

NTP TECHNICAL REPORT
ON THE
TOXICOLOGY AND CARCINOGENESIS
STUDIES OF
FURFURYL ALCOHOL
(CAS NO. 98-00-0)
IN F344/N RATS AND B6C3F₁ MICE
(INHALATION STUDIES)

February 1999

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

NTP TR 482

NIH Publication No. 99-3972

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. 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 available at the NTP's World Wide Web site: <http://ntp-server.niehs.nih.gov>.

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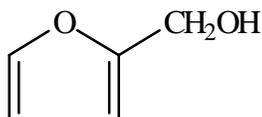
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ABSTRACT



FURFURYL ALCOHOL

CAS No. 98-00-0

Chemical Formula: $C_5H_6O_2$ Molecular Weight: 98.10

Synonyms: 2-Furancarbinol; 2-furanmethanol; furfuralcohol; α -furylcarbinol; 2-furylcarbinol; 2-hydroxymethylfuran

Furfuryl alcohol-based resins are used as binding agents in foundry sand and as corrosion inhibitors in mortar, grout, and cement. Because of their heat resistance, furan resins are used in the manufacture of fiberglass-reinforced plastic equipment. Furfuryl alcohol was selected for evaluation because of the absence of data on its carcinogenic potential and its large production volume, widespread use in manufacturing, and ubiquitous presence in consumer goods. Male and female F344/N rats and B6C3F₁ mice were exposed to furfuryl alcohol (greater than 98% pure) by inhalation for 16 days, 14 weeks, or 2 years. Genetic toxicology studies were conducted in *Salmonella typhimurium*, cultured Chinese hamster ovary cells, and mouse bone marrow cells.

16-DAY STUDY IN RATS

Groups of five male and five female rats were exposed to concentrations of 0, 16, 31, 63, 125, or 250 ppm furfuryl alcohol by inhalation, 6 hours per day, 5 days per week for 16 days. All male and female rats exposed to 250 ppm died by day 2 of the study, and one male rat exposed to 125 ppm died on day 5. Final mean body weights of male and female rats exposed to 125 ppm were significantly less than those of the chamber control groups. Male rats exposed to 31, 63, or 125 ppm and

female rats exposed to 125 ppm gained less weight than the chamber control groups. Clinical findings included dyspnea, hypoactivity, and nasal and ocular discharge in males and females exposed to 63, 125, or 250 ppm. All exposed animals developed lesions in the nasal respiratory epithelium and olfactory epithelium, and the severities of these lesions generally increased with increasing exposure concentration.

16-DAY STUDY IN MICE

Groups of five male and five female mice were exposed to concentrations of 0, 16, 31, 63, 125, or 250 ppm furfuryl alcohol by inhalation, 6 hours per day, 5 days per week for 16 days. All male and female mice exposed to 250 ppm died by day 4 of the study, and one female mouse exposed to 125 ppm died on day 14. Mean body weights of male and female mice exposed to 63 or 125 ppm were significantly less than those of the chamber control groups. All exposed animals except one 16 ppm male developed lesions in the nasal respiratory epithelium and/or olfactory epithelium, and the severities of these lesions generally increased with increasing exposure concentration.

14-WEEK STUDY IN RATS

Groups of 10 male and 10 female rats were exposed to furfuryl alcohol at concentrations of 0, 2, 4, 8, 16, or 32 ppm, 6 hours per day, 5 days per week for 14 weeks. All rats survived to the end of the study. The mean body weight gain of females exposed to 32 ppm was less than that of the chamber control group. Exposure-related increases in the incidences of squamous metaplasia of the respiratory and transitional epithelium, goblet cell hyperplasia of the respiratory epithelium, and hypertrophy of the respiratory epithelium lining the nasopharyngeal duct were observed in the nose of male and female rats. The incidences of degeneration, hyperplasia, metaplasia, and surface exudate of the olfactory epithelium generally increased with increasing exposure concentration in males and females.

14-WEEK STUDY IN MICE

Groups of 10 male and 10 female mice were exposed to furfuryl alcohol at concentrations of 0, 2, 4, 8, 16, or 32 ppm, 6 hours per day, 5 days per week for 14 weeks. All mice survived to the end of the study. Heart weights of 32 ppm males were significantly less than those of the chamber controls. Exposure-related histologic changes included degeneration, metaplasia, and chronic inflammation of the olfactory epithelium; hyaline droplets of the respiratory epithelium; and squamous metaplasia of the submucosal gland of the cuboidal epithelium in males and females.

2-YEAR STUDY IN RATS

Groups of 50 male and 50 female rats were exposed to furfuryl alcohol by inhalation, 6 hours per day, 5 days per week for 105 weeks, at concentrations of 0, 2, 8, or 32 ppm.

Survival and Body Weights

All male rats exposed to 32 ppm died by week 99; survival of all other exposed groups of male and female rats was similar to that of the chamber control groups. Mean body weights of 32 ppm males were less than those of the chamber control group beginning at week 19.

Pathology Findings

All groups of exposed male and female rats had significantly increased incidences of nonneoplastic histologic changes of the nose compared to the chamber control groups. An adenoma of the lateral wall of the nose was observed in one 2 ppm male and one 8 ppm female, an adenoma of the respiratory epithelium was observed in one 8 ppm male and one 32 ppm female, one carcinoma of the respiratory epithelium was observed in a 32 ppm male, and squamous cell carcinomas of the nose were observed in three 32 ppm males. Renal tubule adenomas were present in one chamber control male, one 2 ppm male, two 8 ppm males, and two 32 ppm females. One 2 ppm female had a renal tubule carcinoma. Additional histologic sections from the kidney revealed the presence of additional hyperplasias in all groups of males and females; one additional renal tubule adenoma was observed in each of the chamber control, 2 ppm, and 8 ppm male groups, and four additional adenomas were observed in 32 ppm males. In females, two additional adenomas were found in the 8 ppm group, one adenoma in the 32 ppm group, and one carcinoma in the 2 ppm group. The severities of nephropathy relative to the chamber controls were increased in 32 ppm males and females. Males exposed to 32 ppm had extrarenal signs indicative of marked nephropathy including parathyroid gland hyperplasia and fibrous osteodystrophy.

2-YEAR STUDY IN MICE

Groups of 50 male and 50 female mice were exposed to furfuryl alcohol by inhalation, 6 hours per day, 5 days per week for 105 weeks, at concentrations of 0, 2, 8, or 32 ppm.

Survival, Body Weights, and Clinical Findings

Survival of exposed males and females was similar to that of the chamber control groups. Mean body weights of exposed males were generally similar to those of the chamber control group throughout the study. Mean body weights of exposed females were less than those of the chamber control group during year 2 of the study. Female mice exposed to 32 ppm developed focal corneal opacities.

Pathology Findings

The incidences of renal tubule neoplasms were increased in 32 ppm male mice compared to the chamber control group and exceeded the historical control range for inhalation studies. Step sectioning revealed the presence of additional hyperplasias in the chamber control and exposed groups and one adenoma in 32 ppm males. The severity of nephropathy increased with increasing exposure concentration in male mice. The incidence of renal tubule degeneration in male mice exposed to 32 ppm was significantly greater than in the chamber control group. Incidences of a variety of nonneoplastic lesions of the nose were significantly greater in all exposed groups of male and female mice than in the chamber control groups. The incidence of degeneration of the cornea was significantly greater in 32 ppm female mice compared to the chamber control group.

GENETIC TOXICOLOGY

Furfuryl alcohol was not mutagenic in *Salmonella typhimurium* strain TA98, TA100, TA1535, or TA1537, with or without S9. It did induce sister chromatid exchanges in cultured Chinese hamster ovary cells in the absence of S9, but not in the presence of S9. No induction of chromosomal aberrations was noted in cultured Chinese hamster ovary cells treated with furfuryl alcohol in the absence

of S9, but in the presence of S9 an equivocal result was obtained. *In vivo*, no induction of sister chromatid exchanges, chromosomal aberrations, or micronuclei was noted in bone marrow cells of male mice after treatment with furfuryl alcohol.

CONCLUSIONS

Under the conditions of these 2-year inhalation studies, there was *some evidence of carcinogenic activity** of furfuryl alcohol in male F344/N rats based on increased incidences of combined neoplasms of the nose. There was *equivocal evidence of carcinogenic activity* of furfuryl alcohol in female F344/N rats based on marginally increased incidences of neoplasms of the nose and renal tubule neoplasms. There was *some evidence of carcinogenic activity* of furfuryl alcohol in male B6C3F₁ mice based on increased incidences of renal tubule neoplasms. There was *no evidence of carcinogenic activity* of furfuryl alcohol in female B6C3F₁ mice exposed to 2, 8, or 32 ppm.

Exposure of male and female rats and male mice to furfuryl alcohol was associated with increased incidences of nonneoplastic lesions of the nose and increased severities of nephropathy. Exposure of female mice to furfuryl alcohol was associated with increased incidences of nonneoplastic lesions of the nose and corneal degeneration.

* Explanation of Levels of Evidence of Carcinogenic Activity is on page 10. A summary of the Technical Reports Review Subcommittee comments and the public discussion on this Technical Report appears on page 12.

Summary of the 2-Year Carcinogenesis and Genetic Toxicology Studies of Furfuryl Alcohol

	Male F344/N Rats	Female F344/N Rats	Male B6C3F₁ Mice	Female B6C3F₁ Mice
Concentrations in air	0, 2, 8, or 32 ppm	0, 2, 8, or 32 ppm	0, 2, 8, or 32 ppm	0, 2, 8, or 32 ppm
Body weights	32 ppm group less than chamber control group	Exposed groups similar to chamber control group	Exposed groups similar to chamber control group	Exposed groups less than chamber control group
Survival rates	8/50, 5/50, 9/50, 0/50	26/50, 26/50, 22/49, 16/50	34/50, 36/50, 30/50, 38/50	34/50, 33/49, 32/50, 40/50
Nonneoplastic effects	<p><u>Nose (all sites)</u>: suppurative inflammation (3/50, 6/50, 17/50, 44/50); glands, hyperplasia (0/50, 0/50, 22/50, 49/50); lateral wall hyperplasia (1/50, 49/50, 50/50, 50/50); lateral wall, squamous metaplasia (1/50, 1/50, 8/50, 33/50)</p> <p><u>Nose (olfactory epithelium)</u>: atrophy (1/50, 12/50, 47/50, 50/50); hyaline degeneration (42/50, 48/50, 50/50, 47/50); fibrosis (0/50, 1/50, 26/50, 40/50); hyperplasia (0/50, 1/50, 42/50, 40/50); metaplasia (1/50, 8/50, 37/50, 49/50)</p> <p><u>Nose (respiratory epithelium)</u>: hyaline degeneration (12/50, 14/50, 45/50, 3/50); hyperplasia (0/50, 26/50, 50/50, 50/50); squamous metaplasia (0/50, 0/50, 3/50, 26/50)</p> <p><u>Kidney (all sites)</u>: severity of nephropathy (2.9, 2.9, 3.1, 3.7)</p>	<p><u>Nose (all sites)</u>: suppurative inflammation (4/49, 1/50, 5/48, 23/49); glands, hyperplasia (0/49, 0/50, 24/48, 46/49); lateral wall hyperplasia (0/49, 39/50, 48/48, 49/49); lateral wall, squamous metaplasia (0/49, 1/50, 0/48, 24/49)</p> <p><u>Nose (olfactory epithelium)</u>: atrophy (0/49, 6/50, 44/48, 49/49); hyaline degeneration (43/49, 50/50, 47/48, 48/49); fibrosis (0/49, 0/50, 16/48, 31/49); hyperplasia (0/49, 0/50, 31/48, 41/49); metaplasia (0/49, 5/50, 37/48, 48/49)</p> <p><u>Nose (respiratory epithelium)</u>: hyaline degeneration (23/49, 39/50, 45/48, 6/49); hyperplasia (0/49, 18/50, 40/48, 49/49); squamous metaplasia (0/49, 0/50, 2/48, 10/49)</p> <p><u>Kidney (all sites)</u>: severity of nephropathy (1.9, 1.9, 1.9, 2.4)</p>	<p><u>Nose (all sites)</u>: suppurative inflammation (7/50, 11/49, 27/49, 28/50); glands, hyperplasia (0/50, 10/49, 48/49, 46/50); glands, squamous metaplasia (0/50, 6/49, 35/49, 47/50); lateral wall, squamous metaplasia (0/50, 9/49, 10/49, 20/50)</p> <p><u>Nose (olfactory epithelium)</u>: atrophy (3/50, 15/49, 49/49, 50/50); hyaline degeneration (2/50, 3/49, 21/49, 39/50); metaplasia (0/50, 12/49, 49/49, 50/50)</p> <p><u>Nose (respiratory epithelium)</u>: hyaline degeneration (5/50, 18/49, 42/49, 45/50); squamous metaplasia (0/50, 2/49, 10/49, 20/50); regeneration (0/50, 1/49, 13/49, 21/50)</p> <p><u>Kidney (all sites)</u>: severity of nephropathy (1.2, 1.4, 1.5, 1.8)</p>	<p><u>Nose (all sites)</u>: suppurative inflammation (5/50, 12/48, 25/49, 42/50); glands, hyperplasia (0/50, 33/48, 46/49, 47/50); glands, squamous metaplasia (1/50, 1/48, 34/49, 46/50); lateral wall, squamous metaplasia (3/50, 14/48, 16/49, 36/50)</p> <p><u>Nose (olfactory epithelium)</u>: atrophy (2/50, 35/48, 49/49, 50/50); hyaline degeneration (7/50, 14/48, 28/49, 45/50); metaplasia (0/50, 31/48, 49/49, 49/50)</p> <p><u>Nose (respiratory epithelium)</u>: hyaline degeneration (19/50, 44/48, 49/49, 48/50); squamous metaplasia (1/50, 9/48, 21/49, 39/50); regeneration (0/50, 0/48, 9/49, 13/50)</p> <p><u>Eye</u>: cornea, degeneration (3/49, 1/49, 4/49, 26/50)</p>
Neoplastic effects	<u>Nose (all sites)</u> : adenoma, carcinoma, or squamous cell carcinoma (0/50, 1/50, 1/50, 4/50)	None	<u>Kidney (renal tubule)</u> : adenoma (standard evaluation - 0/50, 0/49, 0/49, 2/50; standard and extended evaluations combined - 0/50, 0/49, 0/49, 3/50); carcinoma (standard evaluation - 0/50, 0/49, 0/49, 2/50; standard and extended evaluations combined - 0/50, 0/49, 0/49, 2/50); adenoma or carcinoma (standard evaluation - 0/50, 0/49, 0/49, 4/50; standard and extended evaluations combined - 0/50, 0/49, 0/49, 5/50)	None

Summary of the 2-Year Carcinogenesis and Genetic Toxicology Studies of Furfuryl Alcohol

	Male F344/N Rats	Female F344/N Rats	Male B6C3F ₁ Mice	Female B6C3F ₁ Mice
Uncertain findings	None	<p><u>Nose (all sites):</u> lateral wall, adenoma (0/49, 0/50, 1/48, 0/49)</p> <p><u>Nose (respiratory epithelium):</u> adenoma (0/49, 0/50, 0/48, 1/49); lateral wall, adenoma (0/49, 0/50, 1/48, 0/49)</p> <p><u>Kidney (renal tubule):</u> adenoma (standard evaluation - 0/50, 0/49, 0/49, 2/50; standard and extended evaluations combined - 0/50, 0/49, 2/49, 2/50); carcinoma (standard evaluation - 0/50, 1/49, 0/49, 0/50; standard and extended evaluations combined - 0/50, 1/49, 0/49, 0/50); adenoma or carcinoma (standard evaluation - 0/50, 1/49, 0/49, 2/50; standard and extended evaluations combined - 0/50, 1/49, 2/49, 2/50)</p>	None	None
Level of evidence of carcinogenic activity	Some evidence	Equivocal evidence	Some evidence	No evidence
Genetic toxicology				
<i>Salmonella typhimurium</i> gene mutations:		Negative in strains TA98, TA100, TA1535, and TA1537 with and without S9		
Sister chromatid exchanges				
Cultured Chinese hamster ovary cells <i>in vitro</i> :		Positive without S9; negative with S9		
Mouse bone marrow <i>in vivo</i> :		Negative		
Chromosomal aberrations				
Cultured Chinese hamster ovary cells <i>in vitro</i> :		Negative without S9; equivocal with S9		
Mouse bone marrow <i>in vivo</i> :		Negative		
Micronucleated erythrocytes				
Mouse bone marrow <i>in vivo</i> :		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.

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The members of the Technical Reports Review Subcommittee who evaluated the draft NTP Technical Report on furfuryl alcohol on 10 December 1997 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 10 December 1997 the draft Technical Report on the toxicity and carcinogenicity studies of furfuryl alcohol received public review by the National Toxicology Programs's Board of Scientific Counselor's Technical Reports Review Subcommittee. The review meeting was held at the National Institute of Environmental Health Sciences, Research Triangle Park, NC.

Dr. R.D. Irwin, NIEHS, introduced the toxicity and carcinogenesis studies of furfuryl alcohol 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 *some evidence of carcinogenic activity* in male F344/N rats and male B6C3F₁ mice, *equivocal evidence of carcinogenic activity* in female F344/N rats, and *no evidence of carcinogenic activity* in female B6C3F₁ mice.

Drs. Cullen and J. Russo, principal reviewers, agreed with the proposed conclusions.

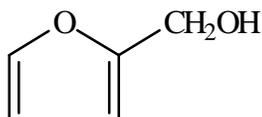
Dr. Bus, a principal reviewer, agreed with the proposed conclusions. He noted that the proposed conclusion for female rats was partly based on the observation of renal tubule neoplasms, particularly when they are observed in extended evaluation step sections. Dr. Bus also noted that the proposed conclusion for male mice was based entirely on the same observation. He stated that it is unclear whether the neoplasms observed in the step sections were new or the same neoplasms observed in the standard evaluation (see p. 43). Dr. Bus commented that more attention should have been paid to the 14-week rat study results in setting exposure concentrations for the 2-year study, in that 32 ppm appeared to exceed the maximum tolerated dose and 2 ppm was above the no-effect

level. Dr. Irwin said that in setting exposure concentrations for the 2-year study, mean body weights at 32 ppm were within 10% of the controls and the shape of the growth curve indicating this would probably not change much or that these animals might recover. In the 2-year study, mean body weights of 32 ppm female rats were observed to be approximately the same as those of the chamber controls.

Dr. Carlson commented on the rationale for studying furfuryl alcohol as part of a class study with furan and furfural, noting that cholangiocarcinomas and other hepatocellular neoplasms were significant neoplastic findings with furan and furfural. He noted that no liver response was seen with furfuryl alcohol in contrast with the other two analogues. Dr. Bailer said he thought the proposed level of evidence in male rats should have been *clear evidence of carcinogenic activity* based on an exposure-related response and four malignant neoplasms in the high exposure group. Dr. J.K. Haseman, NIEHS, said that although there were no squamous cell carcinomas of the nose in the chamber control groups for inhalation studies, there have been one or two in some control groups in other concurrent studies. Dr. Irwin said that the lack of supporting data in females also entered into the decision to go with the proposed conclusion of *some evidence of carcinogenic activity* for male rats.

Dr. Bus moved that the Technical Report on furfuryl alcohol be accepted with the revisions discussed and the conclusions as written for male rats and mice, *some evidence of carcinogenic activity*; for female rats, *equivocal evidence of carcinogenic activity*; and for female mice, *no evidence of carcinogenic activity*. Dr. Cullen seconded the motion, which was accepted by six yes votes to two no votes (Drs. Bailer and Goldsworthy).

INTRODUCTION



FURFURYL ALCOHOL

CAS No. 98-00-0

Chemical Formula: $C_5H_6O_2$ Molecular Weight: 98.10

Synonyms: 2-Furancarbinol; 2-furanmethanol; furfuralcohol; α -furylcarbinol; 2-furylcarbinol; 2-hydroxymethylfuran

CHEMICAL AND PHYSICAL PROPERTIES

Furfuryl alcohol is a member of an industrially important class of compounds containing the furan ring. It is a clear liquid under standard conditions, with a vapor pressure of 0.4 mm Hg at 20° C and a boiling point of 170° C. Furfuryl alcohol is soluble in water, alcohol, benzene, and chloroform but insoluble in paraffinic hydrocarbons (*Kirk-Othmer*, 1985).

PRODUCTION, USE, AND HUMAN EXPOSURE

Furfuryl alcohol is produced by high-pressure reduction (hydrogenation) of furfural in the liquid or vapor phase over a copper catalyst (*Kirk-Othmer*, 1985). The current production volume is not listed by the United States International Trade Commission (USITC, 1994).

The major industrial uses of furfuryl alcohol are based on its ability to undergo acid-catalyzed polymerization into linear, branched, and cross-linked polymers or resins often called furan resins. The resins are heat stable and resistant to acid, alkali, and solvents. Furfuryl alcohol also forms copolymers with furfural, formaldehyde, urea, and phenolic derivatives. A major application involves the use of these resins as binders of foundry sand. The resin is mixed with foundry sand (sufficient resin is added to equal approximately 1% of the weight of the sand) and exposed to catalyst (heat, acid) to initiate "curing" (polymerization). As the curing proceeds, it causes the

sand to become dimensionally stable. Because polymerization is a highly exothermic reaction, some furfuryl alcohol is vaporized as the resin cures. Furan resins are also added to mortars, grouts, and cements as corrosion inhibitors. Because of their heat resistance, furan resins are used in the manufacture of fiberglass-reinforced plastic equipment (*Kirk-Othmer*, 1980; Quaker Oats, 1985).

Furfuryl alcohol is also used as a viscosity reducer in epoxy resins, as an accelerator or liquefier for amine curatives of epoxy resins, as a solvent in textile printing and in alkaline paint strippers, and as an intermediate in the synthesis of numerous other organic chemicals (*Kirk-Othmer*, 1980; Quaker Oats, 1985).

The numerous uses of furfuryl alcohol and furfuryl alcohol-based resins provide considerable potential for occupational exposure. Furfuryl alcohol is regulated as an air contaminant by the National Institute for Occupational Safety and Health; recommended exposure limits for airborne concentrations were lowered in 1993 from a maximum of 50 ppm (200 mg/m³) to 10 ppm (40 mg/m³) determined as a time-weighted average for up to a 10-hour work shift or 40-hour work week (NIOSH, 1997). The American Conference of Governmental Industrial Hygienists suggests an 8-hour, time-weighted average threshold limit value (TLV) of 10 ppm and a 15-minute, time-weighted exposure limit of 15 ppm (ACGIH, 1997). The National Occupational Hazard Survey conducted by NIOSH from 1972 to 1974

estimated that 11,577 workers in 2,939 plants were potentially exposed to furfuryl alcohol (NIOSH, 1976). Occupations with the largest number of exposed workers were carpentry, tile setting, metal molding, packaging and filling machine operation, and casting. A second workplace survey conducted from 1981 to 1983 estimated that 5,358 workers in 74 plants were potentially exposed (NIOSH, 1990). The stone, clay, glass, primary metal, and chemical and allied industries employ the largest number of exposed workers.

A NIOSH health hazard survey conducted at a foundry in Salt Lake City, Utah, examined 10 workers potentially exposed to furfuryl alcohol (Burton and Rivera, 1972). Five of the ten were core makers with measured exposures of 11, 25, 30, 32, and 66 mg/m³. In another health hazard survey at a foundry in Tigard, Oregon, furfuryl alcohol concentrations ranging from 2.2 to 15.8 ppm were recorded during a casting cycle with the furfuryl alcohol concentration dependent on the temperature of the sand used in core production (Apol, 1973). Virtamo and Tossavainen (1976) examined the furfuryl alcohol and formaldehyde concentrations in the air around core-making facilities at 10 iron and steel foundries in Finland. The mean concentration of furfuryl alcohol was 4.3 ppm, but the actual measured concentration exceeded the TLV of 5 ppm in 22% of the determinations.

More recently, Ahman *et al.* (1991) conducted lung function evaluations of molders and core makers exposed to furan resin sand as well as unexposed controls before and after a work shift. The time-weighted average concentration of furfuryl alcohol was 7 mg/m³ with peak values exceeding the short-term exposure limit of 40 mg/m³. During the work shift, exposed workers exhibited an average decrease in forced vital capacity and had more complaints of airway symptoms than unexposed workers; however, no decrease in any other lung function variable was detected. Exposed workers evaluated after work exhibited a post-shift decrease in total lung capacity. In spite of these acute responses, no evidence of chronic lung impairment was detected.

Furfuryl alcohol and furfural are present in thermally processed foods because of the dehydration of pentoses in reactions similar to those that occur during the commercial preparation of furfural from agricultural

waste. Consumer products that contain furfuryl alcohol include cocoa, tea, coffee, dehydrated orange products, cooked beef and pork, milk products, nuts, bread, popcorn, and vegetables. Furfuryl alcohol is a component of cigarette smoke (Maga, 1979).

ABSORPTION, DISTRIBUTION, METABOLISM, AND EXCRETION

Experimental Animals

The metabolites present in the urine of male F344/N rats administered [¹⁴C]-furfural or [¹⁴C]-furfuryl alcohol by gavage in corn oil have been examined by Irwin *et al.* (1985). A diagram of the urinary metabolites of furfuryl alcohol is presented in Figure 1. Greater than 70% of the administered dose was recovered as urinary metabolites. Furoylglycine was identified as the major metabolite present in urine after administration of either compound; the minor urinary metabolites, furoic acid and furanacrylic acid, were also the same for either furfural or furfuryl alcohol. These results were interpreted as indicating that the major route of metabolic transformation of furfuryl alcohol is oxidation to furfural, which is then further oxidized to furoic acid and conjugated with glycine to form furoylglycine. A secondary route involves the formation of furanacrylic acid.

Nomeir *et al.* (1992) examined the metabolism and disposition of furfural and furfuryl alcohol in F344 rats following oral administration of [¹⁴C]-furfuryl alcohol (corn oil gavage) at doses of 0.275, 2.75, or 27.5 mg/kg or [¹⁴C]-furfural at doses of 0.127, 1.15, or 12.5 mg/kg. Both compounds were well absorbed from the gastrointestinal tract and metabolized extensively prior to excretion. Of the administered doses, 83% to 88% was eliminated in the urine and 2% to 4% was eliminated in the feces. Furoylglycine was the major metabolite present in the urine (73%-80%); furoic acid (1%-6%) and furanacrylic acid (3%-8%) were identified as minor metabolites. Approximately 7% of the label from the 12.5 mg/kg dose of furfural was eliminated as CO₂; none was detected after administration of furfuryl alcohol. At 72 hours after administration, the pattern of tissue distribution was very similar for both compounds with

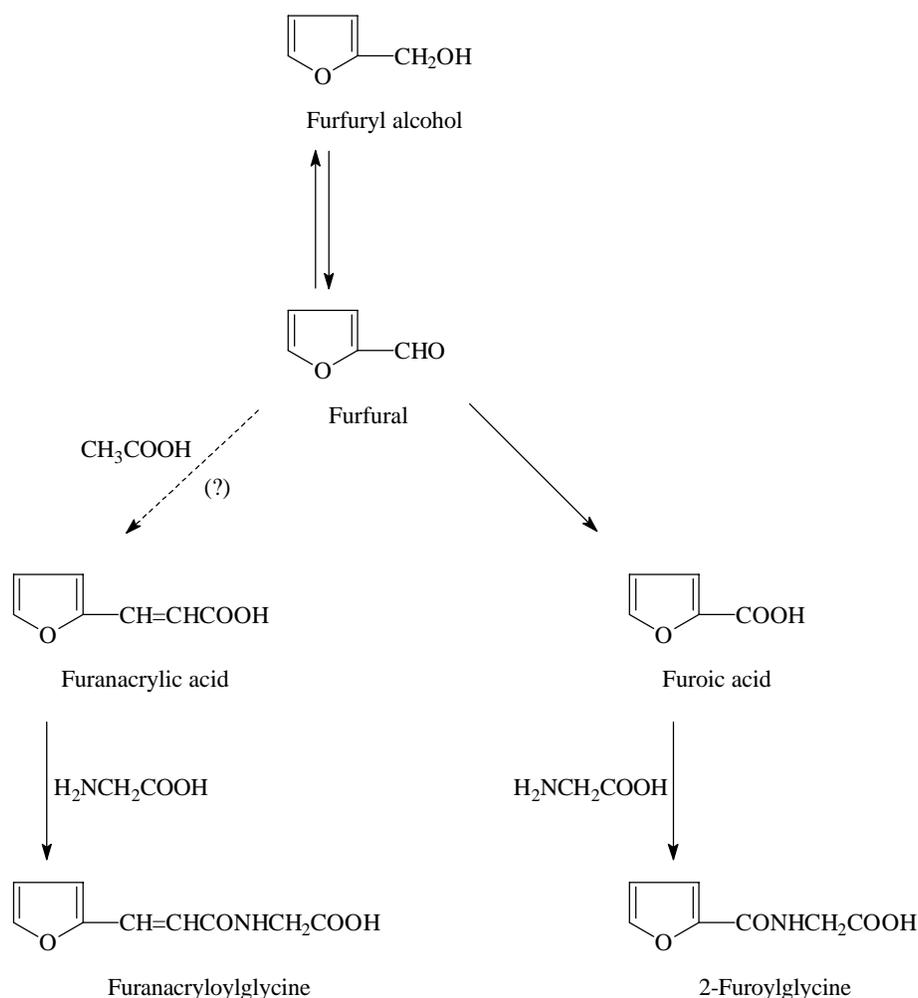


FIGURE 1
Metabolic Pathway of Furfuryl Alcohol

the highest concentration being present in the liver and kidney and the lowest in the brain. In general, the amount of radioactivity present in a given tissue was proportional to the dose. Based on these results, the authors concluded that furfuryl alcohol is oxidized to furfural, which is then oxidized to furoic acid and conjugated with glycine or is converted to furanacrylic acid.

Parkash and Caldwell (1994) examined the metabolism of furfural in F344 rats administered single oral doses of 1, 10, or 60 mg/kg and CD-1 mice administered 1, 20, or 200 mg/kg. They also confirmed that the major route of elimination was in urine for both rats and mice, with only small amounts eliminated in the feces or as CO₂. In both

species, the major urinary metabolite was furoylglycine, which accounted for approximately 80% of the dose in male rats and 85% to 89% of the total dose in male mice. However, the second most abundant metabolite was furanacryloylglycine, the glycine conjugate of furanacrylic acid. Free furoic acid was detected only at the highest doses as a minor metabolite (approximately 2% in rats and male mice and 4%-10% in female mice). These authors suggested that furanacryloyl-CoA is formed from furanacrylic acid and then conjugated with glycine to form furanacryloylglycine.

Humans

A similar metabolic profile has been determined for humans exposed to furfural. In a series of experiments,

human volunteers were exposed to furfural vapors for periods of up to 8 hours. The mean pulmonary retention was determined to be 77.9% and was not dependent on the exposure concentrations over the range of exposure; analysis of the metabolites present in urine revealed that furoylglycine was the major metabolite and furan acrylic acid a minor metabolite. No furoic acid was detected in freshly expressed urine (Sedivec and Flek, 1978).

Dermal absorption was also found to be significant in human volunteers exposed to furfural vapor or liquid. In this series of experiments, subjects were placed in a room and exposed to an atmosphere containing 30 mg/m³ furfural vapor while breathing pure air through a breathing tube attached to a mask. An 8-hour exposure under these conditions resulted in percutaneous absorption of 20% to 30% of the dose retained by the lungs under the same exposure conditions, based on the quantity of metabolites recovered in urine. Moreover, increasing the temperature or humidity of the air substantially increased the percutaneous absorption of furfural. In another experiment, three subjects immersed their left hands, up to the wrist, in a vessel of pure liquid furfural for 15 minutes; the amount absorbed was determined based on the quantity of urinary metabolites excreted. The results indicated that the 15-minute immersion in liquid furfural resulted in percutaneous absorption of the same amount of furfural as would be absorbed during an 8-hour inhalation exposure to atmospheres containing 10 mg/m³ (Sedivec and Flek, 1978).

Total urinary furoic acid concentration has been suggested as a measure of furfuryl alcohol exposure in foundry workers. Furfuryl alcohol exposure was determined by collecting urine samples from six foundry workers; their excretion of urinary furoic acid was then determined after alkaline hydrolysis of the glycine conjugates. The product of the sampling time and vapor concentration of furfuryl alcohol correctly predicted total urinary furoic acid concentration (Pfaffli *et al.*, 1985).

TOXICITY IN EXPERIMENTAL ANIMALS

The acute toxicity of furfuryl alcohol has been evaluated in several studies, and the results of these studies indicate that in experimental animals furfuryl alcohol is absorbed and is toxic when administered dermally, orally, or by inhalation.

The oral toxicity of furfuryl alcohol has been examined in two prechronic studies. In one study, reported only in an abstract, furfuryl alcohol was administered to rats in

drinking water for 20 days; the only effect observed was weight loss. Unfortunately, no details were included in the report (Gajewski and Alsdorf, 1949).

In 14-day and 13-week studies furfuryl alcohol was administered in corn oil by gavage (NTP, unpublished data). During the 14-day studies, compound-related mortality and clinical findings were observed among both F344/N rats and B6C3F₁ mice but there were no significant gross observations at necropsy. During the 13-week studies, rats received doses of 0, 38, 75, 150, or 300 mg furfuryl alcohol per kg body weight in corn oil, and mice received doses of 0, 38, 75, 150, 300, or 600 mg/kg in corn oil. All male and female rats receiving 150 or 300 mg/kg died prior to the end of the study, and significant mortality was also observed in male and female mice receiving 300 or 600 mg/kg. Mean body weights of rats receiving 38, 75, or 150 mg/kg were similar to those of the controls; because of the significant early mortality, mean body weights of rats receiving 150 or 300 mg/kg were not calculated. Mean body weights of male and female mice receiving 600 mg/kg were 15% lower than those of the controls while other dose groups were within 10% of the controls. Mean absolute liver and kidney weights of male and female rats receiving 75 mg/kg were significantly greater than those of the controls ($P < 0.05$); no significant organ weight differences were observed among dosed and control mice.

Histopathologic lesions of the liver and kidney were observed in rats receiving 75, 150, or 300 mg furfuryl alcohol/kg body weight and in mice receiving 300 or 600 mg/kg. The renal and liver lesions in rats were mild and consisted of degeneration of individual hepatocytes and tubular epithelial cells in the renal cortex, accompanied by some cytoplasmic vacuolization. In mice, the lesions were more severe and included necrosis and cytoplasmic vacuolization. In a prechronic inhalation study, 15 rats and eight mice (sex and strain not specified) were exposed to 19 ppm furfuryl alcohol 6 hours per day, 5 days per week for 3 weeks. One rat died after the third exposure and one mouse died after the ninth exposure; exposed and control animals exhibited similar mean body weight gains. At necropsy, diffuse congestion was noted in the entire respiratory tract but no other organs or tissues were grossly affected (Comstock and Oberst, 1952).

In a prechronic inhalation study, 3-month-old Wistar rats (20 per group) were exposed to 25, 50, or 100 ppm furfuryl alcohol 6 hours per day, 5 days per week for 16 weeks (Savolainen and Pfaffli, 1983). Mean body weights of all groups of exposed animals were less than

those of the controls throughout the study, and animals exposed to 100 ppm exhibited muscle hypotonia (unspecified) after 13 weeks of exposure. After 4, 9, 13, or 16 weeks of exposure, five animals per group were sacrificed and their brains removed. The specific activity of creatinine kinase (a marker for astroglial cells) in homogenates of the cerebellum was elevated in all exposed groups and was significantly greater ($P < 0.01$) than control activity for animals exposed to 50 or 100 ppm. In the same homogenates, however, the specific activity of succinate dehydrogenase, a general glial cell marker, was reduced in a dose-dependent manner and was also found to be lower in glial cell preparations. These results were interpreted as an indication that exposure to furfuryl alcohol may be cytotoxic for glial cells, resulting in increased proliferation of astroglial cells.

Analysis of cerebral extracts by electrophoresis in polyacrylamide gels containing sodium dodecyl sulfate revealed an apparent reduction in the relative amount of myelin basic protein. Moreover, the specific activity of an acid protease was significantly elevated ($P < 0.05$) in the glial cell fraction. Because degradation of myelin basic protein by an acid protease is an early step in the process of demyelination, the observed changes may be an indication of demyelination caused by chemical exposure, which is consistent with primary effects on glial cells (Savolainen and Pfaffli, 1983).

CARCINOGENICITY IN EXPERIMENTAL ANIMALS

There are no published studies that have examined the carcinogenicity of furfuryl alcohol in experimental animals; however, the NTP has completed 2-year carcinogenicity studies of two related compounds, furan and furfural. The vehicle in both of these gavage studies was corn oil. In the furan study (NTP, 1993), F344/N rats received doses of 2, 4, or 8 mg/kg, and B6C3F₁ mice received doses of 8 or 15 mg/kg. The liver was the major target organ in rats and mice. Among groups of rats, the incidences of cholangiocarcinoma were 0/50 for vehicle controls, 43/50, 48/50, and 49/50 for 2, 4, and 8 mg/kg males, and 49/50, 50/50, and 48/50 for 2, 4, and 8 mg/kg females, respectively. Incidences of hepatocellular adenoma and carcinoma were also significantly increased in dosed male rats, and the incidences of hepatocellular adenoma were significantly increased in dosed female rats. A separate stop-exposure group of 50 male rats was administered a single dose of 30 mg/kg furan for 13 weeks and then maintained for the remainder of the

2-year period without additional chemical exposure. Groups of 10 animals were evaluated for the presence of neoplasms at the end of the 13-week exposure period and at 9 and 15 months. Cholangiocarcinoma was present in all 10 animals examined at the 9- and 15-month interim evaluations and occurred with an overall incidence of 100% in the stop-exposure group of rats. Among mice, the incidence of hepatocellular carcinoma was 7/50, 32/50, and 34/50 for vehicle control, 8 mg/kg, and 15 mg/kg males, and 2/50, 7/50, and 27/50 for vehicle control, 8 mg/kg, and 15 mg/kg females. No stop-exposure study was conducted with mice.

In the 2-year study of furfural, F344/N rats received doses of 30 or 60 mg/kg and mice received doses of 50, 100, or 150 mg/kg (NTP, 1990). Cholangiocarcinomas were present in two 60 mg/kg male rats, and two additional 60 mg/kg males had bile duct dysplasia with fibrosis, a precursor lesion for cholangiocarcinoma. The incidences of hepatocellular adenoma and carcinoma were increased in dosed male mice, and the incidences of hepatocellular adenoma were increased in dosed female mice.

GENETIC TOXICITY

There is little published mutagenicity data for furfuryl alcohol, and the available data show little evidence for genotoxic activity. Florin *et al.* (1980) and Mortelmans *et al.* (1986) reported no increase in gene reversion after treatment with furfuryl alcohol, with or without liver metabolic activation enzymes (S9), in various strains of *Salmonella typhimurium*. There was one report of chromosomal aberration induction in cultured Chinese hamster ovary cells treated with furfuryl alcohol with and without S9 (Stich *et al.*, 1981); however, these data were presented in a way that made independent assessment difficult, and the results require confirmation. No increases in sister chromatid exchanges were noted in cultured human lymphocytes after exposure to furfuryl alcohol (Gomez-Arroyo and Souza S., 1985; Jansson *et al.*, 1986). And finally, no evidence for mutagenic activity of furfuryl alcohol was seen in a *Drosophila melanogaster* sex-linked recessive lethal assay or a sex-chromosome loss test; both these germ cell tests employed adult injection and larval feeding as routes of administration (Rodriguez-Arnaiz *et al.*, 1989).

STUDY RATIONALE

Furfuryl alcohol, furfural, and furan were selected for evaluation as a class study because of the absence of data

on carcinogenic potential and because their large production volume, widespread use in manufacturing, and ubiquitous presence in consumer goods and foodstuffs suggested the potential for widespread human exposure.

Furfuryl alcohol was evaluated in 14-day and 13-week corn oil gavage studies (NTP, unpublished data) as part of the comparative class study with furan and furfural. However, human exposure to furfuryl alcohol occurs predominantly in occupational settings where inhalation is the major route of exposure. Therefore, it was considered most appropriate to evaluate the carcinogenic potential of furfuryl alcohol by inhalation.

MATERIALS AND METHODS

PROCUREMENT AND CHARACTERIZATION OF FURFURYL ALCOHOL

Furfuryl alcohol was obtained from QO Chemicals, Inc. (Memphis, TN), in one lot (7B19M-2), which was used during the 16-day, 14-week, and 2-year studies. Identity, purity, and stability analyses were conducted by the analytical chemistry laboratory, Midwest Research Institute (Kansas City, MO). Reports on analyses performed in support of the furfuryl alcohol studies are on file at the National Institute of Environmental Health Sciences.

The chemical, a clear yellow liquid, was identified as furfuryl alcohol by infrared, ultraviolet/visible, and nuclear magnetic resonance spectroscopy. The purity of lot 7B19M-2 was determined by elemental analyses, Karl Fischer water analysis, and gas chromatography. Elemental analyses for carbon and hydrogen were in agreement with the theoretical values for furfuryl alcohol. Karl Fischer water analysis indicated $0.098\% \pm 0.008\%$ water. Gas chromatography by two systems indicated one major peak and five impurities with areas greater than 0.1% relative to the major peak area; the combined impurity peak areas were 1.36% by one system and 1.17% by the second system. Major peak comparison between lot 7B19M-2 and lot Q0112979, a previously analyzed lot not used in the current studies, indicated a purity of $100.9\% \pm 0.6\%$ for lot 7B19M-2 relative to lot Q0112979. The overall purity was determined to be greater than 98%.

During the studies, the bulk chemical was stored under a nitrogen blanket in its original shipping containers at approximately -20°C . Stability was monitored by the study laboratory throughout the studies with gas chromatography; no degradation of the bulk chemical was detected.

VAPOR GENERATION AND EXPOSURE SYSTEM

Furfuryl alcohol was pumped into the top of a glass evaporation column filled with glass beads. A heated nitrogen stream entered the column from below, vaporized the furfuryl alcohol, and carried it to a heated condenser column. During the 2-year studies, the evaporation column was heated by wrapping with heat tape; additional heated nitrogen was added to the furfuryl alcohol vapor leaving the evaporation column to dilute the vapor. Detailed descriptions of the inhalation chamber and vapor generation system are provided in Appendix J.

During the 16-day and 14-week studies, the vapor was drawn through a heated line and injected into the inlet air stream of a mixing chamber and then pumped through a pneumatic valve into the distribution line. The charcoal- and HEPA-filtered air was conditioned to room temperature and maintained at minimum relative humidity to prevent the vapor from condensing. During the 16-day studies, condensation particles were filtered from the vapor with Teflon-membrane filters before entering the distribution line. In the 2-year studies, no mixing chamber was used; the vapor was drawn through a heated line and then mixed with heated air at the entrance of a short vapor distribution manifold. An automatic controller maintained constant flow in the distribution manifold.

From the distribution manifold, individual temperature-controlled delivery lines carried the vapor to each exposure chamber. The study laboratory designed the inhalation exposure chamber so that uniform vapor concentrations could be maintained throughout the chamber with the catch pans 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 furfuryl alcohol vapor, and not aerosol, was produced. The minimum resolvable level of the detector is approximately 200 particles per cubic centimeter. During the 16-day studies, without animals in the chambers, particle concentrations were below the limit of detection in the 16 and 31 ppm chambers but ranged up to 600 particles/cm³ in the 63 ppm chambers and 8,400 particles/cm³ in the 125 ppm chambers; concentrations in the 250 ppm chambers ranged from 8,400 to 36,000 particles/cm³. With animals in the chambers, concentrations were below the limit of detection in all but the 125 and 250 ppm chambers, which had concentrations of 1,470 and 11,200 particles/cm³, respectively. During the 14-week studies, particle concentrations in the 32 ppm chamber were 200 particles/cm³ without animals present and 245 particles/cm³ with animals; concentrations in all other chambers were below the limit of detection, with and without animals present. During the 2-year studies, the 32 ppm mouse chamber had a concentration of 370 particles/cm³ with no animals present; all other rat and mouse chambers, with and without animals present, had concentrations below the limit of detection.

VAPOR CONCENTRATION MONITORING

The chamber concentrations of furfuryl alcohol were monitored by a Hewlett-Packard Model 5890 on-line gas chromatograph. Samples were drawn through a 12-port stream select valve. The monitoring system was calibrated against a gravimetrically prepared standard of furfuryl alcohol in nitrogen. Additionally, the on-line monitor was calibrated by a comparison of chamber concentration data to grab samples analyzed by an off-line gas chromatograph. The operation of the chamber monitor was checked throughout the day against an on-line standard. The grab samples were collected in bubblers containing dimethylformamide and analyzed by an off-line gas chromatograph. The off-line gas chromatograph was calibrated with gravimetrically prepared furfuryl alcohol standards in dimethylformamide. Chamber concentration uniformity was maintained throughout the studies. Summaries of the chamber concentrations during the studies are presented in Tables J1 through J3.

CHAMBER ATMOSPHERE CHARACTERIZATION

The buildup of vapor concentration in the chamber to 90% of its final stable concentration (T_{90}) at the beginning of exposure and the decay of concentration at the end of exposure to 10% (T_{10}) were measured with and without animals in the chambers. A T_{90} of 12 minutes was initially used for all studies. However, because the actual T_{90} values for the 14-week studies were considerably longer than 12 minutes (16 to 20 minutes), the T_{90} was increased to 20 minutes on the seventeenth exposure day; this value was used until the end of the studies. To compensate for the slow buildup, additional vapor was delivered to the exposure chambers during the first 30 to 60 minutes.

Throughout the studies, stability was monitored by testing furfuryl alcohol samples (collected with bubblers or gas sampling tubes) with gas chromatography. No degradation of furfuryl alcohol was detected.

16-DAY STUDIES

Male and female F344/N rats and B6C3F₁ mice were obtained from Simonsen Laboratories (Gilroy, CA). On receipt, the rats and mice were approximately 4 weeks old. Animals were quarantined for 12 days and were 6 weeks old on the first day of the studies. Before the studies began, five male and five female rats and mice were randomly selected for parasite evaluation and gross observation for evidence of disease.

Groups of five male and five female rats and mice were exposed to concentrations of 0, 16, 31, 63, 125, or 250 ppm furfuryl alcohol by inhalation, 6 hours plus T_{90} (12 minutes) per day, 5 days per week, for 16 days. Rats and mice received a total of 12 exposures, including at least two consecutive exposures before necropsy. Feed was available *ad libitum* except during exposure periods; water was available *ad libitum*. Rats and mice were housed individually. Clinical findings were recorded twice daily for rats and mice. The animals were weighed initially, on day 8, and at the end of the studies. Details of the study design and animal maintenance are summarized in Table 1.

At the end of the 16-day studies, a necropsy was performed on all rats and mice. The heart, right kidney, liver, lung, right testis, and thymus were weighed. Histopathologic examinations were performed on all rats and mice. Table 1 lists the tissues and organs examined.

14-WEEK STUDIES

The 14-week studies were conducted to evaluate the cumulative toxic effects of repeated exposure to furfuryl alcohol and to determine the appropriate exposure concentrations to be used in the 2-year studies.

Male and female F344/N rats and B6C3F₁ mice were obtained from Simonsen Laboratories (Gilroy, CA). On receipt, the rats and mice were approximately 4 weeks old. Animals were quarantined for 12 or 13 days and were 6 weeks old on the first day of the studies. Before the studies began, five male and five female rats and mice were randomly selected for parasite evaluation and gross observation for evidence of disease. At the end of the studies, serologic analyses were performed on five male and five female sentinel rats and control mice using the protocols of the NTP Sentinel Animal Program (Appendix L).

Groups of 10 male and 10 female rats and mice were exposed to furfuryl alcohol at concentrations of 0, 2, 4, 8, 16, or 32 ppm for 6 hours plus T₉₀ (12 minutes through day 16, 20 minutes thereafter) per day, 5 days per week for 14 weeks. Additional groups of 10 male and 10 female rats designated for special clinical pathology evaluations were exposed to the same concentrations of furfuryl alcohol as the core study rats. Feed was available *ad libitum* except during exposure periods; water was available *ad libitum*. Rats and mice were housed individually. Clinical findings were recorded weekly. The core study animals were weighed initially, weekly, and at the end of the studies. Details of the study design and animal maintenance are summarized in Table 1.

