 ± 5.2	38 ± 2.7
	50		38 ± 4.1				42 ± 4.0
	75						54 ± 4.6
	100	Toxic		27 ± 2.5	28 ± 3.7	35 ± 0.9[c]	36 ± 3.8[c]
	150				44 ± 3.0		
	200				32 ± 1.5[c]		
	333	Toxic		16 ± 2.1[c]		Toxic	
Trial summary		Negative	Negative	Negative	Equivocal	Negative	Equivocal
Positive control		2,245 ± 98.6	1,434 ± 19.3	1,121 ± 62.3	1,093 ± 20.9	469 ± 32.3	1,007 ± 55.1

TABLE E1
Mutagenicity of Glutaraldehyde in *Salmonella typhimurium*

Strain	Dose (μg/plate)	Revertants/Plate -S9 Trial 1	-S9 Trial 2	+10% hamster S9 Trial 1	+10% hamster S9 Trial 2	+10% rat S9 Trial 1	+10% rat S9 Trial 2
Study performed at Case Western Reserve University							
TA100	0	92 ± 2.8	98 ± 2.6	117 ± 20.8	113 ± 6.4	85 ± 2.7	111 ± 9.1
	10		91 ± 3.6		116 ± 0.3		175 ± 10.0
	33	99 ± 2.7	93 ± 0.6	101 ± 12.0	114 ± 6.9	95 ± 2.6	137 ± 12.5
	100	96 ± 8.5	93 ± 6.2	98 ± 2.8	160 ± 17.0	114 ± 7.1	163 ± 6.6
	333	99 ± 6.4	87 ± 5.0	130 ± 12.0	Toxic	133 ± 8.7	Toxic
	1,000	Toxic	95 ± 3.5	Toxic	4 ± 4.0	65 ± 9.5	3 ± 3.3
	3,333	0 ± 0.0		0 ± 0.0		0 ± 0.0	
Trial summary		Negative	Negative	Negative	Negative	Equivocal	Equivocal
Positive control		307 ± 18.1	394 ± 78.3	2,397 ± 104.0	2,104 ± 81.4	2,363 ± 61.5	1,230 ± 27.7
TA1535	0	10 ± 2.0	5 ± 1.2	9 ± 2.0	11 ± 0.6	10 ± 1.0	3 ± 0.3
	10		7 ± 0.6		9 ± 1.5		3 ± 1.2
	33	8 ± 2.7	6 ± 0.6	7 ± 0.3	9 ± 0.3	10 ± 1.3	8 ± 0.7
	100	9 ± 1.9	2 ± 0.3	7 ± 1.0	6 ± 0.9	10 ± 1.8	3 ± 0.6
	333	8 ± 1.7	2 ± 0.3	9 ± 2.5	5 ± 1.2	7 ± 0.3	3 ± 0.6
	1,000	5 ± 1.5	0 ± 0.3	4 ± 1.2	2 ± 1.7	4 ± 0.3	3 ± 1.5
	3,333	0 ± 0.0		0 ± 0.0		0 ± 0.0	
Trial summary		Negative	Negative	Negative	Negative	Negative	Negative
Positive control		97 ± 46.8	310 ± 33.8	39 ± 8.1	41 ± 3.8	37 ± 8.4	42 ± 4.3
TA1537	0	4 ± 1.2	3 ± 1.2	6 ± 2.6	8 ± 1.5	8 ± 1.9	8 ± 1.8
	10		4 ± 0.9		7 ± 2.0		5 ± 0.9
	33	2 ± 1.2	2 ± 0.3	7 ± 0.3	6 ± 0.3	7 ± 1.2	8 ± 1.2
	100	4 ± 0.9	2 ± 0.3	7 ± 2.4	3 ± 1.2	12 ± 2.3	5 ± 0.7
	333	4 ± 1.2	1 ± 0.3	6 ± 2.1	2 ± 0.9	10 ± 1.2	1 ± 0.6
	1,000	1 ± 0.7	0 ± 0.3	5 ± 0.9	1 ± 0.6	8 ± 0.9	0 ± 0.3
	3,333	0 ± 0.0		0 ± 0.0		0 ± 0.0	
Trial summary		Negative	Negative	Negative	Negative	Negative	Negative
Positive control		148 ± 19.5	72 ± 38.0	141 ± 4.4	163 ± 27.8	210 ± 58.3	72 ± 8.7
TA98	0	12 ± 1.2	11 ± 0.9	24 ± 1.5	21 ± 3.0	26 ± 1.9	17 ± 1.9
	10		13 ± 1.9		25 ± 1.8		17 ± 4.1
	33	14 ± 1.5	10 ± 0.3	23 ± 3.2	22 ± 1.8	27 ± 2.7	26 ± 2.7
	100	14 ± 1.5	7 ± 3.8	31 ± 5.5	22 ± 5.0	37 ± 11.3	13 ± 1.2
	333	15 ± 1.7	4 ± 1.2	33 ± 2.9	20 ± 2.1	43 ± 9.0	18 ± 1.5
	1,000	8 ± 1.2	5 ± 1.5	19 ± 7.5	17 ± 2.7	Toxic	18 ± 0.6
	3,333	0 ± 0.0		0 ± 0.0		0 ± 0.0	
Trial summary		Negative	Negative	Negative	Negative	Negative	Negative
Positive control		118 ± 11.8	150 ± 24.2	1,775 ± 121.2	1,590 ± 52.8	2,141 ± 79.2	561 ± 12.0

TABLE E1
Mutagenicity of Glutaraldehyde in *Salmonella typhimurium*

Strain	Dose (μg/plate)	Revertants/Plate -S9 Trial 1	-S9 Trial 2	-S9 Trial 3	+10% mouse S9 Trial 1	+10% mouse S9 Trial 2	+10% mouse S9 Trial 3
Study performed at Inveresk Research International							
TA102	0	257 ± 9.2	138 ± 10.4		305 ± 21.0	327 ± 4.5	226 ± 27.0
	25	259 ± 5.0	187 ± 6.5		353 ± 24.8	322 ± 15.9	267 ± 21.6
	50	297 ± 25.9	214 ± 4.7		333 ± 6.5	364 ± 13.3	365 ± 5.9
	100	275 ± 7.3	278 ± 21.3		417 ± 5.0	441 ± 38.4	473 ± 27.0
	200	232 ± 11.3	192 ± 13.8		570 ± 19.7	741 ± 35.8	504 ± 58.2
	300	46 ± 29.7[c]	27 ± 1.8[c]		352 ± 17.3[c]	743 ± 23.2[c]	250 ± 24.5[c]
Trial summary		Negative	Positive		Positive	Positive	Positive
Positive control		634 ± 95.3	898 ± 38.0		443 ± 14.0	562 ± 25.8	478 ± 28.4

Strain	Dose (μg/plate)	+10% rat S9 Trial 1	+10% rat S9 Trial 2
TA102	0	279 ± 19.4	274 ± 9.0
	25	346 ± 10.3	309 ± 53.3
	50	394 ± 41.4	389 ± 34.3
	100	485 ± 34.7	535 ± 15.2
	200	379 ± 57.0	481 ± 39.8
	300	608 ± 8.7[c]	268 ± 68.4[c]
Trial summary		Positive	Positive
Positive control		454 ± 3.0	497 ± 15.3

Strain	Dose (μg/plate)	Revertants/Plate -S9 Trial 1	-S9 Trial 2	-S9 Trial 3	+10% mouse S9 Trial 1	+10% mouse S9 Trial 2
TA104	0	453 ± 13.3	338 ± 12.5	338 ± 8.7	482 ± 21.2	406 ± 7.5
	25	632 ± 10.8	321 ± 3.8	464 ± 36.1	726 ± 40.3	605 ± 36.6
	50	732 ± 13.5	452 ± 17.0	602 ± 6.6	893 ± 25.5	771 ± 19.9
	100	1,018 ± 21.1	600 ± 16.2	715 ± 22.2	1,074 ± 56.5	1,020 ± 21.0
	200	807 ± 44.3	815 ± 33.5	783 ± 28.9	754 ± 20.2	654 ± 123.9
	300	296 ± 68.7[c]	861 ± 14.4[c]	522 ± 110.3[c]	477 ± 55.0[c]	620 ± 65.0[c]
Trial summary		Positive	Positive	Positive	Positive	Positive
Positive control		232 ± 4.7[c]	653 ± 43.5	818 ± 50.4	1,371 ± 21.4	1,052 ± 14.9