Blood was collected from the special clinical pathology groups of rats on days 3 and 23 and from core study rats at the end of the 14-week study. After the day 23 blood collection, the special clinical pathology rats were killed and discarded without a necropsy being performed. The rats were anesthetized with 70% CO₂ and blood was collected from the retroorbital plexus. Blood for hematology determinations was placed in tubes containing potassium EDTA as an anticoagulant. Erythrocyte, total leukocyte, and platelet counts, hematocrit, hemoglobin concentration, mean cell volume,

mean cell hemoglobin, and mean cell hemoglobin concentration were measured on an Ortho ELT-8/ds hematology analyzer (Ortho Instruments, Westwood, MA). Differential leukocyte counts were based on classifying a minimum of 100 leukocytes in blood smears stained with a Gam-Rad automatic stainer (Gam-Rad, Inc., Chilhowie, VA), and these values were calculated in absolute numbers. Reticulocytes were stained with new methylene blue and counted as a reticulocyte/erythrocyte ratio using the Miller disc method. Blood for serum clinical chemistry analyses was collected in containers without anticoagulant but containing a separator gel, allowed to clot, and centrifuged to separate the serum. For the day 3 and day 23 clinical chemistry evaluations, the following were assayed using an Abbott VP chemistry analyzer (Abbott Laboratories, Abbott Park, IL): urea nitrogen, creatinine, total protein, albumin, globulin, alanine aminotransferase, alkaline phosphatase, creatine kinase, and sorbitol dehydrogenase. For the core study samples at the end of the study, only sorbitol dehydrogenase was measured using the Abbott VP analyzer; all other analyses were performed by a Roche Cobas Fara analyzer (Roche Diagnostic Systems, Inc., Montclair, NJ). Total bile acids were determined using a commercially obtained kit (Enzabill®) with the optical density of the colored end-product read on a recording spectrophotometer. The parameters measured are listed in Table 1.

At the end of the 14-week studies, samples were collected for sperm motility and vaginal cytology evaluations on rats and mice exposed to 0, 2, 8, and 32 ppm. The parameters evaluated are listed in Table 1. Methods used were those described in the NTP's sperm morphology and vaginal cytology evaluations protocol (NTP, 1987). For 12 consecutive days prior to scheduled terminal sacrifice, the vaginal vaults of the females were moistened with saline, if necessary, and samples of vaginal fluid and cells were stained. Relative numbers of leukocytes, nucleated epithelial cells, and large squamous epithelial cells were determined and used to ascertain estrous cycle stage (i.e., diestrus, proestrus, estrus, and metestrus). Male animals were evaluated for sperm count and motility. The left testis and left epididymis were isolated and weighed. The tail of the epididymis (cauda epididymis) was then removed from the epididymal body (corpus epididymis) and weighed. Test yolk (rats) or modified Tyrode's buffer (mice) was applied to slides, and a small incision was made at the distal border of the cauda epididymis. The sperm effluxing from the incision were dispersed in the buffer on the slides, and the numbers of motile and nonmotile spermatozoa were counted for five fields per slide by two observers.

Following completion of sperm motility estimates, each left cauda epididymis was placed in buffered saline solution. Caudae were finely minced, and the tissue was incubated in the saline solution and then heat fixed at 65° C. Sperm density was then determined microscopically with the aid of a hemacytometer. To quantify spermatogenesis, the testicular spermatid head count was determined by removing the tunica albuginea and homogenizing the left testis in phosphate-buffered saline containing 10% dimethyl sulfoxide. Homogenization-resistant spermatid nuclei were counted with a hemacytometer.

A necropsy was performed on all core study animals. The heart, right kidney, liver, lung, right testis, and thymus were weighed. Tissues for microscopic examination 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. A complete histopathologic examination was performed on core study rats and mice in the 0 and 32 ppm groups. Additionally, the nose and gross lesions of male and female rats and mice in the 2, 4, 8, and 16 ppm groups were examined. Table 1 lists the tissues and organs routinely examined.

2-YEAR STUDIES

Study Design

Groups of 50 male and 50 female rats and mice were exposed to furfuryl alcohol by inhalation, 6 hours plus T₉₀ (12 minutes) per day, 5 days per week for 105 weeks, at concentrations of 0, 2, 8, or 32 ppm.

Postexposure 16-hour urine samples were collected at study termination from rats from each exposure group. Water was available *ad libitum* during the 16-hour collection periods, and all urine samples were analyzed for volume, creatinine, furoylglycine, and furanacryloylglycine. Analyses were accomplished using solvent extraction followed by derivitization and gas chromatography/mass spectrometry using a Hewlett-Packard Model 5890 gas chromatograph with an HP-5971 mass selective detector and an HP-7673 auto-sampler (Hewlett-Packard, Palo Alto, CA).

Source and Specification of Animals

Male and female F344/N rats and B6C3F₁ mice were obtained from Taconic Farms (Germantown, NY) for use in the 2-year studies. Rats and mice were quarantined for 12 to 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 6 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 L).

Animal Maintenance

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

Clinical Examinations and Pathology

All animals were observed twice daily. Animals were weighed initially, weekly for 12 weeks, monthly until week 91, then every 2 weeks until the end of the studies. Clinical findings were recorded initially, approximately monthly until week 91, then every 2 weeks 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. For extended evaluation of renal proliferative lesions, kidneys were step sectioned at 1-mm (rats) or 0.5-mm (mice) intervals, and four additional sections were obtained from each kidney. 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 adrenal gland, kidney, lung, nose, pituitary gland, and skin of male rats; adrenal gland, bone, lung, nose, and

skin of female rats; adrenal gland, kidney, lung, nose, and pancreatic islets of male mice; and eye, lung, nose, pituitary gland, and thyroid gland of female mice.

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. This group examined the tissues without any knowledge of dose groups or previously rendered diagnoses. 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 Inhalation Studies of Furfuryl Alcohol

16-Day Studies	14-Week Studies	2-Year Studies
Study Laboratory Battelle Pacific Northwest Laboratories (Richland, WA)	Battelle Pacific Northwest Laboratories (Richland, WA)	Battelle Pacific Northwest Laboratories (Richland, WA)
Strain and Species Rats: F344/N Mice: B6C3F ₁	Rats: F344/N Mice: B6C3F ₁	Rats: F344/N Mice: B6C3F ₁
Animal Source Simonsen Laboratories (Gilroy, CA)	Simonsen Laboratories (Gilroy, CA)	Taconic Farms (Germantown, NY)
Time Held Before Studies 12 days	Rats: 12 days (males) or 13 days (females) Mice: 13 days	Rats: 12 days Mice: 14 days
Average Age When Studies Began 6 weeks	6 weeks	6 weeks
Date of First Exposure Rats: 18 July 1988 Mice: 19 July 1988	Rats: 19 (males) or 20 (females) December 1988 Mice: 20 December 1988	Rats: 26 November 1991 Mice: 21 November 1991
Duration of Exposure 6 hours plus T ₉₀ (12 minutes) per day, 5 days per week, for 16 days	6 hours plus T ₉₀ (12 minutes initially, increased to 20 minutes on seventeenth exposure day) per day, 5 days per week, for 14 weeks	6 hours plus T ₉₀ (12 minutes) per day, 5 days per week, for 105 weeks
Date of Last Exposure Rats: 2 August 1988 Mice: 3 August 1988	Rats: 20 (males) or 21 (females) March 1989 Mice: 22 (males) or 23 (females) March 1989	Rats: 24 November 1993 Mice: 19 November 1993
Necropsy Dates Rats: 3 August 1988 Mice: 4 August 1988	Rats: 21 (males) or 22 (females) March 1989 Mice: 23 (males) or 24 (females) March 1989	Rats: 29-30 November 1993 Mice: 22-24 November 1993
Average Age at Necropsy 9 weeks	19 weeks	111 weeks
Size of Study Groups 5 males and 5 females	10 males and 10 females	50 males and 50 females
Method of Distribution Animals were distributed randomly into groups of approximately equal initial mean body weights.	Same as 16-day studies	Same as 16-day studies
Animals per Cage 1	1	1
Method of Animal Identification Tail tattoo	Tail tattoo	Tail tattoo

TABLE 1
Experimental Design and Materials and Methods in the Inhalation Studies of Furfuryl Alcohol

16-Day Studies	14-Week Studies	2-Year Studies
Diet NIH-07 open formula pelleted diet (Zeigler Brothers, Inc., Gardners, PA), available <i>ad libitum</i> except during exposure periods, changed weekly	Same as 16-day studies	NIH-07 open formula pelleted diet (Zeigler Brothers, Inc., Gardners, PA), available <i>ad libitum</i> except during exposure and urine collection periods, changed weekly
Water Distribution Tap water (Richland municipal supply) via automatic watering system (Edstrom Industries, Waterford, WI), available <i>ad libitum</i>	Same as 16-day studies	Same as 16-day studies
Cages Stainless steel (Harford Systems, Aberdeen, MD), changed once per week	Same as 16-day studies	Same as 16-day studies
Bedding Techsorb® untreated cageboard (Shepherd Specialty Papers, Inc., Kalamazoo, MI), changed daily	Same as 16-day studies	Untreated cageboard (Bunzl Cincinnati Paper Co., Cincinnati, OH), changed daily
Chamber Air Supply Filters Single HEPA filter (Flanders Filters, Inc., San Rafael, CA); charcoal filter (RSE, Inc., New Baltimore, MI)	Same as 16-day studies	Same as 16-day studies
Chambers Stainless steel (Harford Systems, Aberdeen, MD), changed once per week	Same as 16-day studies	Same as 16-day studies
Chamber Environment Mean temperature: 22.8°-23.7° C Mean relative humidity: 45%-61% Room fluorescent light: 12 hours/day Chamber air changes: 15/hour	Mean temperature: 23.6°-24.1° C Mean relative humidity: 55%-56% Room fluorescent light: 12 hours/day Chamber air changes: 15/hour	Mean temperature: 23.9°-24.3° C (rats); 23.8°-24.1° C (mice) Mean relative humidity: 55%-57% (rats); 51%- 55% (mice) Room fluorescent light: 12 hours/day Chamber air changes: 15/hour
Exposure Concentrations 0, 16, 31, 63, 125, or 250 ppm	0, 2, 4, 8, 16, or 32 ppm	0, 2, 8, or 32 ppm
Type and Frequency of Observation Observed twice daily; animals were weighed initially, on day 8, and at the end of the studies; clinical findings were recorded twice daily.	Observed twice daily; animals were weighed initially, weekly, and at the end of the studies; clinical findings were recorded weekly.	Observed twice daily; animals were weighed initially, weekly for 12 weeks, monthly until week 91, then every 2 weeks until the end of the studies. Clinical findings were recorded initially, approximately monthly until week 91, then every 2 weeks until the end of the studies.
Method of Sacrifice 70% CO ₂	Same as 16-day studies	Same as 16-day studies
Necropsy Necropsy was performed on all animals. Organs weighed were heart, right kidney, liver, lung, right testis, and thymus.	Necropsy was performed on all core study animals. Organs weighed were heart, right kidney, liver, lung, right testis, and thymus.	Necropsy was performed on all animals.

TABLE 1
Experimental Design and Materials and Methods in the Inhalation Studies of Furfuryl Alcohol

16-Day Studies	14-Week Studies	2-Year Studies
<p>Clinical Pathology None</p>	<p>Blood was collected from special clinical pathology groups on days 3 and 23, and from all core study rats at the end of the study for hematology and clinical chemistry analyses. Blood was collected from the retroorbital plexus of animals anesthetized with 70% CO₂/30% room air after at least two consecutive days of exposure.</p> <p>Hematology: hematocrit; hemoglobin concentration; erythrocyte, reticulocyte, and platelet counts; mean cell volume; mean cell hemoglobin; mean cell hemoglobin concentration; and total leukocyte count and differentials</p> <p>Clinical chemistry: urea nitrogen, creatinine, total protein, albumin, globulin, albumin/globulin ratio, alanine aminotransferase, alkaline phosphatase, creatine kinase, sorbitol dehydrogenase, and total bile acids</p>	None
<p>Histopathology Histopathology was performed on all rats and mice. In addition to gross lesions and tissue masses, the following tissues were examined: larynx, lung, nose, and trachea.</p>	<p>Complete histopathology was performed on core study rats and mice in the 0 and 32 ppm groups. In addition to gross lesions and tissue masses, the following tissues were examined: adrenal gland, bone and marrow, brain, clitoral gland, esophagus, gallbladder (mice), heart and aorta, large intestine (cecum, colon, rectum), small intestine (duodenum, jejunum, ileum), kidney, larynx, liver, lung, lymph nodes (mandibular, mesenteric, bronchial, mediastinal), mammary gland, thigh muscle, nose, ovary, pancreas, parathyroid gland, pharynx, 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, uterus, and vagina. Additionally, the nose and gross lesions of rats and mice in the 2, 4, 8, and 16 ppm groups were examined.</p>	<p>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 and 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 (with skin), nose, ovary, pancreas, parathyroid gland, pituitary gland, preputial gland, prostate gland, salivary gland, spleen, stomach (forestomach and glandular), testis (with epididymis and seminal vesicle), thymus, thyroid gland, trachea, urinary bladder, and uterus.</p>
<p>Sperm Motility and Vaginal Cytology None</p>	<p>Sperm samples were collected from rats and mice in the 0, 2, 8, and 32 ppm groups at the end of the studies and evaluated for sperm count and motility. The left cauda epididymis, left epididymis, and left testis were weighed. Vaginal samples were collected for up to 12 consecutive days prior to the end of the studies and evaluated for the relative frequency of estrous stages and for estrous cycle length.</p>	None

TABLE 1
Experimental Design and Materials and Methods in the Inhalation Studies of Furfuryl Alcohol

16-Day Studies	14-Week Studies	2-Year Studies
Urinary Metabolite Study None	None	Urine samples were obtained from rats from each exposure group at study termination. Samples from fasted animals were collected over ice for 16 hours and stored at -70° C. Parameters measured included volume, creatinine, furoylglycine, and furanacryloylglycine.

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 pregnant 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, C5, 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.

Kidney step sections provide approximately eight additional sections per animal that may have additional proliferative lesions. In the incidence tables and standard statistical analyses given in the appendixes, only the proliferative lesions in the original (typically two) kidney sections are considered. However, separate analyses of the additional lesions found in the step sections and of the combined lesions in original and step section often

provided significant additional information and are given in this report. Since the same large proliferative lesions may be present both on an original section and on subsequent step sections, such a lesion is only counted once in the combination analysis. Animals with proliferative lesions identified in the step-section review are listed in a separate document for the specific study, Report of the Special Pathology Working Group for Kidney Step Sections, and is available on request.

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 B6C3F₁ 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 chamber 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

Two approaches were employed to assess the significance of pairwise comparisons between exposed and chamber control groups in the analysis of continuous variables. Organ and body weight data, which have approximately normal distributions, were analyzed with the parametric multiple comparison procedures of Dunnett (1955) and Williams (1971, 1972). Hematology, clinical chemistry, spermatid, and epididymal spermatozoal data, which have typically skewed distributions, were analyzed using the nonparametric multiple comparison methods of Shirley (1977) and Dunn (1964). Jonckheere's test (Jonckheere, 1954) was used to assess the significance of the dose-related trends and to determine whether a trend-sensitive test (Williams' or Shirley's test) was more appropriate for pairwise comparisons than a test that does not assume a monotonic dose-related trend (Dunnett's or Dunn's test). Prior to statistical analysis, extreme values identified by the outlier test of Dixon and Massey (1951) were examined by NTP personnel, and implausible values were eliminated from the analysis. Average severity values were analyzed for significance with the Mann-Whitney U test (Hollander and Wolfe, 1973). Because vaginal cytology data are proportions (the proportion of the observation period that an animal was in a given estrous stage), an arcsine transformation was used to bring the data into closer conformance with a normality assumption. Treatment effects were investi-

gated by applying a multivariate analysis of variance (Morrison, 1976) to the transformed data to test for simultaneous equality of measurements across exposure concentrations.

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 14-week and 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 furfuryl alcohol was assessed by testing the ability of the chemical to induce mutations in various strains of *Salmonella typhimurium*, sister chromatid exchanges and chromosomal aberrations in cultured Chinese hamster ovary cells and mouse bone marrow cells, and micronucleated erythrocytes in bone marrow of mice. The protocols for these studies and the results are given in Appendix E.

The genetic toxicity studies of furfuryl alcohol 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 chemically 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. But, 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

16-DAY STUDY

All male and female rats exposed to 250 ppm died by day 2 of the study, and one male rat exposed to 125 ppm died on day 5 (Table 2). Final mean body weights of male and female rats exposed to 125 ppm were significantly less than those of the chamber control groups. Male rats

exposed to 31, 63, or 125 ppm and female rats exposed to 125 ppm gained less weight than the chamber control groups. Clinical findings included dyspnea, hypoactivity, and nasal and ocular discharge in males and females exposed to 63, 125, or 250 ppm.

TABLE 2
Survival and Body Weights of Rats in the 16-Day Inhalation Study of Furfuryl Alcohol

Concentration (ppm)	Survival ^a	Mean Body Weight ^b (g)			Final Weight Relative to Controls (%)
		Initial	Final	Change	
Male					
0	5/5	111 ± 3	186 ± 5	76 ± 4	
16	5/5	119 ± 5	194 ± 4	75 ± 2	104
31	5/5	111 ± 2	172 ± 3	61 ± 3*	92
63	5/5	116 ± 4	174 ± 6	58 ± 3**	93
125	4/5 ^c	116 ± 3	159 ± 7**	43 ± 7**	85
250	0/5 ^d	118 ± 4	—	—	—
Female					
0	5/5	94 ± 3	130 ± 4	36 ± 3	
16	5/5	98 ± 2	131 ± 4	33 ± 2	101
31	5/5	94 ± 3	125 ± 3	31 ± 1	96
63	5/5	97 ± 3	126 ± 2	30 ± 2	97
125	5/5	94 ± 3	113 ± 4**	20 ± 2**	87
250	0/5 ^e	97 ± 4	—	—	—

* Significantly different ($P \leq 0.05$) from the chamber control group by Williams' or Dunnett's test

** $P \leq 0.01$

^a Number of animals surviving at 16 days/number initially in group

^b Weights and weight changes are given as mean ± standard error. No final mean body weights were calculated for groups with 100% mortality. Subsequent calculations are based on animals surviving to the end of the study.

^c Day of death: 5

^d Day of death: 2

^e Day of death: 1, 1, 2, 2, 2

Absolute heart and thymus weights of 125 ppm males and females were significantly less than those of the chamber control groups; absolute lung weights were significantly less in 63 and 125 ppm males and 125 ppm females than in the chamber controls (Table G1). These differences were attributed to the lower mean body weights of these groups. All exposed animals exhibited

acute and/or suppurative inflammation; necrosis, regeneration, and squamous metaplasia of the respiratory epithelium; and necrosis and degeneration of the olfactory epithelium (Table 3). The severity of exposure-induced nasal lesions generally increased with increasing exposure concentration. A no-observable-effect level for furfuryl alcohol was not determined in this study.

TABLE 3
Incidences of Nonneoplastic Lesions of the Nose in Rats in the 16-Day Inhalation Study of Furfuryl Alcohol

	Chamber Control	16 ppm	31 ppm	63 ppm	125 ppm	250 ppm
Male						
Number Examined Microscopically	5	5	5	5	5	5
Acute and/or Suppurative Inflammation ^a	0	1	3	4*	5**	5**
Respiratory Epithelium, Necrosis	0	5** (1.2) ^b	5** (1.8)	5** (2.2)	5** (2.2)	0
Respiratory Epithelium, Regeneration	0	4* (1.5)	5** (2.4)	5** (2.4)	5** (1.8)	0
Respiratory Epithelium, Squamous Metaplasia	0	5** (1.2)	5** (1.2)	5** (1.4)	4* (2.8)	0
Olfactory Epithelium, Necrosis	0	4* (1.3)	5** (1.4)	5** (2.8)	5** (2.8)	0
Olfactory Epithelium, Degeneration	0	5** (2.0)	5** (2.6)	5** (2.8)	4* (2.8)	0
Female						
Number Examined Microscopically	5	5	5	5	5	5
Acute and/or Suppurative Inflammation	0	0	0	2	1	5**
Respiratory Epithelium, Necrosis	0	2 (1.0)	4* (1.3)	5** (1.8)	4* (1.8)	0
Respiratory Epithelium, Regeneration	0	5** (1.2)	5** (1.4)	5** (2.2)	5** (1.4)	0
Respiratory Epithelium, Squamous Metaplasia	0	5** (1.0)	5** (1.2)	5** (1.0)	5** (1.4)	0
Olfactory Epithelium, Necrosis	0	0	0	5** (1.6)	4* (1.8)	0
Olfactory Epithelium, Degeneration	0	5** (1.2)	5** (2.8)	5** (3.4)	5** (2.6)	0

* Significantly different ($P \leq 0.05$) from the chamber control group by the Fisher exact 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

14-WEEK STUDY

All rats survived to the end of the study (Table 4). The final mean body weight and body weight gain of females exposed to 32 ppm were significantly less than those of the chamber control group. There were no serious

exposure-related clinical findings. Swelling was observed around the face and eyes of exposed rats, and urine stains were present in all groups of exposed females.

TABLE 4
Survival and Body Weights of Rats in the 14-Week Inhalation Study of Furfuryl Alcohol

Concentration (ppm)	Survival ^a	Mean Body Weight ^b (g)			Final Weight Relative to Controls (%)
		Initial	Final	Change	
Male					
0	10/10	102 ± 3	316 ± 7	213 ± 6	
2	10/10	98 ± 3	315 ± 7	218 ± 6	100
4	10/10	98 ± 2	325 ± 5	227 ± 5	103
8	10/10	99 ± 3	316 ± 5	217 ± 4	100
16	10/10	98 ± 3	302 ± 4	203 ± 5	96
32	10/10	100 ± 2	304 ± 6	204 ± 5	96
Female					
0	10/10	96 ± 2	195 ± 4	99 ± 3	
2	10/10	96 ± 2	194 ± 2	98 ± 2	100
4	10/10	92 ± 2	194 ± 4	102 ± 3	100
8	10/10	93 ± 3	186 ± 4	93 ± 4	96
16	10/10	91 ± 2	187 ± 2	96 ± 2	96
32	10/10	92 ± 2	176 ± 3**	84 ± 3**	90

** Significantly different ($P \leq 0.01$) from the chamber control group by Williams' or Dunnett's test

^a Number of animals surviving at 14 weeks/number initially in group

^b Weights and weight changes are given as mean ± standard error.

Absolute liver and lung weights of 32 ppm females were significantly less than those of the chamber control group (Table G2). However, these differences were small in magnitude and considered to be associated with the lower body weight of this group. The hematology and clinical chemistry data for rats are presented in Table F1. On day 3, a minimal exposure-related erythrocytosis, evidenced by increases in hematocrit values, hemoglobin concentrations, and erythrocyte counts, occurred in males and females exposed to 4 ppm or greater. The increased circulating red cell mass would be consistent with erythrocytosis of dehydration and would be related to hemoconcentration. Hemoconcentration of dehydration was supported by the increases in albumin and total protein concentrations observed in males exposed to 4 ppm or greater. The erythrocytosis was transient, and by day 23, hematocrit values, hemoglobin concentrations, and erythrocyte counts of exposed groups were similar to the chamber control values. On day 3, there was a minimal decrease in the serum alkaline phosphatase

activity of 16 and 32 ppm males and females. Jenkins and Robinson (1975) reported that decreased feed consumption can result in decreased serum alkaline phosphatase activity. The clinical pathology data suggest that by day 3 of the study, exposed rats had decreased water and feed consumption, but that this effect was transient. Changes in other hematology and clinical chemistry variables were minimal, inconsistent between males and females, and within physiological values; they were not considered toxicologically relevant.

The spermatid count and number of spermatid heads per testis were significantly increased in 32 ppm males (Table H1). Spermatid heads per gram of testis were significantly increased in 16 and 32 ppm males. There were no significant differences in vaginal cytology parameters between exposed and chamber control females (Table H2).

Exposure-related increases in the incidences of squamous metaplasia of the respiratory and transitional epithelium, goblet cell hyperplasia of the respiratory epithelium, and hypertrophy of the respiratory epithelium lining the nasopharyngeal duct were observed in the nose of male and female rats (Table 5). The incidences of degeneration, hyperplasia, metaplasia, and surface

exudate of the olfactory epithelium generally increased with increasing exposure concentration in males and females. The incidences of cellular infiltrate of the lamina propria of the nose in males and females in the 16 and 32 ppm groups were significantly increased compared to the chamber control groups.

TABLE 5
Incidences of Nonneoplastic Lesions of the Nose in Rats in the 14-Week Inhalation Study of Furfuryl Alcohol

	Chamber Control	2 ppm	4 ppm	8 ppm	16 ppm	32 ppm
Male						
Number Examined Microscopically	10	10	10	10	10	10
Respiratory Epithelium, Squamous Metaplasia ^a	0	0	0	5* (1.4) ^b	10** (2.0)	10** (2.3)
Respiratory Epithelium, Goblet Cell, Hyperplasia	0	0	0	7** (1.0)	6** (1.3)	10** (1.1)
Transitional (Cuboidal) Epithelium, Squamous Metaplasia	0	9** (1.0)	10** (1.1)	10** (2.1)	10** (2.0)	10** (2.7)
Nasopharyngeal Duct, Epithelium, Hypertrophy	0	0	0	2 (1.0)	6** (1.0)	10** (1.0)
Olfactory Epithelium, Degeneration	0	1 (1.0)	4* (1.0)	9** (1.3)	10** (2.2)	10** (3.0)
Olfactory Epithelium, Hyperplasia	0	0	1 (1.0)	2 (1.0)	9** (1.2)	9** (1.9)
Olfactory Epithelium, Metaplasia	0	0	0	0	0	2 (1.0)
Olfactory Epithelium, Surface Exudate	0	0	0	0	6** (1.0)	7** (1.0)
Lamina Propria, Mixed Cell, Cellular Infiltrate	0	0	0	1 (1.0)	7** (1.0)	10** (1.0)
Female						
Number Examined Microscopically	10	10	10	10	10	10
Respiratory Epithelium, Squamous Metaplasia	0	0	0	6** (1.0)	10** (1.2)	10** (1.6)
Respiratory Epithelium, Goblet Cell, Hyperplasia	0	0	0	2 (1.0)	8** (1.0)	9** (1.0)
Transitional (Cuboidal) Epithelium, Squamous Metaplasia	0	9** (1.0)	10** (1.0)	10** (1.9)	10** (2.2)	10** (2.2)
Nasopharyngeal Duct, Epithelium, Hypertrophy	0	0	0	0	3 (1.0)	9** (1.0)
Olfactory Epithelium, Degeneration	0	3 (1.3)	7** (1.1)	10** (1.4)	10** (2.3)	10** (2.8)
Olfactory Epithelium, Hyperplasia	0	0	0	2 (1.0)	5* (1.4)	10** (1.2)
Olfactory Epithelium, Metaplasia	0	0	0	0	1 (1.0)	5* (1.2)
Olfactory Epithelium, Surface Exudate	0	0	0	2 (1.0)	6** (1.0)	10** (1.0)
Lamina Propria, Mixed Cell, Cellular Infiltrate	0	2 (1.0)	0	3 (1.3)	8** (1.0)	6** (1.0)

* Significantly different ($P \leq 0.05$) from the chamber control group by the Fisher exact 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

Exposure Concentration Selection Rationale: The selection of exposure concentrations for the 2-year rat study was based on the incidences and severities of cytological alterations in the nasal mucosa associated with exposure to furfuryl alcohol. In the 14-week study, squamous metaplasia of the transitional epithelium and degeneration of the olfactory epithelium were present in all exposed groups; however, other chemical-related changes in the nasal mucosa occurred only at concentrations of 8 ppm or greater. Although the incidences of several lesions increased between 8 and 32 ppm, the severity of these lesions generally ranged from minimal to mild and were similar in severity to those observed at 16 or 31 ppm during the 16-day study. The longer exposure time in the 14-week study did not result

in a significant increase in the severity of changes in the nasal mucosa, and it was considered unlikely that the lesions would become life-threatening during a 2-year study. Therefore, 32 ppm was selected as the high exposure concentration for the 2-year rat study. A no-observable-effect level was not achieved in either the 16-day or 14-week studies. Since the three lowest concentrations in the 14-week study were below the currently recommended TLVs (TLV time-weighted average=10 ppm; TLV short-term exposure limit=15 ppm) for occupational exposure, lower concentrations of 2 and 8 ppm were selected for the 2-year study. This provided three concentrations over a range that covered documented occupational exposures.

2-YEAR STUDY

Survival

Estimates of 2-year survival probabilities for male and female rats are shown in Table 6 and in the Kaplan-Meier survival curves (Figure 2). All male rats exposed to 32 ppm died by week 99. Survival of all other exposed groups of male and female rats was similar to that of the chamber control groups.

Body Weights and Clinical Findings

Mean body weights of 32 ppm males were less than those of the chamber controls beginning week 19; mean body weights of 2 and 8 ppm male groups and

all exposed female groups were similar to those of the chamber control groups throughout the study (Tables 7 and 8; Figure 3). There were no exposure-related clinical findings.

Urinary Metabolites

The concentrations of furoylglycine and furan-acryloylglycine, the two major metabolites of furfuryl alcohol, were increased in the urine of exposed rats. For both metabolites, the increase was approximately proportional to exposure concentration.

TABLE 6
Survival of Rats in the 2-Year Inhalation Study of Furfuryl Alcohol

	Chamber Control	2 ppm	8 ppm	32 ppm
Male				
Animals initially in study	50	50	50	50
Moribund	34	43	31	43
Natural deaths	8	2	10	7
Animals surviving to study termination	8 ^d	5	9	0
Percent probability of survival at end of study ^a	16	10	18	0
Mean survival (days) ^b	8	620	630	593
Survival analysis ^c	P<0.001	P=0.597	P=0.915N	P<0.001
Female				
Animals initially in study	50	50	50	50
Pregnant ^e	0	0	1	0
Moribund	23	21	24	32
Natural deaths	1	3	3	2
Animals surviving to study termination	26	26 ^d	22	16
Percent probability of survival at end of study	52	52	45	32
Mean survival (days)	667	683	678	651
Survival analysis	P=0.028	P=0.982N	P=0.681	P=0.094

^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 the study

^e Censored from survival analyses

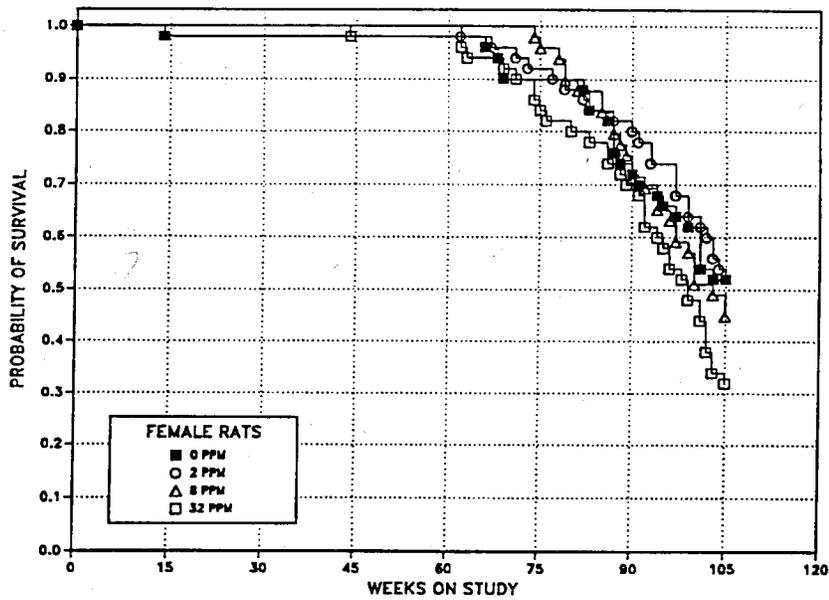
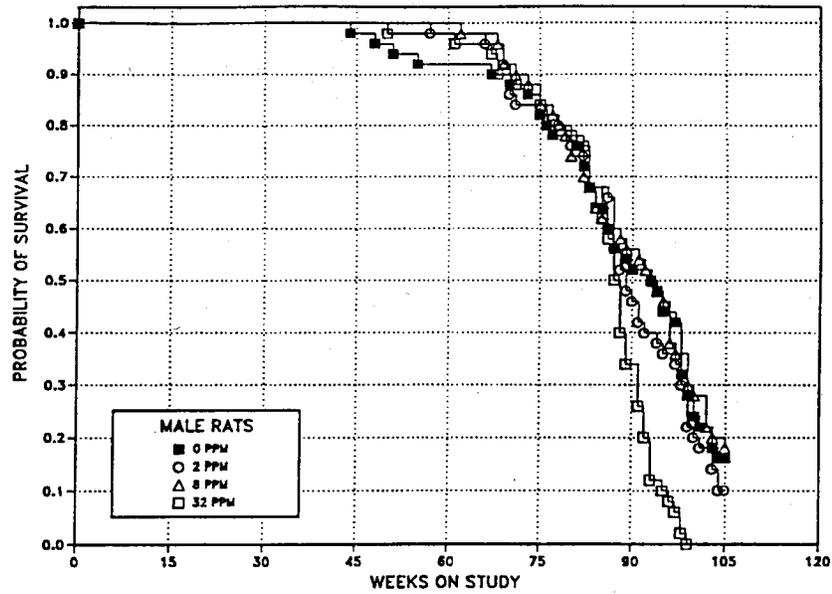


FIGURE 2
Kaplan-Meier Survival Curves for Male and Female Rats Administered Furfuryl Alcohol by Inhalation for 2 Years

TABLE 7
Mean Body Weights and Survival of Male Rats in the 2-Year Inhalation Study of Furfuryl Alcohol

Weeks on Study	Chamber Control		2 ppm			8 ppm			32 ppm		
	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	151	50	149	99	50	148	98	50	144	96	50
2	206	50	202	98	50	201	98	50	193	94	50
3	237	50	234	99	50	233	98	50	225	95	50
4	262	50	260	99	50	256	98	50	248	95	50
5	283	50	282	100	50	279	99	50	267	94	50
6	299	50	298	100	50	297	100	50	285	95	50
7	315	50	313	99	50	313	100	50	300	95	50
8	329	50	326	99	50	327	99	50	316	96	50
9	342	50	338	99	50	340	99	50	330	97	50
10	352	50	349	99	50	350	100	50	336	95	50
12	368	50	365	99	50	366	99	50	352	96	50
15	398	50	395	99	50	396	100	50	380	95	50
19	425	50	418	98	50	416	98	50	399	94	50
23	449	50	441	98	50	441	98	50	423	94	50
27	466	50	457	98	50	457	98	50	435	93	50
31	479	50	468	98	50	469	98	50	446	93	50
35	491	50	482	98	50	482	98	50	459	93	50
39	503	50	491	98	50	493	98	50	468	93	50
44	507	50	499	98	50	497	98	50	469	92	50
47	515	49	506	98	50	510	99	50	482	94	50
51	525	47	513	98	50	516	98	50	491	94	49
55	529	46	516	98	50	519	98	50	491	93	49
59	536	46	523	98	49	525	98	50	497	93	49
63	545	46	531	98	49	533	98	49	503	92	48
67	546	46	525	96	48	537	98	49	501	92	48
71	547	44	534	98	42	536	98	45	503	92	45
75	544	42	532	98	42	529	97	43	499	92	42
80	545	39	528	97	40	535	98	38	489	90	40
83	534	35	510	96	35	529	99	34	472	88	36
87	535	29	492	92	31	520	97	30	444	83	27
91	535	26	484	90	23	515	96	28	409	76	16
93	525	25	493	94	20	509	97	25			
95	511	23	498	97	18	494	97	24			
97	504	22	487	97	17	492	98	19			
99	492	15	471	96	12	504	102	16			
101	501	11	479	96	9	494	99	14			
103	485	9	466	96	8	491	101	10			
Mean for weeks											
1-13	286		283	99		283	99		272	95	
14-52	476		467	98		468	98		445	93	
53-103	526		504	96		516	98		481	91	

TABLE 8
Mean Body Weights and Survival of Female Rats in the 2-Year Inhalation Study of Furfuryl Alcohol

Weeks on Study	Chamber Control		2 ppm			8 ppm			32 ppm		
	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	122	50	118	97	50	118	97	49	117	96	50
2	145	50	144	99	50	143	98	49	138	95	50
3	158	50	154	98	50	156	99	49	149	95	50
4	167	50	166	100	50	163	98	49	159	96	50
5	176	50	175	99	50	175	99	49	168	95	50
6	182	50	180	99	50	181	99	49	175	96	50
7	188	50	186	99	50	186	99	49	179	95	50
8	193	50	191	99	50	191	99	49	185	96	50
9	198	50	195	99	50	196	99	49	191	97	50
10	202	50	200	99	50	200	99	49	191	95	50
12	208	50	205	98	50	206	99	49	201	97	50
15	219	49	216	99	50	219	100	49	211	97	50
19	228	49	224	98	50	223	98	49	221	97	50
23	241	49	237	99	50	235	98	49	234	97	50
27	249	49	244	98	50	243	98	49	241	97	50
31	256	49	253	99	50	252	98	49	252	98	50
35	265	49	262	99	50	259	98	49	258	97	50
39	278	49	272	98	50	272	98	49	269	97	50
44	290	49	284	98	50	282	97	49	280	96	50
47	303	49	296	98	50	297	98	49	296	98	49
51	312	49	308	99	50	311	100	49	308	99	49
55	323	49	317	98	50	317	98	49	318	99	49
59	332	49	325	98	50	327	99	49	328	99	49
63	340	49	333	98	49	336	99	49	337	99	47
67	347	48	339	98	49	343	99	49	346	100	47
71	356	45	347	98	48	351	99	49	353	99	46
75	359	45	348	97	46	353	98	47	358	100	43
80	365	45	357	98	44	360	98	44	364	100	41
83	360	44	358	100	43	359	100	43	363	101	40
87	361	40	360	100	41	359	99	40	356	99	37
91	381	35	363	95	40	369	97	35	364	96	34
93	381	35	361	95	39	362	95	34	361	95	31
95	382	33	365	96	37	365	95	32	356	93	30
97	378	32	367	97	35	358	95	31	356	94	27
99	372	32	363	98	33	361	97	29	352	95	25
101	364	31	359	99	32	373	103	25	348	96	23
103	374	26	364	97	29	368	99	24	361	97	18
Mean for weeks											
1-13	176		174	99		174	99		168	95	
14-52	264		260	98		259	98		257	97	
53-103	361		352	98		354	98		351	97	

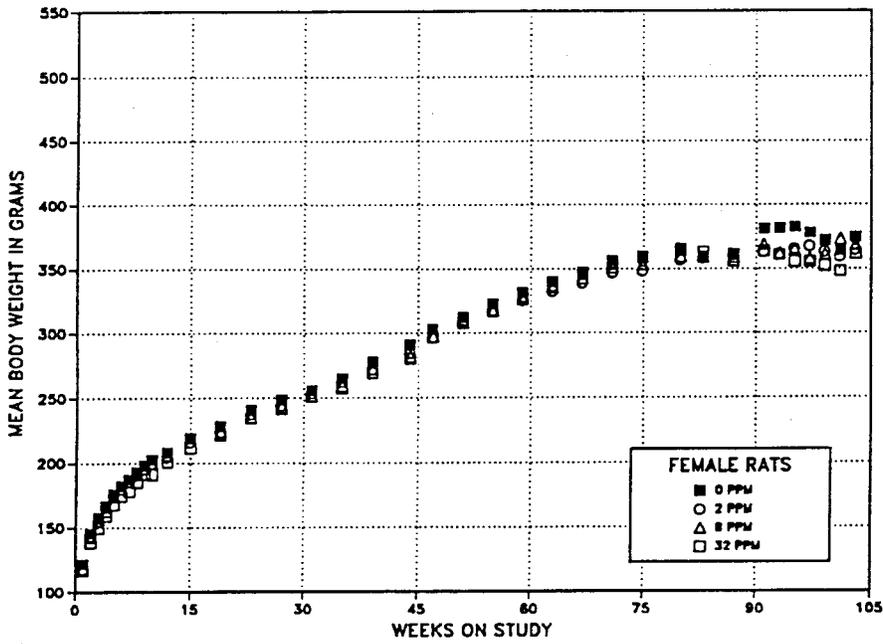
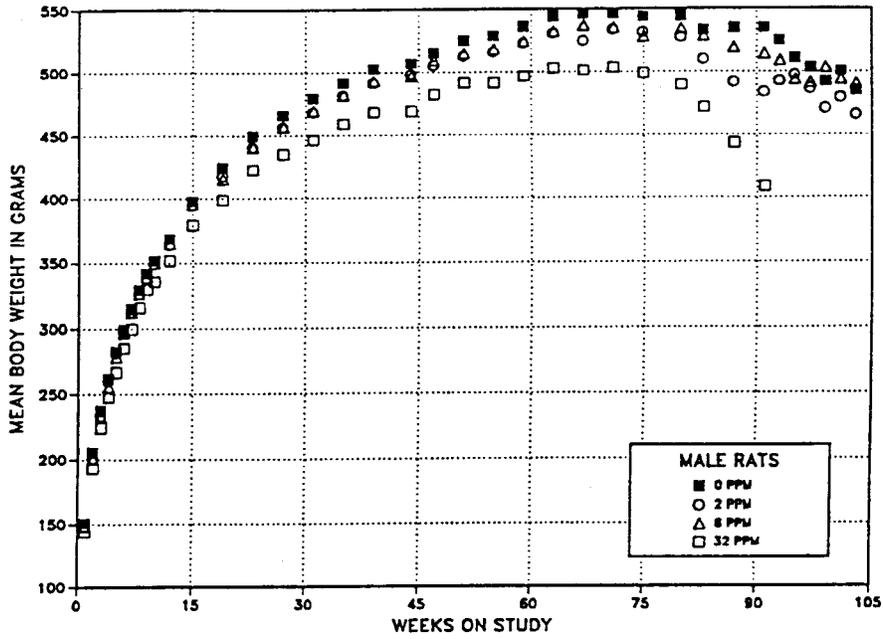


FIGURE 3
Growth Curves for Male and Female Rats
Administered Furfuryl Alcohol by Inhalation for 2 Years

Pathology and Statistical Analyses

This section describes the statistically significant or biologically noteworthy changes in the incidences of neoplasms and nonneoplastic lesions of the nose 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: One lateral wall adenoma was observed in a 2 ppm male and one in an 8 ppm female, one respiratory epithelium adenoma was observed in an 8 ppm male and one in a 32 ppm female, and one carcinoma of the respiratory epithelium and three squamous cell carcinomas were observed in 32 ppm males (Tables 9, A1, and B1). These incidences were not significantly greater than those in the chamber control groups, but squamous cell carcinoma has not been observed in male historical controls (Tables 9 and A4a). All of the neoplasms in the nose were of epithelial origin. The squamous cell carcinomas were masses of pleomorphic stratified squamous epithelium that became protrusions into the nasal cavity and also invaded the underlying lamina propria (Plate 1). The adenomas of the respiratory epithelium and the epithelium of the lateral wall consisted of proliferations of multiple glandular structures (Plate 2).

Furfuryl alcohol was irritating and toxic to the nose. All groups of exposed male and female rats had significantly increased incidences of nonneoplastic lesions in the nose (Tables 9, A5, and B5). In general, the severity increased

with increasing exposure concentration, but the overall architecture of the nasal turbinates was not distorted and the mucosal lining remained intact. Suppurative inflammation consisted of aggregates of neutrophils beneath the epithelial lining or within the nasal lumens. Hyperplastic Bowman's glands had multiple layers of polyhedral epithelium instead of the normal single layer. Hyperplasia of both the respiratory epithelium (Plate 3) and transitional epithelium of the lateral wall consisted of replacement of the normal single layer with multiple layers of polyhedral epithelium. Squamous metaplasia of the transitional epithelium of the lateral wall or of the respiratory epithelium generally occurred within hyperplastic areas and consisted of areas of keratinizing stratified squamous epithelium. Hyperplasia and squamous metaplasia represent conversion of highly specialized nasal epithelium to more resistant types of epithelium and represent adaptive responses to chronic irritation. Hyaline degeneration of both respiratory and olfactory epithelium is a common degenerative change consisting of cytoplasmic accumulations of eosinophilic refractile material. Atrophy of the olfactory epithelium was an attenuation of the normally tall pseudostratified columnar cells. Metaplasia of the olfactory epithelium often accompanied atrophy and consisted of replacement of neurosensory cells by ciliated respiratory-type epithelial cells. Hyperplasia of the olfactory epithelium consisted of replacement of the normally tall pseudostratified columnar cells by densely packed, somewhat disorganized neurosensory cells. Fibrosis of the olfactory epithelium sometimes accompanied hyperplasia. Fibrosis affected the connective tissue underlying olfactory epithelium and consisted of thin bundles of dense collagen.

TABLE 9
Incidences of Neoplasms and Nonneoplastic Lesions of the Nose in Rats in the 2-Year Inhalation Study of Furfuryl Alcohol

	Chamber Control	2 ppm	8 ppm	32 ppm
Male				
Number Examined Microscopically	50	50	50	50
Suppurative Inflammation ^a	3 (1.0) ^b	6 (1.5)	17** (1.7)	44** (2.1)
Glands, Hyperplasia	0	0	22** (1.0)	49** (2.3)
Lateral Wall, Hyperplasia	1 (1.0)	49** (1.5)	50** (2.4)	50** (3.5)
Lateral Wall, Squamous Metaplasia	1 (1.0)	1 (1.0)	8* (1.1)	33** (1.3)
Olfactory Epithelium, Atrophy	1 (1.0)	12** (1.1)	47** (1.8)	50** (2.4)
Olfactory Epithelium, Hyaline Degeneration	42 (1.3)	48 (1.5)	50** (2.6)	47 (2.7)
Olfactory Epithelium, Fibrosis	0	1 (1.0)	26** (1.0)	40** (2.0)
Olfactory Epithelium, Hyperplasia	0	1 (1.0)	42** (1.0)	40** (1.8)
Olfactory Epithelium, Metaplasia	1 (1.0)	8* (1.3)	37** (1.5)	49** (2.2)
Respiratory Epithelium, Hyaline Degeneration	12 (1.0)	14 (1.0)	45** (1.6)	3* (1.7)
Respiratory Epithelium, Hyperplasia	0	26** (1.8)	50** (2.5)	50** (3.5)
Respiratory Epithelium, Squamous Metaplasia	0	0	3 (1.0)	26** (1.4)
Lateral Wall, Adenoma	0	1	0	0
Respiratory Epithelium, Adenoma ^c	0	0	1	0
Respiratory Epithelium, Carcinoma ^d	0	0	0	1
Respiratory Epithelium, Squamous Cell Carcinoma ^d	0	0	0	3
Adenoma, Carcinoma, or Squamous Cell Carcinoma (Combined)	0	1	1	4*
Female				
Number Examined Microscopically	49	50	48	49
Suppurative Inflammation	4 (2.3)	1 (2.0)	5 (1.4)	23** (1.7)
Glands, Hyperplasia	0	0	24** (1.0)	46** (2.2)
Lateral Wall, Hyperplasia	0	39** (1.3)	48** (2.1)	49** (3.3)
Lateral Wall, Squamous Metaplasia	0	1 (1.0)	0	24** (1.0)
Olfactory Epithelium, Atrophy	0	6* (1.3)	44** (1.7)	49** (2.3)
Olfactory Epithelium, Hyaline Degeneration	43 (1.2)	50* (1.6)	47 (2.7)	48 (3.3)
Olfactory Epithelium, Fibrosis	0	0	16** (1.3)	31** (1.7)
Olfactory Epithelium, Hyperplasia	0	0	31** (1.2)	41** (1.5)
Olfactory Epithelium, Metaplasia	0	5* (1.2)	37** (1.5)	48** (2.2)
Respiratory Epithelium, Hyaline Degeneration	23 (1.0)	39** (1.2)	45** (1.9)	6** (2.0)
Respiratory Epithelium, Hyperplasia	0	18** (1.4)	40** (2.1)	49** (3.2)
Respiratory Epithelium, Squamous Metaplasia	0	0	2 (1.0)	10** (1.2)
Lateral Wall, Adenoma	0	0	1	0
Respiratory Epithelium, Adenoma ^e	0	0	0	1
Adenoma (Combined)	0	0	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

^c Historical incidence for 2-year NTP inhalation studies with untreated chamber controls (mean \pm standard deviation): 1/897 (0.1% \pm 0.5%); range, 0%-2%

^d Historical incidence: 0/897

^e Historical incidence: 1/892 (0.1% \pm 0.5%); range, 0%-2%

Kidney: One atypical nephroblastoma and one stromal nephroma occurred in male rats exposed to 8 ppm (Tables 10 and A1). Renal tubule adenomas were observed in one chamber control male, one 2 ppm male, two 8 ppm males, and two 32 ppm females, and one 2 ppm female had a renal tubule carcinoma. These incidences were within the historical control range for male rats but exceeded the historical control range for female rats (Tables 10, A4b, and B4b). Incidences of renal tubule hyperplasia in exposed rats were not significantly different from those in the chamber control groups (Tables 10, A5, and B5).