Strain	Dose (μg/plate)	+10% rat S9 Trial 1	+10% rat S9 Trial 2
TA104	0	417 ± 21.7	495 ± 15.7
	25	506 ± 15.4	689 ± 50.0
	50	543 ± 14.6	1,003 ± 40.8
	100	1,185 ± 121.4	1,174 ± 31.8
	200	667 ± 15.7	861 ± 51.0
	300	173 ± 23.2[c]	541 ± 107.8[c]
Trial summary		Positive	Positive
Positive control		1,133 ± 60.4	976 ± 42.8

TABLE E1
Mutagenicity of Glutaraldehyde in *Salmonella typhimurium*

Strain	Dose (μg/plate)	Revertants/Plate -S9 Trial 1	-S9 Trial 2	-S9 Trial 3	+10% mouse S9 Trial 1	+10% mouse S9 Trial 2	+10% mouse S9 Trial 3
Study performed at Inveresk Research International (continued)							
TA100	0	65 ± 5.5	82 ± 9.0	91 ± 3.6	84 ± 2.0	112 ± 3.6	90 ± 2.7
	25	106 ± 6.5	116 ± 4.9	108 ± 6.4	116 ± 6.2	122 ± 2.9	114 ± 4.3
	50	84 ± 7.4	135 ± 2.2	159 ± 5.4	139 ± 9.7	151 ± 1.7	146 ± 14.0
	100	131 ± 1.2	197 ± 27.4	330 ± 14.7	146 ± 19.5	224 ± 18.2	261 ± 8.2
	200	149 ± 13.0	356 ± 18.1	355 ± 35.7	151 ± 11.0	256 ± 19.6	296 ± 6.5
	300	89 ± 3.8[c]	152 ± 4.4[c]	117 ± 9.1[c]	90 ± 3.5[c]	158 ± 13.2[c]	86 ± 6.8[c]
Trial summary		Positive	Positive	Positive	Weakly Positive	Positive	Positive
Positive control		182 ± 5.3	338 ± 12.5	455 ± 4.4	512 ± 15.5	1,308 ± 105.9	1,253 ± 78.9

Strain	Dose (μg/plate)	+10% rat S9 Trial 1	+10% rat S9 Trial 2
TA100	0	83 ± 1.7	94 ± 5.7
	25	119 ± 4.9	121 ± 4.2
	50	163 ± 3.5	180 ± 3.1
	100	255 ± 3.8	259 ± 16.7
	200	96 ± 9.0	177 ± 11.1
	300	85 ± 4.3[c]	133 ± 10.7[c]
Trial summary		Positive	Positive
Positive control		408 ± 17.6	829 ± 38.0

[a] The detailed protocol and the data for the first two studies are presented by Haworth *et al.* (1983). The protocol and data for the third study (Inveresk Research International) is presented by Dillon *et al.* (1998). 0 μg/plate was the solvent control.
[b] Revertants are presented as mean ± standard error from three plates.
[c] Slight toxicity
[d] The positive controls in the absence of metabolic activation were sodium azide (TA100 and TA1535), 9-aminoacridine (TA1537), 4-nitro-*o*-phenylenediamine (TA98), mitomycin-C (TA102), and methyl methanesulfonate (TA104). The positive control for metabolic activation with all strains was 2-aminoanthracene, and 2-aminoanthracene or sterigmatocystin was used for TA102.

TABLE E2
Induction of Trifluorothymidine Resistance in L5178Y Mouse Lymphoma Cells by Glutaraldehyde[a]

Compound	Concentration (μg/mL)	Cloning Efficiency (%)	Relative Total Growth (%)	Mutant Count	Mutant Fraction[b]	Average Mutant Fraction
-S9						
Trial 1						
Distilled water[c]		68	98	68	33	
		71	89	68	32	
		58	102	55	31	
		77	111	41	18	29
Ethyl methanesulfonate[d]						
	250	70	91	312	149	
		80	84	353	147	148*
Glutaraldehyde						
	0.5	64	106	105	55	
		68	153	48	23	49
	1	62	96	87	47	
		83	154	80	32	40
	2	44	71	120	91	
		80	199	67	28	59*
	4	69	100	98	47	
		75	128	97	43	45
	8	29	26	236	270	
		67	22	285	142	206*
	16	Lethal				
		Lethal				

TABLE E2
Induction of Trifluorothymidine Resistance in L5178Y Mouse Lymphoma Cells by Glutaraldehyde

Compound	Concentration (μg/mL)	Cloning Efficiency (%)	Relative Total Growth (%)	Mutant Count	Mutant Fraction	Average Mutant Fraction
-S9 (continued)						
Trial 2						
Distilled water						
		74	102	79	36	
		59	110	66	38	
		70	88	95	45	39
Ethyl methanesulfonate						
	250	75	55	725	324	
		63	62	615	325	324*
Glutaraldehyde						
	0.5	92	88	160	58	
		80	93	88	37	47
	1	86	98	92	36	
		66	90	57	29	32
	2	64	90	76	40	
		79	87	107	45	43
	4	89	64	187	70	
		72	69	89	41	56
	8	21	2	385	611	
		27	5	283	352	481*
	16	Lethal				
		Lethal				

* Positive response ($P \leq 0.05$) versus the solvent control
[a] Study was performed at Inveresk Research International. The detailed protocol and these data are presented by McGregor *et al*. (1988).
[b] Mutant fraction = mutant cells/10^6 clonable cells
[c] Solvent control
[d] Positive control

TABLE E3
Induction of Sister Chromatid Exchanges in Chinese Hamster Ovary Cells by Glutaraldehyde[a]

Compound	Concentration (μg/mL)	Total Cells Scored	No. of Chromosomes	No. of SCEs	SCEs/ Chromosome	SCEs/ Cell	Hrs in BrdU	Relative Change of SCEs/ Chromosome[b] (%)
Study performed at Litton Bionetics, Inc.								
-S9								
Summary: Positive								
Distilled water[c]		50	1,026	390	0.38	7.8	25.5	
Triethylenemelamine[d]	15	50	1,010	2,079	2.05	41.6	25.5	441.53
Glutaraldehyde	0.36	50	1,031	475	0.46	9.5	25.5	21.20*
	1.08	50	1,034	400	0.38	8.0	25.5	1.77
	3.6	50	1,028	539	0.52	10.8	25.5	37.94*
	10.8	0					25.5	
					P < 0.001[e]			
+S9								
Trial 1								
Summary: Weakly positive								
Distilled water		50	1,035	477	0.46	9.5	25.5	
Cyclophosphamide[d]	1.5	50	1,023	1,348	1.31	27.0	25.5	185.92
Glutaraldehyde	1	50	1,046	501	0.47	10.0	25.5	3.93
	3.6	50	1,045	535	0.51	10.7	25.5	11.09
	10.8	50	1,035	713	0.68	14.3	25.5	49.48*
					P < 0.001			
Trial 2								
Summary: Positive								
Distilled water		50	1,026	394	0.38	7.9	26.0	
Cyclophosphamide	1.5	50	1,052	1,691	1.60	33.8	26.0	318.59
Glutaraldehyde	10	50	1,028	451	0.43	9.0	26.0	14.24
	12.5	50	1,019	560	0.54	11.2	26.0	43.11*
	15	50	1,025	652	0.63	13.0	26.0	65.64*
					P < 0.001			

TABLE E3
Induction of Sister Chromatid Exchanges in Chinese Hamster Ovary Cells by Glutaraldehyde

Compound	Concentration (μg/mL)	Total Cells Scored	No. of Chromo-somes	No. of SCEs	SCEs/ Chromo-some	SCEs/ Cell	Hrs in BrdU	Relative Change of SCEs/ Chromosome (%)
Study performed at Columbia University								
-S9								
Summary: Negative								
Dimethylsulfoxide[c]		50	1,050	524	0.49	10.5	26.0	
Triethylenemelamine	0.015	50	1,050	1,437	1.36	28.7	26.0	174.24
Glutaraldehyde	0.5	50	1,050	545	0.51	10.9	26.0	4.01
	1.6	50	1,049	483	0.46	9.7	26.0	-7.74
	5	50	1,048	531	0.50	10.6	26.0	1.53
	16	25	524	321	0.61	12.8	26.0	22.75*
					P=0.035			
+S9								
Summary: Weakly positive								
Dimethylsulfoxide		100	2,097	915	0.43	9.2	26.0	
Cyclophosphamide	1	100	2,095	2,593	1.23	25.9	26.0	183.66
Glutaraldehyde	1.6	50	1,048	484	0.46	9.7	26.0	5.84
	5	50	1,047	484	0.46	9.7	26.0	5.95
	16	100	2,092	1,167	0.56	11.7	26.0	27.85*
					P<0.001			