Kidney step sections provided approximately eight additional sections per animal to examine for additional proliferative lesions. Separate analyses of the additional lesions found in the step sections and of the combined lesions in original and step sections often provided significant additional information. Since the same large proliferative lesions may be present both on an original section and on subsequent step sections, such a lesion is only counted once in the combination analysis. Animals with proliferative lesions identified in the step-section review are listed in a separate document for the specific study, Report of the Special Pathology Working Group for Kidney Step Sections, which is available on request.

Step sections revealed the presence of one additional renal tubule adenoma in each of the chamber control, 2 ppm, and 8 ppm groups of males and four additional adenomas in 32 ppm males. Two adenomas were observed in 8 ppm females and one in a 32 ppm female, and a carcinoma was observed in a 2 ppm female. Additional hyperplasias were observed in all groups of males and females.

Renal tubule adenomas were small, discrete proliferations of epithelial cells that typically compressed the adjacent parenchyma. Adenomas were five or more renal tubule diameters in size and had no orientation to the tubule basement membrane. Hyperplasia of the renal tubule epithelium was a stratification of the normally single-layered epithelium with the maintenance of cellular orientation to the tubule basement membrane.

Nephropathy was present in virtually all of the animals in this study. Nephropathy is a common spontaneous renal disease of F344/N rats characterized by renal tubule epithelial necrosis and regeneration, interstitial fibrosis, inflammation, and renal tubule dysfunction. The severities of nephropathy relative to chamber controls were increased in 32 ppm males and females. Males exposed to 32 ppm had extrarenal signs of kidney failure including parathyroid gland hyperplasia and fibrous osteodystrophy (Tables 10 and A5).

TABLE 10
Incidences of Selected Neoplasms and Nonneoplastic Lesions in Rats in the 2-Year Inhalation Study of Furfuryl Alcohol

	Chamber Control	2 ppm	8 ppm	32 ppm
Male				
Kidney	50	50	50	50
Single Sections (Standard Evaluation)				
Mineralization ^a	2 (3.0) ^b	2 (3.0)	2 (4.0)	28** (3.3)
Nephropathy	50 (2.9)	49 (2.9)	50 (3.1)	50 (3.7)**
Renal Tubule, Hyperplasia	5 (2.8)	5 (2.0)	2 (1.5)	6 (2.5)
Nephroblastoma	0	0	1	0
Stromal Nephroma	0	0	1	0
Renal Tubule, Adenoma ^c	1	1	2	0

TABLE 10
Incidences of Selected Neoplasms and Nonneoplastic Lesions in Rats in the 2-Year Inhalation Study
of Furfuryl Alcohol

	Chamber Control		2 ppm		8 ppm		32 ppm	
Male (continued)								
Kidney (continued)	50		50		50		50	
Step Sections (Extended Evaluation)								
Renal Tubule, Hyperplasia	7	(1.7)	5	(2.0)	7	(2.3)	23**	(2.7)
Renal Tubule, Adenoma	1		1		1		4	
Single Sections and Step Sections (Combined)								
Renal Tubule, Hyperplasia	10	(2.4)	7	(2.3)	7	(2.3)	25**	(2.8)
Renal Tubule, Adenoma	2		2		3		4	
Parathyroid Gland	49		45		50		49	
Hyperplasia	9	(2.1)	5	(3.0)	12	(2.4)	39**	(3.6)
Bone	50		50		50		50	
Fibrous Osteodystrophy	2	(2.0)	5	(2.2)	6	(2.5)	34**	(3.2)
Female								
Kidney	50		49		49		50	
Single Sections (Standard Evaluation)								
Mineralization	0		1	(2.0)	0		0	
Nephropathy	47	(1.9)	45	(1.9)	47	(1.9)	47	(2.4)**
Renal Tubule, Hyperplasia	0		0		0		2	(2.5)
Renal Tubule, Adenoma ^d	0		0		0		2	
Renal Tubule, Carcinoma ^e	0		1		0		0	
Renal Tubule, Adenoma or Carcinoma ^f	0		1		0		2	
Step Sections (Extended Evaluation)								
Renal Tubule, Hyperplasia	2	(1.0)	1	(2.0)	3	(2.0)	9	(1.9)
Renal Tubule, Adenoma	0		0		2		1	
Renal Tubule, Carcinoma	0		1		0		0	
Renal Tubule, Adenoma or Carcinoma	0		1		2		1	
Single Sections and Step Sections (Combined)								
Renal Tubule, Hyperplasia	2	(1.0)	1	(2.0)	3	(2.0)	11*	(2.0)
Renal Tubule, Adenoma	0		0		2		2	
Renal Tubule, Carcinoma	0		1		0		0	
Renal Tubule, Adenoma or Carcinoma	0		1		2		2	

* Significantly different ($P \leq 0.05$) from the chamber control group by the Poly-3 test

** Significantly different ($P \leq 0.01$) from the chamber control group by the Poly-3 test (incidences) or Mann-Whitney U test (severities)

^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 NTP inhalation studies with untreated chamber controls (mean \pm standard deviation): 9/902 (1.0% \pm 1.2%); range, 0%-4%

^d Historical incidence: 1/898 (0.1% \pm 0.5%); range, 0%-2%

^e Historical incidence: 4/898 (0.5% \pm 0.9%); range, 0%-2%

^f Historical incidence: 5/898 (0.6% \pm 0.9%); range, 0%-2%

MICE**16-DAY STUDY**

All male and female mice exposed to 250 ppm died by day 4 of the study, and one female mouse exposed to 125 ppm died on day 14 (Table 11). Final mean body

weights and body weight gains of male and female mice exposed to 63 or 125 ppm were significantly less than those of the chamber control groups.

TABLE 11
Survival and Body Weights of Mice in the 16-Day Inhalation Study of Furfuryl Alcohol

Concentration (ppm)	Survival ^a	Mean Body Weight ^b (g)			Final Weight Relative to Controls (%)
		Initial	Final	Change	
Male					
0	5/5	24.0 ± 0.4	27.8 ± 0.5	3.8 ± 0.4	
16	5/5	24.2 ± 0.4	28.5 ± 0.3	4.3 ± 0.5	102
31	5/5	23.9 ± 0.3	27.8 ± 0.7	4.0 ± 0.6	100
63	5/5	24.2 ± 0.4	25.8 ± 0.3*	1.6 ± 0.3**	93
125	5/5	24.1 ± 0.4	24.5 ± 0.7**	0.4 ± 0.3**	88
250	0/5 ^c	23.9 ± 0.4	—	—	—
Female					
0	5/5	19.5 ± 0.4	22.6 ± 0.3	3.1 ± 0.3	
16	5/5	20.2 ± 0.3	23.2 ± 0.3	3.0 ± 0.1	103
31	5/5	19.3 ± 0.3	22.6 ± 0.4	3.3 ± 0.3	100
63	5/5	19.9 ± 0.4	21.1 ± 0.3**	1.3 ± 0.2**	93
125	4/5 ^d	19.5 ± 0.3	19.9 ± 0.2**	0.5 ± 0.3**	88
250	0/5 ^e	19.4 ± 0.4	—	—	—

* Significantly different ($P \leq 0.05$) from the chamber control group by Williams' or Dunnett's test

** $P \leq 0.01$

^a Number of animals surviving at 16 days/number initially in group

^b Weights and weight changes are given as mean ± standard error. No final mean body weights were calculated for groups with 100% mortality. Subsequent calculations are based on animals surviving to the end of the study.

^c Day of death: 3, 4, 4, 4

^d Day of death: 14

^e Day of death: 2

Absolute heart and kidney weights of 63 and 125 ppm males and females and absolute thymus weights of 125 ppm males and females were significantly less than those of the chamber controls (Table G3). These differences were attributed to the lower body weights of these groups. All exposed animals except one 16 ppm male had histologic changes in the nasal respiratory

epithelium and/or olfactory epithelium (Table 12). The severities of exposure-related changes increased with increasing exposure concentration. Although a no-observable-effect level for furfuryl alcohol-induced nasal alterations was not achieved in this study, most changes that occurred in mice exposed to 16 ppm were minimal.

TABLE 12
Incidences of Nonneoplastic Lesions of the Nose in Mice in the 16-Day Inhalation Study of Furfuryl Alcohol

	Chamber Control	16 ppm	31 ppm	63 ppm	125 ppm	250 ppm
Male						
Number Examined Microscopically	5	5	5	5	5	5
Acute and/or Suppurative Inflammation ^a	0	0	0	2 (1.0) ^b	4* (1.5)	5** (4.0)
Respiratory Epithelium, Necrosis	0	0	2 (1.0)	2 (1.0)	0	5** (4.0)
Respiratory Epithelium, Squamous Metaplasia	0	3 (1.0)	5** (1.0)	5** (1.0)	5** (1.6)	0
Olfactory Epithelium, Necrosis	0	0	1 (1.0)	4* (1.0)	4* (1.8)	2 (2.5)
Olfactory Epithelium, Degeneration	0	3 (1.0)	5** (2.8)	5** (3.4)	5** (3.4)	0
Female						
Number Examined Microscopically	5	5	5	5	5	5
Acute and/or Suppurative Inflammation	0	0	0	3 (1.0)	5** (1.8)	5** (2.2)
Respiratory Epithelium, Necrosis	0	0	1 (1.0)	2 (1.0)	4* (1.0)	5** (3.4)
Respiratory Epithelium, Squamous Metaplasia	0	3 (1.0)	5** (1.0)	5** (1.2)	5** (1.8)	0
Olfactory Epithelium, Necrosis	0	0	2 (1.0)	5** (1.4)	5** (1.2)	1 (2.0)
Olfactory Epithelium, Degeneration	0	5** (1.6)	5** (3.2)	5** (3.4)	5** (3.2)	1 (2.0)

* Significantly different ($P < 0.05$) from the chamber control group by the Fisher exact test

** $P < 0.01$

^a Number of animals with lesion

^b Average severity grade of lesions in affected animals: 1=minimal, 2=mild, 3=moderate, 4=marked

14-WEEK STUDY

All mice survived to the end of the study (Table 13). The final mean body weight and body weight gain of male mice exposed to 2 ppm were significantly greater

than those of the chamber control group. There were no exposure-related clinical findings.

TABLE 13
Survival and Body Weights of Mice in the 14-Week Inhalation Study of Furfuryl Alcohol

Concentration (ppm)	Survival ^a	Mean Body Weight ^b (g)			Final Weight Relative to Controls (%)
		Initial	Final	Change	
Male					
0	10/10	24.1 ± 0.4	33.1 ± 0.6	9.0 ± 0.6	
2	10/10	24.4 ± 0.2	36.0 ± 0.7*	11.7 ± 0.6*	109
4	10/10	24.1 ± 0.3	35.2 ± 0.8	11.1 ± 0.6	106
8	10/10	24.4 ± 0.4	35.5 ± 0.8	11.2 ± 0.7	107
16	10/10	24.6 ± 0.4	35.5 ± 0.5	10.9 ± 0.5	107
32	10/10	23.9 ± 0.2	32.7 ± 0.7	8.9 ± 0.7	99
Female					
0	10/10	19.2 ± 0.4	30.1 ± 0.8	10.9 ± 0.6	
2	10/10	19.4 ± 0.4	30.7 ± 0.9	11.3 ± 0.7	102
4	10/10	19.1 ± 0.3	30.6 ± 0.9	11.5 ± 0.8	102
8	10/10	19.2 ± 0.3	30.4 ± 0.9	11.3 ± 0.7	101
16	10/10	19.2 ± 0.3	30.6 ± 0.8	11.5 ± 0.7	102
32	10/10	19.3 ± 0.4	28.9 ± 0.7	9.6 ± 0.6	96

* Significantly different ($P \leq 0.05$) from the chamber control group by Williams' or Dunnett's test

^a Number of animals surviving at 14 weeks/number initially in group

^b Weights and weight changes are given as mean ± standard error.

Absolute and relative heart weights of 32 ppm males and the absolute heart weight of 32 ppm females were significantly less than those of the chamber controls (Table G4). There were no significant differences in sperm motility or vaginal cytology parameters between chamber control and exposed mice (Tables H3 and H4).

Exposure-related histologic changes included degeneration, metaplasia, and chronic inflammation of the olfactory epithelium; hyaline droplets of the respiratory epithelium; and squamous metaplasia of the submucosal gland of the cuboidal epithelium (Table 14).

TABLE 14
Incidences of Nonneoplastic Lesions of the Nose in Mice in the 14-Week Inhalation Study of Furfuryl Alcohol

	Chamber Control	2 ppm	4 ppm	8 ppm	16 ppm	32 ppm
Male						
Number Examined Microscopically	10	10	10	10	10	10
Olfactory Epithelium, Degeneration ^a	0	4* (1.0) ^b	5* (1.0)	9** (1.4)	10** (2.3)	10** (2.7)
Olfactory Epithelium, Metaplasia	0	4* (1.0)	2 (1.0)	4* (1.5)	10** (2.3)	10** (2.7)
Olfactory Epithelium, Chronic Inflammation	0	0	4* (1.0)	8** (1.1)	10** (1.4)	10** (1.6)
Respiratory Epithelium, Hyaline Droplets	0	2 (1.0)	3 (1.0)	3 (1.0)	9** (1.2)	10** (1.5)
Cuboidal Epithelium, Submucosal Gland, Squamous Metaplasia	0	0	0	4* (1.0)	9** (1.0)	10** (1.0)
Female						
Number Examined Microscopically	10	10	10	10	10	10
Olfactory Epithelium, Degeneration	0	3 (1.0)	8** (1.1)	10** (1.7)	10** (2.9)	10** (3.1)
Olfactory Epithelium, Metaplasia	0	2 (1.0)	2 (1.0)	8** (1.4)	10** (2.8)	10** (3.0)
Olfactory Epithelium, Chronic Inflammation	0	0	1 (1.0)	10** (1.0)	10** (1.0)	10** (2.0)
Respiratory Epithelium, Hyaline Droplets	0	8** (1.3)	9** (1.1)	10** (1.5)	10** (3.0)	10** (2.9)
Cuboidal Epithelium, Submucosal Gland, Squamous Metaplasia	0	0	0	1 (1.0)	5* (1.0)	10** (1.0)

* Significantly different ($P \leq 0.05$) from the chamber control group by the Fisher exact 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

Exposure Concentration Selection Rationale: The selection of exposure concentrations for the 2-year mouse study was based on the incidences and severities of alterations in the nasal mucosa associated with exposure to furfuryl alcohol. In mice, exposure-related changes in the olfactory and respiratory epithelium were observed in all exposed groups. During the 14-week study, the incidences and severities of changes in the nasal mucosa increased with increasing exposure concentration up to 8 ppm but changed very little between 16 and 32 ppm. Although the lesions were somewhat more severe at the end of the 14-week study than those observed in the 16-day study at comparable exposure concen-

trations, they were within the mild to moderate range of severities and it was considered unlikely that they would progress to become life-threatening during a 2-year study. Therefore, 32 ppm was selected as the high exposure concentration for the 2-year mouse study. A no-observable-effect level was not achieved in either the 16-day or 14-week studies. Since the three lowest concentrations in the 14-week study were below the currently recommended TLVs for occupational exposure, lower concentrations of 2 and 8 ppm were selected for the 2-year study. This provided three concentrations over a range that covered documented occupational exposures.

2-YEAR STUDY

Survival

Estimates of 2-year survival probabilities for male and female mice are shown in Table 15 and in the Kaplan-Meier survival curves (Figure 4). Survival of exposed males and females was similar to that of the chamber control groups.

Body Weights and Clinical Findings

Mean body weights of exposed males were generally similar to those of the chamber control group throughout the study. Mean body weights of females exposed to 2, 8, or 32 ppm were less than those of the chamber control group beginning at weeks 59, 59, or 39, respectively (Figure 5; Tables 16 and 17). Female mice exposed to 32 ppm developed focal corneal opacities.

TABLE 15
Survival of Mice in the 2-Year Inhalation Study of Furfuryl Alcohol

	Chamber Control	2 ppm	8 ppm	32 ppm
Male				
Animals initially in study	50	50	50	50
Moribund	11	10	14	8
Natural deaths	5	4	6	4
Animals surviving to study termination	34	36	30	38
Percent probability of survival at end of study ^a	68	72	60	76
Mean survival (days) ^b	688	682	656	705
Survival analysis ^c	P=0.351N	P=0.838N	P=0.410	P=0.431N
Female				
Animals initially in study	50	50	50	50
Accidental deaths ^d	0	1	1	0
Pregnant ^d	0	1	0	0
Moribund	11	12	15	8
Natural deaths	5	3	2	2
Animals surviving to study termination	34	33	32	40
Percent probability of survival at end of study	68	69	66	80
Mean survival (days)	690	685	690	715
Survival analysis	P=0.145N	P=1.000N	P=1.000	P=0.212N

^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

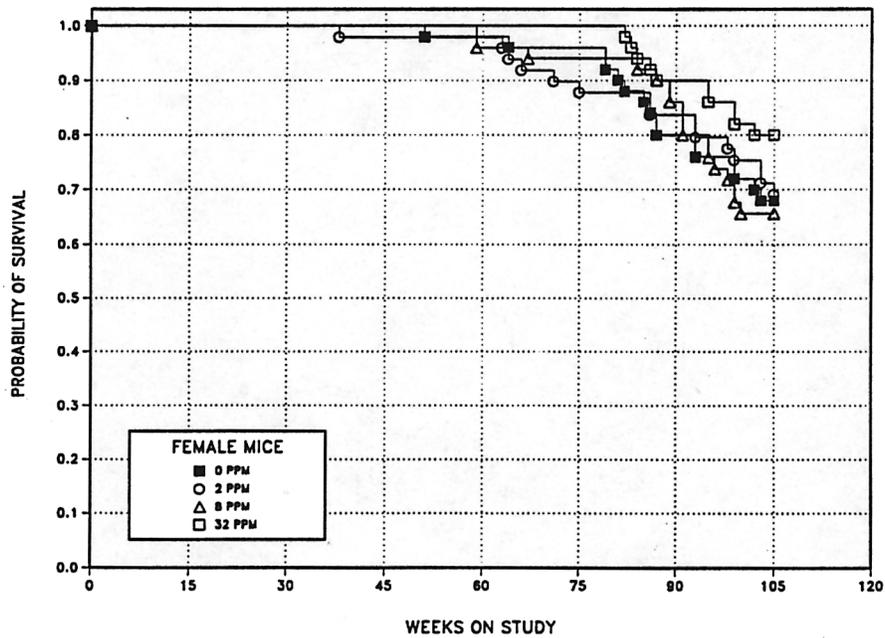
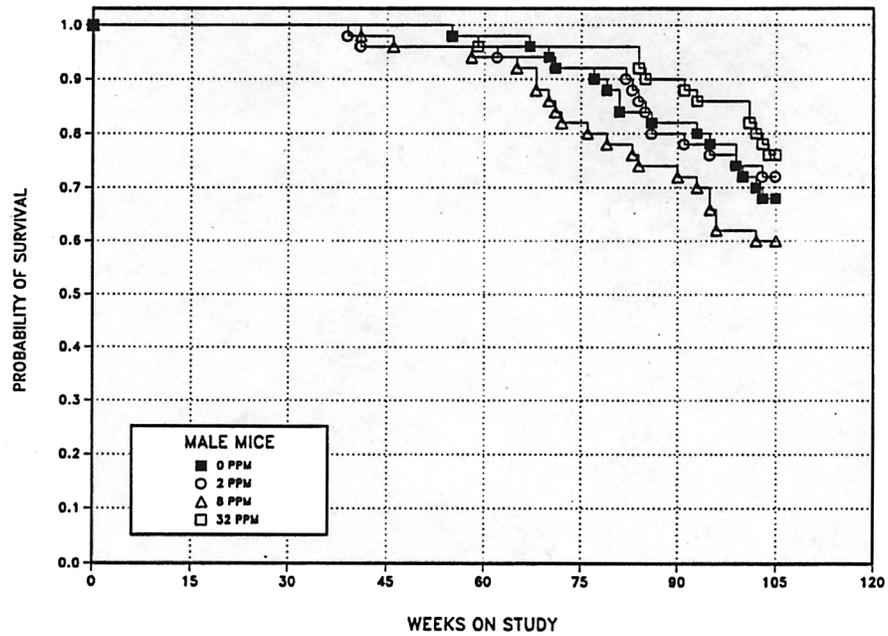


FIGURE 4
Kaplan-Meier Survival Curves for Male and Female Mice
Administered Furfuryl Alcohol by Inhalation for 2 Years

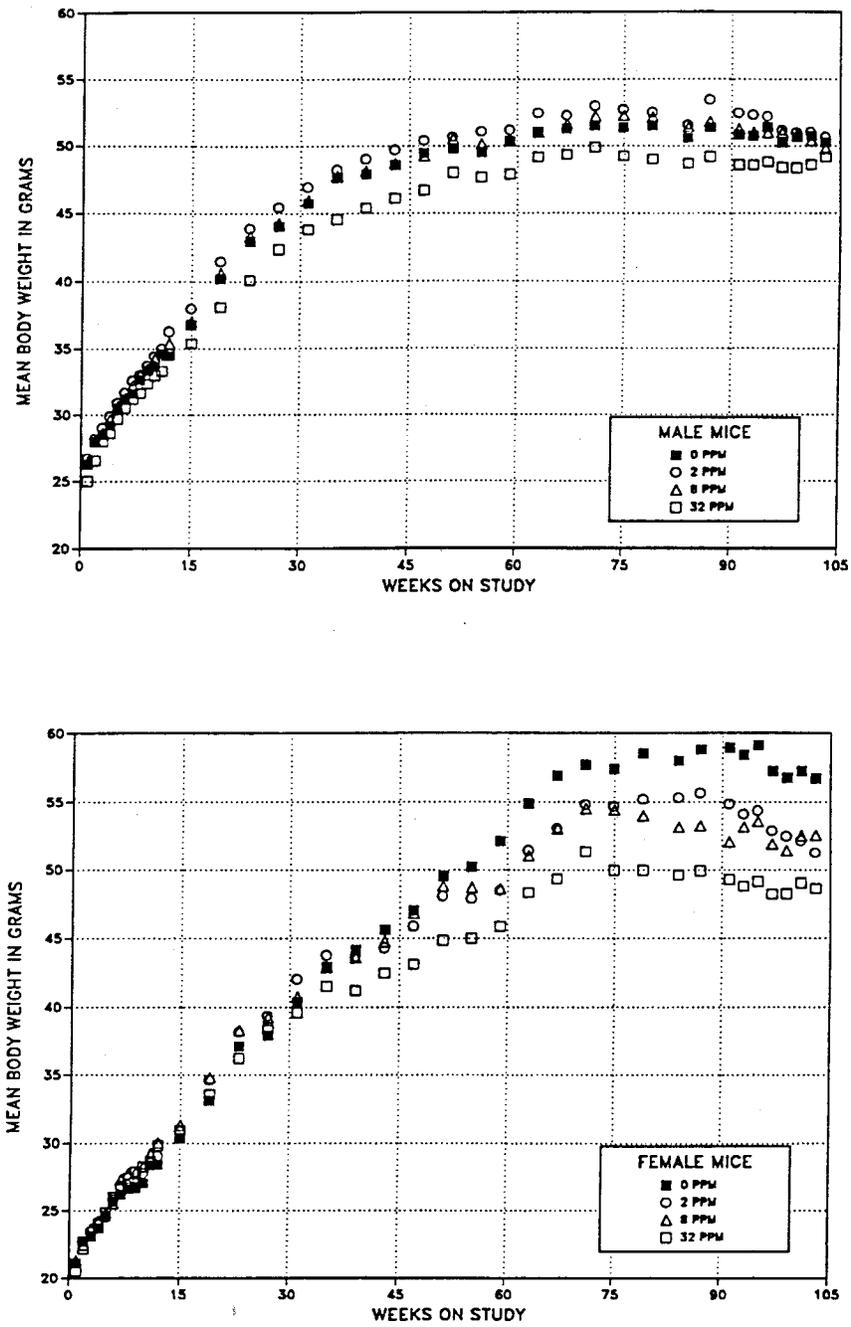


FIGURE 5
Growth Curves for Male and Female Mice
Administered Furfuryl Alcohol by Inhalation for 2 Years

TABLE 16
Mean Body Weights and Survival of Male Mice in the 2-Year Inhalation Study of Furfuryl Alcohol

Weeks on Study	Chamber Control		2 ppm			8 ppm			32 ppm		
	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	26.3	50	26.7	102	50	26.5	101	50	25.0	95	50
2	27.9	50	28.2	101	50	28.1	101	50	26.6	95	50
3	28.5	50	29.1	102	50	28.7	101	50	28.0	98	50
4	29.2	50	29.9	102	50	29.7	102	50	28.6	98	50
5	30.5	50	30.9	101	50	30.7	101	50	29.7	97	50
6	31.1	50	31.7	102	50	31.3	101	50	30.5	98	50
7	31.6	50	32.6	103	50	32.2	102	50	31.2	99	50
8	32.6	50	33.0	101	50	33.0	101	50	31.6	97	50
9	33.3	50	33.7	101	50	33.5	101	50	32.3	97	50
10	33.6	50	34.4	102	50	34.2	102	50	33.0	98	50
11	34.6	50	35.0	101	50	34.5	100	50	33.3	96	50
12	34.5	50	36.3	105	50	35.4	103	50	34.6	100	50
15	36.8	50	38.0	103	50	37.1	101	50	35.4	96	50
19	40.2	50	41.5	103	50	40.6	101	50	38.1	95	50
23	43.0	50	43.9	102	50	43.3	101	50	40.1	93	50
27	44.0	50	45.4	103	50	44.3	101	50	42.4	96	50
31	45.7	50	47.0	103	50	46.0	101	50	43.8	96	50
35	47.7	50	48.3	101	50	47.8	100	50	44.6	94	50
39	47.9	50	49.0	102	48	48.1	100	50	45.4	95	50
43	48.6	50	49.7	102	47	48.7	100	49	46.1	95	50
47	49.4	50	50.4	102	48	49.2	100	48	46.7	95	50
51	49.8	50	50.7	102	48	50.6	102	48	48.0	96	50
55	49.5	50	51.1	103	48	50.2	101	48	47.7	96	49
59	50.4	49	51.2	102	48	50.4	100	47	47.9	95	49
63	51.1	49	52.5	103	47	51.0	100	47	49.2	96	48
67	51.3	48	52.3	102	47	51.7	101	46	49.4	96	48
71	51.5	47	53.0	103	47	52.3	102	43	49.9	97	48
75	51.4	46	52.8	103	46	52.3	102	41	49.2	96	48
79	51.6	44	52.6	102	46	52.2	101	39	49.0	95	48
84	50.6	42	51.6	102	44	51.5	102	38	48.7	96	48
87	51.4	41	53.5	104	40	51.9	101	37	49.2	96	45
91	50.9	41	52.5	103	39	51.3	101	36	48.6	96	45
93	50.7	41	52.4	103	39	51.0	101	36	48.6	96	43
95	51.4	39	52.3	102	39	51.0	99	35	48.8	95	43
97	50.2	39	51.2	102	38	51.0	102	31	48.4	96	43
99	50.6	37	51.0	101	38	50.9	101	31	48.4	96	43
101	50.7	36	51.1	101	37	50.4	99	31	48.6	96	43
103	50.3	35	50.7	101	36	49.8	99	30	49.2	98	39
Mean for weeks											
1-13	31.1		31.8	102		31.5	101		30.4	98	
14-52	45.3		46.4	102		45.6	101		43.1	95	
53-103	50.9		52.0	102		51.2	101		48.8	96	

TABLE 17
Mean Body Weights and Survival of Female Mice in the 2-Year Inhalation Study of Furfuryl Alcohol

Weeks on Study	Chamber Control		2 ppm			8 ppm			32 ppm		
	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	21.1	50	21.2	101	49	21.4	101	50	20.6	98	50
2	22.7	50	22.8	100	49	22.5	99	50	22.2	98	50
3	23.1	50	23.5	102	49	23.7	103	50	23.2	100	50
4	23.7	50	24.2	102	49	24.3	103	50	23.9	101	50
5	24.6	50	24.5	100	49	24.8	101	50	24.9	101	50
6	25.7	50	25.8	100	49	25.5	99	50	26.0	101	50
7	26.2	50	26.9	103	49	27.3	104	50	26.8	102	50
8	26.6	50	26.9	101	49	27.8	105	50	27.4	103	50
9	26.7	50	26.8	100	49	27.8	104	50	27.9	105	50
10	27.0	50	27.8	103	49	28.3	105	50	28.3	105	50
11	28.4	50	28.6	101	49	29.2	103	50	28.7	101	50
12	28.4	50	29.1	103	49	30.0	106	50	29.8	105	50
15	30.4	50	30.9	102	49	31.3	103	50	30.9	102	50
19	33.1	50	34.7	105	49	34.8	105	50	33.6	102	50
23	37.1	50	38.2	103	49	38.3	103	50	36.2	98	50
27	37.9	50	39.4	104	49	39.2	103	50	38.3	101	50
31	40.4	50	42.1	104	49	40.8	101	50	39.6	98	50
35	42.9	50	43.8	102	49	42.9	100	50	41.6	97	50
39	44.2	50	43.7	99	48	43.6	99	50	41.2	93	50
43	45.6	50	44.3	97	48	44.8	98	50	42.5	93	50
47	47.0	50	45.9	98	48	46.8	100	50	43.1	92	50
51	49.5	49	48.1	97	48	48.8	99	50	44.9	91	50
55	50.2	49	47.9	95	48	48.7	97	50	45.0	90	50
59	52.1	49	48.5	93	48	48.6	93	49	45.9	88	50
63	54.9	49	51.4	94	48	51.0	93	48	48.3	88	50
67	56.9	48	53.1	93	45	53.0	93	47	49.3	87	50
71	57.7	48	54.8	95	45	54.6	95	47	51.3	89	50
75	57.4	48	54.7	95	44	54.5	95	47	50.0	87	50
79	58.5	46	55.2	94	43	54.0	92	47	50.0	86	50
84	58.0	44	55.3	95	43	53.1	92	47	49.6	86	48
87	58.8	41	55.7	95	41	53.2	91	45	49.9	85	46
91	58.9	40	54.9	93	41	52.1	89	42	49.3	84	45
93	58.4	40	54.1	93	39	53.2	91	39	48.8	84	45
95	59.1	38	54.4	92	39	53.6	91	39	49.1	83	44
97	57.3	38	52.9	92	39	51.9	91	36	48.2	84	43
99	56.8	37	52.5	92	36	51.4	91	35	48.2	85	42
101	57.2	36	52.2	91	36	52.5	92	32	49.0	86	41
103	56.7	34	51.3	91	36	52.6	93	32	48.6	86	40
Mean for weeks											
1-13	25.4		25.7	101		26.1	103		25.8	102	
14-52	40.8		41.1	101		41.1	101		39.2	96	
53-103	56.8		53.1	93		52.4	92		48.8	86	

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 kidney, nose, and eye. 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 C for male mice and Appendix D for female mice.

Kidney: Male mice exposed to 32 ppm had increased numbers of renal tubule neoplasms (Tables 18 and C1). The incidences of renal tubule adenoma, carcinoma, and adenoma or carcinoma (combined) in males were not significantly greater than in the chamber control group

TABLE 18
Incidences of Neoplasms and Nonneoplastic Lesions of the Kidney in Mice in the 2-Year Inhalation Study of Furfuryl Alcohol

	Chamber Control		2 ppm		8 ppm		32 ppm	
Male								
Number Examined Microscopically	50		49		49		50	
Single Sections (Standard Evaluation)								
Nephropathy ^a	49	(1.2) ^b	48	(1.4)	43	(1.5)	47	(1.8)
Renal Tubule, Degeneration	0		0		1	(1.0)	48**	(1.0)
Renal Tubule, Hyperplasia	1	(1.0)	3	(1.0)	0		3	(1.7)
Renal Tubule, Adenoma ^c	0		0		0		2	
Renal Tubule, Carcinoma ^d	0		0		0		2	
Renal Tubule, Adenoma or Carcinoma ^e	0		0		0		4	
Step Sections (Extended Evaluation)								
Renal Tubule, Hyperplasia	3	(1.7)	5	(1.0)	3	(1.0)	2	(2.5)
Renal Tubule, Adenoma	0		0		0		1	
Renal Tubule, Carcinoma	0		0		0		0	
Renal Tubule, Adenoma or Carcinoma	0		0		0		0	
Single Sections and Step Sections (Combined)								
Renal Tubule, Hyperplasia	4	(1.5)	8	(1.0)	3	(1.0)	5	(2.0)
Renal Tubule, Adenoma	0		0		0		3	
Renal Tubule, Carcinoma	0		0		0		2	
Renal Tubule, Adenoma or Carcinoma	0		0		0		5*	
Female								
Number Examined Microscopically	50		48		49		49	
Nephropathy	41	(1.0)	35	(1.1)	40	(1.2)	39	(1.0)

* Significantly different ($P < 0.05$) 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

^c Historical incidence for 2-year NTP inhalation studies with untreated chamber controls (mean \pm standard deviation): 3/1,093 (0.3% \pm 0.6%); range, 0%-2%

^d Historical incidence: 1/1,093 (0.1% \pm 0.4%); range, 0%-2%

^e Historical incidence: 4/1,093 (0.4% \pm 1.0%); range, 0%-4%

but exceeded historical control ranges for inhalation studies (Tables 18 and C4), and the incidence of renal tubule adenoma or carcinoma (combined) occurred with a positive trend (Table C3). Step sectioning revealed the presence of additional hyperplasias in chamber control and exposed groups and one adenoma in 32 ppm male mice. Renal tubule adenomas were small, discrete (approximately 1 mm in diameter) proliferations of epithelial cells in clusters and tubular structures (Plate 4). Renal tubule carcinomas were 1- to 2-cm-diameter masses that replaced much of the kidney. Carcinomas had solid, highly pleomorphic clusters of cells.

Nephropathy was observed in all groups of male and female mice (Tables 18, C5, and D4). The severity of nephropathy increased with increasing exposure concentration in male mice. Nephropathy consisted of necrosis and regeneration of renal tubule epithelium and inflammation and fibrosis in the interstitium. The incidence of renal tubule degeneration in male mice exposed to 32 ppm was significantly greater than in the chamber control group. Renal tubule degeneration was separately diagnosed and consisted of slightly distended tubules with lumens containing eosinophilic, finely granular material. Some degenerate tubules had one to a few enlarged epithelial cells with large, sometimes pleomorphic, nuclei.

Nose: There were no exposure-related neoplasms in the nose of males or females. Incidences of a variety of nonneoplastic histologic changes in the nose were significantly greater in all exposed groups than in the

chamber control groups (Tables 19, C5, and D4). Furfuryl alcohol was irritating and toxic to the nose. Suppurative inflammation consisted of aggregates of neutrophils beneath the epithelial lining or within the nasal lumens. Hyperplastic Bowman's glands had multiple layers of polyhedral epithelium instead of the normal single layer. Metaplasia of Bowman's glands generally affected the ducts, which had replacement of the normally cuboidal epithelium by squamous epithelium. Metaplasia of both the respiratory epithelium and the transitional epithelium of the lateral wall consisted of replacement of the normal single layer of cuboidal or columnar cells by areas of stratified squamous epithelium. Squamous metaplasia represents conversion of highly specialized nasal epithelium to a more resistant type of epithelium and represents adaptive responses to chronic irritation. Hyaline degeneration of both respiratory and olfactory epithelium was increased in all exposed groups. Atrophy of the olfactory epithelium was an attenuation of the normally tall pseudostratified columnar cells. Metaplasia of the olfactory epithelium often accompanied atrophy and consisted of replacement of neurosensory cells by ciliated respiratory-type epithelial cells. Necrosis of respiratory epithelium was observed in only a very few mice, but regeneration of the respiratory epithelium was increased in 8 and 32 ppm male and female mice. Despite the numerous nonneoplastic alterations in the nasal epithelium of exposed mice, the overall architecture of the nasal turbinates was not distorted. Except for the very few mice with focal necrosis of the respiratory epithelium, the mucosa lining remained intact.

TABLE 19
Incidences of Nonneoplastic Lesions of the Nose in Mice in the 2-Year Inhalation Study
of Furfuryl Alcohol

	Chamber		2 ppm	8 ppm	32 ppm
	Control				
Male					
Number Examined Microscopically	50		49	49	50
Suppurative Inflammation ^a	7 (1.4) ^b		11 (1.2)	27** (1.3)	28** (1.7)
Glands, Hyperplasia	0		10** (1.0)	48** (1.8)	46** (3.3)
Glands, Squamous Metaplasia	0		6* (1.0)	35** (1.1)	47** (1.5)
Lateral Wall, Squamous Metaplasia	0		9** (1.0)	10** (1.7)	20** (1.5)
Olfactory Epithelium, Atrophy	3 (1.0)		15** (1.2)	49** (2.2)	50** (3.6)
Olfactory Epithelium, Hyaline Degeneration	2 (1.5)		3 (1.7)	21** (1.3)	39** (2.0)
Olfactory Epithelium, Metaplasia	0		12** (1.1)	49** (2.1)	50** (3.5)
Respiratory Epithelium, Hyaline Degeneration	5 (1.0)		18** (1.1)	42** (1.3)	45** (1.2)
Respiratory Epithelium, Squamous Metaplasia	0		2 (1.0)	10** (1.1)	20** (1.4)
Respiratory Epithelium, Necrosis	1 (2.0)		0	0	1 (1.0)
Respiratory Epithelium, Regeneration	0		1 (1.0)	13** (1.0)	21** (1.0)
Female					
Number Examined Microscopically	50		48	49	50
Suppurative Inflammation	5 (1.2)		12* (1.1)	25** (1.5)	42** (2.0)
Glands, Hyperplasia	0		33** (1.1)	46** (2.8)	47** (3.1)
Glands, Squamous Metaplasia	1 (1.0)		1 (1.0)	34** (1.1)	46** (1.5)
Lateral Wall, Squamous Metaplasia	3 (1.0)		14** (1.4)	16** (1.4)	36** (1.9)
Olfactory Epithelium, Atrophy	2 (1.0)		35** (1.2)	49** (3.0)	50** (3.6)
Olfactory Epithelium, Hyaline Degeneration	7 (1.3)		14 (1.4)	28** (1.8)	45** (2.2)
Olfactory Epithelium, Metaplasia	0		31** (1.2)	49** (3.0)	49** (3.6)
Respiratory Epithelium, Hyaline Degeneration	19 (1.4)		44** (1.5)	49** (1.3)	48** (1.4)
Respiratory Epithelium, Squamous Metaplasia	1 (1.0)		9** (1.8)	21** (1.7)	39** (1.9)
Respiratory Epithelium, Necrosis	0		0	2 (2.5)	3 (1.3)
Respiratory Epithelium, Regeneration	0		0	9** (1.0)	13** (1.2)

* 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

Eye: There was a high incidence of degeneration of the cornea in 32 ppm female mice (3/49, 1/49, 4/49, 26/50; Table D4). Corneal degeneration consisted of mineralization of the stroma immediately beneath the corneal epithelium (Plate 5). Mineralization was positive in a von Kossa stain for minerals and an X-ray elemental

analysis which showed peaks for both calcium and phosphorus. In more severe cases, there was thickening (hyperplasia) and/or ulceration of the overlying epithelium and/or a slight infiltrate of inflammatory cells at the site of mineralization.

GENETIC TOXICOLOGY

Furfuryl alcohol (33-10,000 µg/plate) was not mutagenic in *Salmonella typhimurium* strain TA98, TA100, TA1535, or TA1537, with or without S9 metabolic activation enzymes (Mortelmans *et al.*, 1986; Table E1). It did induce sister chromatid exchanges in cultured Chinese hamster ovary cells in each of two trials conducted in the absence of S9 (Table E2). In the second trial without S9, significant cell cycle delay occurred at the highest dose (500 µg/mL) requiring harvest of additional cells at a later time (31 hours culture time) to provide sufficient cells for analysis. No induction of sister chromatid exchanges was noted following treatment with furfuryl alcohol in the presence of S9. Furfuryl alcohol did not induce chromosomal aberrations in cultured Chinese hamster ovary cells treated with furfuryl alcohol in the absence of S9, but in the presence of S9, an equivocal result was obtained (Table E3). In the chromosomal aberrations test with S9, the first trial

showed a clear dose-related increase in aberrations, with significant elevations seen at 500 and 1,000 µg/mL. Results of the second trial were negative, and the assay overall was determined to be equivocal. *In vivo*, no induction of sister chromatid exchanges (Table E4), chromosomal aberrations (Table E5), or micronuclei (Table E6) was noted in bone marrow cells of male B6C3F₁ mice after administration of furfuryl alcohol by intraperitoneal injection. In the chromosomal aberrations test, results of the initial 36-hour trial were positive (P=0.003). However, results of two additional 36-hour trials were negative and the assay was concluded to be negative overall.

In conclusion, with the exception of the positive response observed in the sister chromatid exchange test in cultured Chinese hamster ovary cells *in vitro*, no indication of genetic activity was seen with furfuryl alcohol.

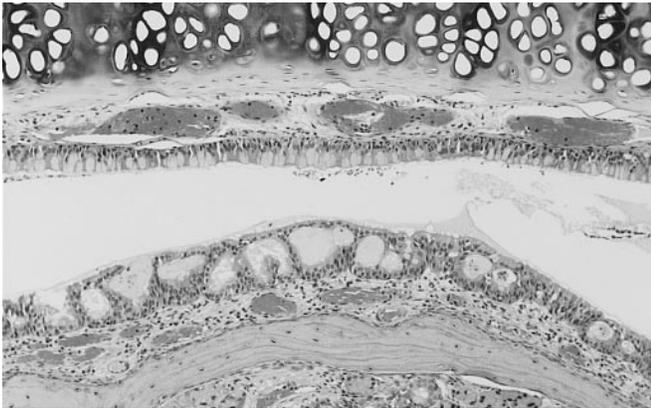


PLATE 1

Nose from a male F344 rat exposed to 32 ppm furfuryl alcohol via inhalation for 2 years. There is a squamous cell carcinoma of the respiratory epithelium along the nasal septum. This solid proliferation of keratinizing squamous epithelium shows limited invasion of the underlying tissue but the cells are strikingly disorganized. H&E; 25 ×

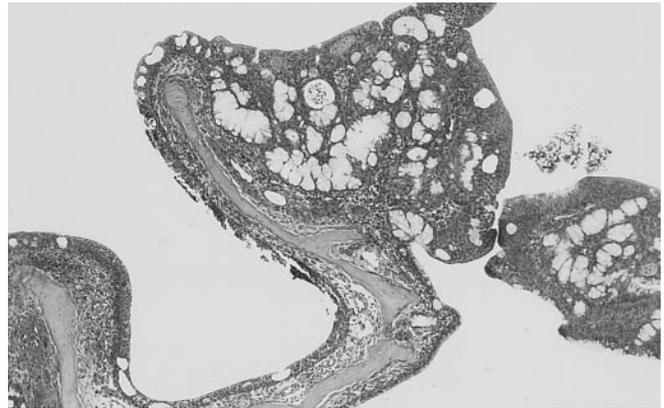


PLATE 2

Nose from a male F344 rat exposed to 8 ppm furfuryl alcohol via inhalation for 2 years. Adenoma of the respiratory epithelium consists of a single neoplastic proliferation protruding from the nasal turbinate (the separation is an artefact). H&E; 20 ×

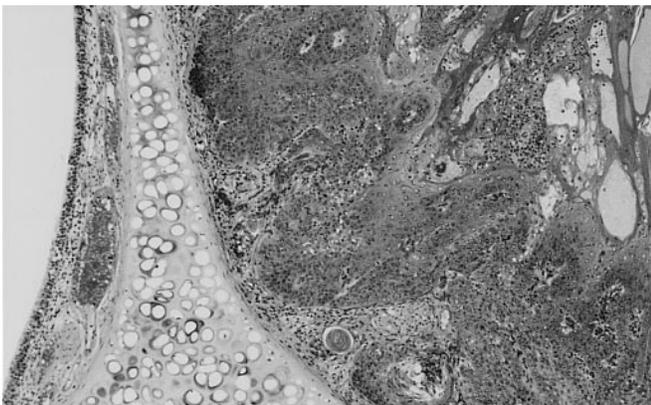


PLATE 3

Nose from a male F344 rat exposed to 32ppm furfuryl alcohol via inhalation for 2 years. Compare the hyperplasia of the respiratory epithelium to the more normal single layer of columnar epithelium on the septum (top). The hyperplastic epithelium has additional cell layers and forms cyst-like spaces. H&E; 33 ×

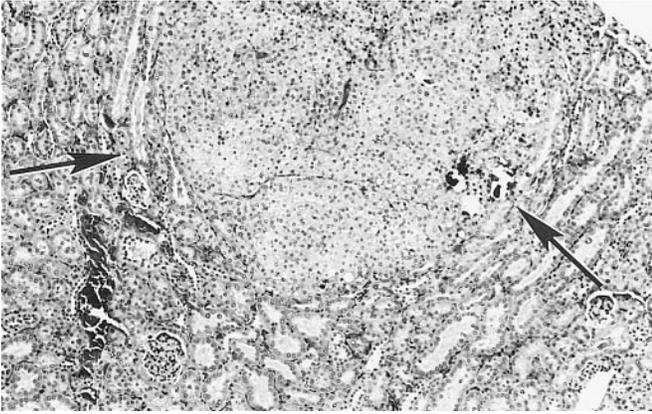


PLATE 4

Kidney from a male B6C3F1 mouse exposed to 32 ppm furfuryl alcohol via inhalation for 2 years. A renal tubule adenoma compresses (arrows) the surrounding parenchyma. H&E; 25 ×

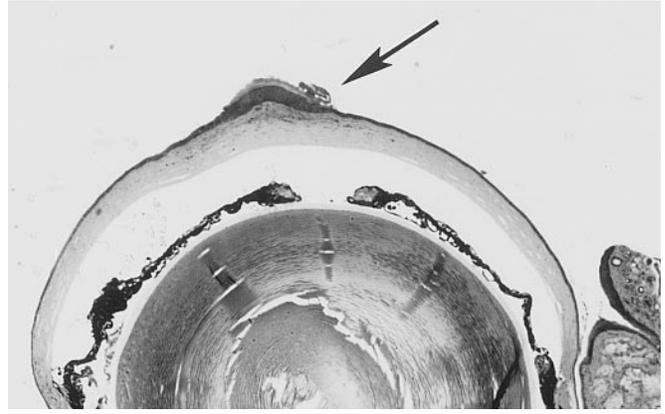


PLATE 5

Eye from a female B6C3F1 mouse exposed to 8 ppm furfuryl alcohol via inhalation for 2 years. The cornea has focal degeneration and mineralization. H&E; 10 ×

DISCUSSION AND CONCLUSIONS

Furan, furfural, and furfuryl alcohol are commercially important compounds which are produced in large quantities and have many industrial applications. Furfuryl alcohol is used in numerous industrial and manufacturing processes with considerable potential for occupational exposure. Occupations with the greatest number of exposed workers include carpentry, tile setting, and metal molding and casting, in which workers are exposed through the use of grouts, mortars, and furan resin sand containing furfuryl alcohol-based resins, and packaging and filling machine operation, in which workers are exposed to furfuryl alcohol in solvents. The stone, clay, glass, primary metal, and chemical and allied industries employ the largest number of exposed workers (NIOSH, 1976, 1990). Furfuryl alcohol is regulated as an air contaminant by the Occupational Safety and Health Administration with exposure limits for airborne concentrations currently recommended not to exceed 50 ppm (200 mg/m³) determined as a time-weighted average for up to a 10-hour work shift or 40-hour work week. The American Conference of Governmental Industrial Hygienists suggests an 8-hour, time-weighted average threshold limit value (TLV) of 10 ppm and a 15-minute, time-weighted exposure limit of 15 ppm (ACGIH, 1997). Therefore, the exposure concentrations used in the present studies are well within the range allowable for occupational exposure.