* Positive response (≥20% increase over solvent control)
[a] The detailed protocol and these data are presented by Galloway *et al*. (1985). SCE=sister chromatid exchange; BrdU=bromodeoxyuridine
[b] SCEs/chromosome in treated cells versus SCEs/chromosome in solvent control cells
[c] Solvent control
[d] Positive control
[e] Significance tested by the linear regression trend test versus log of the dose

TABLE E4
Induction of Chromosomal Aberrations in Chinese Hamster Ovary Cells by Glutaraldehyde[a]

Compound	Concentration (μg/mL)	Total Cells Scored	Number of Aberrations	Aberrations/ Cell	Cells with Aberrations (%)
Study performed at Litton Bionetics, Inc.					
-S9					
Harvest time: 10.5 hours					
Summary: Negative					
Distilled water[b]		100	3	0.03	3.0
Triethylenemelamine[c]	50	100	19	0.19	18.0
Glutaraldehyde	0.3	100	0	0.00	0.0
	1	100	1	0.01	1.0
	3	100	1	0.01	1.0
	10	0			
					P=0.843[d]
+S9					
Harvest time: 10.5 hours					
Summary: Negative					
Distilled water		100	8	0.08	6.0
Cyclophosphamide[c]	50	100	43	0.43	23.0
Glutaraldehyde	1	100	2	0.02	2.0
	3	100	2	0.02	2.0
	10	100	5	0.05	5.0
	15	0			
	30	0			
					P=0.631

TABLE E4
Induction of Chromosomal Aberrations in Chinese Hamster Ovary Cells by Glutaraldehyde

Compound	Concentration (μg/mL)	Total Cells Scored	Number of Aberrations	Aberrations/ Cell	Cells with Aberrations (%)
Study performed at Columbia University					
-S9					
Harvest time: 14.0 hours					
Summary: Weakly positive					
Dimethylsulfoxide[b]		100	1	0.01	1.0
Triethylenemelamine	0.15	100	23	0.23	20.0
Glutaraldehyde	1.6	100	4	0.04	4.0
	5	100	6	0.06	5.0
	16	100	12	0.12	11.0*
					P=0.001
+S9					
Harvest time: 14.0 hours					
Summary: Negative					
Dimethylsulfoxide		100	1	0.01	1.0
Cyclophosphamide	15	100	23	0.23	19.0
Glutaraldehyde	1.6	100	1	0.01	1.0
	5	100	4	0.04	3.0
	16	100	7	0.07	7.0*
					P=0.004

* Positive response ($P \leq 0.01$) versus the solvent control
[a] The detailed protocol and these data are presented by Galloway *et al.* (1985).
[b] Solvent control
[c] Positive control
[d] Significance of percent cells with aberrations tested by the linear regression trend test versus log of the dose

TABLE E5
Induction of Sex-Linked Recessive Lethal Mutations in *Drosophila melanogaster* by Glutaraldehyde[a]

Route of Exposure	Dose (ppm)	Incidence of Death (%)	Incidence of Sterility (%)	No. of Lethals/No. Of Chromosomes Tested			Total[b]
				Mating 1	Mating 2	Mating 3	
Injection	3,000	2	0	6/1,792	1/1,146	3/1,688	10/4,626 (0.22%)
	0			4/1,125	3/1,146	1/1,133	8/3,404 (0.24%)
Injection	4,000	22	54	0/486	2/855	0/578	2/1,919 (0.10%)
	0			1/1,009	1/1,297	0/865	2/3,171 (0.06%)
Feeding	7,500	27	37	2/1,947	3/2,194	1/1,828	6/5,969 (0.10%)
	0			3/1,858	0/1,832	1/2,090	4/5,780 (0.07%)
Feeding	10,000	68	2	0/742	0/618	0/698	0/2,058 (0.00%)
	0			2/724	1/706	1/443	4/1,873 (0.21%)
Larva Feeding	3,500	10	0	4/2,694	2/2,686	0/000	6/5,380 (0.11%)
	0			2/2,598	2/2,630	0/000	4/5,228 (0.08%)

[a] Study was performed at Brown University. The detailed protocol and the data from the adult feeding and injection studies are presented by Yoon *et al*. (1985). The detailed protocol and the data from the larval feeding study are presented by Zimmering *et al*. (1989). Results were not significant at the 5% level (Margolin *et al*., 1983). The mean mutant frequency from 518 negative control experiments is 0.074% (Mason *et al*., 1992).

[b] Total number of lethal mutations/total number of X chromosomes tested for three mating trials

TABLE E6
Induction of Chromosomal Aberrations in Bone Marrow Cells of Male Mice Treated with Glutaraldehyde by Intraperitoneal Injection[a]

	Dose (mg/kg)	Aberrant Cells[b] (%)	Pairwise P Value[c]
Trial 1 (Harvest time: 17 hours)			
Phosphate-buffered saline[d]		0.00 ± 0.00	
Mitomycin-C[e]	1	1.75 ± 0.96	0.007
Glutaraldehyde	15	1.50 ± 0.73	0.011
	30	0.75 ± 0.53	0.052
	60	0.75 ± 0.37	0.052
		P=0.323[f]	
Trial 2 (Harvest time: 36 hours)			
Phosphate-buffered saline		0.50 ± 0.33	
Mitomycin-C	1	6.50 ± 2.06	0.001
Glutaraldehyde	15	1.50 ± 0.63	0.138
	30	3.25 ± 1.13	0.014
	50	5.25 ± 1.28	0.001
	60	5.75 ± 1.28	0.001
		P<0.001	
Trial 3 (Harvest time: 36 hours)			
Phosphate-buffered saline		0.50 ± 0.33	
Mitomycin-C	2	6.75 ± 1.85	0.001
Glutaraldehyde	15	0.75 ± 0.53	0.327
	30	0.75 ± 0.37	0.327
	50	0.75 ± 0.53	0.327
	60	3.00 ± 1.07	0.004
		P=0.003	

[a] Study was performed at Environmental Health Research and Testing, Inc. The 17-hour treatment protocol is presented by Shelby *et al.* (1989) and the 36-hour treatment protocol is presented by McFee *et al.* (1992). Fifty first-division metaphase cells were scored for each of eight animals per dose group.
[b] Mean ± standard error. Gaps were excluded from data.
[c] Pairwise comparison of treated group to solvent control group; significant at P≤0.008 (Trial 1) or P≤0.006 (Trials 2 and 3) (ILS, 1990)
[d] Solvent control
[e] Positive control
[f] Significance tested by a one-tailed trend test; significant at P≤0.025 (ILS, 1990)

TABLE E7
Induction of Micronuclei in Bone Marrow Polychromatic Erythrocytes of Male Mice Treated with Glutaraldehyde by Intraperitoneal Injection: Single-Injection Protocol[a]

Compound	Dose (mg/kg)	Number of Mice with Erythrocytes Scored	Micronucleated PCEs/ 1,000 PCEs[b]	Pairwise P Value[c]
Phosphate-buffered saline[d]		5	0.70 ± 0.37	
Mitomycin-C[e]	1	5	15.80 ± 0.60	0.001
	2	5	36.50 ± 3.07	0.001
Glutaraldehyde	15	5	1.50 ± 0.35	0.044
	30	4	1.38 ± 0.55	0.077
	50	5	1.90 ± 0.33	0.009
	60	5	1.60 ± 0.19	0.030
			P=0.028[f]	

[a] Study was performed at Environmental Health Research and Testing, Inc., in conjunction with Trial 2 for chromosomal aberrations (Table E6). The 36-hour treatment protocol is presented by McFee *et al*. (1992) and the scoring protocol is presented by Shelby *et al*. (1993).
[b] Mean ± standard error. PCE=polychromatic erythrocyte
[c] Pairwise comparison of treated group to solvent control group; significant at P≤0.006 (ILS, 1990)
[d] Solvent control
[e] Positive control
[f] Significance of micronucleated PCEs/1,000 PCEs tested by a one-tailed trend test; significant at P≤0.025 (ILS, 1990)

TABLE E8
Induction of Micronuclei in Bone Marrow Polychromatic Erythrocytes of Male Mice Treated with Glutaraldehyde by Intraperitoneal Injection: Three-Injection Protocol[a]