In the 16-day studies, exposure to 125 or 250 ppm furfuryl alcohol was associated with lower survival rates and decreased mean body weights and body weight gains in male and female rats and mice compared to the chamber control groups. Histologic lesions associated with furfuryl alcohol exposure occurred only in the nose in both rats and mice, and the incidences and severities of these lesions increased with increasing exposure concentration. Exposure to 63 ppm did not reduce survival or decrease mean body weights in rats; however, the severities of nasal lesions in rats at this concentration were nearly the same as those observed at 125 ppm. Moreover, a no-observable-effect level was not achieved. Based on these results, 32 ppm was selected as the highest exposure concentration for the 14-week studies.

Exposure to concentrations of furfuryl alcohol up to 32 ppm for 14 weeks produced few overt signs of toxicity. The mean body weight of female rats exposed to 32 ppm was less than that of the chamber controls, but body weights of other groups of rats and of male and female mice were unaffected. The most significant response occurred in the nose, where exposure to furfuryl alcohol vapor produced a spectrum of inflammatory, degenerative, and proliferative lesions of the respiratory, transitional, and olfactory epithelium of rats and of the respiratory and olfactory epithelium of mice. In general, the changes were more severe in the anterior portion than in the posterior portion of the nose; however, at no point was the integrity of the nasal mucosa or nasal passages disrupted. Squamous metaplasia of the transitional epithelium and degeneration of the olfactory epithelium were observed in all exposed groups of rats and increased in severity with increasing exposure concentration. Squamous metaplasia and goblet cell hyperplasia of the respiratory epithelium, as well as hyperplasia and metaplasia of the olfactory epithelium, were observed primarily at an exposure concentration of 8 ppm or greater. In mice, nasal lesions of the olfactory and respiratory epithelium were observed in all exposed groups. In rats and mice, the lesions were mostly of minimal to mild severity at 2, 4, and 8 ppm, and even at 16 and 32 ppm the mean severities were minimal to moderate. Moreover, the nasal lesions were considered unlikely to progress and become life-threatening during a 2-year study. Based on this response, exposure concentrations of 2, 8, and 32 ppm were selected for the 2-year studies.

Chronic exposure to furfuryl alcohol vapor 6 hours per day, 5 days per week for up to 105 weeks resulted in concentration-related increases in the incidences and severities of inflammatory, degenerative, and proliferative lesions of the nasal epithelium, including degeneration, hyperplasia, and metaplasia of the respiratory and olfactory epithelium in exposed groups of rats and degeneration and metaplasia of the respiratory and olfactory epithelium in exposed groups of mice. There was no evidence of a response in the lung during the

14-week or 2-year studies, suggesting that the majority of furfuryl alcohol vapors were removed by the upper respiratory tract.

Neoplasms of the respiratory epithelium occurred only in rats and were present in one male exposed to 2 ppm, one male and one female exposed to 8 ppm, and four males and one female exposed to 32 ppm. Neoplasms of the epithelium lining the nasal cavity are uncommon in control F344/N rats. Their presence in exposed groups of males and females and the increase of combined incidences of neoplasms in 32 ppm males relative to controls was associated with furfuryl alcohol exposure. However, the low incidence and lack of an increase in females against the significant background of nonneoplastic proliferative lesions was a weak response even for an uncommon neoplasm.

Nephropathy was observed in all groups of rats but was most severe in males, especially in the 32 ppm group, in which the associated parathyroid gland hyperplasia and fibrous osteodystrophy were markedly increased in incidence and severity. In the standard evaluation of kidney sections, renal tubule adenomas were observed in one chamber control male, one 2 ppm male, two 8 ppm males, and two 32 ppm females. In addition, a renal tubule carcinoma was observed in one 2 ppm female. No renal tubule neoplasms were observed in 32 ppm males, although nephropathy was marked in this group and the kidneys were fibrotic with diffuse loss of most of the renal tubules. In order to confirm this response, the kidneys of male and female rats were step sectioned and examined for the presence of previously undetected lesions. In males, analysis of the extended evaluation revealed one additional adenoma in each of the chamber control, 2 ppm, and 8 ppm groups, and four previously undetected adenomas in the 32 ppm group. Additional hyperplasias were also observed. The initial review of single sections combined with the analysis of step sections indicates a significant increase in renal tubule hyperplasia in 32 ppm males, but only a marginal, nonsignificant increase in the incidence of renal tubule adenomas. The presence of two adenomas in chamber control animals and the marginal increase in 32 ppm males over a 16-fold increase in exposure concentration do not support an association between renal tubule adenomas and exposure to furfuryl alcohol.

The extended analysis of step sections from female rats identified two previously unidentified animals with adenomas in the 8 ppm group and one in the 32 ppm group as well as additional hyperplasias in all groups. The combination of single section and step section

analyses indicates a slight increase in the incidence of combined renal tubule neoplasms in exposed groups. Renal tubule neoplasms are uncommon in female F344/N rats and the slight exposure and treatment-related increase is suggestive of an association with furfuryl alcohol exposure. However, the relationship of these neoplasms to furfuryl alcohol exposure is considered uncertain for several reasons. Both the 8 and 32 ppm groups had two adenomas, but renal tubule hyperplasias were increased only in the 32 ppm group relative to chamber controls. In addition, the step section analysis identified additional adenomas in the 8 ppm group but only one new renal tubule neoplasm in the 32 ppm group. Therefore, over a 16-fold increase in exposure concentration (from 2 to 32 ppm) the incidence of renal tubule adenomas increased only marginally, and over a fourfold increase in exposure concentration (8 to 32 ppm) and against a background of increasing renal tubule hyperplasia, the incidence of adenomas did not increase.

Nephropathy was also observed in male and female mice, and the severity was slightly increased in the 32 ppm male group. Renal tubule degeneration was observed in 48 of 50 male mice in the 32 ppm group but did not involve the loss or destruction of tubules. In the standard microscopic evaluation of kidney sections, incidences of renal tubule hyperplasia did not increase with increasing exposure concentration; however, two renal tubule adenomas and two renal tubule carcinomas were observed in 32 ppm males. Renal tubule neoplasms are uncommon in male B6C3F₁ mice, and their presence in four 32 ppm males is consistent with an exposure-related carcinogenic response. Therefore, to determine whether additional hyperplasias or neoplasms were present, the kidneys of male mice were step sectioned. The extended evaluation revealed one additional adenoma in a 32 ppm male. Additional hyperplasias were also observed in chamber control and exposed groups.

Exposure to furfuryl alcohol clearly exacerbated age-related nephropathy in both rats and mice. As illustrated in Figure 1, the major biotransformation pathway for furfuryl alcohol in rodents and humans is oxidation to furfural, which is further oxidized to furoic acid. Furoic acid is then conjugated with glycine to form furoylglycine and eliminated in urine. Furfuryl alcohol is also converted to furanacrylic acid and conjugated with glycine to form furanacryloylglycine, which is also eliminated in urine. The data in Appendix I indicate that elevated concentrations of these two major metabolites were present in the urine of rats at the end of the 2-year studies. Although the liver is the primary site of these biotransformations, the kidney also contains the

necessary enzymes. Therefore, the increased severity of nephropathy in rats may be associated with the renal metabolism and/or urinary elimination of furfuryl alcohol and its metabolites.

Corneal degeneration involving mineralization of the stroma immediately beneath the corneal epithelium was observed in all groups of female mice and was significantly increased relative to chamber controls in the 32 ppm group. Corneal degeneration is a typical response to irritation, and the increase in the 32 ppm group is associated with furfuryl alcohol exposure. However, it is unclear why this lesion was observed only in female mice. Other clinical observations in female mice were similar to those in males. Moreover, cages were rotated within the inhalation chambers weekly and, therefore, it was unlikely to be associated with cage position. Mean body weights of exposed female mice were less than those of chamber controls throughout much of the study. This was especially true for the 32 ppm female group, which had body weights that were considerably less than other groups. By contrast, the mean body weight of 32 ppm males was only slightly less than the other groups. This indicates that furfuryl alcohol was more toxic to female mice than to males. As a result, 32 ppm females, the group with the lowest body weights, may have been less inclined to close their eyes to avoid the irritating effects of furfuryl alcohol vapor than less severely affected groups.

The results of the present studies demonstrate that furfuryl alcohol is an obvious nasal irritant in both rats and mice. However, it is unknown if the primary irritant is the parent alcohol or a metabolite. At vapor concentrations similar to those used in the present study, simple aliphatic alcohols such as methanol and ethanol are essentially nontoxic to the nose (Andrews *et al.*, 1987; Poon *et al.*, 1994). By contrast, their respective aldehydes, formaldehyde and acetaldehyde, are nasal toxicants and nasal carcinogens (Swenberg *et al.*, 1980; Appelman *et al.*, 1982; Woutersen *et al.*, 1984; Monticello *et al.*, 1996). Furfural, an aldehyde, is the

major metabolite of furfuryl alcohol. In the only inhalation study of furfural in which the nose was examined histologically, Syrian golden hamsters were exposed to 0, 20, 115, or 552 ppm furfural, 6 hours per day, 5 days per week for 13 weeks (Feron *et al.*, 1979). In this study, the nose was the only target organ; 20 ppm was the no-observable-effect level, while 115 and 552 ppm caused atrophy and hyperplasia of the olfactory epithelium but were without effect on the respiratory epithelium. These results indicate that furfural is considerably less toxic to the nose than furfuryl alcohol.

At concentrations well below the currently recommended TLVs, exposure to furfuryl alcohol is associated with significant toxicity to the nasal mucosa in rodents. Moreover, because the concentration of metabolites was proportional to dose throughout the range of doses used, the metabolic capacity did not appear to be exceeded. Toxicity was evident in both the olfactory and respiratory epithelium even at the 2 ppm exposure concentration. Therefore, the no-observable-effect level for chronic exposure is probably significantly less than 2 ppm. Studies of other nasal irritants such as formaldehyde or chlorine gas suggest that rodent nasal passages are more sensitive and exhibit an irritant response at exposure concentrations somewhat lower than observed in nonhuman primates such as monkeys or as recorded in documented human exposures (Swenberg *et al.*, 1980; Monticello *et al.*, 1996). However, the present studies clearly indicate that furfuryl alcohol has the potential to be a nasal irritant at exposure concentrations less than those normally encountered in occupational settings.

CONCLUSIONS

Under the conditions of these 2-year inhalation studies, there was *some evidence of carcinogenic activity** of furfuryl alcohol in male F344/N rats based on increased incidences of combined neoplasms of the nose. There was *equivocal evidence of carcinogenic activity* of furfuryl alcohol in female F344/N rats based on

marginally increased incidences of neoplasms of the nose and renal tubule neoplasms. There was *some evidence of carcinogenic activity* of furfuryl alcohol in male B6C3F₁ mice based on increased incidences of renal tubule neoplasms. There was *no evidence of carcinogenic activity* of furfuryl alcohol in female B6C3F₁ mice exposed to 2, 8, or 32 ppm.

Exposure of male and female rats and male mice to furfuryl alcohol was associated with increased incidences of nonneoplastic lesions of the nose and increased severities of nephropathy. Exposure of female mice to furfuryl alcohol was associated with increased incidences of nonneoplastic lesions of the nose and corneal degeneration.

* Explanation of Levels of Evidence of Carcinogenic Activity is on page 10. A summary of the Technical Reports Review Subcommittee comments and the public discussion on this Technical Report appears on page 12.

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

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TABLE A1
Summary of the Incidence of Neoplasms in Male Rats in the 2-Year Inhalation Study of Furfuryl Alcohol^a

	Chamber Control	2 ppm	8 ppm	32 ppm
Disposition Summary				
Animals initially in study	50	50	50	50
Early deaths				
Moribund	34	43	31	43
Natural deaths	8	2	10	7
Survivors				
Died last week of study	1			
Terminal sacrifice	7	5	9	
Animals examined microscopically	50	50	50	50
Alimentary System				
Intestine large, colon	(49)	(50)	(48)	(47)
Intestine large, cecum	(46)	(49)	(44)	(45)
Intestine small, duodenum	(50)	(50)	(50)	(49)
Intestine small, jejunum	(46)	(50)	(43)	(44)
Carcinoma		1 (2%)		
Intestine small, ileum	(47)	(49)	(43)	(45)
Liver	(50)	(50)	(50)	(50)
Hepatocellular adenoma	1 (2%)	1 (2%)		
Histiocytic sarcoma			2 (4%)	
Mesentery	(11)	(13)	(9)	(26)
Oral mucosa	(1)	(1)	(1)	(1)
Pharyngeal, squamous cell papilloma				1 (100%)
Pancreas	(50)	(50)	(50)	(49)
Adenoma		1 (2%)	1 (2%)	
Carcinoma, metastatic, kidney			1 (2%)	
Salivary glands	(47)	(50)	(49)	(49)
Histiocytic sarcoma			1 (2%)	
Stomach, forestomach	(50)	(50)	(50)	(50)
Squamous cell papilloma			1 (2%)	
Stomach, glandular	(50)	(50)	(50)	(49)
Cardiovascular System				
Heart	(50)	(50)	(50)	(50)
Carcinoma, metastatic, kidney			1 (2%)	
Endocrine System				
Adrenal cortex	(50)	(50)	(50)	(50)
Adenoma		1 (2%)		
Carcinoma, metastatic, kidney			1 (2%)	
Bilateral, adenoma			1 (2%)	
Adrenal medulla	(50)	(50)	(50)	(50)
Carcinoma, metastatic, kidney			1 (2%)	
Pheochromocytoma malignant	1 (2%)		2 (4%)	1 (2%)
Pheochromocytoma complex			1 (2%)	
Pheochromocytoma benign	11 (22%)	13 (26%)	12 (24%)	6 (12%)
Bilateral, pheochromocytoma benign	8 (16%)	14 (28%)	10 (20%)	20 (40%)
Islets, pancreatic	(50)	(50)	(50)	(49)
Adenoma	3 (6%)		2 (4%)	
Carcinoma	1 (2%)	1 (2%)	1 (2%)	
Parathyroid gland	(49)	(45)	(50)	(49)
Adenoma		1 (2%)		

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

	Chamber Control	2 ppm	8 ppm	32 ppm
Endocrine System (continued)				
Pituitary gland	(50)	(50)	(48)	(50)
Pars distalis, adenoma	36 (72%)	37 (74%)	39 (81%)	31 (62%)
Thyroid gland	(49)	(49)	(49)	(47)
C-cell, adenoma	5 (10%)	6 (12%)	5 (10%)	
C-cell, carcinoma		1 (2%)	1 (2%)	
Follicular cell, adenoma			2 (4%)	
Follicular cell, carcinoma			1 (2%)	
General Body System				
Peritoneum	(1)	(1)	(1)	
Genital System				
Epididymis	(50)	(50)	(50)	(50)
Preputial gland	(49)	(50)	(49)	(50)
Adenoma	2 (4%)	3 (6%)	2 (4%)	2 (4%)
Carcinoma	3 (6%)	2 (4%)	5 (10%)	2 (4%)
Schwannoma malignant				1 (2%)
Bilateral, carcinoma				1 (2%)
Prostate	(50)	(50)	(50)	(50)
Adenoma	1 (2%)	1 (2%)	1 (2%)	
Seminal vesicle	(49)	(49)	(46)	(47)
Adenoma		1 (2%)		
Testes	(50)	(50)	(50)	(50)
Bilateral, interstitial cell, adenoma	28 (56%)	27 (54%)	27 (54%)	18 (36%)
Interstitial cell, adenoma	7 (14%)	8 (16%)	10 (20%)	14 (28%)
Hematopoietic System				
Bone marrow	(50)	(50)	(50)	(49)
Lymph node	(10)	(8)	(10)	(12)
Lymph node, bronchial	(39)	(28)	(33)	(22)
Carcinoma, metastatic, kidney			1 (3%)	
Lymph node, mandibular	(44)	(42)	(48)	(46)
Lymph node, mesenteric	(48)	(50)	(50)	(45)
Carcinoma, metastatic, kidney			1 (2%)	
Lymph node, mediastinal	(45)	(47)	(46)	(44)
Carcinoma, metastatic, kidney			1 (2%)	
Spleen	(50)	(50)	(50)	(50)
Histiocytic sarcoma			1 (2%)	
Thymus	(43)	(40)	(41)	(38)
Thymoma benign				1 (3%)
Integumentary System				
Mammary gland	(30)	(25)	(29)	(27)
Carcinoma			2 (7%)	
Carcinoma, multiple	1 (3%)			
Fibroadenoma	2 (7%)	1 (4%)	5 (17%)	

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

	Chamber Control	2 ppm	8 ppm	32 ppm
Integumentary System (continued)				
Skin	(50)	(50)	(50)	(50)
Basal cell adenoma		1 (2%)	3 (6%)	
Basal cell carcinoma	2 (4%)		1 (2%)	
Keratoacanthoma	5 (10%)	1 (2%)	7 (14%)	4 (8%)
Squamous cell carcinoma			1 (2%)	
Squamous cell papilloma		2 (4%)		
Sebaceous gland, carcinoma	2 (4%)			
Subcutaneous tissue, fibroma	4 (8%)	2 (4%)	5 (10%)	1 (2%)
Subcutaneous tissue, fibroma, multiple			1 (2%)	
Subcutaneous tissue, histiocytic sarcoma			1 (2%)	
Subcutaneous tissue, schwannoma malignant	2 (4%)	1 (2%)		
Musculoskeletal System				
Bone	(50)	(50)	(50)	(50)
Osteoma	1 (2%)			
Turbinates, osteosarcoma		1 (2%)		
Nervous System				
Brain	(50)	(50)	(50)	(50)
Meningioma malignant	1 (2%)			
Respiratory System				
Lung	(50)	(50)	(50)	(50)
Alveolar/bronchiolar adenoma		2 (4%)	1 (2%)	
Alveolar/bronchiolar carcinoma			1 (2%)	
Alveolar/bronchiolar carcinoma, metastatic, lung			1 (2%)	
Carcinoma, metastatic, kidney			1 (2%)	
Carcinoma, metastatic, preputial gland			1 (2%)	
Histiocytic sarcoma			1 (2%)	
Pheochromocytoma malignant, metastatic, adrenal medulla			1 (2%)	
Nose	(50)	(50)	(50)	(50)
Lateral wall, adenoma		1 (2%)		
Respiratory epithelium, adenoma			1 (2%)	
Respiratory epithelium, carcinoma				1 (2%)
Respiratory epithelium, squamous cell carcinoma				3 (6%)
Special Senses System				
Zymbal's gland	(1)		(1)	(3)
Adenoma			1 (100%)	
Carcinoma	1 (100%)			3 (100%)

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

	Chamber Control	2 ppm	8 ppm	32 ppm
Urinary System				
Kidney	(50)	(50)	(50)	(50)
Histiocytic sarcoma			1 (2%)	
Lipoma		1 (2%)		
Nephroblastoma			1 (2%)	
Stromal nephroma			1 (2%)	
Renal tubule, adenoma	1 (2%)	1 (2%)	2 (4%)	
Transitional epithelium, carcinoma			1 (2%)	
Urinary bladder	(50)	(50)	(50)	(50)
Systemic Lesions				
Multiple organs ^b	(50)	(50)	(50)	(50)
Histiocytic sarcoma			2 (4%)	
Leukemia mononuclear	29 (58%)	31 (62%)	28 (56%)	15 (30%)
Mesothelioma malignant	3 (6%)	2 (4%)	1 (2%)	
Neoplasm Summary				
Total animals with primary neoplasms ^c	50	50	50	50
Total primary neoplasms	161	166	189	125
Total animals with benign neoplasms	47	50	49	47
Total benign neoplasms	115	126	139	98
Total animals with malignant neoplasms	35	35	34	26
Total malignant neoplasms	46	40	50	27
Total animals with metastatic neoplasms			4	
Total metastatic neoplasms			11	

^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 Furfuryl Alcohol: Chamber Control

Number of Days on Study	3	3	3	3	4	4	4	5	5	5	5	5	5	5	5	5	5	5	5	5	6	6	6	6	6	
	0	3	5	8	6	9	0	2	2	3	3	6	7	7	7	8	9	9	9	9	0	0	1	2	4	
	2	3	1	2	9	0	7	2	5	2	6	1	2	4	8	1	1	5	9	9	6	9	7	4	8	
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	
	3	1	1	0	2	2	0	4	2	0	4	1	4	0	0	3	4	3	0	4	1	5	2	1	0	
	8	6	1	9	1	6	3	2	4	7	6	4	8	4	8	5	7	9	5	9	0	0	2	9	6	
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Intestine large, colon	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Intestine large, rectum	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Intestine large, cecum	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Intestine small, jejunum	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Intestine small, ileum	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Hepatocellular adenoma																										
Mesentery																										
Oral mucosa																										
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Cardiovascular System																										
Blood vessel																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Pheochromocytoma malignant																										
Pheochromocytoma benign												X	X								X		X			
Bilateral, pheochromocytoma benign																X										
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Adenoma																									X	
Carcinoma																										
Parathyroid gland	+	+	+	+	+	+	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																									X	
General Body System																										
Peritoneum																										
Genital System																										
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Adenoma																									X	
Carcinoma																									X	
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Adenoma																										
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Bilateral, interstitial cell, adenoma																									X	
Interstitial cell, adenoma																									X	
																									X	
																									X	

+: 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 Furfuryl Alcohol: 32 ppm

Number of Days on Study	3	4	4	4	4	4	5	5	5	5	5	5	5	5	5	5	5	5	5	5	6	6	6	6	6		
	4	2	6	7	7	9	2	2	2	3	5	6	8	8	8	8	8	8	8	9	9	0	0	0	0		
	7	1	9	2	6	7	1	2	6	2	5	8	0	0	1	1	3	5	4	9	1	4	6	9	9		
Carcass ID Number	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6		
	3	4	0	2	1	4	2	3	1	1	1	0	2	4	0	2	3	3	0	4	1	2	0	0	2		
	8	5	5	0	2	8	9	3	4	5	6	4	7	6	8	4	4	0	2	3	7	6	3	9	5		
Hematopoietic System																											
Bone marrow	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Lymph node									+					+						+		+					
Lymph node, bronchial	+	M	+	+	+	+	+	+	+	M	+	M	+	M	+	M	+	M	M	+	M	+	M	M	+	+	
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	M	+	+	+	
Lymph node, mesenteric	+	+	+	+	A	+	+	+	+	+	+	M	+	+	+	+	+	+	M	+	+	+	+	+	+	+	
Lymph node, mediastinal	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	M	
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Thymus	+	M	+	M	+	+	+	+	+	M	M	M	M	+	M	+	+	+	+	+	+	+	+	+	+	M	
Thymoma benign																										X	
Integumentary System																											
Mammary gland	+	+	M	+	+	M	M	M	+	M	M	+	M	M	M	M	M	M	M	M	+	M	+	+	+	M	
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Keratoacanthoma													X														
Subcutaneous tissue, fibroma																											
Musculoskeletal System																											
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Nervous System																											
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Respiratory System																											
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Respiratory epithelium, carcinoma																											
Respiratory epithelium, squamous cell carcinoma																										X	
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Special Senses System																											
Eye		+				+																					
Harderian gland																											
Zymbal's gland	+																									+	
Carcinoma	X																									X	
Urinary System																											
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Systemic Lesions																											
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Leukemia mononuclear		X	X	X	X	X	X		X				X	X	X				X	X							

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

	Chamber Control	2 ppm	8 ppm	32 ppm
Adrenal Medulla: Benign Pheochromocytoma				
Overall rate ^a	19/50 (38%)	27/50 (54%)	22/50 (44%)	26/50 (52%)
Adjusted rate ^b	52.3%	68.0%	55.9%	69.7%
Terminal rate ^c	5/8 (63%)	4/5 (80%)	4/9 (44%)	0/0
First incidence (days)	532	490	492	555
Poly-3 test ^d	P=0.150	P=0.097	P=0.462	P=0.069
Adrenal Medulla: Benign, Complex, or Malignant Pheochromocytoma				
Overall rate	19/50 (38%)	27/50 (54%)	24/50 (48%)	26/50 (52%)
Adjusted rate	52.3%	68.0%	59.8%	69.7%
Terminal rate	5/8 (63%)	4/5 (80%)	4/9 (44%)	0/0
First incidence (days)	532	490	492	555
Poly-3 test	P=0.162	P=0.097	P=0.319	P=0.069
Kidney (Renal Tubule): Adenoma (Single and Step Sections)				
Overall rate	2/50 (4%)	2/50 (4%)	3/50 (6%)	4/50 (8%)
Adjusted rate	6.1%	6.3%	8.9%	13.9%
Terminal rate	0/8 (0%)	1/5 (20%)	0/9 (0%)	0/0
First incidence (days)	681	726	700	609
Poly-3 test	P=0.186	P=0.687	P=0.514	P=0.273
Mammary Gland: Fibroadenoma				
Overall rate	2/50 (4%)	1/50 (2%)	5/50 (10%)	0/50 (0%)
Adjusted rate	6.1%	3.1%	14.8%	0.0%
Terminal rate	1/8 (13%)	0/5 (0%)	4/9 (44%)	0/0
First incidence (days)	648	578	592	— ^e
Poly-3 test	P=0.273N	P=0.505N	P=0.223	P=0.278N
Mammary Gland: Fibroadenoma or Carcinoma				
Overall rate	3/50 (6%)	1/50 (2%)	6/50 (12%)	0/50 (0%)
Adjusted rate	9.1%	3.1%	17.5%	0.0%
Terminal rate	1/8 (13%)	0/5 (0%)	4/9 (44%)	0/0
First incidence (days)	648	578	554	—
Poly-3 test	P=0.203N	P=0.309N	P=0.257	P=0.152N
Nose: Squamous Cell Carcinoma				
Overall rate	0/50 (0%)	0/50 (0%)	0/50 (0%)	3/50 (6%)
Adjusted rate	0.0%	0.0%	0.0%	10.5%
Terminal rate	0/8 (0%)	0/5 (0%)	0/9 (0%)	0/0
First incidence (days)	—	—	—	606
Poly-3 test	P=0.006	— ^f	—	P=0.094
Nose: Adenoma, Carcinoma, or Squamous Cell Carcinoma				
Overall rate	0/50 (0%)	1/50 (2%)	1/50 (2%)	4/50 (8%)
Adjusted rate	0.0%	3.1%	3.0%	13.8%
Terminal rate	0/8 (0%)	0/5 (0%)	0/9 (0%)	0/0
First incidence (days)	—	721	585	606
Poly-3 test	P=0.013	P=0.496	P=0.509	P=0.044
Pancreatic Islets: Adenoma				
Overall rate	3/50 (6%)	0/50 (0%)	2/50 (4%)	0/49 (0%)
Adjusted rate	9.1%	0.0%	6.0%	0.0%
Terminal rate	1/8 (13%)	0/5 (0%)	2/9 (22%)	0/0
First incidence (days)	624	—	735 (T)	—
Poly-3 test	P=0.229N	P=0.122N	P=0.495N	P=0.154N

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

	Chamber Control	2 ppm	8 ppm	32 ppm
Pancreatic Islets: Adenoma or Carcinoma				
Overall rate	4/50 (8%)	1/50 (2%)	3/50 (6%)	0/49 (0%)
Adjusted rate	12.1%	3.1%	8.9%	0.0%
Terminal rate	2/8 (25%)	1/5 (20%)	2/9 (22%)	0/0
First incidence (days)	624	735 (T)	666	—
Poly-3 test	P=0.128N	P=0.185N	P=0.489N	P=0.085N
Pituitary Gland (Pars Distalis): Adenoma				
Overall rate	36/50 (72%)	37/50 (74%)	39/48 (81%)	31/50 (62%)
Adjusted rate	82.8%	82.3%	89.9%	75.5%
Terminal rate	7/8 (88%)	4/5 (80%)	9/9 (100%)	0/0
First incidence (days)	333	399	478	472
Poly-3 test	P=0.146N	P=0.598N	P=0.220	P=0.260N
Preputial Gland: Adenoma				
Overall rate	2/49 (4%)	3/50 (6%)	2/49 (4%)	2/50 (4%)
Adjusted rate	6.1%	9.2%	6.2%	7.2%
Terminal rate	0/8 (0%)	0/5 (0%)	1/9 (11%)	0/0
First incidence (days)	572	616	730	609
Poly-3 test	P=0.608N	P=0.501	P=0.695	P=0.640
Preputial Gland: Carcinoma				
Overall rate	3/49 (6%)	2/50 (4%)	5/49 (10%)	3/50 (6%)
Adjusted rate	9.2%	6.1%	14.7%	10.3%
Terminal rate	0/8 (0%)	0/5 (0%)	2/9 (22%)	0/0
First incidence (days)	572	399	554	522
Poly-3 test	P=0.495	P=0.495N	P=0.379	P=0.614
Preputial Gland: Adenoma or Carcinoma				
Overall rate	4/49 (8%)	5/50 (10%)	7/49 (14%)	5/50 (10%)
Adjusted rate	12.2%	14.9%	20.6%	16.8%
Terminal rate	0/8 (0%)	0/5 (0%)	3/9 (33%)	0/0
First incidence (days)	572	399	554	522
Poly-3 test	P=0.445	P=0.515	P=0.272	P=0.434
Skin: Keratoacanthoma				
Overall rate	5/50 (10%)	1/50 (2%)	7/50 (14%)	4/50 (8%)
Adjusted rate	15.1%	3.1%	19.8%	13.8%
Terminal rate	1/8 (13%)	1/5 (20%)	1/9 (11%)	0/0
First incidence (days)	591	735 (T)	492	555
Poly-3 test	P=0.441	P=0.105N	P=0.424	P=0.589N
Skin: Squamous Cell Papilloma or Keratoacanthoma				
Overall rate	5/50 (10%)	3/50 (6%)	7/50 (14%)	4/50 (8%)
Adjusted rate	15.1%	9.3%	19.8%	13.8%
Terminal rate	1/8 (13%)	1/5 (20%)	1/9 (11%)	0/0
First incidence (days)	591	644	492	555
Poly-3 test	P=0.561	P=0.369N	P=0.424	P=0.589N
Skin: Basal Cell Adenoma				
Overall rate	0/50 (0%)	1/50 (2%)	3/50 (6%)	0/50 (0%)
Adjusted rate	0.0%	3.1%	8.9%	0.0%
Terminal rate	0/8 (0%)	0/5 (0%)	0/9 (0%)	0/0
First incidence (days)	—	705	666	—
Poly-3 test	P=0.513N	P=0.497	P=0.124	—

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

	Chamber Control	2 ppm	8 ppm	32 ppm
Skin: Basal Cell Adenoma or Basal Cell Carcinoma				
Overall rate	2/50 (4%)	1/50 (2%)	4/50 (8%)	0/50 (0%)
Adjusted rate	6.1%	3.1%	11.8%	0.0%
Terminal rate	1/8 (13%)	0/5 (0%)	1/9 (11%)	0/0
First incidence (days)	690	705	666	—
Poly-3 test	P=0.267N	P=0.507N	P=0.351	P=0.276N
Skin: Squamous Cell Papilloma, Keratoacanthoma, or Squamous Cell Carcinoma				
Overall rate	5/50 (10%)	3/50 (6%)	8/50 (16%)	4/50 (8%)
Adjusted rate	15.1%	9.3%	22.5%	13.8%
Terminal rate	1/8 (13%)	1/5 (20%)	1/9 (11%)	0/0
First incidence (days)	591	644	492	555
Poly-3 test	P=0.570	P=0.369N	P=0.314	P=0.589N
Skin: Squamous Cell Papilloma, Keratoacanthoma, Basal Cell Adenoma, Basal Cell Carcinoma, or Squamous Cell Carcinoma				
Overall rate	7/50 (14%)	4/50 (8%)	11/50 (22%)	4/50 (8%)
Adjusted rate	21.0%	12.4%	30.8%	13.8%
Terminal rate	2/8 (25%)	1/5 (20%)	2/9 (22%)	0/0
First incidence (days)	591	644	492	555
Poly-3 test	P=0.379N	P=0.270N	P=0.253	P=0.340N
Skin (Subcutaneous Tissue): Fibroma				
Overall rate	4/50 (8%)	2/50 (4%)	6/50 (12%)	1/50 (2%)
Adjusted rate	12.0%	6.2%	17.2%	3.6%
Terminal rate	1/8 (13%)	0/5 (0%)	1/9 (11%)	0/0
First incidence (days)	525	652	547	638
Poly-3 test	P=0.261N	P=0.349N	P=0.396	P=0.235N
Testes: Adenoma				
Overall rate	35/50 (70%)	35/50 (70%)	37/50 (74%)	32/50 (64%)
Adjusted rate	84.9%	85.1%	85.9%	79.2%
Terminal rate	7/8 (88%)	5/5 (100%)	9/9 (100%)	0/0
First incidence (days)	469	477	428	469
Poly-3 test	P=0.202N	P=0.644	P=0.594	P=0.316N
Thyroid Gland (C-cell): Adenoma				
Overall rate	5/49 (10%)	6/49 (12%)	5/49 (10%)	0/47 (0%)
Adjusted rate	15.2%	18.7%	14.8%	0.0%
Terminal rate	0/8 (0%)	3/5 (60%)	0/9 (0%)	0/0
First incidence (days)	522	571	554	—
Poly-3 test	P=0.034N	P=0.482	P=0.620N	P=0.053N
Thyroid Gland (C-cell): Adenoma or Carcinoma				
Overall rate	5/49 (10%)	7/49 (14%)	5/49 (10%)	0/47 (0%)
Adjusted rate	15.2%	21.6%	14.8%	0.0%
Terminal rate	0/8 (0%)	3/5 (60%)	0/9 (0%)	0/0
First incidence (days)	522	571	554	—
Poly-3 test	P=0.027N	P=0.362	P=0.620N	P=0.053N
Thyroid Gland (Follicular Cell): Adenoma or Carcinoma				
Overall rate	0/49 (0%)	0/49 (0%)	3/49 (6%)	0/47 (0%)
Adjusted rate	0.0%	0.0%	9.2%	0.0%
Terminal rate	0/8 (0%)	0/5 (0%)	1/9 (11%)	0/0
First incidence (days)	—	—	692	—
Poly-3 test	P=0.662N	—	P=0.123	—

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

	Chamber Control	2 ppm	8 ppm	32 ppm
Zymbal's Gland: Carcinoma				
Overall rate	1/50 (2%)	0/50 (0%)	0/50 (0%)	3/50 (6%)
Adjusted rate	3.0%	0.0%	0.0%	10.3%
Terminal rate	0/8 (0%)	0/5 (0%)	0/9 (0%)	0/0
First incidence (days)	609	—	—	347
Poly-3 test	P=0.039	P=0.507N	P=0.497N	P=0.259
Zymbal's Gland: Adenoma or Carcinoma				
Overall rate	1/50 (2%)	0/50 (0%)	1/50 (2%)	3/50 (6%)
Adjusted rate	3.0%	0.0%	3.0%	10.3%
Terminal rate	0/8 (0%)	0/5 (0%)	1/9 (11%)	0/0
First incidence (days)	609	—	735 (T)	347
Poly-3 test	P=0.064	P=0.507N	P=0.759N	P=0.259
All Organs: Mononuclear Cell Leukemia				
Overall rate	29/50 (58%)	31/50 (62%)	28/50 (56%)	15/50 (30%)
Adjusted rate	67.9%	75.3%	65.9%	42.2%
Terminal rate	6/8 (75%)	4/5 (80%)	6/9 (67%)	0/0
First incidence (days)	302	490	428	421
Poly-3 test	P<0.001N	P=0.285	P=0.515N	P=0.011N
All Organs: Malignant Mesothelioma				
Overall rate	3/50 (6%)	2/50 (4%)	1/50 (2%)	0/50 (0%)
Adjusted rate	9.1%	6.2%	3.0%	0.0%
Terminal rate	1/8 (13%)	1/5 (20%)	1/9 (11%)	0/0
First incidence (days)	561	627	735 (T)	—
Poly-3 test	P=0.126N	P=0.514N	P=0.300N	P=0.154N
All Organs: Benign Neoplasms				
Overall rate	47/50 (94%)	50/50 (100%)	49/50 (98%)	47/50 (94%)
Adjusted rate	99.3%	100.0%	99.4%	98.6%
Terminal rate	8/8 (100%)	5/5 (100%)	9/9 (100%)	0/0
First incidence (days)	333	399	428	469
Poly-3 test	P=0.606N	P=1.000	P=0.997	P=0.925N
All Organs: Malignant Neoplasms				
Overall rate	35/50 (70%)	35/50 (70%)	34/50 (68%)	26/50 (52%)
Adjusted rate	77.7%	81.5%	76.8%	63.5%
Terminal rate	6/8 (75%)	5/5 (100%)	7/9 (78%)	0/0
First incidence (days)	302	399	428	347
Poly-3 test	P=0.023N	P=0.419	P=0.565N	P=0.086N

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

	Chamber Control	2 ppm	8 ppm	32 ppm
All Organs: Benign or Malignant Neoplasms				
Overall rate	50/50 (100%)	50/50 (100%)	50/50 (100%)	50/50 (100%)
Adjusted rate	100.0%	100.0%	100.0%	100.0%
Terminal rate	8/8 (100%)	5/5 (100%)	9/9 (100%)	0/0
First incidence (days)	302	399	428	347
Poly-3 test	—	—	—	—

(T)Terminal sacrifice

^a Number of neoplasm-bearing animals/number of animals examined. Denominator is number of animals examined microscopically for adrenal gland, kidney, nose, 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 A4a
Historical Incidence of Nasal Neoplasms in Chamber Control Male F344/N Rats^a

Study	Incidence in Controls		
	Adenoma	Carcinoma	Squamous Cell Carcinoma
Historical Incidence at Battelle Pacific Northwest Laboratories			
Acetonitrile	0/48	0/48	0/48
α -Chloroacetophenone	0/46	0/46	0/46
Cobalt Sulfate Heptahydrate	0/50	0/50	0/50
Epinephrine Hydrochloride	1/50	0/50	0/50
Hexachlorocyclopentadiene	0/48	0/48	0/48
Isobutyraldehyde	0/50	0/50	0/50
Molybdenum Trioxide	0/50	0/50	0/50
Nitromethane	0/50	0/50	0/50
<i>o</i> -Chlorobenzalmononitrile	0/50	0/50	0/50
Ozone	0/50	0/50	0/50
Tetrafluoroethylene	0/50	0/50	0/50
Tetrahydrofuran	0/50	0/50	0/50
Overall Historical Incidence			
Total	1/897 (0.1%)	0/897	0/897
Standard deviation	0.5%		
Range	0%-2%		

^a Data as of 15 October 1996

TABLE A4b
Historical Incidence of Renal Tubule Neoplasms in Chamber Control Male F344/N Rats^a

Study	Incidence in Controls		
	Adenoma	Carcinoma	Adenoma or Carcinoma
Historical Incidence at Battelle Pacific Northwest Laboratories			
Acetonitrile	1/48	0/48	1/48
α -Chloroacetophenone	1/49	0/49	1/49
Cobalt Sulfate Heptahydrate	1/50	0/50	1/50
Epinephrine Hydrochloride	0/50	0/50	0/50
Hexachlorocyclopentadiene	0/50	0/50	0/50
Isobutyraldehyde	0/50	0/50	0/50
Molybdenum Trioxide	1/50	0/50	1/50
Nitromethane	0/50	0/50	0/50
<i>o</i> -Chlorobenzalmononitrile	1/50	0/50	1/50
Ozone	2/50	0/50	2/50
Tetrafluoroethylene	0/50	1/50	1/50
Tetrahydrofuran	1/50	0/50	1/50
Overall Historical Incidence			
Total	9/902 (1.0%)	1/902 (0.1%)	10/902 (1.1%)
Standard deviation	1.2%	0.5%	1.2%
Range	0%-4%	0%-2%	0%-4%

^a Data as of 15 October 1996

TABLE A5
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 2-Year Inhalation Study of Furfuryl Alcohol^a

	Chamber Control	2 ppm	8 ppm	32 ppm
Disposition Summary				
Animals initially in study	50	50	50	50
Early deaths				
Moribund	34	43	31	43
Natural deaths	8	2	10	7
Survivors				
Died last week of study	1			
Terminal sacrifice	7	5	9	
Animals examined microscopically	50	50	50	50
Alimentary System				
Esophagus	(50)	(48)	(49)	(50)
Inflammation, suppurative	1 (2%)			
Intestine large, colon	(49)	(50)	(48)	(47)
Mineralization			1 (2%)	9 (19%)
Parasite metazoan	3 (6%)	4 (8%)	6 (13%)	5 (11%)
Intestine large, rectum	(47)	(50)	(48)	(47)
Mineralization				2 (4%)
Parasite metazoan	1 (2%)	3 (6%)	4 (8%)	1 (2%)
Intestine large, cecum	(46)	(49)	(44)	(45)
Parasite metazoan	2 (4%)	2 (4%)	8 (18%)	4 (9%)
Intestine small, duodenum	(50)	(50)	(50)	(49)
Inflammation, suppurative			1 (2%)	1 (2%)
Intestine small, ileum	(47)	(49)	(43)	(45)
Inflammation, suppurative				1 (2%)
Mineralization				1 (2%)
Parasite metazoan		1 (2%)	1 (2%)	
Liver	(50)	(50)	(50)	(50)
Angiectasis	6 (12%)	2 (4%)	3 (6%)	4 (8%)
Basophilic focus	9 (18%)	12 (24%)	27 (54%)	31 (62%)
Clear cell focus	5 (10%)	1 (2%)	4 (8%)	
Cyst			2 (4%)	
Degeneration, cystic	12 (24%)	18 (36%)	12 (24%)	9 (18%)
Degeneration, fatty	5 (10%)	9 (18%)	3 (6%)	7 (14%)
Eosinophilic focus	4 (8%)	2 (4%)	3 (6%)	4 (8%)
Hepatodiaphragmatic nodule		1 (2%)	4 (8%)	6 (12%)
Mixed cell focus		1 (2%)	2 (4%)	2 (4%)
Necrosis		2 (4%)		2 (4%)
Regeneration	1 (2%)	3 (6%)	2 (4%)	
Tension lipidosis			1 (2%)	
Vacuolization cytoplasmic, focal	1 (2%)			
Bile duct, hyperplasia	28 (56%)	31 (62%)	30 (60%)	13 (26%)
Centrilobular, necrosis	12 (24%)	17 (34%)	15 (30%)	8 (16%)
Mesentery	(11)	(13)	(9)	(26)
Pigmentation			1 (11%)	
Thrombosis				1 (4%)
Artery, inflammation, chronic active				3 (12%)
Artery, mineralization		2 (15%)		22 (85%)
Fat, hemorrhage		2 (15%)	1 (11%)	2 (8%)
Fat, necrosis	10 (91%)	6 (46%)	7 (78%)	4 (15%)
Oral mucosa	(1)	(1)	(1)	(1)
Gingival, inflammation, chronic active	1 (100%)			
Pharyngeal, hyperplasia			1 (100%)	

^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 Furfuryl Alcohol

	Chamber Control	2 ppm	8 ppm	32 ppm
Alimentary System (continued)				
Pancreas	(50)	(50)	(50)	(49)
Atrophy	22 (44%)	22 (44%)	23 (46%)	17 (35%)
Basophilic focus	3 (6%)	1 (2%)	2 (4%)	1 (2%)
Hyperplasia	5 (10%)	2 (4%)		2 (4%)
Artery, inflammation		1 (2%)		5 (10%)
Artery, mineralization			1 (2%)	3 (6%)
Salivary glands	(47)	(50)	(49)	(49)
Atrophy	1 (2%)	1 (2%)		
Inflammation, chronic active		1 (2%)		
Stomach, forestomach	(50)	(50)	(50)	(50)
Hyperplasia, squamous		1 (2%)		
Inflammation, acute	1 (2%)	1 (2%)		
Mineralization	1 (2%)	2 (4%)	2 (4%)	12 (24%)
Necrosis	9 (18%)	6 (12%)	10 (20%)	6 (12%)
Stomach, glandular	(50)	(50)	(50)	(49)
Mineralization	2 (4%)	2 (4%)	3 (6%)	32 (65%)
Necrosis	7 (14%)	3 (6%)	4 (8%)	4 (8%)
Cardiovascular System				
Blood vessel	(2)	(2)	(3)	(31)
Aorta, mineralization	2 (100%)	2 (100%)	2 (67%)	31 (100%)
Heart	(50)	(50)	(50)	(50)
Cardiomyopathy	38 (76%)	32 (64%)	40 (80%)	42 (84%)
Inflammation, suppurative				1 (2%)
Artery, mineralization	2 (4%)	2 (4%)	2 (4%)	29 (58%)
Atrium, thrombosis	3 (6%)	6 (12%)	1 (2%)	3 (6%)
Endocrine System				
Adrenal cortex	(50)	(50)	(50)	(50)
Hyperplasia	15 (30%)	19 (38%)	20 (40%)	24 (48%)
Hypertrophy	3 (6%)	3 (6%)	1 (2%)	4 (8%)
Necrosis			2 (4%)	1 (2%)
Vacuolization cytoplasmic	4 (8%)	3 (6%)	4 (8%)	8 (16%)
Adrenal medulla	(50)	(50)	(50)	(50)
Hyperplasia	30 (60%)	17 (34%)	24 (48%)	19 (38%)
Islets, pancreatic	(50)	(50)	(50)	(49)
Hyperplasia				1 (2%)
Parathyroid gland	(49)	(45)	(50)	(49)
Hyperplasia	9 (18%)	5 (11%)	12 (24%)	39 (80%)
Necrosis				1 (2%)
Pituitary gland	(50)	(50)	(48)	(50)
Mineralization	1 (2%)			
Pars distalis, angiectasis				1 (2%)
Pars distalis, hemorrhage	1 (2%)			
Pars distalis, hyperplasia	4 (8%)	8 (16%)	3 (6%)	11 (22%)
Pars intermedia, hyperplasia		1 (2%)		
Thyroid gland	(49)	(49)	(49)	(47)
C-cell, hyperplasia	27 (55%)	33 (67%)	30 (61%)	21 (45%)
Follicular cell, hyperplasia	1 (2%)	1 (2%)	2 (4%)	2 (4%)
General Body System				
None				

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

	Chamber Control	2 ppm	8 ppm	32 ppm
Genital System				
Preputial gland	(49)	(50)	(49)	(50)
Hyperplasia	1 (2%)		1 (2%)	
Inflammation, chronic active	1 (2%)		2 (4%)	4 (8%)
Prostate	(50)	(50)	(50)	(50)
Hyperplasia	7 (14%)	3 (6%)	5 (10%)	
Inflammation, chronic active	9 (18%)	8 (16%)	3 (6%)	5 (10%)
Seminal vesicle	(49)	(49)	(46)	(47)
Inflammation, suppurative	1 (2%)			
Mineralization			1 (2%)	3 (6%)
Testes	(50)	(50)	(50)	(50)
Atrophy	1 (2%)	1 (2%)	3 (6%)	5 (10%)
Artery, inflammation, chronic active	3 (6%)	1 (2%)	4 (8%)	8 (16%)
Interstitial cell, hyperplasia	4 (8%)	6 (12%)	4 (8%)	7 (14%)
Hematopoietic System				
Bone marrow	(50)	(50)	(50)	(49)
Necrosis		2 (4%)		
Lymph node	(10)	(8)	(10)	(12)
Ectasia				1 (8%)
Iliac, ectasia				1 (8%)
Renal, ectasia				4 (33%)
Renal, hemorrhage	1 (10%)		1 (10%)	3 (25%)
Lymph node, mandibular	(44)	(42)	(48)	(46)
Infiltration cellular, plasma cell	1 (2%)	1 (2%)		
Lymph node, mediastinal	(45)	(47)	(46)	(44)
Hemorrhage				2 (5%)
Spleen	(50)	(50)	(50)	(50)
Accessory spleen	3 (6%)			1 (2%)
Angiectasis			1 (2%)	
Fibrosis	14 (28%)	13 (26%)	10 (20%)	12 (24%)
Hematopoietic cell proliferation	1 (2%)	2 (4%)	2 (4%)	4 (8%)
Hemorrhage				3 (6%)
Hyperplasia, focal	1 (2%)		1 (2%)	
Necrosis	2 (4%)	2 (4%)	3 (6%)	2 (4%)
Thymus	(43)	(40)	(41)	(38)
Cyst		1 (3%)		
Integumentary System				
Mammary gland	(30)	(25)	(29)	(27)
Degeneration	1 (3%)		1 (3%)	
Galactocele	6 (20%)	2 (8%)	6 (21%)	7 (26%)
Skin	(50)	(50)	(50)	(50)
Cyst epithelial inclusion		2 (4%)		
Fibrosis, focal				1 (2%)
Inflammation, acute		2 (4%)		
Inflammation, chronic active	1 (2%)	2 (4%)	2 (4%)	2 (4%)
Inflammation, granulomatous			1 (2%)	
Mineralization				1 (2%)
Necrosis		1 (2%)		
Subcutaneous tissue, edema		1 (2%)		
Tail, hyperkeratosis	1 (2%)			
Tail, inflammation, chronic active	1 (2%)	2 (4%)	6 (12%)	18 (36%)
Tail, subcutaneous tissue, thrombosis			1 (2%)	