Compound	Dose (mg/kg)	Number of Mice with Erythrocytes Scored	Micronucleated PCEs/ 1,000 PCEs[b]	Pairwise P Value[c]
Trial 1				
Phosphate-buffered saline[d]		5	2.00 ± 0.16	
Mitomycin-C[e]	0.2	5	11.40 ± 2.81	0.001
Glutaraldehyde	5	5	1.30 ± 0.54	0.889
	10	5	1.40 ± 0.56	0.849
	20	4	2.38 ± 0.47	0.295
			P=0.210[f]	
Trial 2				
Phosphate-buffered saline		5	2.30 ± 0.41	
Mitomycin-C	0.2	5	7.70 ± 1.48	0.001
Glutaraldehyde	5	5	2.20 ± 0.30	0.559
	10	5	0.90 ± 0.29	0.993
	20	5	2.20 ± 0.30	0.559
			P=0.651	

[a] Study was performed at Environmental Health Research and Testing, Inc. The protocol is presented by Shelby *et al*. (1993). PCE=polychromatic erythrocyte
[b] Mean ± standard error
[c] Pairwise comparison of treated group to solvent control; significant at P≤0.008 (ILS, 1990)
[d] Solvent control
[e] Positive control
[f] Significance of micronucleated PCEs/1,000 PCEs tested by the one-tailed trend test; significant at P≤0.025 (ILS, 1990)

TABLE E9
Frequency of Micronuclei in Peripheral Blood Erythrocytes of Mice Following Treatment with Glutaraldehyde by Inhalation for 13 Weeks[a]

Compound	Concentration (ppb)	Number of Mice with Erythrocytes Scored	Micronucleated NCEs/ 1,000 NCEs[b]	Pairwise P Value[c]
Male				
Chamber control		10	0.80 ± 0.08	
Urethane[d]	0.2	3	9.60 ± 2.52	0.000
Glutaraldehyde	62.5	10	0.69 ± 0.11	0.784
	125	10	0.68 ± 0.10	0.787
	250	10	0.84 ± 0.09	0.394
	500	10	0.57 ± 0.09	0.954
			P=0.890[e]	
Female				
Chamber control		10	0.43 ± 0.04	
Glutaraldehyde	62.5	10	0.54 ± 0.06	0.140
	125	10	0.63 ± 0.09	0.026
	250	10	0.59 ± 0.06	0.055
	500	8	0.45 ± 0.06	0.442
			P=0.594	

[a] Study was performed at SRI International. The detailed protocol is presented by MacGregor *et al*. (1990). NCE=normochromatic erythrocyte
[b] Mean ± standard error
[c] Pairwise comparison of treated group to chamber control group; significant at P≤0.006 (ILS, 1990)
[d] Positive control; three male mice were administered urethane in drinking water to provide a positive control set of slides for scoring.
[e] Significance of micronucleated NCEs tested by the one-tailed trend test; significant at P≤0.025 (ILS, 1990)

APPENDIX F
CHEMICAL CHARACTERIZATION AND GENERATION OF CHAMBER CONCENTRATIONS

CHEMICAL CHARACTERIZATION AND GENERATION OF CHAMBER CONCENTRATIONS

PROCUREMENT AND CHARACTERIZATION OF GLUTARALDEHYDE

Glutaraldehyde (approximately 25% aqueous solution) was obtained from Union Carbide Corporation (Specialty Chemicals Division, Charleston, WV) in two lots (IS-611699 and IS-678984), which were used during the 2-year studies. A glutaraldehyde reference standard was obtained from Polysciences, Inc. (Warrington, PA). Identity and purity analyses of the bulk chemical were conducted by the study laboratory; the reference standard was analyzed concurrently with each lot. A stability study of the bulk chemical was conducted by the analytical chemistry laboratory, Midwest Research Institute (Kansas City, MO). Reports on analyses performed in support of the glutaraldehyde studies are on file at the National Institute of Environmental Health Sciences.

Both lots of the chemical, a liquid, and the reference standard were identified as glutaraldehyde by infrared, ultraviolet/visible, and C^{13}-nuclear magnetic resonance (NMR) spectroscopy (performed by Chemir/Polytech Laboratories, St. Louis, MO). All spectra were consistent with the structure of aqueous glutaraldehyde, and the nuclear magnetic resonance spectrum was consistent with a literature spectrum (Whipple and Ruta, 1974). The infrared and nuclear magnetic spectra are presented in Figures F1 and F2. Ultraviolet spectroscopy indicated that ratios of absorbance (230 nm:280 nm), used as a relative measure of unsaturated polymer content, ranged from 3.9 to 4.2 for lot IS-611699 and 3.3 to 3.5 for lot IS-678984, with ratios of less than 4 considered acceptable; values for the reference standard were 0.1 and 0.2. ^{13}C-NMR spectroscopy of samples of lot IS-611699 dissolved in d8-dioxane indicated that glutaraldehyde was present in the following forms and at the following estimated equilibrium composition: free aldehyde (7%), hemihydrate (7%), dihydrate (6%), *cis*-cyclic hemiacetal (36%), and *trans*-cyclic hemiacetal (44%). For lot IS-678984, the estimated equilibrium composition was the free aldehyde (7%), hemihydrate (20%), dihydrate (8%), *cis*-cyclic hemiacetal (37%), and *trans*-cyclic hemiacetal (29%).

The purity of each lot and the reference standard was determined by elemental and Karl Fischer water analyses at Galbraith Laboratories (Knoxville, TN) and by pH determination, functional group titration, and gas chromatography at the study laboratory. The pH was measured on diluted samples (1:10) by a titrimeter with a pH combination electrode. For functional group titration, samples were reacted with excess hydroxylamine and back-titrated with 0.5 N hydrochloric acid. Gas chromatography systems used by the study laboratory and the analytical chemistry laboratory are described in Table F1. Major peak comparisons between the reference sample and bulk materials were performed using system A with acetonitrile as a solvent and 2-(2-ethoxyethoxy)-ethanol as an internal standard. Gas chromatography by system B was used to determine methanol, a manufacturing byproduct.

For lot IS-611699, results of elemental analyses for carbon and hydrogen were 16.39% and 10.53%, respectively, compared with theoretical values of 15.66% and 10.39%. Carbon and hydrogen values for the reference standard were 15.48% and 10.73%, respectively, compared with theoretical values of 15.00% and 10.42%, respectively. Less than 0.5% nitrogen was detected. Karl Fischer water analysis indicated 70.64% water for lot IS-611699 and 71.46% for the reference standard. The pH ranged from 3.9 to 4.1 for the bulk chemical and was 3.8 for the reference standard, well within the optimum storage range of 3 to 4.5. Functional group titration indicated a glutaraldehyde content of 26.0% $\pm$ 0.4% for lot IS-611699 and 25.0% $\pm$ 0.4% for the reference standard. Gas chromatography indicated one major peak and one impurity less than 0.6% relative to the major peak area for lot IS-611699. The reference standard also contained one impurity with a relative peak area of 0.2% compared to the major peak. Major peak comparisons indicated a purity of 91.2% to 92.9% for lot IS-611699 relative to the reference standard. Headspace analysis

indicated that the bulk chemical contained less than 0.6% methanol, and the reference standard contained less than 0.3%.

For lot IS-678984 and the reference standard, results of elemental analysis for carbon and hydrogen were 16.26% and 10.46% compared with theoretical values of 15.42% and 10.38%, respectively. Carbon and hydrogen values for the reference sample were 15.52% and 10.63% compared with theoretical values of 15.00% and 10.40%, respectively. Less than 0.5% nitrogen was detected. Karl Fischer analysis indicated 70.71% water for lot IS-678984 and 73.33% water for the reference standard. The pH ranged from 4.2 to 4.3 for the bulk chemical and was 4.4 for the reference standard. Functional group titration indicated a glutaraldehyde content of 25.5% $\pm$ 0.2% for lot IS-678984 and 25.1 $\pm$ 0.1% for the reference standard. Gas chromatography indicated one major peak and four impurity peaks each, with a total relative area of less than 0.7% for lot IS-678984 and less than 0.8% for the reference standard. Major peak comparisons indicated a purity of 94.6% to 94.8% for lot IS-678984 relative to the reference standard. Gas chromatographic headspace analysis indicated less than 0.3% methanol in lot IS-678984 and less than 0.4% methanol in the reference standard.

Stability studies of lot 95296 (50% aqueous solution, not used in the current studies) were performed by the analytical chemistry laboratory using gas chromatography (system C). These studies indicated that glutaraldehyde is stable as a bulk chemical for 2 weeks when stored protected from light at temperatures up to 25° C. To ensure stability, the bulk chemical was stored under nitrogen headspace at approximately 0° C in 1-gallon amber glass bottles. Stability was monitored during the 2-year studies by gas chromatography with flame ionization detection and by ultraviolet/visible spectroscopy (230 nm:280 nm absorbance ratio). No degradation of the bulk chemical was detected.

VAPOR GENERATION AND EXPOSURE SYSTEM

A diagram of the glutaraldehyde generation and delivery system used in the 2-year studies is shown in Figure F3. Glutaraldehyde vapor was generated with a rotary evaporation system (Büchi Rotavapor, Model EL-1315, Brinkman Instruments, Westberry, NY) with a hot-water bath operated at 44° C modified to include a heated stream of nitrogen metered into the flask. The glutaraldehyde and water vapors arising from the flask were carried through the generator by the nitrogen. The generator was maintained at a temperature sufficient to prevent condensation of the vapor as it passed through the generator. Because the evaporation rate of water was faster than that of glutaraldehyde, ultrapure water was pumped into the evaporation flask throughout the generation period to maintain a constant volume in the flask.

Vapor entering the distribution manifold was diluted with heated HEPA- and charcoal-filtered air, and heated transfer lines were used to prevent condensation. Flow to each chamber was controlled by vacuum pumps. A three-way valve, mounted between the distribution manifold and each chamber, directed vapor to the exposure chamber exhaust until a stable concentration of glutaraldehyde vapor was built up in the distribution line. Vapor flowed through separate metering valves for each exposure chamber and was further diluted with filtered air to the appropriate concentration. To overcome the adsorption of the vapor once it entered the exposure chamber, a recirculating system was added to each chamber (including the control chamber) to increase the air velocity through the exposure chambers; this did not affect the normal air exchange rate in the chambers. The increased chamber air circulation helped maintain uniform exposure concentrations.

The study laboratory designed the stainless-steel inhalation exposure chambers (Hazleton H-2000®; Harford Systems Division of Lab Products, Inc., Aberdeen, MD) so that uniform vapor concentrations could be maintained throughout the chambers when catch pans were in place. The total active mixing volume of each chamber was 1.7 m^3. A small particle detector (Type CN, Gardner Associates, Schenectady, NY) was used with and without animals in the exposure chambers to ensure that glutaraldehyde vapor, and not

aerosol, was produced. No particle counts above the minimum resolvable level (approximately 200 particles/cm^3) were detected.

VAPOR CONCENTRATION MONITORING

Vapor concentrations of glutaraldehyde as the free aldehyde in the distribution system were determined to be stable using gas chromatography with system D. Chamber concentrations of glutaraldehyde were monitored by an online gas chromatograph (system E). The monitor was coupled with the inhalation chambers by a computer-controlled 12-port steam select valve. Each chamber was sampled approximately every 45 minutes. Calibrations against gravimetrically prepared standards were performed monthly or when excessive calibration drift was detected by shifts in an on-line standard of 2-butoxyethanol vapor in nitrogen that was checked throughout each exposure day. Additionally, the gas chromatograph was calibrated by a comparison of chamber concentration data to data from grab samples. For approximately the first 9 months of the studies, grab samples were collected with bubblers containing 2,4-dinitrophenylhydrazine and hydrochloric acid (catalyst) in an acetonitrile:water (70:30) solution and with cyclohexanone added as an internal standard. The bubbler grab samples were analyzed by high-performance liquid chromatography; the chromatograph was calibrated with gravimetrically prepared standards of glutaraldehyde. Throughout the remainder of the studies, grab samples were collected with sorbent tubes (ORBO™-23, Supelco, Bellefonte, PA), extracted with toluene, and analyzed by an off-line gas chromatograph/mass spectrometer which was calibrated with gravimetrically prepared standards of glutaraldehyde. Summaries of the chamber concentrations are given in Table F2.

CHAMBER ATMOSPHERE CHARACTERIZATION

The time for vapor concentration in the chamber to build up to 90% of its stable final concentration (T_{90}) and to decay to 10% (T_{10}) were measured with animals in the chambers. At a chamber airflow rate of 15 air changes per hour, the theoretical value for T_{90} and T_{10} is approximately 12.5 minutes. During prestart testing, the values of T_{90} ranged from 25 to 44 minutes and T_{10} ranged from 6 to 10 minutes in the rat chambers; T_{90} values ranged from 18 to 31 minutes and the T_{10} value was 9 or 11 minutes in the mouse chambers. During the studies, the values of T_{90} ranged from 9 to 24 minutes for rats and 7 to 20 minutes for mice; the values for T_{10} were 7 to 10 minutes for rats and 4 to 7 minutes for mice. A T_{90} value of 25 minutes was used for these studies.

The uniformity of glutaraldehyde concentration in the exposure chambers with animals present was measured before the start of the studies and periodically during the studies. The vapor concentration was measured using system E with the automatic 12-port sample valve disabled to allow continuous monitoring from a single line. The chamber uniformity was generally acceptable throughout the studies, except for one set of measurements taken from the 250 ppb mouse chamber midway through the studies.

The persistence of glutaraldehyde in the chambers following exposure was determined by monitoring overnight the concentration in the 750 ppb rat chamber and the 250 ppb mouse chamber with animals present. The concentration of glutaraldehyde in the chambers decreased to less than 1% of the target concentrations within 36 minutes (rats) or 14 minutes (mice) after vapor generation ceased during prestudy testing and within 50 minutes (rats) or 15 minutes (mice) during the studies.

The stability of glutaraldehyde in the exposure system was characterized by gas chromatography (system F) and ultraviolet/visible spectroscopy. Samples from the generator flask, distribution line, and occupied chambers were analyzed and the results were compared with those from the bulk glutaraldehyde and the glutaraldehyde reference standard. Samples from the generator flask were collected during the first and last hours of two exposure days and analyzed with gas chromatography. Relative to the reference standard, the purity of generator flask samples ranged from 98.1% in the first hour to 86.9% in the last. There was a

slight increase in the ultraviolet/visible absorbance ratio at 230 and 280 nm for generator flask samples taken during the last hour. Samples from the distribution line, the 750 ppb rat chamber, and the 62.5 ppb mouse chamber were collected with gas sampling tubes (Supelpak 20F, Supelco); the sorbent beds were eluted with methanol and analyzed by gas chromatography. No degradation products were detected at significant concentrations. Because aldehydes may be oxidized by air to the carboxylic acid, samples from the generator flask (at the beginning and end of an exposure day), distribution line, 750 ppb rat chamber, and 62.5 ppb mouse chamber were analyzed for glutaric acid as well as for polymers and dimers. Samples were collected with ice-chilled bubblers containing ultrapure, deionized water and analyzed for glutaric acid by anion exchange chromatography (Dionex, Sunnyvale, CA) with a water/sodium hydroxide gradient and conductivity detection. No enhancement of glutaric acid, polymers, or dimers was detected in the samples from the exposure system.

The concentrations of methanol, a byproduct of glutaraldehyde synthesis, were measured in the distribution line and the occupied 750 ppb rat chamber and 62.5 ppb mouse chamber. Samples were collected with ORBO-32 large charcoal desorption tubes, desorbed with acetonitrile containing isopropanol as an internal standard, and analyzed with gas chromatography (system D) against calibration standards prepared from gravimetric stock solutions. Immediately after glutaraldehyde generation began, methanol concentrations were 21,000 or 23,000 ppb in the distribution line, 1,700 or 1,800 ppb in the rat chamber, and 190 or 220 ppb in the mouse chamber. Methanol concentrations decreased steadily as the exposure day proceeded and had decreased to 130 or 190 ppb in the distribution line and less than the limit of detection (60 ppb) in the exposure chambers approximately 30 minutes before glutaraldehyde generation ended. Methanol concentrations were less than 20% of the glutaraldehyde concentrations by approximately 45 minutes after generation began. As a result, 45 minutes was established as the minimum period during which the generator was operated before animal exposures began.