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

	Chamber Control	2 ppm	8 ppm	32 ppm
Musculoskeletal System				
Bone	(50)	(50)	(50)	(50)
Fibrous osteodystrophy	2 (4%)	5 (10%)	6 (12%)	34 (68%)
Fracture				1 (2%)
Hyperostosis		5 (10%)	1 (2%)	
Nervous System				
Brain	(50)	(50)	(50)	(50)
Necrosis		2 (4%)		
Respiratory System				
Lung	(50)	(50)	(50)	(50)
Foreign body		1 (2%)		
Hemorrhage			1 (2%)	1 (2%)
Inflammation, granulomatous		1 (2%)		
Inflammation, suppurative		1 (2%)		
Metaplasia, osseous	1 (2%)			1 (2%)
Metaplasia, squamous		1 (2%)		
Mineralization	1 (2%)	2 (4%)	2 (4%)	24 (48%)
Thrombosis		1 (2%)		1 (2%)
Alveolar epithelium, hyperplasia	12 (24%)	7 (14%)	5 (10%)	8 (16%)
Artery, mediastinum, mineralization	1 (2%)	2 (4%)	2 (4%)	26 (52%)
Mediastinum, inflammation, suppurative	1 (2%)			
Perivascular, infiltration cellular, mononuclear cell		1 (2%)		
Nose	(50)	(50)	(50)	(50)
Inflammation, suppurative	3 (6%)	6 (12%)	17 (34%)	44 (88%)
Thrombosis	10 (20%)	15 (30%)	11 (22%)	2 (4%)
Glands, hyperplasia			22 (44%)	49 (98%)
Lateral wall, hyperplasia	1 (2%)	49 (98%)	50 (100%)	50 (100%)
Lateral wall, metaplasia, squamous	1 (2%)	1 (2%)	8 (16%)	33 (66%)
Lateral wall, necrosis	1 (2%)			
Nasopharyngeal duct, inflammation, acute			1 (2%)	
Olfactory epithelium, atrophy	1 (2%)	12 (24%)	47 (94%)	50 (100%)
Olfactory epithelium, degeneration, hyaline	42 (84%)	48 (96%)	50 (100%)	47 (94%)
Olfactory epithelium, fibrosis		1 (2%)	26 (52%)	40 (80%)
Olfactory epithelium, hyperplasia		1 (2%)	42 (84%)	40 (80%)
Olfactory epithelium, metaplasia	1 (2%)	8 (16%)	37 (74%)	49 (98%)
Respiratory epithelium, degeneration, hyaline	12 (24%)	14 (28%)	45 (90%)	3 (6%)
Respiratory epithelium, hyperplasia		26 (52%)	50 (100%)	50 (100%)
Respiratory epithelium, metaplasia, squamous			3 (6%)	26 (52%)
Trachea	(49)	(50)	(50)	(50)
Inflammation, suppurative				1 (2%)
Special Senses System				
Eye		(3)	(1)	(3)
Cataract		1 (33%)	1 (100%)	1 (33%)
Inflammation, chronic active		2 (67%)		1 (33%)
Retina, atrophy		1 (33%)		1 (33%)
Harderian gland		(1)		(1)
Hyperplasia				1 (100%)
Inflammation, chronic active		1 (100%)		

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

	Chamber Control	2 ppm	8 ppm	32 ppm
Urinary System				
Kidney	(50)	(50)	(50)	(50)
Cyst	1 (2%)	3 (6%)		4 (8%)
Hydronephrosis			2 (4%)	
Hyperplasia, oncocytic				1 (2%)
Infarct	1 (2%)	2 (4%)		1 (2%)
Mineralization	2 (4%)	2 (4%)	2 (4%)	28 (56%)
Nephropathy	50 (100%)	49 (98%)	50 (100%)	50 (100%)
Stromal hyperplasia			1 (2%)	
Papilla, necrosis	1 (2%)			
Renal tubule, hyperplasia	5 (10%)	5 (10%)	2 (4%)	6 (12%)
Urinary bladder	(50)	(50)	(50)	(50)
Inflammation, chronic active	1 (2%)	1 (2%)		1 (2%)
Necrosis	1 (2%)			
Transitional epithelium, hyperplasia		1 (2%)		

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

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TABLE B1
Summary of the Incidence of Neoplasms in Female Rats in the 2-Year Inhalation Study of Furfuryl Alcohol^a

	Chamber Control	2 ppm	8 ppm	32 ppm
Disposition Summary				
Animals initially in study	50	50	50	50
Early deaths				
Moribund	23	21	24	32
Natural deaths	1	3	3	2
Survivors				
Died last week of study		1		
Terminal sacrifice	26	25	22	16
Pregnant			1	
Animals examined microscopically	50	50	49	50
Alimentary System				
Intestine large, colon	(50)	(47)	(48)	(48)
Intestine large, rectum	(50)	(47)	(47)	(49)
Fibroma			1 (2%)	
Leiomyosarcoma			1 (2%)	
Intestine large, cecum	(49)	(47)	(46)	(48)
Intestine small, duodenum	(50)	(49)	(47)	(49)
Intestine small, jejunum	(49)	(47)	(47)	(48)
Adenocarcinoma			1 (2%)	
Intestine small, ileum	(49)	(47)	(46)	(48)
Liver	(50)	(49)	(49)	(50)
Hepatocellular adenoma	1 (2%)			
Histiocytic sarcoma		1 (2%)		1 (2%)
Osteosarcoma, metastatic, bone			2 (4%)	
Mesentery	(15)	(8)	(11)	(7)
Carcinoma, metastatic, kidney		1 (13%)		
Sarcoma stromal, metastatic, uterus				1 (14%)
Oral mucosa	(1)	(1)	(1)	
Pharyngeal, squamous cell papilloma	1 (100%)			
Pancreas	(49)	(49)	(48)	(50)
Carcinoma, metastatic, kidney		1 (2%)		
Salivary glands	(49)	(50)	(49)	(50)
Stomach, forestomach	(50)	(50)	(49)	(50)
Leiomyosarcoma				1 (2%)
Stomach, glandular	(50)	(49)	(49)	(50)
Tongue	(1)	(4)	(1)	(3)
Squamous cell carcinoma		1 (25%)		1 (33%)
Squamous cell papilloma		2 (50%)		1 (33%)
Cardiovascular System				
Heart	(50)	(50)	(49)	(50)
Endocrine System				
Adrenal cortex	(50)	(50)	(48)	(50)
Adenoma	2 (4%)			2 (4%)
Histiocytic sarcoma				1 (2%)
Osteosarcoma, metastatic, bone			1 (2%)	

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

	Chamber Control	2 ppm	8 ppm	32 ppm
Endocrine System (continued)				
Adrenal medulla	(50)	(50)	(48)	(50)
Histiocytic sarcoma				1 (2%)
Pheochromocytoma malignant	1 (2%)			
Pheochromocytoma complex		1 (2%)		
Pheochromocytoma benign	4 (8%)	5 (10%)	2 (4%)	5 (10%)
Bilateral, pheochromocytoma benign		2 (4%)	2 (4%)	2 (4%)
Islets, pancreatic	(49)	(48)	(48)	(50)
Adenoma	1 (2%)		3 (6%)	
Carcinoma		1 (2%)	1 (2%)	
Parathyroid gland	(46)	(43)	(44)	(46)
Adenoma				1 (2%)
Pituitary gland	(50)	(49)	(48)	(50)
Pars distalis, adenoma	38 (76%)	35 (71%)	34 (71%)	35 (70%)
Thyroid gland	(49)	(49)	(47)	(48)
C-cell, adenoma	7 (14%)	5 (10%)	6 (13%)	5 (10%)
C-cell, carcinoma	1 (2%)	1 (2%)	2 (4%)	
Follicular cell, adenoma				1 (2%)
Follicular cell, carcinoma		2 (4%)	1 (2%)	
General Body System				
None				
Genital System				
Clitoral gland	(44)	(45)	(46)	(45)
Adenoma	3 (7%)	2 (4%)	2 (4%)	7 (16%)
Carcinoma	3 (7%)		2 (4%)	1 (2%)
Bilateral, adenoma	1 (2%)			
Bilateral, carcinoma				1 (2%)
Ovary	(50)	(50)	(49)	(50)
Granulosa cell tumor benign		1 (2%)	1 (2%)	
Sertoli cell tumor benign				1 (2%)
Uterus	(50)	(50)	(49)	(50)
Adenoma	1 (2%)			
Leiomyosarcoma, metastatic, intestine large, rectum			1 (2%)	
Polyp stromal	5 (10%)	9 (18%)	6 (12%)	2 (4%)
Polyp stromal, multiple	1 (2%)			
Sarcoma stromal				2 (4%)
Schwannoma malignant	2 (4%)	1 (2%)		
Vagina		(1)	(3)	
Leiomyosarcoma, metastatic, intestine large, rectum			1 (33%)	
Polyp			1 (33%)	

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

	Chamber Control	2 ppm	8 ppm	32 ppm
Hematopoietic System				
Bone marrow	(49)	(48)	(48)	(50)
Lymph node	(4)	(5)	(8)	(11)
Lymph node, bronchial	(37)	(30)	(40)	(25)
Carcinoma, metastatic, thyroid gland	1 (3%)			
Histiocytic sarcoma				1 (4%)
Lymph node, mandibular	(46)	(46)	(46)	(42)
Lymph node, mesenteric	(50)	(50)	(49)	(50)
Carcinoma, metastatic, kidney		1 (2%)		
Lymph node, mediastinal	(43)	(37)	(45)	(40)
Carcinoma, metastatic, kidney		1 (3%)		
Spleen	(49)	(49)	(49)	(50)
Hemangiosarcoma	1 (2%)			
Histiocytic sarcoma				1 (2%)
Osteosarcoma, metastatic, bone			1 (2%)	
Sarcoma	1 (2%)			
Thymus	(47)	(44)	(44)	(43)
Integumentary System				
Mammary gland	(50)	(49)	(49)	(50)
Adenoma	1 (2%)			
Carcinoma	7 (14%)	2 (4%)	2 (4%)	5 (10%)
Carcinoma, multiple	2 (4%)			1 (2%)
Fibroadenoma	17 (34%)	17 (35%)	19 (39%)	14 (28%)
Fibroadenoma, multiple	2 (4%)	7 (14%)	6 (12%)	6 (12%)
Skin	(50)	(50)	(48)	(50)
Keratoacanthoma	1 (2%)	2 (4%)		
Squamous cell papilloma				1 (2%)
Subcutaneous tissue, fibroma			3 (6%)	2 (4%)
Musculoskeletal System				
Bone	(50)	(50)	(49)	(50)
Fibroma	1 (2%)			
Osteosarcoma			2 (4%)	1 (2%)
Nervous System				
Brain	(50)	(50)	(49)	(50)
Astrocytoma malignant		1 (2%)		
Histiocytic sarcoma				1 (2%)
Respiratory System				
Larynx	(50)	(49)	(49)	(49)
Carcinoma, metastatic, thyroid gland	1 (2%)			
Lung	(50)	(50)	(49)	(50)
Alveolar/bronchiolar adenoma	1 (2%)			
Alveolar/bronchiolar carcinoma			1 (2%)	
Carcinoma, metastatic, mammary gland		1 (2%)		
Carcinoma, metastatic, thyroid gland	1 (2%)			
Histiocytic sarcoma				1 (2%)
Osteosarcoma, metastatic, bone			2 (4%)	
Mediastinum, osteosarcoma, metastatic, bone			1 (2%)	

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

	Chamber Control	2 ppm	8 ppm	32 ppm
Respiratory System (continued)				
Nose	(49)	(50)	(48)	(49)
Lateral wall, adenoma			1 (2%)	
Respiratory epithelium, adenoma				1 (2%)
Special Senses System				
None				
Urinary System				
Kidney	(50)	(49)	(49)	(50)
Histiocytic sarcoma				1 (2%)
Renal tubule, adenoma				2 (4%)
Renal tubule, carcinoma		1 (2%)		
Transitional epithelium, carcinoma			1 (2%)	
Urinary bladder	(49)	(49)	(49)	(50)
Leiomyosarcoma, metastatic, intestine large, rectum			1 (2%)	
Transitional epithelium, carcinoma		1 (2%)		
Systemic Lesions				
Multiple organs ^b	(50)	(50)	(49)	(50)
Histiocytic sarcoma		1 (2%)		1 (2%)
Leukemia mononuclear	21 (42%)	19 (38%)	18 (37%)	29 (58%)
Lymphoma malignant			1 (2%)	
Neoplasm Summary				
Total animals with primary neoplasms ^c	49	49	49	49
Total primary neoplasms	127	119	120	131
Total animals with benign neoplasms	48	47	46	43
Total benign neoplasms	88	87	87	88
Total animals with malignant neoplasms	31	28	32	36
Total malignant neoplasms	39	32	33	43
Total animals with metastatic neoplasms	1	2	3	1
Total metastatic neoplasms	3	5	10	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 Furfuryl Alcohol: Chamber Control

	0	4	4	4	4	5	5	5	5	6	6	6	6	6	6	6	6	6	7	7	7	7	7	7		
Number of Days on Study	9	5	7	7	7	7	8	8	9	0	0	0	1	2	3	5	6	7	9	0	0	0	0	2	3	
	8	6	0	7	8	3	1	1	9	4	9	9	6	7	1	2	1	3	3	7	7	7	7	1	5	
Carcass ID Number	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	
	3	3	0	2	2	0	0	1	3	4	2	3	0	1	0	3	2	3	0	1	2	3	4	1	0	
	4	3	6	1	0	7	3	6	8	3	8	2	9	8	2	1	9	7	4	2	5	6	2	0	1	
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Hepatocellular adenoma																										
Mesentery								+									+	+	+					+		
Oral mucosa																										
Pharyngeal, squamous cell papilloma								+																		
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Tongue																								+		
Tooth	+																									
Cardiovascular System																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Adenoma																	X									
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Pheochromocytoma malignant																										
Pheochromocytoma benign																							X	X	X	
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	
Adenoma																										
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	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	
C-cell, adenoma							X						X				X							X		
C-cell, carcinoma												X														
General Body System																										
None																										
Genital System																										
Clitoral gland	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	M	+	+	M	M
Adenoma																										
Carcinoma																										
Bilateral, adenoma																						X				
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

+: Tissue examined microscopically
A: Autolysis precludes examination

M: Missing tissue
I: Insufficient tissue

X: Lesion present
Blank: Not examined

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

	Chamber Control	2 ppm	8 ppm	32 ppm
Adrenal Medulla: Benign Pheochromocytoma				
Overall rate ^a	4/50 (8%)	7/50 (14%)	4/48 (8%)	7/50 (14%)
Adjusted rate ^b	9.9%	16.7%	10.2%	18.6%
Terminal rate ^c	1/26 (4%)	5/26 (19%)	1/22 (5%)	3/16 (19%)
First incidence (days)	707	693	679	670
Poly-3 test ^d	P=0.260	P=0.278	P=0.629	P=0.217
Adrenal Medulla: Benign, Complex, or Malignant Pheochromocytoma				
Overall rate	5/50 (10%)	8/50 (16%)	4/48 (8%)	7/50 (14%)
Adjusted rate	12.4%	18.9%	10.2%	18.6%
Terminal rate	2/26 (8%)	5/26 (19%)	1/22 (5%)	3/16 (19%)
First incidence (days)	707	571	679	670
Poly-3 test	P=0.378	P=0.304	P=0.518N	P=0.327
Clitoral Gland: Adenoma				
Overall rate	4/44 (9%)	2/45 (4%)	2/46 (4%)	7/45 (16%)
Adjusted rate	11.3%	5.3%	5.3%	20.1%
Terminal rate	3/24 (13%)	1/23 (4%)	1/21 (5%)	2/14 (14%)
First incidence (days)	693	679	627	518
Poly-3 test	P=0.044	P=0.302N	P=0.307N	P=0.246
Clitoral Gland: Carcinoma				
Overall rate	3/44 (7%)	0/45 (0%)	2/46 (4%)	2/45 (4%)
Adjusted rate	8.5%	0.0%	5.3%	6.0%
Terminal rate	2/24 (8%)	0/23 (0%)	1/21 (5%)	2/14 (14%)
First incidence (days)	707	— ^e	522	735 (T)
Poly-3 test	P=0.514	P=0.105N	P=0.468N	P=0.529N
Clitoral Gland: Adenoma or Carcinoma				
Overall rate	7/44 (16%)	2/45 (4%)	4/46 (9%)	9/45 (20%)
Adjusted rate	19.8%	5.3%	10.5%	25.9%
Terminal rate	5/24 (21%)	1/23 (4%)	2/21 (10%)	4/14 (29%)
First incidence (days)	693	679	522	518
Poly-3 test	P=0.052	P=0.059N	P=0.214N	P=0.372
Mammary Gland: Fibroadenoma				
Overall rate	19/50 (38%)	24/50 (48%)	25/49 (51%)	20/50 (40%)
Adjusted rate	45.5%	54.7%	57.5%	50.4%
Terminal rate	11/26 (42%)	17/26 (65%)	13/22 (59%)	10/16 (63%)
First incidence (days)	627	497	546	497
Poly-3 test	P=0.556N	P=0.254	P=0.176	P=0.407
Mammary Gland: Fibroadenoma or Adenoma				
Overall rate	20/50 (40%)	24/50 (48%)	25/49 (51%)	20/50 (40%)
Adjusted rate	47.9%	54.7%	57.5%	50.4%
Terminal rate	12/26 (46%)	17/26 (65%)	13/22 (59%)	10/16 (63%)
First incidence (days)	627	497	546	497
Poly-3 test	P=0.506N	P=0.333	P=0.242	P=0.496
Mammary Gland: Carcinoma				
Overall rate	9/50 (18%)	2/50 (4%)	2/49 (4%)	6/50 (12%)
Adjusted rate	22.1%	4.7%	5.0%	15.7%
Terminal rate	5/26 (19%)	0/26 (0%)	1/22 (5%)	2/16 (13%)
First incidence (days)	661	497	679	518
Poly-3 test	P=0.433	P=0.019N	P=0.025N	P=0.332N

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

	Chamber Control	2 ppm	8 ppm	32 ppm
Mammary Gland: Adenoma or Carcinoma				
Overall rate	10/50 (20%)	2/50 (4%)	2/49 (4%)	6/50 (12%)
Adjusted rate	24.6%	4.7%	5.0%	15.7%
Terminal rate	6/26 (23%)	0/26 (0%)	1/22 (5%)	2/16 (13%)
First incidence (days)	661	497	679	518
Poly-3 test	P=0.510	P=0.010N	P=0.013N	P=0.243N
Mammary Gland: Fibroadenoma, Adenoma, or Carcinoma				
Overall rate	25/50 (50%)	25/50 (50%)	26/49 (53%)	23/50 (46%)
Adjusted rate	59.2%	56.7%	59.5%	56.8%
Terminal rate	15/26 (58%)	17/26 (65%)	13/22 (59%)	11/16 (69%)
First incidence (days)	627	497	546	497
Poly-3 test	P=0.498N	P=0.494N	P=0.578	P=0.500N
Oral Cavity (Oral Mucosa or Tongue): Squamous Cell Papilloma or Squamous Cell Carcinoma				
Overall rate	1/50 (2%)	3/50 (6%)	0/49 (0%)	2/50 (4%)
Adjusted rate	2.4%	7.1%	0.0%	5.3%
Terminal rate	0/26 (0%)	2/26 (8%)	0/22 (0%)	0/16 (0%)
First incidence (days)	478	469	—	639
Poly-3 test	P=0.535	P=0.318	P=0.506N	P=0.471
Pancreatic Islets: Adenoma				
Overall rate	1/49 (2%)	0/48 (0%)	3/48 (6%)	0/50 (0%)
Adjusted rate	2.6%	0.0%	7.7%	0.0%
Terminal rate	1/26 (4%)	0/26 (0%)	3/22 (14%)	0/16 (0%)
First incidence (days)	735 (T)	—	735 (T)	—
Poly-3 test	P=0.442N	P=0.494N	P=0.304	P=0.511N
Pancreatic Islets: Adenoma or Carcinoma				
Overall rate	1/49 (2%)	1/48 (2%)	4/48 (8%)	0/50 (0%)
Adjusted rate	2.6%	2.5%	10.2%	0.0%
Terminal rate	1/26 (4%)	0/26 (0%)	4/22 (18%)	0/16 (0%)
First incidence (days)	735 (T)	732	735 (T)	—
Poly-3 test	P=0.325N	P=0.754N	P=0.176	P=0.511N
Pituitary Gland (Pars Distalis): Adenoma				
Overall rate	38/50 (76%)	35/49 (71%)	34/48 (71%)	35/50 (70%)
Adjusted rate	82.4%	75.7%	76.4%	79.6%
Terminal rate	21/26 (81%)	20/26 (77%)	17/22 (77%)	12/16 (75%)
First incidence (days)	477	469	546	478
Poly-3 test	P=0.545	P=0.285N	P=0.315N	P=0.466N
Skin (Subcutaneous Tissue): Fibroma				
Overall rate	0/50 (0%)	0/50 (0%)	3/49 (6%)	2/50 (4%)
Adjusted rate	0.0%	0.0%	7.5%	5.4%
Terminal rate	0/26 (0%)	0/26 (0%)	2/22 (9%)	0/16 (0%)
First incidence (days)	—	—	694	711
Poly-3 test	P=0.168	— ^f	P=0.116	P=0.220
Thyroid Gland (C-cell): Adenoma				
Overall rate	7/49 (14%)	5/49 (10%)	6/47 (13%)	5/48 (10%)
Adjusted rate	17.2%	12.0%	15.2%	13.5%
Terminal rate	3/26 (12%)	2/26 (8%)	3/22 (14%)	2/16 (13%)
First incidence (days)	477	679	547	438
Poly-3 test	P=0.500N	P=0.364N	P=0.526N	P=0.443N

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

	Chamber Control	2 ppm	8 ppm	32 ppm
Thyroid Gland (C-cell): Adenoma or Carcinoma				
Overall rate	8/49 (16%)	6/49 (12%)	8/47 (17%)	5/48 (10%)
Adjusted rate	19.4%	14.4%	20.1%	13.5%
Terminal rate	3/26 (12%)	2/26 (8%)	4/22 (18%)	2/16 (13%)
First incidence (days)	477	677	547	438
Poly-3 test	P=0.367N	P=0.374N	P=0.582	P=0.342N
Tongue: Squamous Cell Papilloma or Squamous Cell Carcinoma				
Overall rate	0/50 (0%)	3/50 (6%)	0/49 (0%)	2/50 (4%)
Adjusted rate	0.0%	7.1%	0.0%	5.3%
Terminal rate	0/26 (0%)	2/26 (8%)	0/22 (0%)	0/16 (0%)
First incidence (days)	—	469	—	639
Poly-3 test	P=0.403	P=0.128	—	P=0.222
Uterus: Stromal Polyp				
Overall rate	6/50 (12%)	9/50 (18%)	6/49 (12%)	2/50 (4%)
Adjusted rate	14.7%	21.2%	14.9%	5.3%
Terminal rate	4/26 (15%)	5/26 (19%)	5/22 (23%)	0/16 (0%)
First incidence (days)	581	637	547	599
Poly-3 test	P=0.058N	P=0.314	P=0.612	P=0.158N
Uterus: Stromal Polyp or Stromal Sarcoma				
Overall rate	6/50 (12%)	9/50 (18%)	6/49 (12%)	4/50 (8%)
Adjusted rate	14.7%	21.2%	14.9%	10.2%
Terminal rate	4/26 (15%)	5/26 (19%)	5/22 (23%)	0/16 (0%)
First incidence (days)	581	637	547	429
Poly-3 test	P=0.200N	P=0.314	P=0.612	P=0.397N
All Organs: Mononuclear Cell Leukemia				
Overall rate	21/50 (42%)	19/50 (38%)	18/49 (37%)	29/50 (58%)
Adjusted rate	46.7%	44.0%	41.2%	66.3%
Terminal rate	8/26 (31%)	9/26 (35%)	5/22 (23%)	12/16 (75%)
First incidence (days)	456	628	518	438
Poly-3 test	P=0.011	P=0.484N	P=0.375N	P=0.043
All Organs: Benign Neoplasms				
Overall rate	48/50 (96%)	47/50 (94%)	46/49 (94%)	43/50 (86%)
Adjusted rate	99.5%	96.6%	96.7%	93.8%
Terminal rate	26/26 (100%)	25/26 (96%)	22/22 (100%)	16/16 (100%)
First incidence (days)	470	469	546	438
Poly-3 test	P=0.113N	P=0.358N	P=0.376N	P=0.092N
All Organs: Malignant Neoplasms				
Overall rate	31/50 (62%)	28/50 (56%)	32/49 (65%)	36/50 (72%)
Adjusted rate	67.6%	59.2%	68.5%	77.8%
Terminal rate	15/26 (58%)	10/26 (39%)	12/22 (55%)	13/16 (81%)
First incidence (days)	456	428	518	429
Poly-3 test	P=0.058	P=0.262N	P=0.553	P=0.181

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

	Chamber Control	2 ppm	8 ppm	32 ppm
All Organs: Benign or Malignant Neoplasms				
Overall rate	49/50 (98%)	49/50 (98%)	49/49 (100%)	49/50 (98%)
Adjusted rate	100.0%	98.0%	100.0%	99.9%
Terminal rate	26/26 (100%)	25/26 (96%)	22/22 (100%)	16/16 (100%)
First incidence (days)	456	428	518	429
Poly-3 test	P=0.649	P=0.505N	P=1.000	P=1.000N

(T)Terminal sacrifice

^a Number of neoplasm-bearing animals/number of animals examined. Denominator is number of animals examined microscopically for adrenal gland, clitoral gland, pancreatic islets, 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 Nasal Adenoma in Chamber Control Female F344/N Rats^a

Study	Incidence in Controls
Historical Incidence at Battelle Pacific Northwest Laboratories	
Acetonitrile	0/47
α -Chloroacetophenone	0/48
Cobalt Sulfate Heptahydrate	0/50
Epinephrine Hydrochloride	1/50
Hexachlorocyclopentadiene	0/50
Isobutyraldehyde	0/49
Molybdenum Trioxide	0/48
Nitromethane	0/50
<i>o</i> -Chlorobenzalmononitrile	0/49
Ozone	0/50
Tetrafluoroethylene	0/50
Tetrahydrofuran	0/49
Overall Historical Incidence	
Total	1/892 (0.1%)
Standard deviation	0.5%
Range	0%-2%

^a Data as of 15 October 1996

TABLE B4b
Historical Incidence of Renal Tubule Neoplasms in Chamber Control Female F344/N Rats^a

Study	Incidence in Controls		
	Adenoma	Carcinoma	Adenoma or Carcinoma
Historical Incidence at Battelle Pacific Northwest Laboratories			
Acetonitrile	0/48	0/48	0/48
α -Chloroacetophenone	0/49	0/49	0/49
Cobalt Sulfate Heptahydrate	0/49	1/49	1/49
Epinephrine Hydrochloride	0/50	0/50	0/50
Hexachlorocyclopentadiene	0/50	1/50	1/50
Isobutyraldehyde	0/49	0/49	0/49
Molybdenum Trioxide	0/50	0/50	0/50
Nitromethane	0/50	1/50	1/50
<i>o</i> -Chlorobenzalmononitrile	0/49	0/49	0/49
Ozone	1/50	0/50	1/50
Tetrafluoroethylene	0/50	0/50	0/50
Tetrahydrofuran	0/50	1/50	1/50
Overall Historical Incidence			
Total	1/898 (0.1%)	4/898 (0.5%)	5/898 (0.6%)
Standard deviation	0.5%	0.9%	0.9%
Range	0%-2%	0%-2%	0%-2%

^a Data as of 15 October 1996

TABLE B5
Summary of the Incidence of Nonneoplastic Lesions in Female Rats in the 2-Year Inhalation Study of Furfuryl Alcohol^a

	Chamber Control	2 ppm	8 ppm	32 ppm
Disposition Summary				
Animals initially in study	50	50	50	50
Early deaths				
Moribund	23	21	24	32
Natural deaths	1	3	3	2
Survivors				
Died last week of study		1		
Terminal sacrifice	26	25	22	16
Pregnant			1	
Animals examined microscopically	50	50	49	50
Alimentary System				
Intestine large, colon	(50)	(47)	(48)	(48)
Parasite metazoan	2 (4%)	3 (6%)	2 (4%)	3 (6%)
Intestine large, rectum	(50)	(47)	(47)	(49)
Parasite metazoan	4 (8%)	3 (6%)	3 (6%)	3 (6%)
Intestine large, cecum	(49)	(47)	(46)	(48)
Parasite metazoan	5 (10%)	4 (9%)	8 (17%)	4 (8%)
Intestine small, ileum	(49)	(47)	(46)	(48)
Parasite metazoan	1 (2%)			
Liver	(50)	(49)	(49)	(50)
Angiectasis	3 (6%)	2 (4%)	3 (6%)	5 (10%)
Basophilic focus	30 (60%)	31 (63%)	34 (69%)	22 (44%)
Clear cell focus	5 (10%)	6 (12%)	6 (12%)	3 (6%)
Cyst	1 (2%)			
Degeneration, cystic			1 (2%)	1 (2%)
Degeneration, fatty	13 (26%)	9 (18%)	10 (20%)	17 (34%)
Eosinophilic focus	3 (6%)	2 (4%)	4 (8%)	1 (2%)
Hematopoietic cell proliferation		1 (2%)		
Hepatodiaphragmatic nodule	4 (8%)	7 (14%)	6 (12%)	4 (8%)
Infiltration cellular, histiocyte	1 (2%)			
Inflammation, granulomatous			1 (2%)	
Mixed cell focus	9 (18%)	13 (27%)	9 (18%)	8 (16%)
Necrosis	1 (2%)	1 (2%)		2 (4%)
Regeneration		1 (2%)		1 (2%)
Thrombosis	1 (2%)			
Vacuolization cytoplasmic, focal		1 (2%)		
Bile duct, hyperplasia	6 (12%)	7 (14%)	6 (12%)	7 (14%)
Centrilobular, necrosis	6 (12%)	6 (12%)	8 (16%)	9 (18%)
Mesentery	(15)	(8)	(11)	(7)
Fat, hemorrhage	1 (7%)			
Fat, necrosis	13 (87%)	7 (88%)	11 (100%)	6 (86%)
Oral mucosa	(1)	(1)	(1)	
Pharyngeal, hyperplasia, squamous		1 (100%)	1 (100%)	
Pancreas	(49)	(49)	(48)	(50)
Atrophy	10 (20%)	11 (22%)	11 (23%)	11 (22%)
Basophilic focus	4 (8%)	1 (2%)	1 (2%)	1 (2%)
Hyperplasia	1 (2%)	1 (2%)		
Metaplasia, hepatocyte				1 (2%)
Salivary glands	(49)	(50)	(49)	(50)
Atrophy				1 (2%)
Necrosis				1 (2%)

^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 Furfuryl Alcohol

	Chamber Control	2 ppm	8 ppm	32 ppm
Alimentary System (continued)				
Stomach, forestomach	(50)	(50)	(49)	(50)
Hyperplasia, squamous		1 (2%)	1 (2%)	
Inflammation, acute			1 (2%)	
Mineralization	1 (2%)			
Necrosis	5 (10%)	6 (12%)	5 (10%)	12 (24%)
Stomach, glandular	(50)	(49)	(49)	(50)
Mineralization	2 (4%)	2 (4%)	1 (2%)	1 (2%)
Necrosis	1 (2%)	2 (4%)	3 (6%)	7 (14%)
Tongue	(1)	(4)	(1)	(3)
Hyperplasia, squamous				1 (33%)
Tooth	(1)			(1)
Degeneration				1 (100%)
Pulp, necrosis	1 (100%)			
Cardiovascular System				
Blood vessel		(1)		
Aorta, mineralization		1 (100%)		
Heart	(50)	(50)	(49)	(50)
Cardiomyopathy	29 (58%)	24 (48%)	23 (47%)	19 (38%)
Artery, mineralization		1 (2%)		
Atrium, thrombosis	3 (6%)	3 (6%)		
Endocrine System				
Adrenal cortex	(50)	(50)	(48)	(50)
Angiectasis	1 (2%)		1 (2%)	
Degeneration, cystic		1 (2%)		
Hyperplasia	19 (38%)	22 (44%)	21 (44%)	23 (46%)
Hypertrophy	2 (4%)	4 (8%)	6 (13%)	2 (4%)
Necrosis	4 (8%)	1 (2%)		1 (2%)
Vacuolization cytoplasmic	5 (10%)	3 (6%)	3 (6%)	8 (16%)
Adrenal medulla	(50)	(50)	(48)	(50)
Hyperplasia	12 (24%)	7 (14%)	10 (21%)	14 (28%)
Islets, pancreatic	(49)	(48)	(48)	(50)
Hyperplasia			2 (4%)	
Parathyroid gland	(46)	(43)	(44)	(46)
Hyperplasia	1 (2%)	1 (2%)	1 (2%)	1 (2%)
Pituitary gland	(50)	(49)	(48)	(50)
Cyst			1 (2%)	
Pars distalis, angiectasis			3 (6%)	
Pars distalis, hyperplasia	8 (16%)	10 (20%)	7 (15%)	9 (18%)
Thyroid gland	(49)	(49)	(47)	(48)
C-cell, hyperplasia	40 (82%)	41 (84%)	35 (74%)	39 (81%)
General Body System				
None				

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

	Chamber Control	2 ppm	8 ppm	32 ppm
Genital System				
Clitoral gland	(44)	(45)	(46)	(45)
Hyperplasia	1 (2%)	5 (11%)	2 (4%)	1 (2%)
Inflammation, chronic active	2 (5%)	3 (7%)	1 (2%)	
Ovary	(50)	(50)	(49)	(50)
Cyst	3 (6%)	5 (10%)	6 (12%)	7 (14%)
Hematopoietic System				
Bone marrow	(49)	(48)	(48)	(50)
Hyperplasia, histiocytic	2 (4%)	1 (2%)	1 (2%)	
Lymph node	(4)	(5)	(8)	(11)
Renal, ectasia				1 (9%)
Renal, hemorrhage		1 (20%)	1 (13%)	1 (9%)
Renal, pigmentation			1 (13%)	
Lymph node, mesenteric	(50)	(50)	(49)	(50)
Hemorrhage			1 (2%)	
Lymph node, mediastinal	(43)	(37)	(45)	(40)
Hemorrhage			1 (2%)	1 (3%)
Spleen	(49)	(49)	(49)	(50)
Accessory spleen			2 (4%)	1 (2%)
Fibrosis	5 (10%)	3 (6%)	3 (6%)	5 (10%)
Hematopoietic cell proliferation	2 (4%)	4 (8%)	2 (4%)	5 (10%)
Hemorrhage	1 (2%)		1 (2%)	
Hyperplasia, focal	1 (2%)			
Inflammation, granulomatous	1 (2%)			1 (2%)
Metaplasia, lipocyte	1 (2%)			
Necrosis	1 (2%)	1 (2%)		
Integumentary System				
Mammary gland	(50)	(49)	(49)	(50)
Galactocele	3 (6%)	2 (4%)	1 (2%)	5 (10%)
Hyperplasia, atypical				1 (2%)
Necrosis		1 (2%)		
Skin	(50)	(50)	(48)	(50)
Cyst epithelial inclusion	1 (2%)			
Hyperkeratosis				1 (2%)
Inflammation, chronic active		2 (4%)		
Subcutaneous tissue, necrosis				1 (2%)
Tail, hyperkeratosis				1 (2%)
Tail, inflammation, chronic active				5 (10%)
Musculoskeletal System				
Bone	(50)	(50)	(49)	(50)
Fibrous osteodystrophy		1 (2%)		1 (2%)
Hyperostosis	8 (16%)	14 (28%)	12 (24%)	6 (12%)
Inflammation, chronic				1 (2%)
Nervous System				
None				

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

	Chamber Control	2 ppm	8 ppm	32 ppm
Respiratory System				
Larynx	(50)	(49)	(49)	(49)
Epiglottis, metaplasia, squamous	1 (2%)			
Lung	(50)	(50)	(49)	(50)
Foreign body				1 (2%)
Infiltration cellular, histiocyte	2 (4%)			
Inflammation, granulomatous	1 (2%)		2 (4%)	3 (6%)
Inflammation, suppurative	1 (2%)			
Mineralization		1 (2%)		
Alveolar epithelium, hyperplasia	9 (18%)	16 (32%)	13 (27%)	12 (24%)
Mediastinum, inflammation, granulomatous				1 (2%)
Perivascular, infiltration cellular, mononuclear cell	1 (2%)			
Nose	(49)	(50)	(48)	(49)
Inflammation, suppurative	4 (8%)	1 (2%)	5 (10%)	23 (47%)
Thrombosis	7 (14%)	3 (6%)	6 (13%)	5 (10%)
Glands, hyperplasia			24 (50%)	46 (94%)
Lateral wall, hyperplasia		39 (78%)	48 (100%)	49 (100%)
Lateral wall, metaplasia, squamous		1 (2%)		24 (49%)
Olfactory epithelium, atrophy		6 (12%)	44 (92%)	49 (100%)
Olfactory epithelium, degeneration, hyaline	43 (88%)	50 (100%)	47 (98%)	48 (98%)
Olfactory epithelium, fibrosis			16 (33%)	31 (63%)
Olfactory epithelium, hyperplasia			31 (65%)	41 (84%)
Olfactory epithelium, metaplasia		5 (10%)	37 (77%)	48 (98%)
Respiratory epithelium, degeneration, hyaline	23 (47%)	39 (78%)	45 (94%)	6 (12%)
Respiratory epithelium, hyperplasia		18 (36%)	40 (83%)	49 (100%)
Respiratory epithelium, metaplasia, squamous			2 (4%)	10 (20%)
Special Senses System				
Eye	(1)		(1)	(1)
Cataract	1 (100%)		1 (100%)	
Retina, atrophy	1 (100%)		1 (100%)	
Urinary System				
Kidney	(50)	(49)	(49)	(50)
Cyst				1 (2%)
Hydronephrosis		1 (2%)		
Infarct	2 (4%)	1 (2%)		
Infiltration cellular, histiocyte	1 (2%)			
Mineralization		1 (2%)		
Nephropathy	47 (94%)	45 (92%)	47 (96%)	47 (94%)
Renal tubule, hyperplasia				2 (4%)
Urinary bladder	(49)	(49)	(49)	(50)
Transitional epithelium, hyperplasia			2 (4%)	1 (2%)

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

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TABLE C1
Summary of the Incidence of Neoplasms in Male Mice in the 2-Year Inhalation Study of Furfuryl Alcohol^a

	Chamber Control	2 ppm	8 ppm	32 ppm
Disposition Summary				
Animals initially in study	50	50	50	50
Early deaths				
Moribund	11	10	14	8
Natural deaths	5	4	6	4
Survivors				
Terminal sacrifice	34	36	30	38
Animals examined microscopically	50	50	50	50
Alimentary System				
Intestine small, duodenum	(48)	(48)	(46)	(47)
Intestine small, jejunum	(47)	(47)	(45)	(47)
Carcinoma		1 (2%)	1 (2%)	
Intestine small, ileum	(46)	(48)	(46)	(47)
Liver	(50)	(50)	(49)	(50)
Hemangiosarcoma		5 (10%)		3 (6%)
Hepatoblastoma	1 (2%)			
Hepatocellular carcinoma	13 (26%)	17 (34%)	11 (22%)	12 (24%)
Hepatocellular carcinoma, multiple	2 (4%)	2 (4%)	3 (6%)	1 (2%)
Hepatocellular adenoma	7 (14%)	12 (24%)	5 (10%)	11 (22%)
Hepatocellular adenoma, multiple	6 (12%)	1 (2%)	5 (10%)	2 (4%)
Hepatocholangiocarcinoma		1 (2%)		
Mesentery	(7)	(4)	(7)	(3)
Hemangioma			1 (14%)	
Oral mucosa	(1)			
Pharyngeal, squamous cell carcinoma	1 (100%)			
Pancreas	(50)	(49)	(48)	(49)
Hemangiosarcoma			1 (2%)	
Stomach, forestomach	(50)	(49)	(50)	(50)
Squamous cell carcinoma				1 (2%)
Squamous cell papilloma		1 (2%)		
Stomach, glandular	(50)	(48)	(47)	(48)
Sarcoma			1 (2%)	
Tooth	(2)	(1)	(1)	
Odontoma	1 (50%)	1 (100%)		
Cardiovascular System				
Heart	(50)	(50)	(50)	(50)
Hepatocholangiocarcinoma, metastatic, liver		1 (2%)		1 (2%)
Endocrine System				
Adrenal cortex	(50)	(49)	(49)	(48)
Adenoma	2 (4%)			
Hepatocellular carcinoma, metastatic, liver				1 (2%)
Capsule, adenoma	4 (8%)	2 (4%)		1 (2%)
Adrenal medulla	(50)	(49)	(48)	(48)
Pheochromocytoma malignant			1 (2%)	
Islets, pancreatic	(50)	(49)	(48)	(48)
Adenoma	2 (4%)	1 (2%)	2 (4%)	
Pituitary gland	(50)	(48)	(48)	(49)
Schwannoma malignant, metastatic, nose	1 (2%)			
Pars distalis, adenoma			1 (2%)	
Thyroid gland	(50)	(49)	(49)	(48)
Follicular cell, adenoma	1 (2%)		1 (2%)	

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

	Chamber Control	2 ppm	8 ppm	32 ppm
General Body System				
None				
Genital System				
Epididymis	(50)	(50)	(49)	(50)
Leiomyoma	1 (2%)			
Testes	(50)	(50)	(49)	(50)
Interstitial cell, adenoma		1 (2%)		1 (2%)
Hematopoietic System				
Lymph node	(2)	(2)	(1)	(1)
Lymph node, bronchial	(27)	(22)	(27)	(28)
Alveolar/bronchiolar carcinoma, metastatic, lung			1 (4%)	
Hepatocholangiocarcinoma, metastatic, liver		1 (5%)		1 (4%)
Lymph node, mandibular	(28)	(33)	(23)	(28)
Lymph node, mesenteric	(50)	(46)	(46)	(47)
Lymph node, mediastinal	(40)	(39)	(38)	(31)
Alveolar/bronchiolar carcinoma, metastatic, lung			1 (3%)	
Spleen	(50)	(49)	(49)	(50)
Hemangiosarcoma			1 (2%)	
Thymus	(35)	(31)	(36)	(36)
Hepatocholangiocarcinoma, metastatic, liver		1 (3%)		
Integumentary System				
Skin	(50)	(50)	(48)	(49)
Hemangioma		1 (2%)		
Histiocytic sarcoma			1 (2%)	
Subcutaneous tissue, hemangioma		1 (2%)		
Subcutaneous tissue, hemangiosarcoma			1 (2%)	
Subcutaneous tissue, histiocytic sarcoma			1 (2%)	
Subcutaneous tissue, sarcoma, multiple	1 (2%)			
Subcutaneous tissue, schwannoma malignant				1 (2%)
Musculoskeletal System				
Bone	(50)	(50)	(50)	(50)
Maxilla, hemangiosarcoma	1 (2%)			
Skeletal muscle			(1)	(1)
Hemangiosarcoma				1 (100%)
Nervous System				
Brain	(50)	(50)	(49)	(50)
Meningioma benign				1 (2%)
Meninges, schwannoma malignant, metastatic, nose	1 (2%)			

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

	Chamber Control	2 ppm	8 ppm	32 ppm
Respiratory System				
Lung	(50)	(50)	(49)	(50)
Alveolar/bronchiolar adenoma	14 (28%)	15 (30%)	9 (18%)	12 (24%)
Alveolar/bronchiolar adenoma, multiple	2 (4%)	1 (2%)	1 (2%)	2 (4%)
Alveolar/bronchiolar carcinoma	3 (6%)	7 (14%)	7 (14%)	8 (16%)
Alveolar/bronchiolar carcinoma, multiple	1 (2%)		1 (2%)	
Carcinoma, metastatic, harderian gland	1 (2%)			1 (2%)
Hepatocellular carcinoma, metastatic, liver	2 (4%)	4 (8%)	3 (6%)	4 (8%)
Hepatocholangiocarcinoma, metastatic, liver		1 (2%)		1 (2%)
Mediastinum, alveolar/bronchiolar carcinoma, metastatic, lung			1 (2%)	
Mediastinum, hepatocholangiocarcinoma, metastatic, liver		1 (2%)		1 (2%)
Nose	(50)	(49)	(49)	(50)
Carcinoma, metastatic, harderian gland	1 (2%)			
Schwannoma malignant	1 (2%)			
Special Senses System				
Harderian gland	(4)	(4)	(5)	(3)
Adenoma	3 (75%)	3 (75%)	5 (100%)	2 (67%)
Carcinoma	1 (25%)			1 (33%)
Urinary System				
Kidney	(50)	(49)	(49)	(50)
Hepatocholangiocarcinoma, metastatic, liver		1 (2%)		1 (2%)
Renal tubule, adenoma				2 (4%)
Renal tubule, carcinoma				1 (2%)
Renal tubule, carcinoma, multiple				1 (2%)
Systemic Lesions				
Multiple organs ^b	(50)	(50)	(50)	(50)
Histiocytic sarcoma			2 (4%)	
Lymphoma malignant	3 (6%)	3 (6%)	1 (2%)	2 (4%)
Neoplasm Summary				
Total animals with primary neoplasms ^c	42	44	41	39
Total primary neoplasms	70	76	61	66
Total animals with benign neoplasms	31	31	25	29
Total benign neoplasms	43	40	30	34
Total animals with malignant neoplasms	22	30	26	25
Total malignant neoplasms	27	36	31	32
Total animals with metastatic neoplasms	4	5	5	7
Total metastatic neoplasms	7	10	6	11

^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 C3
Statistical Analysis of Primary Neoplasms in Male Mice in the 2-Year Inhalation Study of Furfuryl Alcohol

	Chamber Control	2 ppm	8 ppm	32 ppm
Adrenal Cortex: Adenoma				
Overall rate ^a	6/50 (12%)	2/49 (4%)	0/49 (0%)	1/48 (2%)
Adjusted rate ^b	13.7%	4.7%	0.0%	2.3%
Terminal rate ^c	4/34 (12%)	2/36 (6%)	0/30 (0%)	0/37 (0%)
First incidence (days)	567	733 (T)	— ^e	646
Poly-3 test ^d	P=0.094N	P=0.139N	P=0.022N	P=0.054N
Harderian Gland: Adenoma				
Overall rate	3/50 (6%)	3/50 (6%)	5/50 (10%)	2/50 (4%)
Adjusted rate	7.0%	6.9%	12.5%	4.4%
Terminal rate	3/34 (9%)	2/36 (6%)	4/30 (13%)	1/38 (3%)
First incidence (days)	733 (T)	632	317	716
Poly-3 test	P=0.330N	P=0.661N	P=0.315	P=0.472N
Harderian Gland: Adenoma or Carcinoma				
Overall rate	4/50 (8%)	3/50 (6%)	5/50 (10%)	3/50 (6%)
Adjusted rate	9.1%	6.9%	12.5%	6.5%
Terminal rate	3/34 (9%)	2/36 (6%)	4/30 (13%)	1/38 (3%)
First incidence (days)	465	632	317	707
Poly-3 test	P=0.427N	P=0.508N	P=0.442	P=0.474N
Kidney (Renal Tubule): Adenoma or Carcinoma (Single Sections)				
Overall rate	0/50 (0%)	0/49 (0%)	0/49 (0%)	4/50 (8%)
Adjusted rate	0.0%	0.0%	0.0%	8.7%
Terminal rate	0/34 (0%)	0/36 (0%)	0/30 (0%)	4/38 (11%)
First incidence (days)	—	—	—	733 (T)
Poly-3 test	P=0.002	— ^f	—	P=0.068
Kidney (Renal Tubule): Adenoma (Single and Step Sections)				
Overall rate	0/50 (0%)	0/49 (0%)	0/49 (0%)	3/50 (6%)
Adjusted rate	0.0%	0.0%	0.0%	6.6%
Terminal rate	0/34 (0%)	0/36 (0%)	0/30 (0%)	3/38 (8%)
First incidence (days)	—	—	—	733 (T)
Poly-3 test	P=0.009	—	—	P=0.130
Kidney (Renal Tubule): Adenoma or Carcinoma (Single and Step Sections)				
Overall rate	0/50 (0%)	0/49 (0%)	0/49 (0%)	5/50 (10%)
Adjusted rate	0.0%	0.0%	0.0%	10.9%
Terminal rate	0/34 (0%)	0/36 (0%)	0/30 (0%)	5/38 (13%)
First incidence (days)	—	—	—	733 (T)
Poly-3 test	P<0.001	—	—	P=0.036
Liver: Hemangiosarcoma				
Overall rate	0/50 (0%)	5/50 (10%)	0/49 (0%)	3/50 (6%)
Adjusted rate	0.0%	11.5%	0.0%	6.5%
Terminal rate	0/34 (0%)	3/36 (8%)	0/30 (0%)	2/38 (5%)
First incidence (days)	—	632	—	637
Poly-3 test	P=0.428	P=0.031	—	P=0.131
Liver: Hepatocellular Adenoma				
Overall rate	13/50 (26%)	13/50 (26%)	10/49 (20%)	13/50 (26%)
Adjusted rate	30.2%	29.0%	24.7%	27.4%
Terminal rate	13/34 (38%)	10/36 (28%)	7/30 (23%)	9/38 (24%)
First incidence (days)	733 (T)	433	471	582
Poly-3 test	P=0.483N	P=0.546N	P=0.374N	P=0.479N

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

	Chamber Control	2 ppm	8 ppm	32 ppm
Liver: Hepatocellular Carcinoma				
Overall rate	15/50 (30%)	19/50 (38%)	14/49 (29%)	13/50 (26%)
Adjusted rate	31.2%	39.8%	30.8%	26.9%
Terminal rate	3/34 (9%)	9/36 (25%)	3/30 (10%)	5/38 (13%)
First incidence (days)	465	270	400	382
Poly-3 test	P=0.208N	P=0.251	P=0.572N	P=0.407N
Liver: Hepatocellular Adenoma or Carcinoma				
Overall rate	28/50 (56%)	27/50 (54%)	23/49 (47%)	22/50 (44%)
Adjusted rate	58.2%	56.6%	49.7%	45.0%
Terminal rate	16/34 (47%)	17/36 (47%)	10/30 (33%)	12/38 (32%)
First incidence (days)	465	270	400	382
Poly-3 test	P=0.108N	P=0.519N	P=0.264N	P=0.135N
Liver: Hepatocellular Carcinoma or Hepatoblastoma				
Overall rate	15/50 (30%)	19/50 (38%)	14/49 (29%)	13/50 (26%)
Adjusted rate	31.2%	39.8%	30.8%	26.9%
Terminal rate	3/34 (9%)	9/36 (25%)	3/30 (10%)	5/38 (13%)
First incidence (days)	465	270	400	382
Poly-3 test	P=0.208N	P=0.251	P=0.572N	P=0.407N
Liver: Hepatocellular Adenoma, Hepatocellular Carcinoma, or Hepatoblastoma				
Overall rate	28/50 (56%)	27/50 (54%)	23/49 (47%)	22/50 (44%)
Adjusted rate	58.2%	56.6%	49.7%	45.0%
Terminal rate	16/34 (47%)	17/36 (47%)	10/30 (33%)	12/38 (32%)
First incidence (days)	465	270	400	382
Poly-3 test	P=0.108N	P=0.519N	P=0.264N	P=0.135N
Lung: Alveolar/bronchiolar Adenoma				
Overall rate	16/50 (32%)	16/50 (32%)	10/49 (20%)	14/50 (28%)
Adjusted rate	37.0%	36.1%	25.6%	30.2%
Terminal rate	15/34 (44%)	13/36 (36%)	9/30 (30%)	12/38 (32%)
First incidence (days)	697	287	712	582
Poly-3 test	P=0.312N	P=0.554N	P=0.189N	P=0.322N
Lung: Alveolar/bronchiolar Carcinoma				
Overall rate	4/50 (8%)	7/50 (14%)	8/49 (16%)	8/50 (16%)
Adjusted rate	9.2%	16.3%	19.9%	17.4%
Terminal rate	3/34 (9%)	7/36 (19%)	6/30 (20%)	7/38 (18%)
First incidence (days)	687	733 (T)	502	716
Poly-3 test	P=0.324	P=0.254	P=0.140	P=0.205
Lung: Alveolar/bronchiolar Adenoma or Carcinoma				
Overall rate	20/50 (40%)	23/50 (46%)	17/49 (35%)	20/50 (40%)
Adjusted rate	46.1%	51.9%	42.2%	43.1%
Terminal rate	18/34 (53%)	20/36 (56%)	14/30 (47%)	17/38 (45%)
First incidence (days)	687	287	502	582
Poly-3 test	P=0.332N	P=0.368	P=0.444N	P=0.470N
All Organs: Hemangiosarcoma				
Overall rate	1/50 (2%)	5/50 (10%)	3/50 (6%)	4/50 (8%)
Adjusted rate	2.3%	11.5%	7.6%	8.7%
Terminal rate	1/34 (3%)	3/36 (8%)	2/30 (7%)	2/38 (5%)
First incidence (days)	733 (T)	632	630	637
Poly-3 test	P=0.431	P=0.102	P=0.273	P=0.200

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

	Chamber Control	2 ppm	8 ppm	32 ppm
All Organs: Hemangioma or Hemangiosarcoma				
Overall rate	1/50 (2%)	7/50 (14%)	4/50 (8%)	4/50 (8%)
Adjusted rate	2.3%	16.1%	10.2%	8.7%
Terminal rate	1/34 (3%)	5/36 (14%)	3/30 (10%)	2/38 (5%)
First incidence (days)	733 (T)	632	630	637
Poly-3 test	P=0.588N	P=0.030	P=0.152	P=0.200
All Organs: Malignant Lymphoma				
Overall rate	3/50 (6%)	3/50 (6%)	1/50 (2%)	2/50 (4%)
Adjusted rate	6.9%	7.0%	2.5%	4.4%
Terminal rate	1/34 (3%)	2/36 (6%)	0/30 (0%)	1/38 (3%)
First incidence (days)	712	693	532	724
Poly-3 test	P=0.416N	P=0.661	P=0.336N	P=0.474N
All Organs: Benign Neoplasms				
Overall rate	31/50 (62%)	31/50 (62%)	25/50 (50%)	29/50 (58%)
Adjusted rate	68.8%	67.0%	58.9%	60.6%
Terminal rate	26/34 (77%)	25/36 (69%)	18/30 (60%)	22/38 (58%)
First incidence (days)	547	287	317	582
Poly-3 test	P=0.260N	P=0.517N	P=0.222N	P=0.268N
All Organs: Malignant Neoplasms				
Overall rate	23/50 (46%)	30/50 (60%)	26/50 (52%)	25/50 (50%)
Adjusted rate	46.8%	61.8%	55.5%	50.8%
Terminal rate	9/34 (27%)	18/36 (50%)	11/30 (37%)	15/38 (40%)
First incidence (days)	385	270	400	382
Poly-3 test	P=0.418N	P=0.099	P=0.259	P=0.424
All Organs: Benign or Malignant Neoplasms				
Overall rate	43/50 (86%)	44/50 (88%)	41/50 (82%)	39/50 (78%)
Adjusted rate	86.5%	88.9%	84.1%	78.0%
Terminal rate	28/34 (82%)	31/36 (86%)	23/30 (77%)	27/38 (71%)
First incidence (days)	385	270	317	382
Poly-3 test	P=0.091N	P=0.476	P=0.477N	P=0.197N

(T)Terminal sacrifice

^a Number of neoplasm-bearing animals/number of animals examined. Denominator is number of animals examined microscopically for adrenal gland, kidney, liver, and lung; 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 C4
Historical Incidence of Renal Tubule Neoplasms in Chamber Control Male B6C3F₁ Mice^a

Study	Incidence in Controls		
	Adenoma	Carcinoma	Adenoma or Carcinoma
Historical Incidence at Battelle Pacific Northwest Laboratories			
1,3-Butadiene	0/50	0/50	0/50
Acetonitrile	0/49	0/49	0/49
Allyl Glycidyl Ether	0/49	0/49	0/49
α -Chloroacetophenone	0/50	0/50	0/50
Cobalt Sulfate Heptahydrate	0/49	0/49	0/49
Epinephrine Hydrochloride	0/50	0/50	0/50
Hexachlorocyclopentadiene	0/50	0/50	0/50
Molybdenum Trioxide	0/49	0/49	0/49
Nitromethane	0/50	0/50	0/50
<i>o</i> -Chlorobenzalmalononitrile	0/49	0/49	0/49
Ozone	1/50	1/50	2/50
Tetrahydrofuran	1/49	0/49	1/49
Overall Historical Incidence			
Total	3/1,093 (0.3%)	1/1,093 (0.1%)	4/1,093 (0.4%)
Standard deviation	0.6%	0.4%	1.0%
Range	0%-2%	0%-2%	0%-4%

^a Data as of 4 October 1996

TABLE C5
Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the 2-Year Inhalation Study of Furfuryl Alcohol^a

	Chamber Control	2 ppm	8 ppm	32 ppm
Disposition Summary				
Animals initially in study	50	50	50	50
Early deaths				
Moribund	11	10	14	8
Natural deaths	5	4	6	4
Survivors				
Terminal sacrifice	34	36	30	38
Animals examined microscopically	50	50	50	50
Alimentary System				
Gallbladder	(45)	(42)	(42)	(43)
Degeneration, hyaline		1 (2%)		
Epithelium, hyperplasia			1 (2%)	1 (2%)
Intestine large, rectum	(48)	(47)	(46)	(46)
Anus, inflammation, chronic active	1 (2%)			
Intestine large, cecum	(48)	(47)	(46)	(48)
Serosa, inflammation, chronic	1 (2%)			
Intestine small, duodenum	(48)	(48)	(46)	(47)
Peyer's patch, hyperplasia		1 (2%)		
Intestine small, ileum	(46)	(48)	(46)	(47)
Peyer's patch, hyperplasia				1 (2%)
Liver	(50)	(50)	(49)	(50)
Angiectasis				2 (4%)
Basophilic focus		5 (10%)		
Clear cell focus		3 (6%)	3 (6%)	1 (2%)
Degeneration, cystic		1 (2%)		
Degeneration, fatty	5 (10%)	1 (2%)		1 (2%)
Eosinophilic focus	13 (26%)	18 (36%)	12 (24%)	14 (28%)
Hematopoietic cell proliferation	2 (4%)	1 (2%)	1 (2%)	1 (2%)
Inflammation, chronic	1 (2%)		1 (2%)	2 (4%)
Necrosis	2 (4%)	4 (8%)	6 (12%)	2 (4%)
Vacuolization cytoplasmic		1 (2%)		3 (6%)
Bile duct, cyst	1 (2%)		1 (2%)	1 (2%)
Bile duct, hyperplasia				1 (2%)
Centrilobular, degeneration			1 (2%)	
Centrilobular, necrosis			1 (2%)	
Mesentery	(7)	(4)	(7)	(3)
Fat, necrosis	7 (100%)	4 (100%)	6 (86%)	3 (100%)
Pancreas	(50)	(49)	(48)	(49)
Atrophy	7 (14%)	3 (6%)	4 (8%)	10 (20%)
Hypertrophy	1 (2%)		2 (4%)	
Inflammation, chronic, focal				1 (2%)
Duct, cyst	1 (2%)		1 (2%)	
Salivary glands	(50)	(49)	(49)	(50)
Hyperplasia	1 (2%)			
Inflammation, chronic		1 (2%)		
Duct, hyperplasia		1 (2%)		
Stomach, forestomach	(50)	(49)	(50)	(50)
Diverticulum		1 (2%)		
Hyperkeratosis		1 (2%)		
Inflammation, suppurative		1 (2%)		1 (2%)
Ulcer			1 (2%)	
Epithelium, hyperplasia	2 (4%)	5 (10%)	2 (4%)	5 (10%)

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

TABLE C5
Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the 2-Year Inhalation Study of Furfuryl Alcohol

	Chamber Control	2 ppm	8 ppm	32 ppm
Alimentary System (continued)				
Stomach, glandular	(50)	(48)	(47)	(48)
Inflammation, suppurative	1 (2%)		2 (4%)	2 (4%)
Necrosis	2 (4%)		1 (2%)	
Tooth	(2)	(1)	(1)	
Developmental malformation	1 (50%)			
Inflammation			1 (100%)	
Cardiovascular System				
Blood vessel		(1)		
Inflammation		1 (100%)		
Heart	(50)	(50)	(50)	(50)
Cardiomyopathy	46 (92%)	47 (94%)	43 (86%)	45 (90%)
Atrium, thrombosis	1 (2%)			
Ventricle, thrombosis	1 (2%)			
Endocrine System				
Adrenal cortex	(50)	(49)	(49)	(48)
Hyperplasia	1 (2%)	1 (2%)	5 (10%)	2 (4%)
Hypertrophy	35 (70%)	37 (76%)	31 (63%)	28 (58%)
Capsule, hyperplasia		1 (2%)		
Adrenal medulla	(50)	(49)	(48)	(48)
Hyperplasia				1 (2%)
Islets, pancreatic	(50)	(49)	(48)	(48)
Hyperplasia	9 (18%)	7 (14%)	10 (21%)	5 (10%)
Pituitary gland	(50)	(48)	(48)	(49)
Pars distalis, hyperplasia	3 (6%)	4 (8%)	1 (2%)	2 (4%)
Pars intermedia, hyperplasia			1 (2%)	
Thyroid gland	(50)	(49)	(49)	(48)
Follicular cell, hyperplasia	8 (16%)	9 (18%)	6 (12%)	13 (27%)
General Body System				
None				
Genital System				
Epididymis	(50)	(50)	(49)	(50)
Hyperplasia			2 (4%)	
Inflammation, chronic	2 (4%)	1 (2%)		2 (4%)
Mineralization			1 (2%)	
Spermatocoele	2 (4%)			
Penis		(2)		
Inflammation		1 (50%)		
Preputial gland	(50)	(49)	(49)	(50)
Cyst	3 (6%)	3 (6%)	2 (4%)	6 (12%)
Inflammation	3 (6%)		1 (2%)	2 (4%)
Prostate	(49)	(48)	(48)	(49)
Inflammation, suppurative	1 (2%)	1 (2%)	1 (2%)	
Seminal vesicle	(50)	(48)	(46)	(49)
Inflammation			1 (2%)	

TABLE C5
Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the 2-Year Inhalation Study of Furfuryl Alcohol

	Chamber Control	2 ppm	8 ppm	32 ppm
Genital System (continued)				
Testes	(50)	(50)	(49)	(50)
Angiectasis			1 (2%)	
Atrophy	4 (8%)	3 (6%)	5 (10%)	2 (4%)
Degeneration			1 (2%)	
Inflammation, focal, granulomatous				1 (2%)
Mineralization		1 (2%)		
Interstitial cell, hyperplasia				1 (2%)
Hematopoietic System				
Bone marrow	(50)	(49)	(49)	(50)
Hyperplasia	2 (4%)	2 (4%)		1 (2%)
Lymph node, bronchial	(27)	(22)	(27)	(28)
Hyperplasia			2 (7%)	
Lymph node, mandibular	(28)	(33)	(23)	(28)
Hyperplasia				1 (4%)
Lymph node, mesenteric	(50)	(46)	(46)	(47)
Angiectasis		1 (2%)	2 (4%)	
Hematopoietic cell proliferation		1 (2%)		1 (2%)
Hyperplasia	1 (2%)	2 (4%)		3 (6%)
Lymph node, mediastinal	(40)	(39)	(38)	(31)
Hematopoietic cell proliferation		1 (3%)		
Hyperplasia	2 (5%)		1 (3%)	1 (3%)
Spleen	(50)	(49)	(49)	(50)
Angiectasis				1 (2%)
Hematopoietic cell proliferation	7 (14%)	12 (24%)	11 (22%)	9 (18%)
Hyperplasia, lymphoid		2 (4%)		
Thymus	(35)	(31)	(36)	(36)
Epithelial cell, hyperplasia			1 (3%)	
Integumentary System				
Skin	(50)	(50)	(48)	(49)
Cyst epithelial inclusion			1 (2%)	
Inflammation, chronic	2 (4%)			
Inflammation, chronic active		1 (2%)		
Mineralization	1 (2%)			
Prepuce, inflammation, chronic active	3 (6%)	2 (4%)	3 (6%)	2 (4%)
Subcutaneous tissue, inflammation, chronic active		2 (4%)	1 (2%)	
Subcutaneous tissue, inflammation, focal, granulomatous		1 (2%)		
Musculoskeletal System				
Bone	(50)	(50)	(50)	(50)
Fibrous osteodystrophy		1 (2%)	2 (4%)	
Hyperostosis		1 (2%)	1 (2%)	1 (2%)
Nervous System				
Brain	(50)	(50)	(49)	(50)
Cyst epithelial inclusion	1 (2%)			
Meninges, infiltration cellular, mononuclear cell	1 (2%)			

TABLE C5
Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the 2-Year Inhalation Study of Furfuryl Alcohol

	Chamber Control	2 ppm	8 ppm	32 ppm
Respiratory System				
Larynx	(50)	(49)	(49)	(48)
Hyperplasia	2 (4%)	1 (2%)	2 (4%)	1 (2%)
Inflammation, suppurative	1 (2%)		1 (2%)	
Lung	(50)	(50)	(49)	(50)
Hematopoietic cell proliferation			1 (2%)	
Hemorrhage		1 (2%)	1 (2%)	2 (4%)
Infiltration cellular, histiocyte	4 (8%)	4 (8%)	5 (10%)	7 (14%)
Inflammation, chronic, focal			1 (2%)	
Alveolar epithelium, hyperplasia	5 (10%)	2 (4%)	2 (4%)	2 (4%)
Mediastinum, angiectasis				1 (2%)
Nose	(50)	(49)	(49)	(50)
Inflammation, suppurative	7 (14%)	11 (22%)	27 (55%)	28 (56%)
Glands, hyperplasia		10 (20%)	48 (98%)	46 (92%)
Glands, metaplasia, squamous		6 (12%)	35 (71%)	47 (94%)
Lateral wall, metaplasia, squamous		9 (18%)	10 (20%)	20 (40%)
Lateral wall, necrosis			3 (6%)	
Olfactory epithelium, atrophy	3 (6%)	15 (31%)	49 (100%)	50 (100%)
Olfactory epithelium, degeneration, hyaline	2 (4%)	3 (6%)	21 (43%)	39 (78%)
Olfactory epithelium, metaplasia		12 (24%)	49 (100%)	50 (100%)
Respiratory epithelium, degeneration, hyaline	5 (10%)	18 (37%)	42 (86%)	45 (90%)
Respiratory epithelium, hyperplasia, polypoid				1 (2%)
Respiratory epithelium, metaplasia, squamous		2 (4%)	10 (20%)	20 (40%)
Respiratory epithelium, necrosis	1 (2%)			1 (2%)
Respiratory epithelium, regeneration		1 (2%)	13 (27%)	21 (42%)
Trachea	(50)	(48)	(48)	(49)
Metaplasia, squamous	2 (4%)			
Special Senses System				
Eye	(50)	(48)	(49)	(49)
Cataract	2 (4%)	1 (2%)	3 (6%)	
Inflammation, chronic active	2 (4%)			1 (2%)
Cornea, dysplasia			1 (2%)	
Cornea, hyperplasia	1 (2%)		2 (4%)	1 (2%)
Cornea, inflammation, chronic active		1 (2%)		
Retina, atrophy		1 (2%)		
Urinary System				
Kidney	(50)	(49)	(49)	(50)
Amyloid deposition				1 (2%)
Cyst	1 (2%)	3 (6%)		
Hydronephrosis	2 (4%)	2 (4%)	1 (2%)	2 (4%)
Inflammation, chronic active	2 (4%)		1 (2%)	
Metaplasia, osseous	3 (6%)	4 (8%)		4 (8%)
Mineralization			1 (2%)	
Nephropathy	49 (98%)	48 (98%)	43 (88%)	47 (94%)
Papilla, necrosis			1 (2%)	
Renal tubule, degeneration			1 (2%)	48 (96%)
Renal tubule, hyperplasia	1 (2%)	3 (6%)		3 (6%)
Renal tubule, hypertrophy			1 (2%)	1 (2%)
Urinary bladder	(50)	(47)	(47)	(50)
Inflammation, chronic active	3 (6%)	1 (2%)		
Inflammation, suppurative			1 (2%)	
Mineralization			1 (2%)	
Necrosis			1 (2%)	
Transitional epithelium, hyperplasia	1 (2%)	1 (2%)		

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

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TABLE D1
Summary of the Incidence of Neoplasms in Female Mice in the 2-Year Inhalation Study of Furfuryl Alcohol^a

	Chamber Control	2 ppm	8 ppm	32 ppm
Disposition Summary				
Animals initially in study	50	50	50	50
Early deaths				
Accidental deaths		1	1	
Moribund	11	12	15	8
Natural deaths	5	3	2	2
Survivors				
Terminal sacrifice	34	33	32	40
Pregnant		1		
Animals examined microscopically	50	49	50	50
Alimentary System				
Intestine large, rectum	(49)	(45)	(49)	(48)
Anus, squamous cell carcinoma	1 (2%)			
Intestine small, duodenum	(47)	(46)	(48)	(48)
Polyp adenomatous	1 (2%)			
Intestine small, jejunum	(45)	(46)	(48)	(48)
Intestine small, ileum	(45)	(47)	(48)	(48)
Liver	(50)	(49)	(49)	(49)
Hemangiosarcoma				1 (2%)
Hepatocellular carcinoma	8 (16%)	12 (24%)	5 (10%)	6 (12%)
Hepatocellular carcinoma, multiple	1 (2%)	3 (6%)		2 (4%)
Hepatocellular adenoma	5 (10%)	5 (10%)	9 (18%)	5 (10%)
Hepatocellular adenoma, multiple	2 (4%)	2 (4%)		
Hepatocholangiocarcinoma			1 (2%)	
Histiocytic sarcoma	2 (4%)			
Sarcoma, metastatic, uncertain primary site			1 (2%)	
Mesentery	(15)	(6)	(11)	(10)
Hemangiosarcoma			1 (9%)	
Hepatocholangiocarcinoma, metastatic, liver			1 (9%)	
Histiocytic sarcoma	1 (7%)			
Sarcoma, metastatic, skin				1 (10%)
Pancreas	(50)	(48)	(49)	(49)
Sarcoma, metastatic, uncertain primary site			1 (2%)	
Salivary glands	(50)	(49)	(49)	(50)
Carcinoma, metastatic, harderian gland		1 (2%)		
Stomach, forestomach	(50)	(48)	(49)	(49)
Squamous cell carcinoma			1 (2%)	
Squamous cell papilloma			3 (6%)	
Stomach, glandular	(50)	(46)	(49)	(48)
Tooth			(2)	
Adamantinoma malignant			1 (50%)	
Cardiovascular System				
Heart	(50)	(49)	(49)	(50)
Sarcoma, metastatic, uncertain primary site			1 (2%)	

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

	Chamber Control	2 ppm	8 ppm	32 ppm
Endocrine System				
Adrenal cortex	(50)	(49)	(50)	(49)
Sarcoma, metastatic, uncertain primary site			1 (2%)	
Capsule, adenoma		2 (4%)		1 (2%)
Adrenal medulla	(48)	(48)	(49)	(49)
Pheochromocytoma benign	1 (2%)			1 (2%)
Sarcoma, metastatic, uncertain primary site			1 (2%)	
Islets, pancreatic	(49)	(48)	(49)	(49)
Adenoma	1 (2%)		1 (2%)	1 (2%)
Pituitary gland	(48)	(48)	(48)	(49)
Pars distalis, adenoma	7 (15%)	7 (15%)	4 (8%)	1 (2%)
Pars intermedia, adenoma	1 (2%)	1 (2%)		
Thyroid gland	(50)	(49)	(49)	(49)
Bilateral, follicular cell, adenoma			1 (2%)	
Follicular cell, adenoma	3 (6%)	1 (2%)	2 (4%)	5 (10%)
Follicular cell, carcinoma		1 (2%)		
General Body System				
None				
Genital System				
Clitoral gland	(43)	(41)	(31)	(41)
Histiocytic sarcoma	1 (2%)			
Ovary	(50)	(49)	(48)	(49)
Alveolar/bronchiolar carcinoma, metastatic, lung		1 (2%)		
Cystadenoma	2 (4%)	1 (2%)	3 (6%)	2 (4%)
Granulosa cell tumor benign			2 (4%)	
Histiocytic sarcoma	2 (4%)			
Luteoma	1 (2%)			1 (2%)
Sarcoma, metastatic, uncertain primary site			1 (2%)	
Yolk sac carcinoma			1 (2%)	
Uterus	(50)	(49)	(49)	(49)
Adenocarcinoma				1 (2%)
Hemangioma		1 (2%)		
Histiocytic sarcoma	2 (4%)		1 (2%)	
Leiomyoma	1 (2%)			
Leiomyosarcoma	1 (2%)			
Polyp stromal	2 (4%)	3 (6%)	4 (8%)	2 (4%)
Sarcoma, metastatic, uncertain primary site			1 (2%)	
Hematopoietic System				
Bone marrow	(50)	(49)	(49)	(49)
Hemangiosarcoma	2 (4%)	1 (2%)		1 (2%)
Lymph node	(6)	(4)	(5)	(4)
Lymph node, bronchial	(33)	(27)	(30)	(37)
Alveolar/bronchiolar carcinoma, metastatic, lung	1 (3%)	1 (4%)	1 (3%)	
Hepatocholangiocarcinoma, metastatic, liver			1 (3%)	
Lymph node, mandibular	(36)	(40)	(43)	(40)
Carcinoma, metastatic, harderian gland		1 (3%)		

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

	Chamber Control	2 ppm	8 ppm	32 ppm
Hematopoietic System (continued)				
Lymph node, mesenteric	(48)	(47)	(47)	(46)
Lymph node, mediastinal	(41)	(34)	(40)	(40)
Alveolar/bronchiolar carcinoma, metastatic, lung		1 (3%)	1 (3%)	
Hepatocholangiocarcinoma, metastatic, liver			1 (3%)	
Sarcoma, metastatic, uncertain primary site			1 (3%)	
Spleen	(50)	(48)	(49)	(49)
Hemangioma				1 (2%)
Hemangiosarcoma		1 (2%)	2 (4%)	
Histiocytic sarcoma		1 (2%)		
Thymus	(42)	(40)	(46)	(38)
Alveolar/bronchiolar carcinoma, metastatic, lung			1 (2%)	
Sarcoma, metastatic, uncertain primary site			1 (2%)	
Integumentary System				
Mammary gland	(50)	(49)	(49)	(50)
Carcinoma		2 (4%)	1 (2%)	
Skin	(50)	(49)	(49)	(50)
Hemangiosarcoma		1 (2%)		
Subcutaneous tissue, hemangioma				1 (2%)
Subcutaneous tissue, hemangioma, multiple			1 (2%)	
Subcutaneous tissue, hemangiosarcoma	1 (2%)		2 (4%)	1 (2%)
Subcutaneous tissue, histiocytic sarcoma			1 (2%)	
Subcutaneous tissue, sarcoma	1 (2%)		1 (2%)	1 (2%)
Subcutaneous tissue, sarcoma, multiple				1 (2%)
Musculoskeletal System				
Bone	(50)	(49)	(50)	(50)
Hemangiosarcoma, metastatic, bone marrow	1 (2%)			
Osteosarcoma				1 (2%)
Skeletal muscle		(1)	(1)	(1)
Alveolar/bronchiolar carcinoma, metastatic, lung		1 (100%)		
Sarcoma, metastatic, skin				1 (100%)
Sarcoma, metastatic, uncertain primary site			1 (100%)	
Nervous System				
Brain	(50)	(49)	(49)	(49)
Meninges, histiocytic sarcoma	1 (2%)			
Respiratory System				
Lung	(50)	(49)	(49)	(50)
Alveolar/bronchiolar adenoma	2 (4%)	4 (8%)	8 (16%)	
Alveolar/bronchiolar carcinoma	4 (8%)	3 (6%)	3 (6%)	1 (2%)
Alveolar/bronchiolar carcinoma, multiple		1 (2%)	1 (2%)	
Carcinoma, metastatic, harderian gland		2 (4%)		1 (2%)
Carcinoma, metastatic, mammary gland			1 (2%)	
Hepatocellular carcinoma, metastatic, liver	2 (4%)	1 (2%)		3 (6%)
Hepatocholangiocarcinoma, metastatic, liver			1 (2%)	
Histiocytic sarcoma	2 (4%)			

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

	Chamber Control	2 ppm	8 ppm	32 ppm
Respiratory System (continued)				
Lung (continued)	(50)	(49)	(49)	(50)
Sarcoma, metastatic, skin	1 (2%)			1 (2%)
Sarcoma, metastatic, uncertain primary site			1 (2%)	
Mediastinum, alveolar/bronchiolar carcinoma, metastatic, lung		1 (2%)	1 (2%)	
Mediastinum, hepatocholangiocarcinoma, metastatic, liver			1 (2%)	
Mediastinum, sarcoma, metastatic, skin				1 (2%)
Nose	(50)	(48)	(49)	(50)
Histiocytic sarcoma	1 (2%)			
Sarcoma, metastatic, uncertain primary site			1 (2%)	
Special Senses System				
Eye	(49)	(49)	(49)	(50)
Sarcoma, metastatic, uncertain primary site			1 (2%)	
Harderian gland	(2)	(5)	(6)	(6)
Adenoma	2 (100%)	2 (40%)	5 (83%)	5 (83%)
Carcinoma		2 (40%)		1 (17%)
Sarcoma, metastatic, uncertain primary site			1 (17%)	
Urinary System				
Kidney	(50)	(48)	(49)	(49)
Hepatocholangiocarcinoma, metastatic, liver			1 (2%)	
Histiocytic sarcoma	1 (2%)		1 (2%)	
Sarcoma, metastatic, uncertain primary site			1 (2%)	
Urinary bladder	(49)	(45)	(49)	(48)
Systemic Lesions				
Multiple organs ^b	(50)	(49)	(50)	(50)
Histiocytic sarcoma	2 (4%)	1 (2%)	2 (4%)	
Lymphoma malignant	6 (12%)	3 (6%)	5 (10%)	8 (16%)
Neoplasm Summary				
Total animals with primary neoplasms ^c	36	37	39	36
Total primary neoplasms	58	60	70	51
Total animals with benign neoplasms	23	23	29	21
Total benign neoplasms	31	29	43	26
Total animals with malignant neoplasms	20	25	23	22
Total malignant neoplasms	27	31	27	25
Total animals with metastatic neoplasms	5	4	4	6
Total metastatic neoplasms	5	10	26	8
Total animals with malignant neoplasms of uncertain primary site			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 D3
Statistical Analysis of Primary Neoplasms in Female Mice in the 2-Year Inhalation Study of Furfuryl Alcohol

	Chamber Control	2 ppm	8 ppm	32 ppm
Harderian Gland: Adenoma				
Overall rate ^a	2/50 (4%)	2/49 (4%)	5/50 (10%)	5/50 (10%)
Adjusted rate ^b	4.6%	4.7%	11.6%	10.6%
Terminal rate ^c	1/34 (3%)	2/33 (6%)	4/32 (13%)	4/40 (10%)
First incidence (days)	712	734 (T)	693	600
Poly-3 test ^d	P=0.211	P=0.685	P=0.215	P=0.252
Harderian Gland: Adenoma or Carcinoma				
Overall rate	2/50 (4%)	4/49 (8%)	5/50 (10%)	6/50 (12%)
Adjusted rate	4.6%	9.3%	11.6%	12.7%
Terminal rate	1/34 (3%)	2/33 (6%)	4/32 (13%)	5/40 (13%)
First incidence (days)	712	525	693	600
Poly-3 test	P=0.210	P=0.332	P=0.215	P=0.162
Liver: Hepatocellular Adenoma				
Overall rate	7/50 (14%)	7/49 (14%)	9/49 (18%)	5/49 (10%)
Adjusted rate	16.0%	16.5%	20.8%	10.8%
Terminal rate	5/34 (15%)	5/33 (15%)	5/32 (16%)	5/40 (13%)
First incidence (days)	595	649	621	734 (T)
Poly-3 test	P=0.226N	P=0.592	P=0.382	P=0.342N
Liver: Hepatocellular Carcinoma				
Overall rate	9/50 (18%)	15/49 (31%)	5/49 (10%)	8/49 (16%)
Adjusted rate	20.6%	34.5%	11.6%	17.1%
Terminal rate	6/34 (18%)	11/33 (33%)	1/32 (3%)	7/40 (18%)
First incidence (days)	651	525	665	582
Poly-3 test	P=0.174N	P=0.111	P=0.198N	P=0.440N
Liver: Hepatocellular Adenoma or Carcinoma				
Overall rate	14/50 (28%)	19/49 (39%)	12/49 (24%)	12/49 (24%)
Adjusted rate	31.7%	43.4%	27.5%	25.7%
Terminal rate	10/34 (29%)	14/33 (42%)	6/32 (19%)	11/40 (28%)
First incidence (days)	595	525	621	582
Poly-3 test	P=0.135N	P=0.179	P=0.421N	P=0.344N
Lung: Alveolar/bronchiolar Adenoma				
Overall rate	2/50 (4%)	4/49 (8%)	8/49 (16%)	0/50 (0%)
Adjusted rate	4.6%	9.4%	18.9%	0.0%
Terminal rate	1/34 (3%)	2/33 (6%)	8/32 (25%)	0/40 (0%)
First incidence (days)	693	649	734 (T)	— ^e
Poly-3 test	P=0.058N	P=0.328	P=0.040	P=0.221N
Lung: Alveolar/bronchiolar Carcinoma				
Overall rate	4/50 (8%)	4/49 (8%)	4/49 (8%)	1/50 (2%)
Adjusted rate	9.0%	9.3%	9.3%	2.1%
Terminal rate	2/34 (6%)	3/33 (9%)	2/32 (6%)	1/40 (3%)
First incidence (days)	547	448	469	734 (T)
Poly-3 test	P=0.099N	P=0.626	P=0.628	P=0.164N
Lung: Alveolar/bronchiolar Adenoma or Carcinoma				
Overall rate	6/50 (12%)	8/49 (16%)	11/49 (22%)	1/50 (2%)
Adjusted rate	13.5%	18.5%	25.5%	2.1%
Terminal rate	3/34 (9%)	5/33 (15%)	9/32 (28%)	1/40 (3%)
First incidence (days)	547	448	469	734 (T)
Poly-3 test	P=0.011N	P=0.364	P=0.122	P=0.049N

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

	Chamber Control	2 ppm	8 ppm	32 ppm
Ovary: Cystadenoma				
Overall rate	2/50 (4%)	1/49 (2%)	3/48 (6%)	2/49 (4%)
Adjusted rate	4.6%	2.4%	7.2%	4.3%
Terminal rate	2/34 (6%)	0/33 (0%)	1/31 (3%)	1/40 (3%)
First incidence (days)	734 (T)	684	637	609
Poly-3 test	P=0.616	P=0.507N	P=0.486	P=0.666N
Pituitary Gland (Pars Distalis): Adenoma				
Overall rate	7/48 (15%)	7/48 (15%)	4/48 (8%)	1/49 (2%)
Adjusted rate	16.8%	16.9%	9.5%	2.2%
Terminal rate	7/33 (21%)	7/33 (21%)	2/32 (6%)	1/40 (3%)
First incidence (days)	734 (T)	734 (T)	617	734 (T)
Poly-3 test	P=0.011N	P=0.608	P=0.251N	P=0.020N
Stomach (Forestomach): Squamous Cell Papilloma				
Overall rate	0/50 (0%)	0/49 (0%)	3/50 (6%)	0/50 (0%)
Adjusted rate	0.0%	0.0%	7.0%	0.0%
Terminal rate	0/34 (0%)	0/33 (0%)	3/32 (9%)	0/40 (0%)
First incidence (days)	—	— ^f	734 (T)	—
Poly-3 test	P=0.545N	— ^f	P=0.118	—
Stomach (Forestomach): Squamous Cell Papilloma or Squamous Cell Carcinoma				
Overall rate	0/50 (0%)	0/49 (0%)	4/50 (8%)	0/50 (0%)
Adjusted rate	0.0%	0.0%	9.3%	0.0%
Terminal rate	0/34 (0%)	0/33 (0%)	4/32 (13%)	0/40 (0%)
First incidence (days)	—	—	734 (T)	—
Poly-3 test	P=0.487N	—	P=0.059	—
Thyroid Gland (Follicular Cell): Adenoma				
Overall rate	3/50 (6%)	1/49 (2%)	3/49 (6%)	5/49 (10%)
Adjusted rate	6.9%	2.4%	7.0%	10.8%
Terminal rate	3/34 (9%)	1/33 (3%)	2/32 (6%)	5/40 (13%)
First incidence (days)	734 (T)	734 (T)	617	734 (T)
Poly-3 test	P=0.159	P=0.313N	P=0.657	P=0.393
Thyroid Gland (Follicular Cell): Adenoma or Carcinoma				
Overall rate	3/50 (6%)	2/49 (4%)	3/49 (6%)	5/49 (10%)
Adjusted rate	6.9%	4.7%	7.0%	10.8%
Terminal rate	3/34 (9%)	2/33 (6%)	2/32 (6%)	5/40 (13%)
First incidence (days)	734 (T)	734 (T)	617	734 (T)
Poly-3 test	P=0.223	P=0.511N	P=0.657	P=0.393
Uterus: Stromal Polyp				
Overall rate	2/50 (4%)	3/49 (6%)	4/50 (8%)	2/50 (4%)
Adjusted rate	4.6%	7.1%	9.1%	4.3%
Terminal rate	2/34 (6%)	3/33 (9%)	1/32 (3%)	2/40 (5%)
First incidence (days)	734 (T)	734 (T)	582	734 (T)
Poly-3 test	P=0.434N	P=0.489	P=0.347	P=0.666N
All Organs: Hemangiosarcoma				
Overall rate	2/50 (4%)	2/49 (4%)	4/50 (8%)	2/50 (4%)
Adjusted rate	4.6%	4.7%	9.1%	4.3%
Terminal rate	1/34 (3%)	2/33 (6%)	1/32 (3%)	2/40 (5%)
First incidence (days)	651	734 (T)	621	734 (T)
Poly-3 test	P=0.522N	P=0.683	P=0.341	P=0.669N

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

	Chamber Control	2 ppm	8 ppm	32 ppm
All Organs: Hemangioma or Hemangiosarcoma				
Overall rate	2/50 (4%)	3/49 (6%)	5/50 (10%)	4/50 (8%)
Adjusted rate	4.6%	7.1%	11.4%	8.6%
Terminal rate	1/34 (3%)	3/33 (9%)	2/32 (6%)	4/40 (10%)
First incidence (days)	651	734 (T)	621	734 (T)
Poly-3 test	P=0.431	P=0.486	P=0.219	P=0.370
All Organs: Malignant Lymphoma				
Overall rate	6/50 (12%)	3/49 (6%)	5/50 (10%)	8/50 (16%)
Adjusted rate	13.4%	7.1%	11.5%	16.9%
Terminal rate	2/34 (6%)	2/33 (6%)	4/32 (13%)	5/40 (13%)
First incidence (days)	573	730	637	663
Poly-3 test	P=0.193	P=0.271N	P=0.521N	P=0.430
All Organs: Benign Neoplasms				
Overall rate	23/50 (46%)	23/49 (47%)	29/50 (58%)	21/50 (42%)
Adjusted rate	51.3%	53.8%	63.2%	44.2%
Terminal rate	18/34 (53%)	19/33 (58%)	20/32 (63%)	19/40 (48%)
First incidence (days)	573	649	582	600
Poly-3 test	P=0.152N	P=0.490	P=0.168	P=0.316N
All Organs: Malignant Neoplasms				
Overall rate	20/50 (40%)	25/49 (51%)	24/50 (48%)	22/50 (44%)
Adjusted rate	41.7%	56.4%	50.3%	45.6%
Terminal rate	9/34 (27%)	18/33 (55%)	11/32 (34%)	16/40 (40%)
First incidence (days)	352	448	411	582
Poly-3 test	P=0.437N	P=0.111	P=0.260	P=0.428
All Organs: Benign or Malignant Neoplasms				
Overall rate	36/50 (72%)	37/49 (76%)	40/50 (80%)	36/50 (72%)
Adjusted rate	73.4%	82.5%	81.7%	73.9%
Terminal rate	22/34 (65%)	28/33 (85%)	24/32 (75%)	29/40 (73%)
First incidence (days)	352	448	411	582
Poly-3 test	P=0.351N	P=0.202	P=0.229	P=0.569

(T)Terminal sacrifice

^a Number of neoplasm-bearing animals/number of animals examined. Denominator is number of animals examined microscopically for liver, lung, ovary, pituitary gland, 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 D4
Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 2-Year Inhalation Study of Furfuryl Alcohol^a

	Chamber Control	2 ppm	8 ppm	32 ppm
Disposition Summary				
Animals initially in study	50	50	50	50
Early deaths				
Accidental deaths		1	1	
Moribund	11	12	15	8
Natural deaths	5	3	2	2
Survivors				
Terminal sacrifice	34	33	32	40
Pregnant		1		
Animals examined microscopically	50	49	50	50
Alimentary System				
Esophagus	(50)	(49)	(48)	(50)
Angiectasis			1 (2%)	
Inflammation	1 (2%)			
Gallbladder	(43)	(45)	(47)	(41)
Degeneration, hyaline	1 (2%)			
Inflammation, suppurative		2 (4%)		
Intestine large, rectum	(49)	(45)	(49)	(48)
Inflammation, suppurative	1 (2%)			
Metaplasia, squamous			1 (2%)	
Intestine small, duodenum	(47)	(46)	(48)	(48)
Inflammation, chronic			1 (2%)	
Necrosis			1 (2%)	
Epithelium, hyperplasia			1 (2%)	
Intestine small, jejunum	(45)	(46)	(48)	(48)
Peyer's patch, hyperplasia			1 (2%)	
Intestine small, ileum	(45)	(47)	(48)	(48)
Peyer's patch, hyperplasia		1 (2%)	1 (2%)	
Liver	(50)	(49)	(49)	(49)
Basophilic focus				2 (4%)
Clear cell focus				2 (4%)
Degeneration, fatty	1 (2%)	1 (2%)	1 (2%)	1 (2%)
Eosinophilic focus	14 (28%)	19 (39%)	20 (41%)	8 (16%)
Hematopoietic cell proliferation	1 (2%)		5 (10%)	5 (10%)
Infiltration cellular, mixed cell				1 (2%)
Inflammation, chronic		4 (8%)	4 (8%)	1 (2%)
Inflammation, focal, granulomatous	1 (2%)	2 (4%)		
Karyomegaly			1 (2%)	
Necrosis	2 (4%)	1 (2%)	4 (8%)	2 (4%)
Pigmentation, bile		1 (2%)		
Regeneration			1 (2%)	
Bile duct, cyst		1 (2%)		
Centrilobular, necrosis		1 (2%)		
Mesentery	(15)	(6)	(11)	(10)
Angiectasis				1 (10%)
Inflammation, chronic	1 (7%)			1 (10%)
Fat, hemorrhage			1 (9%)	1 (10%)
Fat, necrosis	13 (87%)	6 (100%)	8 (73%)	7 (70%)
Oral mucosa				(1)
Pharyngeal, hyperplasia				1 (100%)

^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 Furfuryl Alcohol

	Chamber Control	2 ppm	8 ppm	32 ppm
Alimentary System (continued)				
Pancreas	(50)	(48)	(49)	(49)
Atrophy	7 (14%)	3 (6%)	5 (10%)	9 (18%)
Cytoplasmic alteration		1 (2%)		
Hyperplasia, lymphoid	1 (2%)	1 (2%)		
Hypertrophy	1 (2%)		2 (4%)	1 (2%)
Inflammation, chronic, focal	1 (2%)	1 (2%)		
Duct, cyst				1 (2%)
Stomach, forestomach	(50)	(48)	(49)	(49)
Infiltration cellular, mast cell		1 (2%)		
Inflammation, suppurative		2 (4%)	1 (2%)	
Ulcer		3 (6%)		1 (2%)
Epithelium, hyperplasia	2 (4%)	8 (17%)	6 (12%)	3 (6%)
Stomach, glandular	(50)	(46)	(49)	(48)
Inflammation, suppurative		2 (4%)	2 (4%)	
Necrosis	1 (2%)			
Cardiovascular System				
Blood vessel		(1)		
Inflammation		1 (100%)		
Heart	(50)	(49)	(49)	(50)
Cardiomyopathy	36 (72%)	40 (82%)	46 (94%)	42 (84%)
Mineralization	1 (2%)			
Endocrine System				
Adrenal cortex	(50)	(49)	(50)	(49)
Angiectasis		1 (2%)		
Hematopoietic cell proliferation			1 (2%)	1 (2%)
Hyperplasia		2 (4%)		
Hypertrophy	4 (8%)	1 (2%)	3 (6%)	3 (6%)
Adrenal medulla	(48)	(48)	(49)	(49)
Hyperplasia	4 (8%)	1 (2%)	2 (4%)	4 (8%)
Islets, pancreatic	(49)	(48)	(49)	(49)
Hyperplasia	2 (4%)	1 (2%)	2 (4%)	
Parathyroid gland	(32)	(32)	(29)	(26)
Hyperplasia			1 (3%)	
Pituitary gland	(48)	(48)	(48)	(49)
Angiectasis				1 (2%)
Hemorrhage			1 (2%)	
Pars distalis, angiectasis		1 (2%)		1 (2%)
Pars distalis, cyst	1 (2%)			
Pars distalis, hyperplasia	15 (31%)	17 (35%)	15 (31%)	17 (35%)
Pars intermedia, hyperplasia		1 (2%)		
Thyroid gland	(50)	(49)	(49)	(49)
Inflammation	1 (2%)			
Follicular cell, cyst	1 (2%)			
Follicular cell, hyperplasia	17 (34%)	21 (43%)	17 (35%)	30 (61%)
General Body System				
None				

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

	Chamber Control	2 ppm	8 ppm	32 ppm
Genital System				
Ovary	(50)	(49)	(48)	(49)
Angiectasis		2 (4%)	1 (2%)	
Atrophy	4 (8%)	3 (6%)	1 (2%)	2 (4%)
Cyst	14 (28%)	14 (29%)	18 (38%)	15 (31%)
Hemorrhage		1 (2%)		
Hyperplasia, lymphoid		1 (2%)		
Infiltration cellular, mononuclear cell	1 (2%)			
Inflammation, chronic		1 (2%)		
Inflammation, suppurative			1 (2%)	
Thrombosis		1 (2%)		
Corpus luteum, hemorrhage	1 (2%)			
Corpus luteum, hyperplasia		1 (2%)		
Germinal epithelium, hyperplasia	1 (2%)			
Interstitial cell, hyperplasia	1 (2%)	2 (4%)	1 (2%)	
Uterus	(50)	(49)	(49)	(49)
Angiectasis	3 (6%)		4 (8%)	2 (4%)
Hemorrhage		1 (2%)	1 (2%)	
Hydrometra	5 (10%)	5 (10%)	4 (8%)	3 (6%)
Hyperplasia, cystic	4 (8%)	3 (6%)	2 (4%)	
Inflammation, chronic			1 (2%)	
Inflammation, suppurative	1 (2%)	1 (2%)		1 (2%)
Thrombosis	1 (2%)	2 (4%)	1 (2%)	
Endometrium, hyperplasia			1 (2%)	1 (2%)
Endometrium, metaplasia				1 (2%)
Myometrium, hyperplasia			1 (2%)	
Hematopoietic System				
Bone marrow	(50)	(49)	(49)	(49)
Hyperplasia			1 (2%)	1 (2%)
Lymph node	(6)	(4)	(5)	(4)
Angiectasis	4 (67%)	3 (75%)	2 (40%)	
Necrosis	1 (17%)			
Renal, hyperplasia		1 (25%)	1 (20%)	
Lymph node, bronchial	(33)	(27)	(30)	(37)
Hyperplasia	1 (3%)	1 (4%)	1 (3%)	2 (5%)
Lymph node, mandibular	(36)	(40)	(43)	(40)
Hyperplasia	1 (3%)	2 (5%)		2 (5%)
Infiltration cellular, mast cell			1 (2%)	
Lymph node, mesenteric	(48)	(47)	(47)	(46)
Angiectasis		1 (2%)		2 (4%)
Hematopoietic cell proliferation				1 (2%)
Hyperplasia		2 (4%)	1 (2%)	1 (2%)
Lymph node, mediastinal	(41)	(34)	(40)	(40)
Hyperplasia	4 (10%)	1 (3%)	3 (8%)	2 (5%)
Spleen	(50)	(48)	(49)	(49)
Hematopoietic cell proliferation	11 (22%)	11 (23%)	12 (24%)	17 (35%)
Hyperplasia, lymphoid	8 (16%)	8 (17%)	4 (8%)	5 (10%)
Thymus	(42)	(40)	(46)	(38)
Angiectasis		1 (3%)	1 (2%)	
Hyperplasia, lymphoid			1 (2%)	1 (3%)

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

	Chamber Control	2 ppm	8 ppm	32 ppm
Integumentary System				
Mammary gland	(50)	(49)	(49)	(50)
Hyperplasia		2 (4%)	1 (2%)	2 (4%)
Skin	(50)	(49)	(49)	(50)
Hemorrhage			1 (2%)	
Inflammation, chronic active	1 (2%)		1 (2%)	1 (2%)
Subcutaneous tissue, angiectasis	1 (2%)		1 (2%)	
Subcutaneous tissue, hemorrhage	1 (2%)			1 (2%)
Subcutaneous tissue, inflammation, focal, granulomatous				1 (2%)
Musculoskeletal System				
Bone	(50)	(49)	(50)	(50)
Fibrous osteodystrophy	16 (32%)	19 (39%)	15 (30%)	22 (44%)
Fracture		1 (2%)		
Hyperostosis			1 (2%)	
Nervous System				
Brain	(50)	(49)	(49)	(49)
Gliosis				1 (2%)
Necrosis		2 (4%)	1 (2%)	
Meninges, infiltration cellular, mononuclear cell	4 (8%)	4 (8%)	2 (4%)	4 (8%)
Peripheral nerve			(1)	
Degeneration			1 (100%)	
Spinal cord	(2)		(2)	(1)
Degeneration			1 (50%)	
Respiratory System				
Larynx	(49)	(49)	(50)	(49)
Hyperplasia	5 (10%)	9 (18%)	3 (6%)	5 (10%)
Inflammation, suppurative		3 (6%)		1 (2%)
Epiglottis, metaplasia, squamous	1 (2%)			
Lung	(50)	(49)	(49)	(50)
Hematopoietic cell proliferation		1 (2%)		
Hemorrhage			1 (2%)	
Hyperplasia, lymphoid	1 (2%)			
Infiltration cellular, histiocyte	3 (6%)	5 (10%)	2 (4%)	3 (6%)
Inflammation, chronic, focal	1 (2%)			1 (2%)
Pigmentation, hemosiderin				1 (2%)
Alveolar epithelium, hyperplasia	2 (4%)		1 (2%)	2 (4%)
Mediastinum, inflammation, chronic		1 (2%)	1 (2%)	

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

	Chamber Control	2 ppm	8 ppm	32 ppm
Respiratory System (continued)				
Nose	(50)	(48)	(49)	(50)
Inflammation, suppurative	5 (10%)	12 (25%)	25 (51%)	42 (84%)
Glands, hyperplasia		33 (69%)	46 (94%)	47 (94%)
Glands, metaplasia, squamous	1 (2%)	1 (2%)	34 (69%)	46 (92%)
Lateral wall, metaplasia, squamous	3 (6%)	14 (29%)	16 (33%)	36 (72%)
Lateral wall, necrosis			4 (8%)	1 (2%)
Olfactory epithelium, atrophy	2 (4%)	35 (73%)	49 (100%)	50 (100%)
Olfactory epithelium, degeneration, hyaline	7 (14%)	14 (29%)	28 (57%)	45 (90%)
Olfactory epithelium, metaplasia		31 (65%)	49 (100%)	49 (98%)
Respiratory epithelium, degeneration, hyaline	19 (38%)	44 (92%)	49 (100%)	48 (96%)
Respiratory epithelium, hyperplasia, polypoid				1 (2%)
Respiratory epithelium, metaplasia, squamous	1 (2%)	9 (19%)	21 (43%)	39 (78%)
Respiratory epithelium, necrosis			2 (4%)	3 (6%)
Respiratory epithelium, regeneration			9 (18%)	13 (26%)
Trachea	(50)	(48)	(49)	(48)
Metaplasia, squamous			1 (2%)	
Special Senses System				
Eye	(49)	(49)	(49)	(50)
Cataract	2 (4%)	1 (2%)		1 (2%)
Inflammation, acute		1 (2%)		
Inflammation, chronic		1 (2%)		
Inflammation, chronic active			2 (4%)	
Cornea, degeneration	3 (6%)	1 (2%)	4 (8%)	26 (52%)
Cornea, fibrosis	1 (2%)			
Cornea, hyperplasia	2 (4%)		4 (8%)	7 (14%)
Cornea, inflammation, chronic active	1 (2%)		1 (2%)	3 (6%)
Urinary System				
Kidney	(50)	(48)	(49)	(49)
Metaplasia, osseous	1 (2%)	3 (6%)	2 (4%)	4 (8%)
Mineralization			1 (2%)	
Nephropathy	41 (82%)	35 (73%)	40 (82%)	39 (80%)

APPENDIX E

GENETIC TOXICOLOGY

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GENETIC TOXICOLOGY

SALMONELLA MUTAGENICITY TEST PROTOCOL

Testing was performed as reported by Mortelmans *et al.* (1986). Furfuryl alcohol was sent to the laboratory as a coded aliquot from Radian Corporation (Austin, TX). It was incubated with the *Salmonella typhimurium* tester strains TA98, TA100, TA1535, and TA1537 either in buffer or S9 mix (metabolic activation enzymes and cofactors from Aroclor 1254-induced male Sprague-Dawley rat or Syrian hamster 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 furfuryl alcohol. The high dose was limited by experimental design to 10,000 µg/plate. 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.