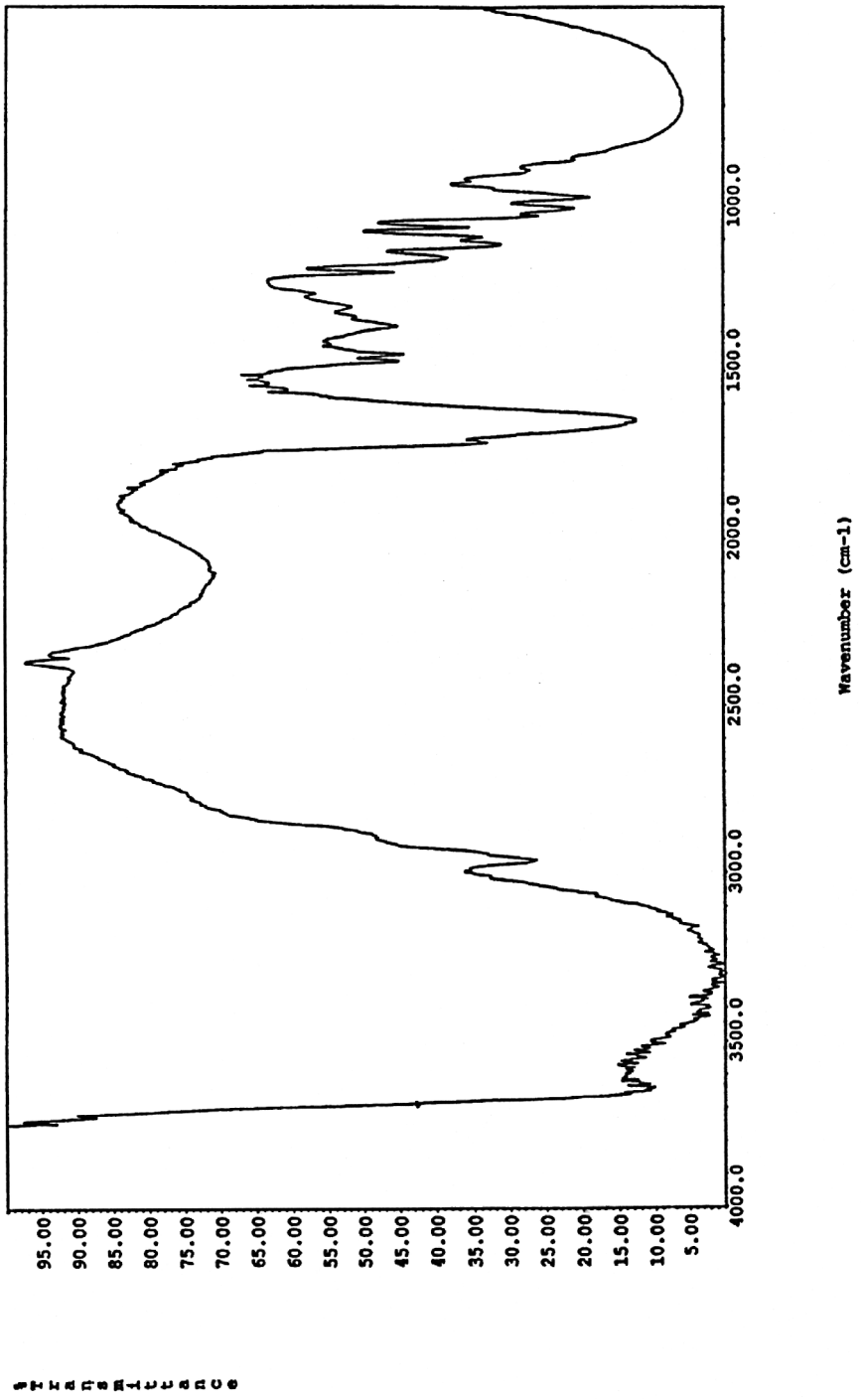

FIGURE F1
Infrared Absorption Spectrum of Glutaraldehyde

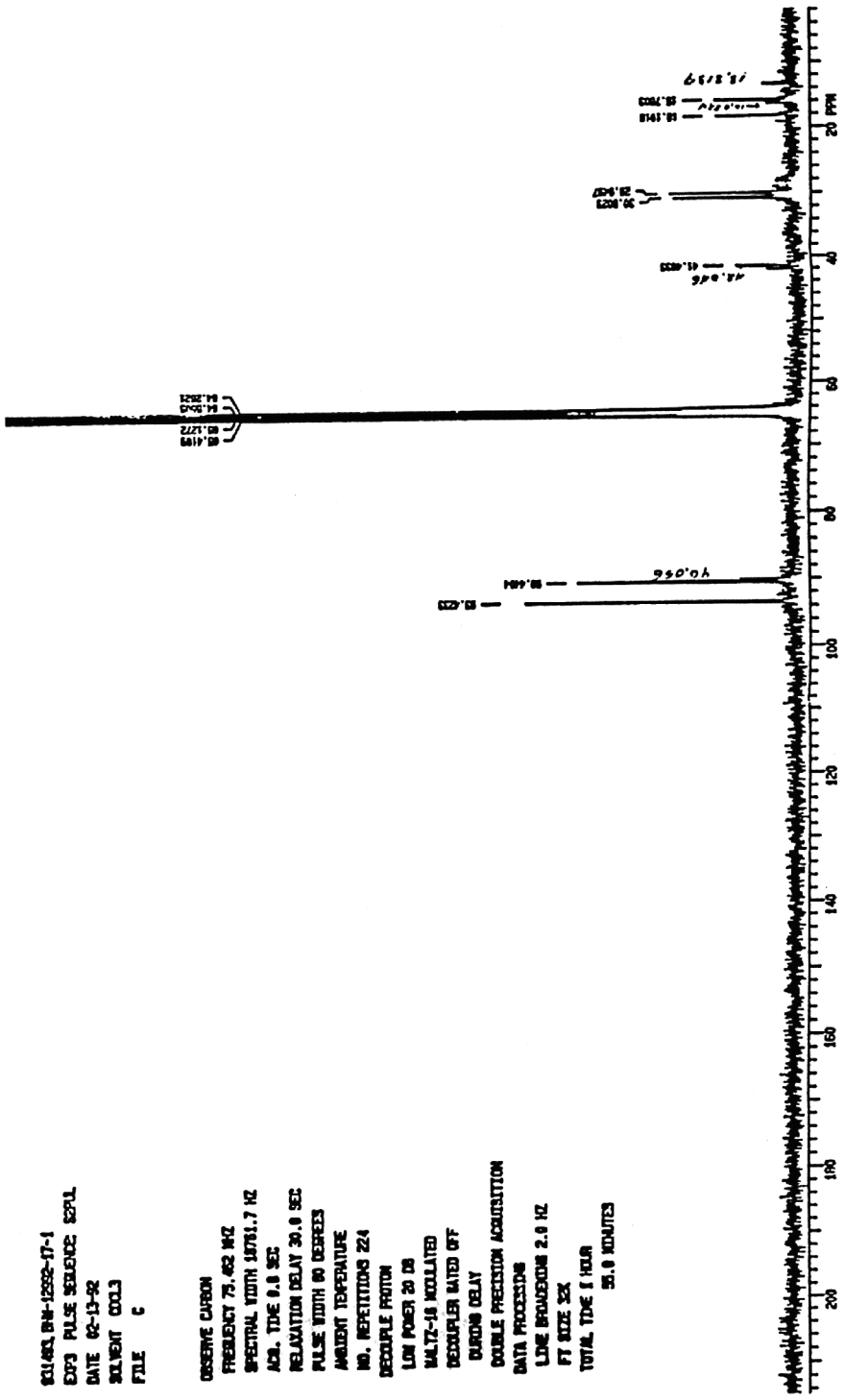

FIGURE F2
Nuclear Magnetic Resonance Spectrum of Glutaraldehyde

TABLE F1
Gas Chromatography Systems Used in the 2-Year Inhalation Studies of Glutaraldehyde[a]

Detection System	Column	Carrier Gas	Oven Temperature Program
System A			
Flame ionization	Rtx-1701 fused silica, 30 m × 0.53 mm, 1 μm film (Restek, Bellefonte, PA)	Helium at 5 psi	80° C for 0.5 minutes, then 5° C/minute to 140° C, held for 1 minute (on-column injection)
System B			
Flame ionization	Rtx-volatiles fused silica, 60 m × 0.53 mm, 2 μm film (Restek)	Nitrogen at 18 psi	1° C for 5 minutes, then 5° C/minute to 40° C, then 20° C/minute to 230° C, held for 2 minutes (headspace sampling injection)
System C			
Flame ionization	Carbowax 20M glass on 80/100 Chromosorb WAW (prepared by the analytical chemistry laboratory)	Nitrogen at 70 mL/minute	100° to 150° C at 10° C/minute, held for 5 minutes
System D			
Flame ionization	DB-5, 15 m × 0.53 mm fused silica, 1.5 μm film (J&W Scientific, Folsom, CA)	Nitrogen at 30 mL/minute	40° C for 0.5 minutes, then 20° C/minute to 80° C, with no hold
System E			
Flame ionization	DB-5, 15 m × 0.53 mm fused silica, 1.5 μm film (J&W Scientific)	Nitrogen at 30 mL/minute	40° C/minute to 100° C, with no hold
System F			
Flame ionization	Rtx-1701 fused silica, 30 m × 0.53 mm, 1 μm film (Restek)	Helium at 5 psi	55° C for 2 minutes, then 15° C/minute to 220° C, held for 5 minutes (cool-on-column injection)

[a] System C was manufactured by Varian Associates, Inc. (Palo Alto, CA); all other gas chromatographs were manufactured by Hewlett-Packard (Palo Alto, CA).