CHINESE HAMSTER OVARY CELL CYTOGENETICS PROTOCOLS

Testing was performed as reported by Galloway *et al.* (1987). Furfuryl alcohol was sent to the laboratory 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 furfuryl alcohol; the high dose was limited by toxicity. A single flask per dose was used, and tests yielding equivocal or positive results were repeated.

Sister Chromatid Exchange Test: In the SCE test without S9, CHO cells were incubated for 26 hours with furfuryl alcohol in supplemented McCoy's 5A medium. Bromodeoxyuridine (BrdU) was added 2 hours after culture initiation. After 26 hours, the medium containing furfuryl alcohol 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 furfuryl alcohol, serum-free medium, and S9 for 2 hours. The medium was then removed and replaced with medium containing serum and BrdU and no furfuryl alcohol. Incubation proceeded for an additional 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. Because significant chemical-induced cell cycle delay was seen at 500 µg/mL in the second trial without S9, incubation time was lengthened to ensure a sufficient number of scorable (second-division metaphase) cells.

Statistical analyses were conducted on the slopes of the dose-response curves and the individual dose points (Galloway *et al.*, 1987). 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 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 furfuryl alcohol for 10 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 furfuryl alcohol and S9 for 2 hours, after which the treatment medium was removed and the cells were incubated for 11 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. Two 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 ($P \leq 0.05$) difference for one dose point and a significant trend ($P \leq 0.015$) were considered weak evidence for a positive 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.*, 1987). Ultimately, the trial calls were based on a consideration of the statistical analyses as well as the biological information available to the reviewers.

MOUSE BONE MARROW CYTOGENETIC TEST PROTOCOLS

Sister Chromatid Exchange Test: A dose range-finding study was performed in the absence of adequate toxicity information from the literature; the high dose was limited by toxicity. Furfuryl alcohol was tested for the induction of SCEs in mouse bone marrow by two protocols. Male B6C3F₁ mice (five animals per dose group) were injected intraperitoneally with furfuryl alcohol dissolved in corn oil (injection volume=0.4 mL). Solvent control mice received equivalent injections of corn oil only. The positive control was dimethylbenzanthracene.

The first protocol had a standard harvest time of 23 hours, and the second protocol had a delayed harvest time of 42 hours. The mice were implanted subcutaneously with a BrdU tablet (McFee *et al.*, 1983) 24 hours before harvest (1 hour before furfuryl alcohol treatment in the case of the standard protocol). The use of BrdU allowed selection of the appropriate cell population (cells in the second metaphase following furfuryl alcohol treatment) for scoring. Two hours before sacrifice, the mice received an intraperitoneal injection of colchicine in saline. The animals were killed 23 or 42 hours after treatment. One or both femurs were removed, and the marrow was flushed out with phosphate-buffered saline (pH 7.0). The 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 fluorescence-plus-Giemsa and scored.

Twenty-five second-division metaphase cells were scored from each of four animals per treatment. Responses were evaluated as SCEs/cell, and the data were analyzed by a trend test (Margolin *et al.*, 1986).

Chromosomal Aberrations Test: Doses were set based on the information obtained from the range-finding study conducted prior to the SCE test. Furfuryl alcohol 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, and the second protocol used a delayed harvest time of 36 hours.

Male B6C3F₁ mice (10 animals per dose group) were injected intraperitoneally with furfuryl alcohol dissolved in corn oil (injection volume = 0.4 mL). Solvent control mice received equivalent injections of corn oil only. The positive control was dimethylbenzanthracene. The mice 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 furfuryl alcohol 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 mice received an intraperitoneal injection of colchicine in saline. The animals were killed 17 or 36 hours after furfuryl alcohol 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 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, and pairwise comparisons were made between each dosed group and the control group (Margolin *et al.*, 1986).

Micronucleus Test: The standard three-exposure protocol is described in detail by Shelby *et al.* (1993). Male B6C3F₁ mice were injected intraperitoneally three times at 24-hour intervals with furfuryl alcohol dissolved in phosphate-buffered saline; the total dosing volume 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 cyclophosphamide. The mice were killed 24 hours after the third injection, and 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 each of five animals per dose group. In addition, the percentage of PCEs among the total erythrocyte population in the bone marrow was scored for each dose group as a measure of toxicity.

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 (Margolin *et al.*, 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 magnitude of those effects.

RESULTS

Furfuryl alcohol (33-10,000 µg/plate) was not mutagenic in *Salmonella typhimurium* strain TA98, TA100, TA1535, or TA1537, with or without S9 metabolic activation enzymes (Mortelmans *et al.*, 1986; Table E1). It did induce sister chromatid exchanges in cultured CHO cells in each of two trials conducted in the absence of S9 (Table E2). In the second trial without S9, significant cell cycle delay occurred at the highest dose (500 µg/mL) requiring harvest of additional cells at a later time (31 hours culture time) to provide sufficient cells for analysis. No induction of SCEs was noted following treatment with furfuryl alcohol in the presence of S9. Furfuryl alcohol did not induce Abs in cultured CHO cells treated with furfuryl alcohol in the absence of S9, but in the presence of S9, an equivocal result was obtained (Table E3). In the Abs test with S9, the first trial showed a clear dose-related increase in aberrations, with significant elevations seen at 500 and 1,000 µg/mL. Results of the second trial were negative, and the assay overall was determined to be equivocal. *In vivo*, no induction of SCEs (Table E4), Abs

(Table E5), or micronuclei (Table E6) was noted in bone marrow cells of male B6C3F₁ mice after administration of furfuryl alcohol by intraperitoneal injection. In the Abs test, results of the initial 36-hour trial were positive (P=0.003). However, results of two additional 36-hour trials were negative and the assay was concluded to be negative overall.

In conclusion, with the exception of the positive response observed in the SCE test in cultured CHO cells *in vitro*, no indication of genetic activity was seen with furfuryl alcohol.

TABLE E1
Mutagenicity of Furfuryl Alcohol in *Salmonella typhimurium*^a

Strain	Dose ($\mu\text{g}/\text{plate}$)	Revertants/plate ^b					
		S9		+10% hamster S9		+10% rat S9	
		Trial 1	Trial 2	Trial 1	Trial 2	Trial 1	Trial 2
TA100	0	100 \pm 6.2	95 \pm 3.9	156 \pm 4.5	144 \pm 6.2	137 \pm 4.6	129 \pm 7.5
	100	122 \pm 8.7	98 \pm 9.6	152 \pm 5.6	139 \pm 1.8	158 \pm 2.9	135 \pm 7.2
	333	114 \pm 6.2	104 \pm 4.3	152 \pm 1.2	141 \pm 8.1	171 \pm 20.7	137 \pm 17.0
	1,000	116 \pm 2.4	97 \pm 6.5	157 \pm 9.9	146 \pm 14.4	145 \pm 2.9	135 \pm 5.6
	3,333	103 \pm 12.0	93 \pm 5.8	158 \pm 13.3	135 \pm 9.2	187 \pm 2.9	154 \pm 11.0
	10,000	Toxic	92 \pm 8.0	61 \pm 4.4	73 \pm 8.7	117 \pm 15.4	115 \pm 2.7
	Trial summary	Negative	Negative	Negative	Negative	Negative	Negative
Positive control ^c	494 \pm 20.0	620 \pm 83.1	1,775 \pm 96.1	2,509 \pm 107.6	1,044 \pm 25.4	1,091 \pm 111.2	
TA1535	0	3 \pm 0.7	5 \pm 1.5	5 \pm 0.3	4 \pm 1.2	4 \pm 1.8	4 \pm 0.3
	100	3 \pm 0.9	3 \pm 1.2	3 \pm 0.6	3 \pm 0.9	3 \pm 1.5	3 \pm 0.0
	333	1 \pm 0.0	1 \pm 0.7	5 \pm 0.3	4 \pm 0.3	4 \pm 0.3	3 \pm 0.7
	1,000	7 \pm 3.3	5 \pm 3.7	3 \pm 0.9	3 \pm 0.3	2 \pm 0.9	5 \pm 1.8
	3,333	2 \pm 0.7	2 \pm 1.2	6 \pm 0.3	3 \pm 1.2	5 \pm 0.6	4 \pm 0.7
	10,000	3 \pm 0.0	3 \pm 1.3	4 \pm 1.2	2 \pm 1.2	2 \pm 0.6	3 \pm 0.7
	Trial summary	Negative	Negative	Negative	Negative	Negative	Negative
Positive control	163 \pm 28.0	108 \pm 7.1	60 \pm 1.0	93 \pm 26.7	78 \pm 11.8	115 \pm 2.7	
TA1537	0	S9		+10% hamster S9			
		Trial 1	Trial 2	Trial 1	Trial 2	Trial 3	
	33	3 \pm 0.6	6 \pm 2.4	5 \pm 1.3	5 \pm 0.6	10 \pm 1.5	
	100		3 \pm 1.2				
	333	2 \pm 0.6	2 \pm 0.9	5 \pm 0.7	6 \pm 1.2	15 \pm 1.7	
	1,000	2 \pm 0.9	4 \pm 1.5	3 \pm 0.9	5 \pm 0.9	12 \pm 1.9	
	3,333	2 \pm 0.7	4 \pm 0.3	4 \pm 0.7	3 \pm 0.7	10 \pm 2.6	
	10,000	3 \pm 1.0	3 \pm 1.5	8 \pm 1.0	6 \pm 0.9	13 \pm 1.3	
	Trial summary	Negative	Negative	Negative	Negative	Negative	
	Positive control	787 \pm 60.9	918 \pm 78.8	110 \pm 12.9	63 \pm 1.3	675 \pm 15.3	
TA1537	0	+10% rat S9					
		Trial 1	Trial 2	Trial 3			
	100	2 \pm 1.3	3 \pm 0.5	12 \pm 3.0			
	333	1 \pm 0.3	5 \pm 1.9	14 \pm 2.6			
	1,000	3 \pm 1.0	7 \pm 1.3	12 \pm 1.5			
	3,333	7 \pm 2.5	7 \pm 1.0	16 \pm 0.9			
	10,000	6 \pm 1.8	5 \pm 1.8	14 \pm 1.9			
Trial summary	Negative	Negative	Negative				
Positive control	53 \pm 4.4	79 \pm 7.9	121 \pm 4.1				

TABLE E1
Mutagenicity of Furfuryl Alcohol in *Salmonella typhimurium*

Strain	Dose ($\mu\text{g}/\text{plate}$)	Revertants/plate					
		S9		+10% hamster S9		+10% rat S9	
		Trial 1	Trial 2	Trial 1	Trial 2	Trial 1	Trial 2
TA98	0	15 \pm 2.0	15 \pm 0.9	21 \pm 1.9	23 \pm 1.7	26 \pm 1.2	20 \pm 3.1
	33		14 \pm 2.6				
	100	11 \pm 2.1	16 \pm 3.3	18 \pm 0.7	20 \pm 1.3	24 \pm 1.0	23 \pm 1.9
	333	13 \pm 2.4	15 \pm 1.9	24 \pm 0.9	23 \pm 4.0	24 \pm 2.3	20 \pm 2.6
	1,000	12 \pm 3.2	12 \pm 0.3	26 \pm 0.9	31 \pm 4.0	23 \pm 0.6	18 \pm 4.3
	3,333	2 \pm 0.6	12 \pm 5.4	22 \pm 0.3	23 \pm 5.2	23 \pm 0.9	17 \pm 1.9
	10,000	Toxic		22 \pm 1.5	22 \pm 4.2	13 \pm 2.3	15 \pm 2.9
	Trial summary	Negative	Negative	Negative	Negative	Negative	Negative
Positive control	156 \pm 12.2	301 \pm 5.3	2,223 \pm 24.6	2,369 \pm 46.4	462 \pm 34.5	617 \pm 103.7	

^a Study was performed at Case Western Reserve University. The detailed protocol and these data are presented in Mortelmans *et al.* (1986).
0 $\mu\text{g}/\text{plate}$ was the solvent control.

^b Revertants are presented as mean \pm standard error from three plates.

^c The positive controls in the absence of metabolic activation were sodium azide (TA100 and TA1535), 9-aminoacridine (TA1537), and 4-nitro-*o*-phenylenediamine (TA98). The positive control for metabolic activation with all strains was 2-aminoanthracene.

TABLE E2
Induction of Sister Chromatid Exchanges in Chinese Hamster Ovary Cells by Furfuryl Alcohol^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 (%)
S9								
Trial 1								
Summary: Weakly positive								
Dimethylsulfoxide ^c		50	1,045	422	0.40	8.4	26.0	
Mitomycin-C ^d	0.0005	50	1,046	558	0.53	11.2	26.0	32.10
	0.0050	10	210	384	1.82	38.4	26.0	352.82
Furfuryl alcohol	16	50	1,050	444	0.42	8.9	26.0	4.71
	50	50	1,051	451	0.42	9.0	26.0	6.26
	160	50	1,049	416	0.39	8.3	26.0	1.80
	500	50	1,051	572	0.54	11.4	26.0	34.77*
					P<0.001 ^e			
Trial 2								
Summary: Positive								
Dimethylsulfoxide		50	1,049	459	0.43	9.2	26.0	
Mitomycin-C	0.0008	50	1,046	551	0.52	11.0	26.0	20.39
	0.0050	10	209	259	1.23	25.9	26.0	183.22
Furfuryl alcohol	16	50	1,044	435	0.41	8.7	26.0	4.78
	50	50	1,048	436	0.41	8.7	26.0	4.92
	160	50	1,046	555	0.53	11.1	26.0	21.26*
	500	3 ^f	61	41	0.67	13.7	26.0	53.61*
	500	50	1,051	587	0.55	11.7	31.0 ^g	27.64*
					P<0.001			

TABLE E2
Induction of Sister Chromatid Exchanges in Chinese Hamster Ovary Cells by Furfuryl Alcohol

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 (%)
+S9								
Summary: Negative								
Dimethylsulfoxide		50	1,050	452	0.43	9.0	26.0	
Cyclophosphamide ^d	0.1	50	1,051	567	0.53	11.3	26.0	25.32
	0.6	10	210	202	0.96	20.2	26.0	123.45
Furfuryl alcohol	16	50	1,049	400	0.38	8.0	26.0	11.42
	50	50	1,050	458	0.43	9.2	26.0	1.33
	160	50	1,050	482	0.45	9.6	26.0	6.64
	500	50	1,050	512	0.48	10.2	26.0	13.27
P=0.001								

* Positive response (20% increase over solvent control)

^a Study was performed at Environmental Health Research and Testing, Inc. The detailed protocol is presented in Galloway *et al.* (1987).
 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 of SCEs/chromosome tested by the linear regression trend test versus log of the dose

^f Only three second-division metaphase cells were evaluated due to the cytostatic nature of the chemical at this concentration. This concentration was retested using an extended culture time.

^g Due to cell cycle delay, harvest time was extended to maximize the number of second-division metaphase cells available for analysis.

TABLE E3
Induction of Chromosomal Aberrations in Chinese Hamster Ovary Cells by Furfuryl Alcohol^a

Compound	Concentration (µg/mL)	Total Cells Scored	Number of Aberrations	Aberrations/Cell	Cells with Aberrations (%)
S9					
Harvest time: 12 hours					
Summary: Negative					
Dimethylsulfoxide ^b		200	3	0.02	1.5
Mitomycin-C ^c	0.0625	200	39	0.20	16.0
	0.25	50	20	0.40	36.0
Furfuryl alcohol	160	200	3	0.02	1.5
	300	200	3	0.02	1.5
	500	200	7	0.04	3.5
					P=0.094 ^d
+S9					
Trial 1					
Harvest time: 13 hours					
Summary: Positive					
Dimethylsulfoxide		200	0	0.00	0.0
Cyclophosphamide ^c	2.5	200	35	0.18	14.5
	7.5	50	21	0.42	32.0
Furfuryl alcohol	300	200	1	0.01	0.5
	500	200	6	0.03	3.0*
	1,000	200	11	0.06	3.0*
					P<0.001
Trial 2					
Harvest time: 13 hours					
Summary: Negative					
Dimethylsulfoxide		200	1	0.01	0.5
Cyclophosphamide	2.5	200	22	0.11	10.5
	7.5	50	18	0.36	32.0
Furfuryl alcohol	500	200	4	0.02	1.5
	1,000	200	6	0.03	3.0
	1,600	200	1	0.01	0.5
					P=0.286

* Positive (P≤0.05)

^a Study was performed at Environmental Health Research and Testing, Inc. The detailed protocol is presented in Galloway *et al.* (1987).

^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 E4
Induction of Sister Chromatid Exchanges in Mouse Bone Marrow Cells by Furfuryl Alcohol^a

Compound	Dose (mg/kg)	SCEs/Cell
Trial 1		
Harvest time: 23 hours		
Corn oil ^b	0	4.47 ± 0.40
Dimethylbenzanthracene ^c	2.5	9.15 ± 0.10
Furfuryl alcohol	75	4.15 ± 0.73
	150	5.70 ± 0.50
	300	4.63 ± 1.03
		P=0.335 ^d
Trial 2		
Harvest time: 42 hours		
Corn oil	0	6.14 ± 1.06
Dimethylbenzanthracene	100	18.39 ± 1.09
Furfuryl alcohol	37.5	5.73 ± 0.44
	75	6.82 ± 1.00
	150	5.40 ± 0.84
		P=0.320

^a Study was performed at Oak Ridge Associated Universities. The detailed protocols are presented in McFee (1991). Data for SCEs/cell are given as mean ± standard error. SCE=sister chromatid exchange. Twenty-five second-division metaphase cells were analyzed from each of four animals per group.

^b Solvent control

^c Positive control

^d Significance tested by the one-tailed trend test; significant at P<0.025 (Margolin *et al.*, 1986)

TABLE E5
Induction of Chromosomal Aberrations in Mouse Bone Marrow Cells by Furfuryl Alcohol^a

Compound	Dose (mg/kg)	Total Aberrations	Aberrations/Cell ^b	Cells with Aberrations (%)	Pairwise P Values ^c
Trial 1					
Harvest time: 17 hours					
Corn oil ^d		1.1	0.02	2.00	
Dimethylbenzanthracene ^e	100	14.0	0.17	17.00	0.000
Furfuryl alcohol	75	1.6	0.02	2.00	0.500
	150	2.6	0.04	4.00	0.097
	300	0.4	0.00	0.00	0.987
				P=0.935 ^f	
Trial 2					
Harvest time: 36 hours					
Corn oil ^g		1.4	0.02	1.43	
Dimethylbenzanthracene	100	40.3	0.67	27.50	0.000
Furfuryl alcohol	50	1.5	0.02	2.00	0.275
	100	2.9	0.04	4.00	0.017
	200	3.0	0.05	4.50	0.008
				P=0.003	
Trial 3					
Harvest time: 36 hours					
Corn oil		3.5	0.04	1.50	
Dimethylbenzanthracene ^g	50	47.4	0.69	24.86	0.000
Furfuryl alcohol	50	1.3	0.02	1.50	0.500
	100	1.1	0.02	1.75	0.390
	200	2.0	0.02	2.00	0.295
				P=0.267	

TABLE E5
Induction of Chromosomal Aberrations in Mouse Bone Marrow Cells by Furfuryl Alcohol

Compound	Dose (mg/kg)	Total Aberrations	Aberrations/Cell	Cells with Aberrations (%)	Pairwise P Values
Trial 4					
Harvest time: 36 hours					
Corn oil		2.0	0.02	1.75	
Dimethylbenzanthracene	50	25.3	0.33	18.00	0.000
Furfuryl alcohol	50	0.9	0.01	1.25	0.720
	100	0.5	0.01	0.75	0.899
	200	1.0	0.02	1.50	0.610
				P=0.603	

^a Study was performed at Oak Ridge Associated Universities. The detailed protocols are presented in McFee (1991). Fifty cells were scored in each of eight animals per dose group unless otherwise noted.

^b Mean

^c Comparison of individual treatment groups to the concurrent solvent control. Significant at $P \leq 0.008$.

^d Solvent control

^e Positive control

^f Significance tested by the one-tailed trend test; significant at $P \leq 0.025$ (Margolin *et al.*, 1986)

^g n=7

TABLE E6
Induction of Micronuclei in Bone Marrow Polychromatic Erythrocytes of Mice
Treated with Furfuryl Alcohol by Intraperitoneal Injection^a

Compound	Dose (mg/kg)	Number of Mice with Erythrocytes Scored	Micronucleated PCEs/1,000 PCEs ^b	Pairwise P Values ^c	PCEs ^b (%)
Phosphate-buffered saline ^d		5	1.00 ± 0.16		53.22 ± 2.68
Cyclophosphamide ^e	15	5	8.80 ± 1.34	0.000	48.04 ± 2.56
Furfuryl alcohol	15.625	5	1.50 ± 0.69	0.159	55.22 ± 2.03
	31.25	5	1.00 ± 0.32	0.500	58.74 ± 4.04
	62.5	5	1.40 ± 0.56	0.207	59.18 ± 2.11
	125	5	1.40 ± 0.19	0.207	52.98 ± 3.34
	250	Lethal			
			P=0.266 ^f		

^a Study was performed at Environmental Health Research and Testing, Inc. The detailed protocol is presented in Shelby *et al.* (1993).

^b PCE=polychromatic erythrocyte.

^c Mean ± standard error

^d Comparison of individual treatment groups to the concurrent solvent control, significant at P≤0.006

^e Solvent control

^f Positive control

^f Significance of micronucleated PCEs/1,000 PCEs tested by the one-tailed trend test, significant at P≤0.025 (ILS, 1990)

APPENDIX F HEMATOLOGY AND CLINICAL CHEMISTRY RESULTS

TABLE F1	Hematology and Clinical Chemistry Data for Rats in the 14-Week Inhalation Study of Furfuryl Alcohol	212
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TABLE F1
Hematology and Clinical Chemistry Data for Rats in the 14-Week Inhalation Study of Furfuryl Alcohol^a

	Chamber Control	2 ppm	4 ppm	8 ppm	16 ppm	32 ppm
Male						
n						
Day 3	10	10	10	10	10	10
Day 23	10	9	9	10	10	10
Week 14	10	10	10	10	10	10
Hematology						
Hematocrit (mL/dL)						
Day 3	39.8 ± 0.3	40.3 ± 0.3	42.9 ± 1.0**	40.7 ± 0.6*	42.3 ± 0.3**	41.8 ± 0.4**
Day 23	42.9 ± 0.4	42.7 ± 0.5	43.0 ± 0.4	42.1 ± 0.3	42.9 ± 0.4	43.0 ± 0.4
Week 14	46.0 ± 0.5	46.7 ± 0.3	46.2 ± 0.5	46.5 ± 0.4	46.6 ± 0.2	46.6 ± 0.2
Hemoglobin (g/dL)						
Day 3	12.9 ± 0.1	13.1 ± 0.1	13.9 ± 0.3**	13.3 ± 0.2*	13.7 ± 0.1**	13.6 ± 0.1**
Day 23	15.0 ± 0.1	15.0 ± 0.2	15.1 ± 0.1	14.7 ± 0.1	14.9 ± 0.1	15.0 ± 0.1
Week 14	15.1 ± 0.2	15.1 ± 0.2	14.9 ± 0.1	15.1 ± 0.1	15.2 ± 0.1	15.2 ± 0.0
Erythrocytes (10⁶/μL)						
Day 3	6.63 ± 0.07	6.73 ± 0.07	7.28 ± 0.18**	6.90 ± 0.12*	7.15 ± 0.06**	7.02 ± 0.12**
Day 23	7.81 ± 0.09	7.78 ± 0.10	7.84 ± 0.09	7.68 ± 0.09	7.77 ± 0.07	7.75 ± 0.09
Week 14	8.81 ± 0.11	8.96 ± 0.04	8.86 ± 0.08	8.95 ± 0.06	9.05 ± 0.04	8.94 ± 0.02
Reticulocytes (10⁶/μL)						
Day 3	0.49 ± 0.02	0.52 ± 0.03	0.49 ± 0.03	0.46 ± 0.03	0.42 ± 0.03	0.43 ± 0.02
Day 23	0.14 ± 0.01	0.11 ± 0.01	0.12 ± 0.01	0.13 ± 0.01	0.15 ± 0.01	0.18 ± 0.01*
Week 14	0.14 ± 0.01	0.14 ± 0.01	0.13 ± 0.01	0.15 ± 0.01	0.15 ± 0.02	0.11 ± 0.01
Nucleated erythrocytes (10³/μL)						
Day 3	0.19 ± 0.03	0.14 ± 0.03	0.11 ± 0.03	0.12 ± 0.03	0.11 ± 0.03	0.08 ± 0.02
Day 23	0.02 ± 0.01	0.00 ± 0.00	0.01 ± 0.01	0.01 ± 0.01	0.01 ± 0.01	0.01 ± 0.01
Week 14	0.02 ± 0.01	0.01 ± 0.01	0.01 ± 0.01	0.03 ± 0.02	0.02 ± 0.01	0.02 ± 0.01
Mean cell volume (fL)						
Day 3	60.0 ± 0.2	59.9 ± 0.3	59.0 ± 0.3	59.0 ± 0.5	59.3 ± 0.3	59.5 ± 0.5
Day 23	55.0 ± 0.3	54.9 ± 0.4	54.9 ± 0.3	54.6 ± 0.3	55.3 ± 0.2	55.5 ± 0.3
Week 14	52.3 ± 0.2	52.2 ± 0.1	52.0 ± 0.0	51.9 ± 0.4*	51.5 ± 0.2**	52.0 ± 0.1*
Mean cell hemoglobin (pg)						
Day 3	19.4 ± 0.1	19.4 ± 0.1	19.1 ± 0.1	19.3 ± 0.1	19.2 ± 0.1	19.4 ± 0.2
Day 23	19.2 ± 0.1	19.3 ± 0.1	19.3 ± 0.1	19.1 ± 0.1	19.2 ± 0.0	19.3 ± 0.1
Week 14	17.1 ± 0.1	16.8 ± 0.1	16.9 ± 0.0	16.9 ± 0.1	16.8 ± 0.1	17.0 ± 0.1
Mean cell hemoglobin concentration (g/dL)						
Day 3	32.4 ± 0.2	32.5 ± 0.1	32.3 ± 0.1	32.7 ± 0.1	32.4 ± 0.1	32.5 ± 0.1
Day 23	34.9 ± 0.1	35.2 ± 0.1	35.1 ± 0.1	34.9 ± 0.1	34.8 ± 0.1	34.8 ± 0.1
Week 14	32.7 ± 0.1	32.3 ± 0.2	32.4 ± 0.1	32.5 ± 0.1	32.7 ± 0.1	32.6 ± 0.1
Platelets (10³/μL)						
Day 3	750.6 ± 12.3	773.7 ± 6.4	762.9 ± 12.5	758.0 ± 17.0	785.2 ± 15.4	792.6 ± 43.4
Day 23	537.5 ± 9.2	543.0 ± 15.4	540.3 ± 17.5	546.9 ± 7.1	539.0 ± 7.2	552.5 ± 7.5
Week 14	489.2 ± 7.3 ^b	474.9 ± 10.2	507.0 ± 6.3	517.3 ± 10.4	481.4 ± 8.1	486.2 ± 9.2
Leukocytes (10³/μL)						
Day 3	7.78 ± 0.31	8.49 ± 0.29	8.62 ± 0.28	8.16 ± 0.38	8.75 ± 0.44	7.62 ± 0.53
Day 23	5.81 ± 0.32	6.16 ± 0.32	6.84 ± 0.33	5.99 ± 0.13	6.44 ± 0.31	6.43 ± 0.31
Week 14	6.70 ± 0.30	7.14 ± 0.34	7.32 ± 0.39	6.87 ± 0.26	5.89 ± 0.29	6.27 ± 0.24
Segmented neutrophils (10³/μL)						
Day 3	1.29 ± 0.09	1.18 ± 0.09	1.01 ± 0.10	1.10 ± 0.09	1.07 ± 0.22*	0.78 ± 0.07**
Day 23	0.57 ± 0.04	0.64 ± 0.07	0.78 ± 0.12	0.86 ± 0.07**	1.01 ± 0.11**	0.92 ± 0.10**
Week 14	1.19 ± 0.08	1.02 ± 0.08	1.13 ± 0.17	0.98 ± 0.08	1.06 ± 0.06	1.08 ± 0.11

TABLE F1
Hematology and Clinical Chemistry Data for Rats in the 14-Week Inhalation Study of Furfuryl Alcohol

	Chamber Control	2 ppm	4 ppm	8 ppm	16 ppm	32 ppm
Male (continued)						
n						
Day 3	10	10	10	10	10	10
Day 23	10	9	9	10	10	10
Week 14	10	10	10	10	10	10
Hematology (continued)						
Lymphocytes (10³/μL)						
Day 3	6.05 ± 0.22	6.87 ± 0.26	7.27 ± 0.30*	6.79 ± 0.32	7.33 ± 0.36*	6.67 ± 0.49
Day 23	5.14 ± 0.31	5.39 ± 0.29	5.86 ± 0.36	4.94 ± 0.12	5.22 ± 0.27	5.10 ± 0.26
Week 14	5.37 ± 0.26	5.99 ± 0.30	6.08 ± 0.29	5.72 ± 0.26	4.73 ± 0.25	5.00 ± 0.19
Monocytes (10³/μL)						
Day 3	0.40 ± 0.08	0.38 ± 0.06	0.33 ± 0.06	0.21 ± 0.04	0.31 ± 0.05	0.16 ± 0.03**
Day 23	0.10 ± 0.02	0.09 ± 0.03	0.18 ± 0.04	0.15 ± 0.04	0.14 ± 0.03	0.30 ± 0.04**
Week 14	0.09 ± 0.02	0.08 ± 0.03	0.08 ± 0.02	0.09 ± 0.03	0.05 ± 0.02	0.07 ± 0.02
Eosinophils (10³/μL)						
Day 3	0.05 ± 0.02	0.05 ± 0.02	0.00 ± 0.00	0.06 ± 0.02	0.04 ± 0.01	0.02 ± 0.01
Day 23	0.01 ± 0.01	0.04 ± 0.02	0.01 ± 0.01	0.04 ± 0.02	0.07 ± 0.03	0.10 ± 0.04*
Week 14	0.06 ± 0.02	0.05 ± 0.02	0.03 ± 0.02	0.07 ± 0.02	0.04 ± 0.02	0.12 ± 0.03
Clinical Chemistry						
Urea nitrogen (mg/dL)						
Day 3	12.4 ± 0.5	11.6 ± 0.4	12.6 ± 0.7	11.2 ± 0.3	12.9 ± 0.6	13.4 ± 0.3
Day 23	12.6 ± 0.4	12.8 ± 0.3	13.1 ± 0.3	12.7 ± 0.3	13.3 ± 0.2	12.8 ± 0.3
Week 14	17.9 ± 0.6	18.7 ± 0.6	18.9 ± 0.7	17.5 ± 0.7	17.8 ± 0.5	17.1 ± 0.7
Creatinine (mg/dL)						
Day 3	0.45 ± 0.02	0.51 ± 0.01	0.47 ± 0.02	0.45 ± 0.02	0.46 ± 0.02	0.46 ± 0.02
Day 23	0.74 ± 0.02	0.77 ± 0.02	0.73 ± 0.02	0.69 ± 0.02	0.74 ± 0.02	0.78 ± 0.01
Week 14	0.67 ± 0.02	0.70 ± 0.02	0.65 ± 0.02	0.64 ± 0.02	0.64 ± 0.02	0.66 ± 0.02
Total protein (g/dL)						
Day 3	5.2 ± 0.0	5.4 ± 0.1	5.6 ± 0.2**	5.4 ± 0.1*	5.5 ± 0.1**	5.5 ± 0.1**
Day 23	6.4 ± 0.1	6.5 ± 0.1	6.4 ± 0.1	6.2 ± 0.1*	6.2 ± 0.1*	6.2 ± 0.1*
Week 14	7.1 ± 0.1	7.0 ± 0.1	7.0 ± 0.1	7.0 ± 0.1	7.1 ± 0.1	6.9 ± 0.1
Albumin (g/dL)						
Day 3	3.2 ± 0.0	3.2 ± 0.0	3.4 ± 0.1	3.3 ± 0.1	3.4 ± 0.1*	3.4 ± 0.1*
Day 23	4.4 ± 0.1	4.4 ± 0.1	4.3 ± 0.0	4.2 ± 0.1	4.4 ± 0.1	4.4 ± 0.1
Week 14	3.9 ± 0.1	4.0 ± 0.0	4.0 ± 0.0	4.0 ± 0.1	4.1 ± 0.0	3.9 ± 0.0
Globulin (g/dL)						
Day 3	2.0 ± 0.1	2.1 ± 0.0	2.2 ± 0.1	2.1 ± 0.1	2.1 ± 0.1	2.1 ± 0.0
Day 23	2.0 ± 0.1	2.1 ± 0.1	2.1 ± 0.0	2.0 ± 0.1	1.8 ± 0.1*	1.8 ± 0.1*
Week 14	3.1 ± 0.1	3.0 ± 0.1	3.0 ± 0.1	3.0 ± 0.1	3.0 ± 0.1	3.0 ± 0.1
A/G ratio						
Day 3	1.6 ± 0.1	1.5 ± 0.0	1.6 ± 0.0	1.6 ± 0.1	1.7 ± 0.1	1.6 ± 0.0
Day 23	2.2 ± 0.1	2.1 ± 0.1	2.1 ± 0.1	2.2 ± 0.1	2.5 ± 0.1*	2.6 ± 0.1*
Week 14	1.3 ± 0.1	1.3 ± 0.0	1.4 ± 0.0	1.3 ± 0.0	1.4 ± 0.0	1.3 ± 0.0
Alanine aminotransferase (IU/L)						
Day 3	47 ± 1	44 ± 1*	44 ± 2	42 ± 3*	38 ± 1**	41 ± 1**
Day 23	35 ± 1	36 ± 1	39 ± 3	35 ± 1	34 ± 1	33 ± 1
Week 14	66 ± 4	66 ± 4 ^b	60 ± 3	72 ± 3	65 ± 4	53 ± 2*

TABLE F1
Hematology and Clinical Chemistry Data for Rats in the 14-Week Inhalation Study of Furfuryl Alcohol

	Chamber Control	2 ppm	4 ppm	8 ppm	16 ppm	32 ppm
Male (continued)						
n						
Day 3	10	10	10	10	10	10
Day 23	10	9	9	10	10	10
Week 14	10	10	10	10	10	10
Clinical Chemistry (continued)						
Alkaline phosphatase (IU/L)						
Day 3	692 ± 12	718 ± 12	679 ± 12	647 ± 12	580 ± 12**	641 ± 20**
Day 23	568 ± 16	579 ± 17	561 ± 17	570 ± 18	554 ± 14	576 ± 15
Week 14	294 ± 7	285 ± 7	271 ± 8	273 ± 10	296 ± 9	283 ± 3
Creatine kinase (IU/L)						
Day 3	408 ± 25	374 ± 20	360 ± 26	496 ± 86	391 ± 54	507 ± 50
Day 23	238 ± 32	379 ± 58	250 ± 22	310 ± 48	287 ± 36	259 ± 39
Week 14	143 ± 14	167 ± 20	138 ± 19	143 ± 15	138 ± 17	149 ± 20
Sorbitol dehydrogenase (IU/L)						
Day 3	8 ± 1	7 ± 0	7 ± 1	6 ± 1	7 ± 1	8 ± 1
Day 23	8 ± 0	8 ± 1	9 ± 2	9 ± 1	9 ± 0	10 ± 0*
Week 14	12 ± 0	12 ± 1 ^b	12 ± 1	12 ± 1	12 ± 1	10 ± 1
Bile acids (µmol/L)						
Day 3	8.4 ± 1.0	7.1 ± 0.7	8.5 ± 0.9	6.4 ± 1.1	6.2 ± 0.4	7.6 ± 0.7
Day 23	5.4 ± 0.6	7.2 ± 1.7	6.1 ± 0.8	4.4 ± 0.5	8.1 ± 2.5	5.0 ± 0.5
Week 14	4.4 ± 0.3	4.2 ± 0.7 ^b	6.5 ± 1.1	4.7 ± 0.7	4.6 ± 0.8	4.2 ± 0.9
Female						
n	10	10	10	10	10	10
Hematology						
Hematocrit (mL/dL)						
Day 3	41.5 ± 0.5	42.3 ± 0.2	42.8 ± 0.7	42.9 ± 0.4*	43.4 ± 0.5*	43.7 ± 0.6*
Day 23	44.7 ± 0.3	43.6 ± 0.3	44.3 ± 0.4	44.8 ± 0.3	44.1 ± 0.4	44.1 ± 0.3
Week 14	47.1 ± 0.4	48.0 ± 0.3	47.8 ± 0.4	48.1 ± 0.5	47.6 ± 0.7	47.8 ± 0.6
Hemoglobin (g/dL)						
Day 3	13.6 ± 0.2	14.0 ± 0.1*	14.1 ± 0.2*	14.1 ± 0.1*	14.2 ± 0.2*	14.3 ± 0.2**
Day 23	15.6 ± 0.1	15.3 ± 0.1	15.6 ± 0.1	15.7 ± 0.1	15.5 ± 0.1	15.5 ± 0.1
Week 14	15.3 ± 0.1	15.5 ± 0.1	15.5 ± 0.1	15.5 ± 0.1	15.3 ± 0.3	15.5 ± 0.1
Erythrocytes (10 ⁶ /µL)						
Day 3	7.17 ± 0.09	7.39 ± 0.05	7.53 ± 0.15*	7.42 ± 0.08*	7.62 ± 0.11**	7.56 ± 0.12**
Day 23	8.03 ± 0.07	7.91 ± 0.07	8.02 ± 0.08	8.10 ± 0.07	7.97 ± 0.11	7.96 ± 0.06
Week 14	8.50 ± 0.07	8.62 ± 0.05	8.62 ± 0.08	8.68 ± 0.08	8.55 ± 0.13	8.61 ± 0.11
Reticulocytes (10 ⁶ /µL)						
Day 3	0.29 ± 0.02	0.28 ± 0.02	0.30 ± 0.02	0.29 ± 0.01	0.24 ± 0.02	0.31 ± 0.03
Day 23	0.10 ± 0.01	0.07 ± 0.01	0.12 ± 0.01	0.11 ± 0.01	0.11 ± 0.01	0.11 ± 0.01
Week 14	0.19 ± 0.01	0.18 ± 0.02	0.19 ± 0.02	0.16 ± 0.01	0.16 ± 0.01	0.16 ± 0.02
Nucleated erythrocytes (10 ³ /µL)						
Day 3	0.15 ± 0.03	0.13 ± 0.04	0.19 ± 0.03	0.11 ± 0.03	0.04 ± 0.03	0.08 ± 0.03
Day 23	0.02 ± 0.01	0.00 ± 0.00	0.01 ± 0.01	0.01 ± 0.01	0.00 ± 0.00	0.01 ± 0.01
Week 14	0.04 ± 0.02	0.04 ± 0.02	0.04 ± 0.02	0.03 ± 0.02	0.05 ± 0.02	0.06 ± 0.02

TABLE F1
Hematology and Clinical Chemistry Data for Rats in the 14-Week Inhalation Study of Furfuryl Alcohol