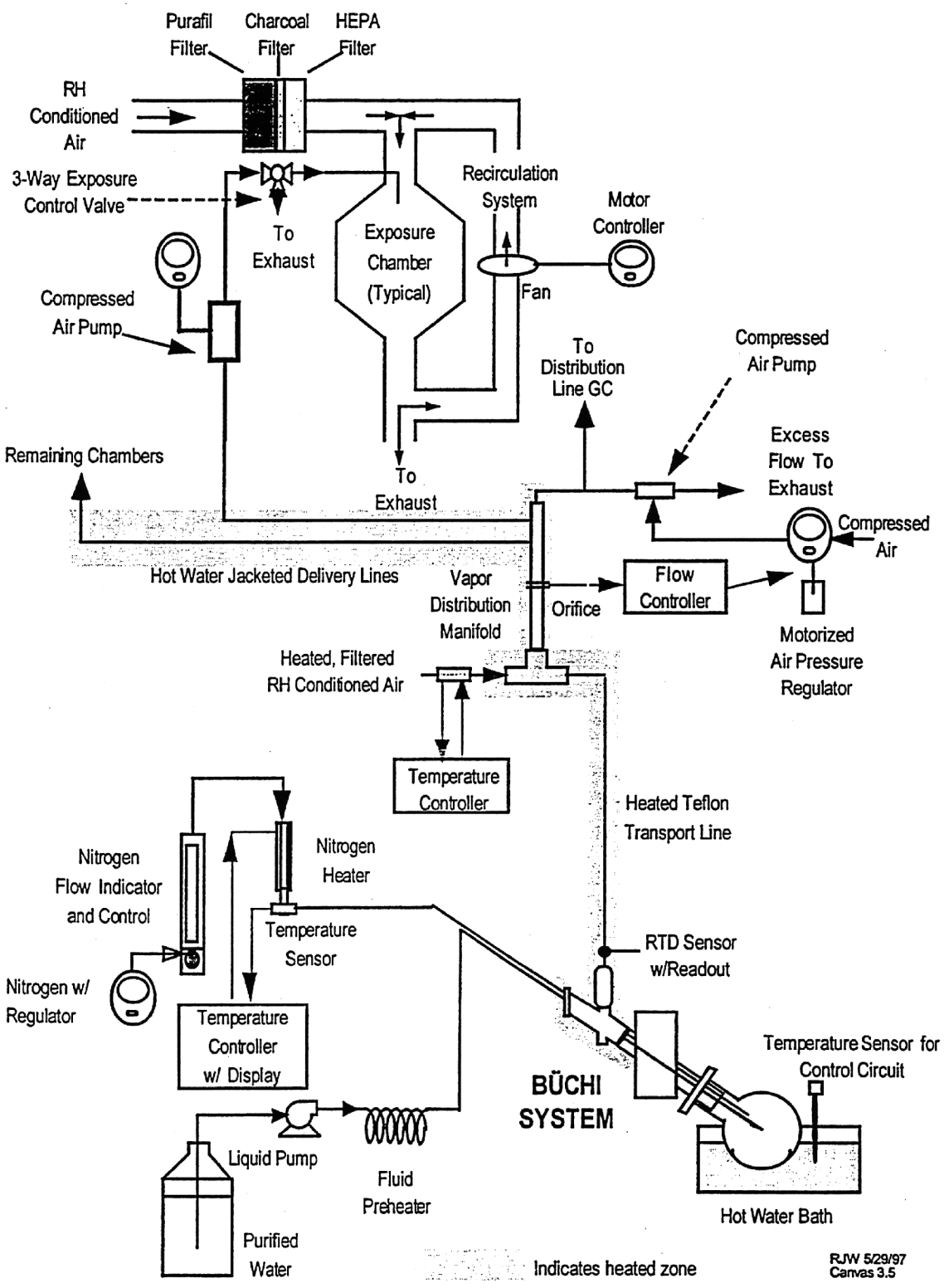

FIGURE F3
Nuclear Magnetic Resonance Spectrum of Glutaraldehyde

TABLE F2
Summary of Chamber Concentrations in the 2-Year Inhalation Studies of Glutaraldehyde

Target Concentration (ppb)	Total Number of Readings	Average Concentration[a] (ppb)
Rat Chambers		
250	3,890	253 ± 25
500	3,788	503 ± 49
750	3,813	754 ± 75
Mouse Chambers		
62.5	3,937	62.4 ± 7.4
125	3,826	127 ± 12
250	3,847	252 ± 24

[a] Mean ± standard deviation

APPENDIX G
INGREDIENTS, NUTRIENT COMPOSITION, AND CONTAMINANT LEVELS IN NIH-07 RAT AND MOUSE RATION

TABLE G1
Ingredients of NIH-07 Rat and Mouse Ration[a]

Ingredients[b]	Percent by Weight
Ground #2 yellow shelled corn	24.50
Ground hard winter wheat	23.00
Soybean meal (49% protein)	12.00
Fish meal (60% protein)	10.00
Wheat middlings	10.00
Dried skim milk	5.00
Alfalfa meal (dehydrated, 17% protein)	4.00
Corn gluten meal (60% protein)	3.00
Soy oil	2.50
Dried brewer's yeast	2.00
Dry molasses	1.50
Dicalcium phosphate	1.25
Ground limestone	0.50
Salt	0.50
Premixes (vitamin and mineral)	0.25

[a] NCI, 1976; NIH, 1978
[b] Ingredients were ground to pass through a U.S. Standard Screen No. 16 before being mixed.

TABLE G2
Vitamins and Minerals in NIH-07 Rat and Mouse Ration[a]

	Amount	Source
Vitamins		
A	5,500,000 IU	Stabilized vitamin A palmitate or acetate
D_3	4,600,000 IU	D-activated animal sterol
K_3	2.8 g	Menadione
d-α-Tocopheryl acetate	20,000 IU	
Choline	560.0 g	Choline chloride
Folic acid	2.2 g	
Niacin	30.0 g	
d-Pantothenic acid	18.0 g	*d*-Calcium pantothenate
Riboflavin	3.4 g	
Thiamine	10.0 g	Thiamine mononitrate
B_{12}	4,000 μg	
Pyridoxine	1.7 g	Pyridoxine hydrochloride
Biotin	140.0 mg	*d*-Biotin
Minerals		
Iron	120.0 g	Iron sulfate
Manganese	60.0 g	Manganous oxide
Zinc	16.0 g	Zinc oxide
Copper	4.0 g	Copper sulfate
Iodine	1.4 g	Calcium iodate
Cobalt	0.4 g	Cobalt carbonate

[a] Per ton (2,000 lb) of finished product

TABLE G3
Nutrient Composition of NIH-07 Rat and Mouse Ration

Nutrient	Mean ± Standard Deviation	Range	Number of Samples
Protein (% by weight)	22.76 ± 0.49	23.6 - 21.8	24
Crude fat (% by weight)	5.39 ± 0.26	5.00 - 6.10	24
Crude fiber (% by weight)	3.43 ± 0.34	3.00 - 4.30	24
Ash (% by weight)	6.34 ± 0.23	5.72 - 6.82	24
Amino Acids (% of total diet)			
Arginine	1.272 ± 0.083	1.100 - 1.390	12
Cystine	0.307 ± 0.068	0.181 - 0.400	12
Glycine	1.152 ± 0.051	1.060 - 1.220	12
Histidine	0.581 ± 0.029	0.531 - 0.630	12
Isoleucine	0.913 ± 0.034	0.867 - 0.965	12
Leucine	1.969 ± 0.053	1.850 - 2.040	12
Lysine	1.269 ± 0.050	1.200 - 1.370	12
Methionine	0.436 ± 0.104	0.306 - 0.699	12
Phenylalanine	0.999 ± 0.114	0.665 - 1.110	12
Threonine	0.899 ± 0.059	0.824 - 0.985	12
Tryptophan	0.216 ± 0.146	0.107 - 0.671	12
Tyrosine	0.690 ± 0.091	0.564 - 0.794	12
Valine	1.079 ± 0.057	0.962 - 1.170	12
Essential Fatty Acids (% of total diet)			
Linoleic	2.389 ± 0.223	1.830 - 2.570	11
Linolenic	0.257 ± 0.062	0.100 - 0.320	11
Vitamins			
Vitamin A (IU/kg)	6,383 ± 524	5,460 - 7,260	24
Vitamin D (IU/kg)	4,450 ± 1,382	3,000 - 6,300	4
α-Tocopherol (ppm)	35.24 ± 8.58	22.5 - 48.9	12
Thiamine (ppm)	18.77 ± 3.94	13.9 - 26.0	24
Riboflavin (ppm)	7.78 ± 0.899	6.10 - 9.00	12
Niacin (ppm)	98.73 ± 23.21	65.0 - 150.0	12
Pantothenic acid (ppm)	32.94 ± 8.92	23.0 - 59.2	12
Pyridoxine (ppm)	9.28 ± 2.49	5.60 - 14.0	12
Folic acid (ppm)	2.56 ± 0.70	1.80 - 3.70	12
Biotin (ppm)	0.265 ± 0.046	0.190 - 0.354	12
Vitamin B_{12} (ppb)	41.6 ± 18.6	10.6 - 65.0	12
Choline (ppm)	2,955 ± 382	2,300 - 3,430	11
Minerals			
Calcium (%)	1.19 ± 0.06	1.03 - 1.30	24
Phosphorus (%)	0.94 ± 0.04	0.870 - 1.010	24
Potassium (%)	0.886 ± 0.059	0.772 - 0.971	10
Chloride (%)	0.531 ± 0.082	0.380 - 0.635	10
Sodium (%)	0.316 ± 0.031	0.258 - 0.371	12
Magnesium (%)	0.165 ± 0.010	0.148 - 0.181	12
Sulfur (%)	0.266 ± 0.060	0.208 - 0.420	11
Iron (ppm)	348.0 ± 83.7	255.0 - 523.0	12
Manganese (ppm)	93.27 ± 5.62	81.7 - 102.0	12
Zinc (ppm)	59.42 ± 9.7	46.1 - 81.6	12
Copper (ppm)	11.63 ± 2.46	8.09 - 15.4	12
Iodine (ppm)	3.49 ± 1.14	1.52 - 5.83	11
Chromium (ppm)	1.57 ± 0.53	0.60 - 2.09	12
Cobalt (ppm)	0.81 ± 0.27	0.49 - 1.23	8

TABLE G4
Contaminant Levels in NIH-07 Rat and Mouse Ration[a]

	Mean ± Standard Deviation[b]	Range	Number of Samples
Contaminants			
Arsenic (ppm)	0.57 ± 0.13	0.34 - 0.80	23
Cadmium (ppm)	0.06 ± 0.02	0.04 - 0.13	23
Lead (ppm)	0.25 ± 0.11	0.12 - 0.50	23
Mercury (ppm)	<0.02		23
Selenium (ppm)	0.32 ± 0.09	0.20 - 0.50	23
Aflatoxins (ppm)	<5.0		23
Nitrate nitrogen (ppm)[c]	8.27 ± 4.29	2.90 - 18.3	23
Nitrite nitrogen (ppm)[c]	1.01 ± 0.70	0.30 - 2.10	23
BHA (ppm)[d]	0.97 ± 1.09	0.01 - 5.0	23
BHT (ppm)[d]	1.27 ± 1.21	0.10 - 5.00	23
Aerobic plate count (CFU/g)	159,048 ± 162,405	3,200 - 460,000	23
Coliform (MPN/g)	167 ± 580	3 - 2,800	23
Escherichia coli (MPN/g)	<10		23
Salmonella (MPN/g)	Negative		23
Total nitrosoamines (ppb)[e]	10.22 ± 2.45	4.0 - 14.7	23
N-Nitrosodimethylamine (ppb)[e]	8.57 ± 2.42	3.0 - 13.00	23
N-Nitrosopyrrolidine (ppb)[e]	1.65 ± 0.59	1.0 - 3.3	23
Pesticides (ppm)			
α-BHC	<0.01		23
β-BHC	<0.02		23
γ-BHC	<0.01		23
δ-BHC	<0.01		23
Heptachlor	<0.01		23
Aldrin	<0.01		23
Heptachlor epoxide	<0.01		23
DDE	<0.01		23
DDD	<0.01		23
DDT	<0.01		23
HCB	<0.01		23
Mirex	<0.01		23
Methoxychlor	<0.05		23
Dieldrin	<0.01		23
Endrin	<0.01		23
Telodrin	<0.01		23
Chlordane	<0.05		23
Toxaphene	<0.10		23
Estimated PCBs	<0.20		23
Ronnel	<0.01		23
Ethion	<0.02		23
Trithion	<0.05		23
Diazinon	<0.10		23
Methyl parathion	<0.02		23
Ethyl parathion	<0.02		23
Malathion	0.15 ± 0.22	0.02 - 0.83	23
Endosulfan I	<0.01		23
Endosulfan II	<0.01		23
Endosulfan sulfate	<0.03		23

[a] CFU=colony-forming units; MPN=most probable number; BHC=hexachlorocyclohexane or benzene hexachloride
[b] For values less than the limit of detection, the detection limit is given as the mean.
[c] Sources of contamination: alfalfa, grains, and fish meal
[d] Sources of contamination: soy oil and fish meal
[e] All values were corrected for percent recovery.

APPENDIX H
SENTINEL ANIMAL PROGRAM

SENTINEL ANIMAL PROGRAM

METHODS

Rodents used in the Carcinogenesis Program of the National Toxicology Program are produced in optimally clean facilities to eliminate potential pathogens that may affect study results. The Sentinel Animal Program is part of the periodic monitoring of animal health that occurs during the toxicologic evaluation of chemical compounds. Under this program, the disease state of the rodents is monitored via serology on sera from extra (sentinel) animals in the study rooms. These animals and the study animals are subject to identical environmental conditions. The sentinel animals come from the same production source and weanling groups as the animals used for the studies of chemical compounds.

Serum samples were collected from randomly selected rats and mice during the 2-year studies. Blood from each animal was collected and allowed to clot, and the serum was separated. The samples were processed appropriately and sent to Microbiological Associates, Inc. (Bethesda, MD), for determination of antibody titers. The laboratory serology methods and viral agents for which testing was performed are tabulated below; the times at which blood was collected during the studies are also listed.

Method and Test	Time of Analysis
RATS	
ELISA	
Mycoplasma arthritidis	Study termination
Mycoplasma pulmonis	Study termination
PVM (pneumonia virus of mice)	6, 12, and 18 months, study termination
RCV/SDA (rat coronavirus/sialodacryoadenitis virus)	6, 12, and 18 months, study termination
Sendai	6, 12, and 18 months, study termination
Hemagglutination Inhibition	
H-1 (Toolan's H-1 virus)	6, 12, and 18 months, study termination
KRV (Kilham rat virus)	6, 12, and 18 months, study termination

MICE

ELISA	
Ectromelia virus	6, 12, and 18 months, study termination
EDIM (epizootic diarrhea of infant mice)	6, 12, and 18 months, study termination
GDVII (mouse encephalomyelitis virus)	6, 12, and 18 months, study termination
LCM (lymphocytic choriomeningitis virus)	6, 12, and 18 months, study termination
Mouse adenoma virus-FL	6, 12, and 18 months, study termination
MHV (mouse hepatitis virus)	6, 12, and 18 months, study termination
M. arthritidis	Study termination
M. pulmonis	Study termination
PVM	6, 12, and 18 months, study termination
Reovirus 3	6, 12, and 18 months, study termination
Sendai	6, 12, and 18 months, study termination
Immunofluorescence Assay	
GDVII	Study termination
LCM	18 months, study termination
MCMV (mouse cytomegalovirus)	Study termination
MHV	18 months, study termination
Hemagglutination Inhibition	
K (papovavirus)	6, 12, and 18 months, study termination
MVM (minute virus of mice)	6, 12, and 18 months, study termination
Polyoma virus	6, 12, and 18 months, study termination

RESULTS

Six rats had positive titers for *M. arthritidis* at the end of the study. Further evaluation of samples positive for *M. arthritidis* by immunoblot and Western blot procedures indicated that the positive titers may have been due to cross reaction with antibodies of nonpathogenic *Mycoplasma* or other agents. There were no clinical findings or histopathologic changes of *M. arthritidis* infection in animals with positive titers. Accordingly, *M. arthritidis*-positive titers were considered false positives.