	Chamber Control	2 ppm	4 ppm	8 ppm	16 ppm	32 ppm
Female (continued)						
n	10	10	10	10	10	10
Hematology (continued)						
Mean cell volume (fL)						
Day 3	58.0 ± 0.2	57.2 ± 0.2	56.9 ± 0.4	57.9 ± 0.2	56.8 ± 0.5*	57.9 ± 0.4
Day 23	55.6 ± 0.2	55.1 ± 0.2	55.1 ± 0.2	55.4 ± 0.3	55.2 ± 0.4	55.3 ± 0.3
Week 14	55.3 ± 0.2	55.8 ± 0.1	55.6 ± 0.2	55.6 ± 0.2	55.5 ± 0.2	55.5 ± 0.3
Mean cell hemoglobin (pg)						
Day 3	19.0 ± 0.1	19.0 ± 0.1	18.7 ± 0.1	19.0 ± 0.1	18.7 ± 0.1	18.9 ± 0.1
Day 23	19.5 ± 0.1	19.4 ± 0.1	19.5 ± 0.1	19.4 ± 0.1	19.5 ± 0.2	19.5 ± 0.1
Week 14	18.0 ± 0.0	18.0 ± 0.1	18.0 ± 0.1	17.9 ± 0.1	17.9 ± 0.2	18.0 ± 0.1
Mean cell hemoglobin concentration (g/dL)						
Day 3	32.7 ± 0.1	33.1 ± 0.1	32.8 ± 0.1	32.8 ± 0.1	32.8 ± 0.1	32.7 ± 0.1
Day 23	35.0 ± 0.1	35.2 ± 0.1	35.3 ± 0.1	35.0 ± 0.1	35.2 ± 0.1	35.3 ± 0.1
Week 14	32.5 ± 0.1	32.4 ± 0.1	32.5 ± 0.1	32.3 ± 0.1	32.2 ± 0.2	32.4 ± 0.2
Platelets (10 ³ /μL)						
Day 3	781.8 ± 14.8	786.0 ± 17.4	774.5 ± 24.3	786.4 ± 15.9	769.6 ± 25.2	774.0 ± 29.4
Day 23	544.8 ± 7.5	512.5 ± 17.8	532.8 ± 9.7	534.3 ± 9.2	499.5 ± 18.1	528.6 ± 12.0
Week 14	506.2 ± 7.6	520.3 ± 9.1	516.7 ± 10.6	526.9 ± 7.2	502.2 ± 10.8	521.7 ± 5.4
Leukocytes (10 ³ /μL)						
Day 3	8.75 ± 0.41	8.50 ± 0.36	8.77 ± 0.44	8.55 ± 0.46	8.78 ± 0.35	8.61 ± 0.47
Day 23	8.03 ± 0.57	7.91 ± 0.22	8.22 ± 0.43	7.57 ± 0.36	7.50 ± 0.41	6.07 ± 0.24**
Week 14	7.23 ± 0.34	6.94 ± 0.45	6.60 ± 0.46	7.87 ± 0.64	6.81 ± 0.56	7.14 ± 0.55
Segmented neutrophils (10 ³ /μL)						
Day 3	0.87 ± 0.11	1.05 ± 0.12	0.90 ± 0.09	0.92 ± 0.09	1.01 ± 0.13	0.90 ± 0.08
Day 23	0.83 ± 0.10	0.68 ± 0.07	0.78 ± 0.09	0.99 ± 0.14	0.72 ± 0.11	0.94 ± 0.11
Week 14	1.03 ± 0.11	1.00 ± 0.14	0.99 ± 0.10	1.11 ± 0.12	0.99 ± 0.08	1.01 ± 0.17
Lymphocytes (10 ³ /μL)						
Day 3	7.62 ± 0.34	7.24 ± 0.28	7.56 ± 0.40	7.38 ± 0.41	7.60 ± 0.37	7.40 ± 0.46
Day 23	6.96 ± 0.51	6.97 ± 0.21	7.18 ± 0.40	6.31 ± 0.32	6.46 ± 0.33	4.93 ± 0.18**
Week 14	6.05 ± 0.31	5.77 ± 0.38	5.48 ± 0.44	6.55 ± 0.57	5.65 ± 0.48	5.95 ± 0.43
Monocytes (10 ³ /μL)						
Day 3	0.20 ± 0.05	0.18 ± 0.06	0.28 ± 0.09	0.22 ± 0.05	0.12 ± 0.03	0.26 ± 0.05
Day 23	0.22 ± 0.05	0.22 ± 0.05	0.22 ± 0.06	0.23 ± 0.05	0.20 ± 0.05	0.15 ± 0.03
Week 14	0.15 ± 0.03	0.12 ± 0.04	0.08 ± 0.03	0.13 ± 0.04	0.08 ± 0.02	0.06 ± 0.03
Eosinophils (10 ³ /μL)						
Day 3	0.06 ± 0.02	0.04 ± 0.02	0.03 ± 0.01	0.04 ± 0.01	0.05 ± 0.02	0.05 ± 0.02
Day 23	0.03 ± 0.02	0.04 ± 0.02	0.05 ± 0.02	0.04 ± 0.01	0.12 ± 0.03	0.05 ± 0.02
Week 14	0.01 ± 0.01	0.04 ± 0.02	0.04 ± 0.02	0.08 ± 0.03*	0.10 ± 0.04**	0.12 ± 0.02**
Clinical Chemistry						
Urea nitrogen (mg/dL)						
Day 3	15.9 ± 0.8	14.6 ± 0.6	13.7 ± 0.6	14.0 ± 0.6	14.7 ± 0.6	13.5 ± 0.6
Day 23	14.7 ± 0.5	14.8 ± 0.4	14.3 ± 0.5	15.7 ± 0.4	13.8 ± 0.4	14.1 ± 0.7
Week 14	19.0 ± 0.8	18.0 ± 0.5	18.0 ± 0.4	18.7 ± 0.6	17.9 ± 0.5	16.6 ± 0.7
Creatinine (mg/dL)						
Day 3	0.52 ± 0.01	0.52 ± 0.02	0.53 ± 0.02	0.51 ± 0.02	0.50 ± 0.02	0.46 ± 0.02
Day 23	0.68 ± 0.01	0.65 ± 0.02	0.70 ± 0.02	0.70 ± 0.02	0.66 ± 0.02	0.66 ± 0.02
Week 14	0.67 ± 0.03	0.63 ± 0.02	0.65 ± 0.02	0.60 ± 0.00	0.64 ± 0.02	0.62 ± 0.02

TABLE F1
Hematology and Clinical Chemistry Data for Rats in the 14-Week Inhalation Study of Furfuryl Alcohol

	Chamber Control	2 ppm	4 ppm	8 ppm	16 ppm	32 ppm
Female (continued)						
n	10	10	10	10	10	10
Clinical Chemistry (continued)						
Total protein (g/dL)						
Day 3	5.2 ± 0.1	5.5 ± 0.1	5.4 ± 0.1	5.3 ± 0.1	5.2 ± 0.1	5.3 ± 0.1
Day 23	6.3 ± 0.1	6.1 ± 0.1	6.2 ± 0.1	6.3 ± 0.0	6.2 ± 0.1	6.0 ± 0.1
Week 14	7.2 ± 0.1	7.1 ± 0.1	7.2 ± 0.1	7.2 ± 0.0	7.1 ± 0.1	7.1 ± 0.1
Albumin (g/dL)						
Day 3	3.3 ± 0.1	3.5 ± 0.0	3.5 ± 0.1	3.4 ± 0.1	3.5 ± 0.1	3.4 ± 0.1
Day 23	4.5 ± 0.1	4.2 ± 0.1**	4.3 ± 0.0	4.5 ± 0.0	4.4 ± 0.1	4.4 ± 0.1
Week 14	4.3 ± 0.1	4.3 ± 0.1	4.3 ± 0.0	4.3 ± 0.0	4.3 ± 0.1	4.3 ± 0.1
Globulin (g/dL)						
Day 3	1.9 ± 0.1	1.9 ± 0.1	1.9 ± 0.0	2.0 ± 0.1	1.8 ± 0.1	1.9 ± 0.1
Day 23	1.8 ± 0.1	1.9 ± 0.1	1.9 ± 0.1	1.9 ± 0.1	1.8 ± 0.1	1.6 ± 0.1
Week 14	2.9 ± 0.1	2.8 ± 0.1	2.9 ± 0.1	3.0 ± 0.1	2.8 ± 0.0	2.8 ± 0.1
A/G ratio						
Day 3	1.8 ± 0.1	1.9 ± 0.1	1.9 ± 0.1	1.7 ± 0.1	2.0 ± 0.1	1.9 ± 0.1
Day 23	2.5 ± 0.1	2.2 ± 0.1	2.4 ± 0.1	2.4 ± 0.1	2.5 ± 0.1	2.7 ± 0.1
Week 14	1.5 ± 0.1	1.5 ± 0.1	1.5 ± 0.0	1.5 ± 0.0	1.5 ± 0.0	1.5 ± 0.0
Alanine aminotransferase (IU/L)						
Day 3	40 ± 1	44 ± 2	41 ± 1	43 ± 1	42 ± 1	38 ± 1
Day 23	29 ± 2	30 ± 1	33 ± 1	30 ± 1	28 ± 2	24 ± 1
Week 14	44 ± 3	48 ± 3	47 ± 3	44 ± 1	48 ± 2	42 ± 2
Alkaline phosphatase (IU/L)						
Day 3	543 ± 9	548 ± 15	528 ± 11	519 ± 15	485 ± 19*	421 ± 15**
Day 23	443 ± 14	430 ± 10	459 ± 17	453 ± 13	440 ± 12	412 ± 19
Week 14	234 ± 9	232 ± 6	240 ± 11	232 ± 10	234 ± 8	224 ± 6
Creatine kinase (IU/L)						
Day 3	428 ± 29	352 ± 15	364 ± 39	407 ± 44	419 ± 41	487 ± 52
Day 23	205 ± 28	327 ± 44	294 ± 42	248 ± 26	230 ± 19	285 ± 45
Week 14	90 ± 10	85 ± 12	105 ± 12	99 ± 11	113 ± 9	107 ± 12
Sorbitol dehydrogenase (IU/L)						
Day 3	9 ± 1	10 ± 1	10 ± 1	10 ± 1	9 ± 0	7 ± 0
Day 23	11 ± 1	12 ± 0	11 ± 0	11 ± 1	11 ± 1	10 ± 1
Week 14	9 ± 1	8 ± 1	8 ± 1	8 ± 1	9 ± 1	8 ± 0
Bile acids (µmol/L)						
Day 3	9.1 ± 1.1	11.8 ± 2.0	11.9 ± 1.3	10.1 ± 1.2	9.1 ± 1.0	6.5 ± 0.7
Day 23	5.5 ± 0.9	6.2 ± 1.1	7.1 ± 1.1	7.7 ± 1.9	9.9 ± 2.9	8.5 ± 2.1
Week 14	14.5 ± 3.7	11.4 ± 2.2	9.0 ± 1.9	11.5 ± 2.7	15.7 ± 5.1	11.4 ± 4.5

* Significantly different ($P \leq 0.05$) from the chamber control group by Dunn's or Shirley's test

** $P \leq 0.01$

^a Mean ± standard error. Statistical tests were performed on unrounded data.

^b n=9

APPENDIX G

ORGAN WEIGHTS AND ORGAN-WEIGHT-TO-BODY-WEIGHT RATIOS

TABLE G1	Organ Weights and Organ-Weight-to-Body-Weight Ratios for Rats in the 16-Day Inhalation Study of Furfuryl Alcohol	218
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TABLE G1
Organ Weights and Organ-Weight-to-Body-Weight Ratios for Rats in the 16-Day Inhalation Study of Furfuryl Alcohol^a

	Chamber Control	16 ppm	31 ppm	63 ppm	125 ppm
Male					
n	5	5	5	5	4
Necropsy body wt	186 ± 5	194 ± 4	172 ± 3	174 ± 6	159 ± 7**
Heart					
Absolute	0.674 ± 0.021	0.696 ± 0.015	0.622 ± 0.011	0.660 ± 0.042	0.578 ± 0.027*
Relative	3.62 ± 0.03	3.58 ± 0.05	3.62 ± 0.07	3.80 ± 0.19	3.64 ± 0.06
R. Kidney					
Absolute	0.814 ± 0.034	0.878 ± 0.017	0.786 ± 0.012	0.822 ± 0.027	0.800 ± 0.014
Relative	4.37 ± 0.10	4.52 ± 0.10	4.58 ± 0.09	4.74 ± 0.02*	5.07 ± 0.16**
Liver					
Absolute	8.684 ± 0.365	9.660 ± 0.272	8.140 ± 0.162	8.578 ± 0.322	7.553 ± 0.370
Relative	46.58 ± 1.05	49.68 ± 0.47*	47.35 ± 0.52	49.40 ± 0.55	47.66 ± 1.44
Lung					
Absolute	1.494 ± 0.079	1.406 ± 0.035	1.366 ± 0.080	1.206 ± 0.079**	1.073 ± 0.048**
Relative	8.01 ± 0.31	7.26 ± 0.32	7.96 ± 0.51	6.97 ± 0.48	6.79 ± 0.32
R. Testis					
Absolute	1.053 ± 0.030	1.080 ± 0.041	1.027 ± 0.018	1.032 ± 0.041	1.047 ± 0.031
Relative	5.65 ± 0.10	5.55 ± 0.14	5.98 ± 0.17	5.94 ± 0.07	6.62 ± 0.15**
Thymus					
Absolute	0.422 ± 0.023	0.492 ± 0.019	0.474 ± 0.020	0.443 ± 0.012	0.343 ± 0.033*
Relative	2.26 ± 0.09	2.55 ± 0.16	2.76 ± 0.10*	2.57 ± 0.12*	2.15 ± 0.15
Female					
n	5	5	5	5	5
Necropsy body wt	130 ± 4	131 ± 4	125 ± 3	126 ± 2	113 ± 4**
Heart					
Absolute	0.506 ± 0.014	0.546 ± 0.016	0.486 ± 0.005	0.504 ± 0.027	0.444 ± 0.017*
Relative	3.90 ± 0.08	4.16 ± 0.13	3.89 ± 0.04	4.00 ± 0.21	3.92 ± 0.07
R. Kidney					
Absolute	0.592 ± 0.013	0.638 ± 0.018	0.618 ± 0.012	0.638 ± 0.014	0.600 ± 0.024
Relative	4.57 ± 0.08	4.86 ± 0.09	4.95 ± 0.06*	5.06 ± 0.12**	5.31 ± 0.15**
Liver					
Absolute	5.520 ± 0.163	5.884 ± 0.191	5.568 ± 0.126	5.802 ± 0.144	5.226 ± 0.231
Relative	42.50 ± 0.19	44.77 ± 0.81	44.58 ± 0.90	46.02 ± 1.18*	46.20 ± 1.44*
Lung					
Absolute	1.136 ± 0.043	1.188 ± 0.076	1.048 ± 0.093	1.248 ± 0.056	0.878 ± 0.027*
Relative	8.76 ± 0.29	9.00 ± 0.35	8.39 ± 0.74	9.90 ± 0.46	7.80 ± 0.39
Thymus					
Absolute	0.372 ± 0.014	0.393 ± 0.016	0.383 ± 0.014	0.374 ± 0.023	0.287 ± 0.022*
Relative	2.89 ± 0.19	2.99 ± 0.13	3.07 ± 0.14	2.96 ± 0.18	2.54 ± 0.20

* Significantly different ($P \leq 0.05$) from the chamber control group by Williams' or Dunnett's test

** $P \leq 0.01$

^a Organ weights (absolute weights) and body weights are given in grams; organ-weight-to-body-weight ratios (relative weights) are given as mg organ weight/g body weight (mean ± standard error). All 250 ppm rats died before the end of the study.

TABLE G2
Organ Weights and Organ-Weight-to-Body-Weight Ratios for Rats in the 14-Week Inhalation Study of Furfuryl Alcohol^a

	Chamber Control	2 ppm	4 ppm	8 ppm	16 ppm	32 ppm
n	10	10	10	10	10	10
Male						
Necropsy body wt	325 ± 7	322 ± 7	332 ± 5	323 ± 5	307 ± 4	311 ± 6
Heart						
Absolute	0.925 ± 0.030	0.923 ± 0.016	0.959 ± 0.017	0.925 ± 0.012	0.908 ± 0.016	0.928 ± 0.021
Relative	2.84 ± 0.05	2.87 ± 0.03	2.89 ± 0.03	2.87 ± 0.03	2.96 ± 0.03*	2.99 ± 0.02**
R. Kidney						
Absolute	1.048 ± 0.025	1.053 ± 0.026	1.092 ± 0.021	1.104 ± 0.023	1.050 ± 0.013	1.082 ± 0.023
Relative	3.23 ± 0.05	3.27 ± 0.02	3.29 ± 0.04	3.42 ± 0.07**	3.42 ± 0.04**	3.48 ± 0.03**
Liver						
Absolute	10.667 ± 0.188	11.035 ± 0.381	11.317 ± 0.324	11.471 ± 0.395	10.629 ± 0.368	10.362 ± 0.385
Relative	32.87 ± 0.33	34.20 ± 0.73	34.10 ± 0.80	35.46 ± 0.83	34.59 ± 0.97	33.30 ± 0.73
Lung						
Absolute	1.531 ± 0.037	1.511 ± 0.051	1.572 ± 0.043	1.708 ± 0.072	1.570 ± 0.054	1.668 ± 0.101
Relative	4.74 ± 0.17	4.69 ± 0.13	4.74 ± 0.10	5.28 ± 0.19	5.11 ± 0.15	5.35 ± 0.24*
R. Testis						
Absolute	1.323 ± 0.016	1.297 ± 0.033	1.368 ± 0.021	1.322 ± 0.024	1.314 ± 0.023	1.363 ± 0.032
Relative	4.08 ± 0.07	4.03 ± 0.08	4.12 ± 0.04	4.10 ± 0.07	4.29 ± 0.09	4.39 ± 0.06**
Thymus						
Absolute	0.337 ± 0.010	0.327 ± 0.011	0.354 ± 0.010	0.320 ± 0.016	0.315 ± 0.010 ^b	0.303 ± 0.014
Relative	1.04 ± 0.03	1.02 ± 0.04	1.07 ± 0.04	0.99 ± 0.04	1.02 ± 0.04 ^b	0.97 ± 0.03
Female						
Necropsy body wt	198 ± 4	198 ± 3	197 ± 4	189 ± 3	188 ± 3	178 ± 4**
Heart						
Absolute	0.619 ± 0.012	0.622 ± 0.008	0.631 ± 0.014	0.624 ± 0.006	0.619 ± 0.008	0.595 ± 0.010
Relative	3.14 ± 0.05	3.14 ± 0.03	3.20 ± 0.06	3.31 ± 0.05*	3.29 ± 0.07*	3.36 ± 0.06**
R. Kidney						
Absolute	0.641 ± 0.013	0.646 ± 0.010	0.656 ± 0.018	0.689 ± 0.048	0.635 ± 0.009	0.617 ± 0.011
Relative	3.25 ± 0.05	3.27 ± 0.04	3.32 ± 0.06	3.64 ± 0.24	3.38 ± 0.05	3.48 ± 0.08
Liver						
Absolute	6.164 ± 0.194	6.022 ± 0.088	6.258 ± 0.140	6.093 ± 0.095	6.037 ± 0.131	5.560 ± 0.134*
Relative	31.16 ± 0.58	30.43 ± 0.23	31.71 ± 0.34	32.29 ± 0.62	32.06 ± 0.51	31.34 ± 0.59
Lung						
Absolute	1.117 ± 0.033	1.116 ± 0.026	1.067 ± 0.034	1.093 ± 0.023	1.077 ± 0.030	1.002 ± 0.026**
Relative	5.65 ± 0.11	5.64 ± 0.10	5.40 ± 0.12	5.80 ± 0.15	5.72 ± 0.13	5.65 ± 0.13
Thymus						
Absolute	0.271 ± 0.008	0.254 ± 0.008	0.275 ± 0.008	0.247 ± 0.010	0.251 ± 0.009	0.244 ± 0.008
Relative	1.38 ± 0.05	1.28 ± 0.04	1.39 ± 0.04	1.30 ± 0.04	1.33 ± 0.03	1.37 ± 0.04

* Significantly different ($P < 0.05$) from the chamber control group by Williams' or Dunnett's test

** $P < 0.01$

^a Organ weights (absolute weights) and body weights are given in grams; organ-weight-to-body-weight ratios (relative weights) are given as mg organ weight/g body weight (mean ± standard error).

^b n=9

TABLE G3
Organ Weights and Organ-Weight-to-Body-Weight Ratios for Mice in the 16-Day Inhalation Study of Furfuryl Alcohol^a

	Chamber Control	16 ppm	31 ppm	63 ppm	125 ppm
Male					
n	5	5	5	5	5
Necropsy body wt	27.8 ± 0.5	28.5 ± 0.3	27.8 ± 0.7	25.8 ± 0.3*	24.5 ± 0.7**
Heart					
Absolute	0.126 ± 0.002	0.142 ± 0.007	0.124 ± 0.004	0.112 ± 0.002*	0.114 ± 0.002*
Relative	4.54 ± 0.11	5.00 ± 0.29	4.45 ± 0.06	4.33 ± 0.06	4.66 ± 0.12
R. Kidney					
Absolute	0.278 ± 0.005	0.298 ± 0.007	0.268 ± 0.009	0.250 ± 0.000*	0.256 ± 0.007*
Relative	10.01 ± 0.16	10.47 ± 0.17	9.63 ± 0.25	9.68 ± 0.10	10.44 ± 0.18
Liver					
Absolute	1.536 ± 0.042	1.656 ± 0.035	1.584 ± 0.047	1.524 ± 0.030	1.574 ± 0.071
Relative	55.22 ± 0.58	58.20 ± 1.19	56.87 ± 0.31	58.97 ± 0.91*	64.11 ± 1.58**
Lung					
Absolute	0.210 ± 0.004	0.218 ± 0.010	0.206 ± 0.007	0.196 ± 0.005	0.198 ± 0.009
Relative	7.55 ± 0.11	7.67 ± 0.38	7.40 ± 0.19	7.59 ± 0.26	8.07 ± 0.20
R. Testis					
Absolute	0.107 ± 0.003	0.103 ± 0.001	0.103 ± 0.002	0.104 ± 0.003	0.103 ± 0.004
Relative	3.83 ± 0.04	3.64 ± 0.06	3.72 ± 0.13	4.04 ± 0.11	4.21 ± 0.07**
Thymus					
Absolute	0.045 ± 0.003	0.044 ± 0.003	0.045 ± 0.002	0.041 ± 0.002	0.033 ± 0.004**
Relative	1.63 ± 0.12	1.55 ± 0.09	1.63 ± 0.09	1.59 ± 0.08	1.33 ± 0.17
Female					
n	5	5	5	5	4
Necropsy body wt	22.6 ± 0.3	23.2 ± 0.3	22.6 ± 0.4	21.1 ± 0.3**	19.9 ± 0.2**
Heart					
Absolute	0.110 ± 0.003	0.114 ± 0.002	0.108 ± 0.004	0.098 ± 0.002**	0.093 ± 0.003**
Relative	4.86 ± 0.12	4.91 ± 0.09	4.77 ± 0.10	4.64 ± 0.05	4.65 ± 0.08
R. Kidney					
Absolute	0.190 ± 0.004	0.194 ± 0.005	0.192 ± 0.004	0.172 ± 0.005*	0.165 ± 0.005**
Relative	8.39 ± 0.14	8.36 ± 0.23	8.49 ± 0.20	8.14 ± 0.14	8.29 ± 0.17
Liver					
Absolute	1.230 ± 0.034	1.360 ± 0.018	1.300 ± 0.040	1.158 ± 0.039	1.248 ± 0.043
Relative	54.30 ± 0.96	58.58 ± 0.69	57.41 ± 1.34	54.80 ± 1.40	62.64 ± 1.43**
Lung					
Absolute	0.192 ± 0.009	0.198 ± 0.006	0.200 ± 0.005	0.178 ± 0.010	0.183 ± 0.008
Relative	8.47 ± 0.29	8.53 ± 0.24	8.84 ± 0.27	8.42 ± 0.42	9.16 ± 0.27
Thymus					
Absolute	0.069 ± 0.004	0.070 ± 0.005	0.068 ± 0.002	0.062 ± 0.003	0.049 ± 0.003**
Relative	3.03 ± 0.17	3.02 ± 0.25	3.03 ± 0.11	2.95 ± 0.15	2.47 ± 0.14

* Significantly different ($P \leq 0.05$) from the chamber control group by Williams' or Dunnett's test

** $P \leq 0.01$

^a Organ weights (absolute weights) and body weights are given in grams; organ-weight-to-body-weight ratios (relative weights) are given as mg organ weight/g body weight (mean ± standard error). All 250 ppm mice died before the end of the study.

TABLE G4
Organ Weights and Organ-Weight-to-Body-Weight Ratios for Mice in the 14-Week Inhalation Study of Furfuryl Alcohol^a

	Chamber Control	2 ppm	4 ppm	8 ppm	16 ppm	32 ppm
n	10	10	10	10	10	10
Male						
Necropsy body wt	34.5 ± 0.6	36.9 ± 0.8	36.3 ± 0.8	36.6 ± 0.8	36.5 ± 0.6	34.0 ± 0.8
Heart						
Absolute	0.160 ± 0.004	0.158 ± 0.003	0.162 ± 0.002	0.160 ± 0.004	0.161 ± 0.002	0.143 ± 0.003**
Relative	4.65 ± 0.12	4.29 ± 0.04*	4.47 ± 0.08	4.38 ± 0.07	4.42 ± 0.09	4.22 ± 0.06**
R. Kidney						
Absolute	0.307 ± 0.011	0.330 ± 0.009	0.335 ± 0.008	0.332 ± 0.007	0.322 ± 0.004	0.306 ± 0.006
Relative	8.88 ± 0.23	8.95 ± 0.17	9.24 ± 0.19	9.09 ± 0.18	8.85 ± 0.20	9.03 ± 0.13
Liver						
Absolute	1.617 ± 0.043	1.616 ± 0.060	1.644 ± 0.033	1.654 ± 0.036	1.604 ± 0.026	1.523 ± 0.043
Relative	46.85 ± 0.91	43.78 ± 1.14	45.36 ± 0.79	45.25 ± 0.67	44.05 ± 0.79	44.84 ± 0.67
Lung						
Absolute	0.244 ± 0.005	0.248 ± 0.008	0.243 ± 0.008	0.242 ± 0.010	0.247 ± 0.007	0.219 ± 0.007
Relative	7.07 ± 0.12	6.74 ± 0.20	6.70 ± 0.19	6.63 ± 0.27	6.80 ± 0.25	6.44 ± 0.13
R. Testis						
Absolute	0.124 ± 0.003	0.131 ± 0.003	0.128 ± 0.003	0.129 ± 0.002	0.131 ± 0.004	0.122 ± 0.003
Relative	3.59 ± 0.07	3.55 ± 0.10	3.54 ± 0.13	3.54 ± 0.10	3.59 ± 0.12	3.59 ± 0.09
Thymus						
Absolute	0.036 ± 0.001	0.040 ± 0.002	0.038 ± 0.002	0.037 ± 0.002	0.041 ± 0.003	0.040 ± 0.003
Relative	1.03 ± 0.04	1.08 ± 0.04	1.06 ± 0.05	1.02 ± 0.03	1.11 ± 0.06	1.18 ± 0.11
Female						
Necropsy body wt	30.9 ± 0.9	31.7 ± 1.0	32.1 ± 1.0	31.3 ± 1.0	32.3 ± 0.9	30.2 ± 0.8
Heart						
Absolute	0.139 ± 0.002	0.136 ± 0.003	0.136 ± 0.003	0.135 ± 0.002	0.133 ± 0.002	0.126 ± 0.002**
Relative	4.53 ± 0.14	4.31 ± 0.11	4.27 ± 0.10	4.34 ± 0.12	4.15 ± 0.12	4.19 ± 0.09
R. Kidney						
Absolute	0.210 ± 0.006	0.221 ± 0.003	0.221 ± 0.005	0.226 ± 0.003	0.225 ± 0.005	0.207 ± 0.004
Relative	6.82 ± 0.18	7.02 ± 0.18	6.92 ± 0.17	7.27 ± 0.21	7.01 ± 0.22	6.88 ± 0.11
Liver						
Absolute	1.437 ± 0.034	1.471 ± 0.029	1.552 ± 0.043	1.510 ± 0.041	1.560 ± 0.034	1.418 ± 0.042
Relative	46.61 ± 0.36	46.58 ± 0.76	48.54 ± 1.01	48.37 ± 0.88	48.44 ± 0.92	47.06 ± 0.95
Lung						
Absolute	0.222 ± 0.006	0.225 ± 0.007	0.224 ± 0.006	0.228 ± 0.006	0.227 ± 0.006	0.221 ± 0.007
Relative	7.21 ± 0.17	7.13 ± 0.21	7.01 ± 0.13	7.32 ± 0.21	7.05 ± 0.19	7.35 ± 0.25
Thymus						
Absolute	0.055 ± 0.002	0.057 ± 0.002	0.059 ± 0.003	0.057 ± 0.003	0.062 ± 0.004	0.059 ± 0.003
Relative	1.78 ± 0.06	1.79 ± 0.05	1.83 ± 0.08	1.83 ± 0.09	1.93 ± 0.10	1.95 ± 0.09

* Significantly different (P<0.05) from the chamber control group by Williams' or Dunnett's test

** P<0.01

^a Organ weights (absolute weights) and body weights are given in grams; organ-weight-to-body-weight ratios (relative weights) are given as mg organ weight/g body weight (mean ± standard error).

APPENDIX H

REPRODUCTIVE TISSUE EVALUATIONS AND ESTROUS CYCLE CHARACTERIZATION

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TABLE H1
Summary of Reproductive Tissue Evaluations for Male Rats in the 14-Week Inhalation Study of Furfuryl Alcohol^a

	Chamber Control	2 ppm	8 ppm	32 ppm
n	10	10	10	10
Weights (g)				
Necropsy body wt	325 ± 7	322 ± 7	323 ± 5	311 ± 6
L. cauda epididymis	0.1637 ± 0.0079	0.1627 ± 0.0042	0.1578 ± 0.0064	0.1626 ± 0.0064
L. epididymis	0.4514 ± 0.0184	0.4406 ± 0.0085	0.4315 ± 0.0098	0.4586 ± 0.0075
L. testis	1.3579 ± 0.0389	1.3626 ± 0.0262	1.3569 ± 0.0278	1.4049 ± 0.0304
Spermatid measurements				
Spermatid heads (10 ⁷ /g testis)	10.43 ± 0.57	12.20 ± 0.68	12.32 ± 0.61*	12.96 ± 0.54**
Spermatid heads (10 ⁷ /testis)	14.26 ± 0.96	16.65 ± 1.05	16.65 ± 0.74	18.13 ± 0.61**
Spermatid count (mean/10 ⁻⁴ mL suspension)	71.30 ± 4.80	83.25 ± 5.25	83.23 ± 3.69	90.63 ± 3.07**
Epididymal spermatozoal measurements				
Motility (%)	87.48 ± 7.80	93.35 ± 1.16	88.02 ± 4.91	92.53 ± 0.58
Concentration (10 ⁶ /g cauda epididymal tissue)	443 ± 46	511 ± 21	460 ± 19	442 ± 15

* Significantly different ($P \leq 0.05$) from the chamber control group by Shirley's test

** $P \leq 0.01$

^a Data are presented as mean ± standard error. Differences from the chamber control group are not significant by Dunnett's test (body and tissue weights) or Dunn's test (epididymal spermatozoal measurements).

TABLE H2
Estrous Cycle Characterization for Female Rats in the 14-Week Inhalation Study of Furfuryl Alcohol^a

	Chamber Control	2 ppm	8 ppm	32 ppm
n	10	10	10	10
Necropsy body wt (g)	198 ± 4	198 ± 3	189 ± 3	178 ± 4**
Estrous cycle length (days)	4.80 ± 0.11	4.85 ± 0.11	4.90 ± 0.10	4.80 ± 0.11
Estrous stages (% of cycle)				
Diestrus	42.5	42.5	39.2	40.0
Proestrus	19.2	15.8	15.8	14.2
Estrus	21.7	22.5	25.0	28.3
Metestrus	16.7	18.3	16.7	15.0
Uncertain diagnoses	0.0	0.8	3.3	2.5

** Significantly different ($P \leq 0.05$) from the chamber control group by Williams' test

^a Necropsy body weight and estrous cycle length data are presented as mean ± standard error. Differences from the chamber control group for estrous cycle length are not significant by Dunn's test. By multivariate analysis of variance, exposed females do not differ significantly from the chamber control females in the relative length of time spent in the estrous stages.

TABLE H3
Summary of Reproductive Tissue Evaluations for Male Mice in the 14-Week Inhalation Study of Furfuryl Alcohol^a

	Chamber Control	2 ppm	8 ppm	32 ppm
n	10	10	10	10
Weights (g)				
Necropsy body wt	34.5 ± 0.6	36.9 ± 0.8	36.6 ± 0.8	34.0 ± 0.8
L. cauda epididymis	0.0162 ± 0.0008	0.0173 ± 0.0009	0.0155 ± 0.0006	0.0162 ± 0.0010
L. epididymis	0.0462 ± 0.0016	0.0472 ± 0.0010	0.0453 ± 0.0009	0.0439 ± 0.0014
L. testis	0.1187 ± 0.0027	0.1264 ± 0.0022	0.1229 ± 0.0011	0.1134 ± 0.0031
Spermatid measurements				
Spermatid heads (10 ⁷ /g testis)	24.94 ± 0.76	24.31 ± 0.88	24.26 ± 1.06	25.56 ± 1.24
Spermatid heads (10 ⁷ /testis)	2.95 ± 0.08	3.06 ± 0.08	2.98 ± 0.13	2.87 ± 0.09
Spermatid count (mean/10 ⁻⁴ mL suspension)	92.18 ± 2.57	95.63 ± 2.57	93.10 ± 3.95	89.80 ± 2.92
Epididymal spermatozoal measurements				
Motility (%)	91.17 ± 1.52	90.27 ± 1.49	94.26 ± 0.97	93.34 ± 0.84
Concentration (10 ⁶ /g cauda epididymal tissue)	996 ± 56	914 ± 63	1,029 ± 40	876 ± 93

^a Data are presented as mean ± standard error. Differences from the chamber control group were not significant by Dunnett's test (body and tissue weights) or Dunn's test (spermatid and epididymal spermatozoal measurements).

TABLE H4
Estrous Cycle Characterization for Female Mice in the 14-Week Inhalation Study of Furfuryl Alcohol^a

	Chamber Control	2 ppm	8 ppm	32 ppm
n	10	10	10	10
Necropsy body wt (g)	30.9 ± 0.9	31.7 ± 1.0	31.3 ± 1.0	30.2 ± 0.8
Estrous cycle length (days)	4.10 ± 0.10	4.20 ± 0.13	4.40 ± 0.22	4.10 ± 0.07
Estrous stages (% of cycle)				
Diestrus	31.7	30.8	32.5	34.2
Proestrus	14.2	20.0	22.5	22.5
Estrus	35.8	30.8	27.5	28.3
Metestrus	16.7	18.3	15.0	14.2
Uncertain diagnoses	1.7	0.0	2.5	0.8

^a Necropsy body weight and estrous cycle length data are presented as mean ± standard error. Differences from the chamber control group are not significant by Dunnett's test (body weights) or Dunn's test (estrous cycle length). By multivariate analysis of variance, exposed females do not differ significantly from the chamber control females in the relative length of time spent in the estrous stages.

APPENDIX I

URINARY METABOLITE STUDY

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TABLE II
Urinary Metabolite Data for Rats in the 2-Year Inhalation Study of Furfuryl Alcohol^a

	Chamber Control	2 ppm	8 ppm	32 ppm
Male				
n	5	5	3	0 ^d
Volume (mL/16 hr)	8.9 ± 1.2	10.6 ± 1.3	12.8 ± 1.5	
Creatinine (mg/16 hr)	6.92 ± 0.94	8.90 ± 0.66	8.47 ± 0.07	
Furoylglycine (µg/16 hr)	16.8 ± 4.1	1,000.6 ± 155.9**	3,920.3 ± 136.1**	
Furanacryloylglycine (µg/16 hr)	3.50 ± 1.70 ^b	46.20 ± 7.69 ^c	369.47 ± 108.26*	
Female				
n	5	5	5	5
Volume (mL/16 hr)	5.5 ± 0.5	6.2 ± 0.9	5.4 ± 0.5	5.7 ± 0.5
Creatinine (mg/16 hr)	4.96 ± 0.32	4.94 ± 0.82	5.12 ± 0.61	4.52 ± 0.25
Furoylglycine (µg/16 hr)	13.6 ± 1.0	516.8 ± 128.4**	2,387.8 ± 332.7**	7,598.0 ± 942.6**
Furanacryloylglycine (µg/16 hr)	3.15 ± 0.25 ^b	24.96 ± 5.19	98.18 ± 11.49**	328.48 ± 61.11**

* Significantly different ($P \leq 0.05$) from the chamber control group by Dunn's or Shirley's test

** $P \leq 0.01$

^a Mean ± standard error. Statistical tests were performed on unrounded data.

^b n=2

^c n=3

^d No data available due to 100% mortality in this exposure group

APPENDIX J

CHEMICAL CHARACTERIZATION AND GENERATION OF CHAMBER CONCENTRATIONS

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CHEMICAL CHARACTERIZATION AND GENERATION OF CHAMBER CONCENTRATIONS

PROCUREMENT AND CHARACTERIZATION OF FURFURYL ALCOHOL

Furfuryl alcohol was obtained from QO Chemicals, Inc. (Memphis, TN), in one lot (7B19M-2), which was used during the 16-day, 14-week, and 2-year studies. Identity, purity, and stability analyses were conducted by the analytical chemistry laboratory, Midwest Research Institute (Kansas City, MO). Reports on analyses performed in support of the furfuryl alcohol studies are on file at the National Institute of Environmental Health Sciences.

The chemical, a clear yellow liquid, was identified as furfuryl alcohol by infrared, ultraviolet/visible, and nuclear magnetic resonance spectroscopy. All spectra were consistent with the literature spectra (*Sadtler Standard Spectra*, 1970; Weast, 1975) of furfuryl alcohol. The infrared and nuclear magnetic spectra are presented in Figures J1 and J2.

The purity of lot 7B19M-2 was determined by elemental analyses, Karl Fischer water analysis, and gas chromatography. Gas chromatography was performed using a flame ionization detector. Two systems were used:

- A) 20% SP-2100/0.1% Carbowax 1500 on 100/120 Supelcoport glass column, with a nitrogen carrier gas at a flow rate of 70 mL/minute and an oven temperature program of 50° C for 5 minutes, then 50° to 170° C at 10° C per minute, and
- B) DB-Wax capillary fused silica column, with a helium carrier gas at a flow rate of 8 mL/minute, a nitrogen makeup gas at a flow rate of 22 mL/minute, and an oven temperature program of 50° C for 5 minutes, then 50° to 225° C at 10° C per minute.

Elemental analyses for carbon and hydrogen were in agreement with the theoretical values for furfuryl alcohol. Karl Fischer water analysis indicated 0.098% ± 0.008% water. Gas chromatography by each system indicated one major peak and five impurities with areas greater than 0.1% relative to the major peak area; the combined impurity peak areas were 1.36% for system A and 1.17% for system B. Major peak comparison between lot 7B19M-2 and lot Q0112979, a previously analyzed lot not used in the current studies, indicated a purity of 100.9% ± 0.6% for lot 7B19M-2 relative to lot Q0112979. The overall purity was determined to be greater than 98%.

Stability studies of lot Q0112979 of the bulk chemical performed by the analytical chemistry laboratory indicated that furfuryl alcohol was stable as a bulk chemical when stored at or below 25° C, protected from light, and under a nitrogen headspace. Literature obtained from the manufacturer indicated that furfuryl alcohol was stable up to 6 months at ambient temperatures and that stability during storage was improved by maintaining the chemical under nitrogen.

During the studies, the bulk chemical was stored under a nitrogen blanket in its original shipping containers at approximately -20° C. Stability was monitored by the study laboratory throughout all studies with gas chromatography; no degradation of the bulk chemical was detected.

VAPOR GENERATION AND EXPOSURE SYSTEM

Schematic diagrams of the furfuryl alcohol generation and delivery system are shown in Figures J3a and J3b. Furfuryl alcohol was pumped through a calibrated volume tube into the top of a glass evaporation column filled with glass beads, which increased the surface area for evaporation. A heated nitrogen stream entered the column from below, vaporized the furfuryl alcohol, and carried it to a heated condenser column. During the 2-year studies, the evaporation column was heated by wrapping with heat tape; additional heated nitrogen was added to the furfuryl alcohol vapor leaving the evaporation column to dilute the vapor. Condensation in the condenser controlled the furfuryl alcohol vapor concentration produced by the generator; condensate was collected in a waste flask at the bottom of the condenser. The refluxing action also tended to remove less volatile impurities from the vapor. The saturated vapor leaving the condenser was transported to the exposure room through a heated Teflon line to prevent condensation. During the 16-day and 14-week studies, the vapor was drawn through the heated line and injected into the inlet air stream of a mixing chamber (an exposure chamber with the cages removed) and then pumped through a pneumatic valve into the distribution line. The charcoal- and HEPA-filtered air was conditioned to room temperature and maintained at minimum relative humidity to prevent the vapor from condensing. During the 16-day studies, condensation particles were filtered from the vapor with Teflon-membrane filters before entering the distribution line. In the 2-year studies, no mixing chamber was used; the vapor was mixed with additional heated air at the entrance of a short vapor distribution manifold. An automatic controller maintained constant flow (and thus constant concentration) in the distribution manifold.

From the distribution manifold, individual temperature-controlled delivery lines carried the vapor to each exposure chamber (Harford Systems Division of Lab Products, Inc., Aberdeen, MD). The study laboratory designed the inhalation exposure chamber so that uniform vapor concentrations could be maintained throughout the chamber with the catch pans in place. The total active mixing volume of each chamber was 1.7 m³. Vapor was drawn through the system by compressed-air-driven vacuum pumps located at the chamber end of each delivery line. A three-way valve, mounted in the line from the distribution manifold to each chamber, directed vapor to the exposure chamber exhaust until the generation system was stable. When equilibrium was reached, each valve was opened to allow the flow of vapor into the chamber. At each chamber, the vapor was injected into the chamber inlet duct where it was further diluted with filtered chamber air to achieve the desired exposure concentration. A small particle detector (Type CN, Gardner Associates, Schenectady, NY) was used with and without animals in the exposure chambers to ensure that furfuryl alcohol vapor, and not aerosol, was produced. The minimum resolvable level of the detector is approximately 200 particles per cubic centimeter. During the 16-day studies, no particles were detected in the distribution line. Without animals in the chambers, particle concentrations were below the limit of detection in the 16 and 31 ppm chambers but ranged up to 600 particles/cm³ in the 63 ppm chambers and 8,400 particles/cm³ in the 125 ppm chambers; concentrations in the 250 ppm chambers ranged from 8,400 to 36,000 particles/cm³. With animals in the chambers, concentrations were below the limit of detection in all but the 125 and 250 ppm chambers, which had concentrations of 1,470 and 11,200 particles/cm³, respectively. During the 14-week studies, particle concentrations in the 32 ppm chamber were 200 particles/cm³ without animals present and 245 particles/cm³ with animals; concentrations in all other chambers were below the limit of detection, with and without animals present. During the 2-year study prestart phase, the 32 ppm mouse chamber had a concentration of 370 particles/cm³ with no animals present; all other rat and mouse chambers, with and without animals present, had concentrations below the limit of detection.

VAPOR CONCENTRATION MONITORING

The chamber concentrations of furfuryl alcohol were monitored by a Hewlett-Packard Model 5890 on-line gas chromatograph (Hewlett-Packard, Palo Alto, CA). During the 2-year studies, samples were drawn from each exposure chamber, the control chamber, the exposure suite, on-line standards, and a nitrogen blank approximately every 36 minutes through a 12-port stream select valve.

The monitoring system was calibrated against a gravimetrically prepared standard of furfuryl alcohol in nitrogen. Additionally, the on-line monitor was calibrated by a comparison of chamber concentration data to grab samples analyzed by an off-line gas chromatograph at least once per month. The operation of the chamber monitor was checked throughout the day against an on-line standard. The grab samples were collected in bubblers containing dimethylformamide and analyzed by an off-line gas chromatograph. The volumes of gas were sampled at a constant flow rate ensured by a calibrated critical orifice. The off-line gas chromatograph was calibrated with gravimetrically prepared furfuryl alcohol standards in dimethylformamide.

Summaries of the chamber concentrations during the studies are presented in Tables J1 through J3.

CHAMBER ATMOSPHERE CHARACTERIZATION

The buildup of vapor concentration in the chamber to 90% of its final stable concentration (T_{90}) at the beginning of exposure and the decay of concentration at the end of exposure to 10% (T_{10}) were measured with and without animals in the chambers. At a chamber airflow rate of 15 air changes/hour, the theoretical value for both T_{90} and T_{10} is approximately 12.5 minutes. For the 16-day studies without animals present, the values of T_{90} ranged from 8 to 12 minutes and T_{10} from 8 to 11 minutes; with animals present, the values for both T_{90} and T_{10} ranged from 11 to 18 minutes. For the 14-week studies without animals present, the values of T_{90} and T_{10} ranged from 10 to 13 minutes; with animals present, the values ranged from 16 to 20 minutes for T_{90} and 13 to 21 minutes for T_{10} . For the 2-year studies without animals present, the values of T_{90} were 11 to 12 minutes for rats and 11 minutes for mice; the values of T_{10} ranged from 11 to 13 minutes for rats and 10 to 13 minutes for mice. With animals present, a much slower buildup phase was noted. The values of T_{90} ranged from 12 to 25 minutes for rats and 15 to 22 minutes for mice and the values for T_{10} were between 30 and 33 minutes for rats and 33 and 59 minutes for mice. To compensate for the slow buildup, additional vapor was delivered to the exposure chambers during the first 30 to 60 minutes. A value for T_{10} could not be determined for the 2 ppm chambers because 10% of the target concentration (0.2 ppm) was below the limit of quantitation (0.27 ppm). A T_{90} of 12 minutes was initially used for all studies. However, because the actual T_{90} values for the 14-week studies were considerably longer than 12 minutes (16 to 20 minutes), the T_{90} was increased to 20 minutes on the seventeenth exposure day; this value was used until the end of the studies.

Vapor concentration uniformity in the exposure chambers without animals in the chambers was measured before each of the studies began. Concentration uniformity with animals present was measured once during the 16-day and 14-week studies and at approximately 90-day intervals during the 2-year studies. Vapor concentration was measured by the on-line gas chromatograph with the automatic 12-port sample valve disabled to allow continuous monitoring from a single input line. Samples taken from several positions within each exposure chamber were analyzed. Chamber concentration uniformity was maintained throughout the studies.

In order to determine the persistence of furfuryl alcohol in the chambers after exposure, the time for the concentration to decay to less than 1% of the stable concentration was measured in the 250 ppm (16-day study) or 32 ppm (14-week and 2-year studies) chamber. Monitoring was performed before the start of the studies without animals and during the studies with animals present. In the 16-day studies, the concentration of furfuryl alcohol fell to below 1% in approximately 30 minutes without animals present and in approximately 50 minutes with animals in the chambers. In the 14-week studies, the concentration fell to below 1% in approximately 27 minutes without animals present and in approximately 103 minutes with animals present. In the 2-year studies, the concentration of furfuryl alcohol in the rat chambers failed to fall below 1% within 945 minutes with animals in

the chamber, although the concentration decayed to less than 1% in 52 minutes without animals. The concentration of furfuryl alcohol in the mouse chambers fell to less than 1% within 367 minutes with animals present and within 58 minutes without animals in the chamber.

Furfuryl alcohol samples collected with bubblers or gas sampling tubes from the vapor generator reservoir were tested for stability during the 16-day and 14-week studies by gas chromatography with a furfuryl alcohol reference. Results indicated that furfuryl alcohol was stable in the reservoir for 8 hours at room temperature under a blanket of nitrogen. Although a brown-black tar, indicative of polymerization, was noted in the evaporation column, the refluxing action of the condenser column apparently removed the heavier, less volatile degradation products; no significant degeneration of furfuryl alcohol was detected. During prestudy testing, 0.5% furfural was detected in the transport line, although concentrations elsewhere in the exposure system ranged from 0.02% to 0.17%; the furfural in the transport line was considered to be a sampling artifact. Furoic acid, furan, and formaldehyde concentrations were at or below the limits of detection. Additionally, aged samples of furfuryl alcohol were analyzed with gas chromatography/mass spectroscopy and gas chromatography/Fourier transform infrared spectroscopy; eight degradation products were tentatively identified in the aged furfuryl alcohol sample.

During the 16-day studies, stability was monitored by testing furfuryl alcohol samples for furfural, formaldehyde, and volatile organic impurities by gas chromatography. Samples were collected with bubblers or gas sampling tubes from the generator reservoir, transport and distribution lines, and the 16 and 250 ppm chambers, with and without animals present. An impurity with a relative area of 0.1% was detected in the 16 ppm chamber, and two impurities with a combined relative area of approximately 0.4% were detected in the occupied 250 ppm chamber. No more than 0.4% furfural (approximately the amount present in the bulk chemical) was detected in any sample; formaldehyde concentrations were at or below the limit of detection. During the 14-week studies, samples collected by gas sampling tube from the distribution line and the 2 and 32 ppm chambers, with animals present, were tested by gas chromatography for oxidation products, polymers, dimers, and the oxazolidine derivatives formaldehyde and 2-furaldehyde; major peak comparisons of samples from the evaporation and condenser column collection flasks and the generator reservoir were also performed with gas chromatography. No degradation of furfuryl alcohol was detected; 2-furaldehyde concentrations in the exposure system ranged from approximately 0.1% to 0.2%, similar to the concentration detected in the bulk chemical (0.22%), and formaldehyde concentrations were at or below the limit of detection in all samples. Stability in the 2-year studies was monitored by gas chromatographic analysis of 2-furaldehyde concentrations in the generator reservoir, condenser column collection flask, distribution line, and 0, 2, and 32 ppm chambers with animals present. Concentrations of 2-furaldehyde ranged from 0.11% in the condenser column collection flask to 0.35% in the 2 ppm chamber (at the end of an exposure day), indicating that no degradation of furfuryl alcohol occurred.

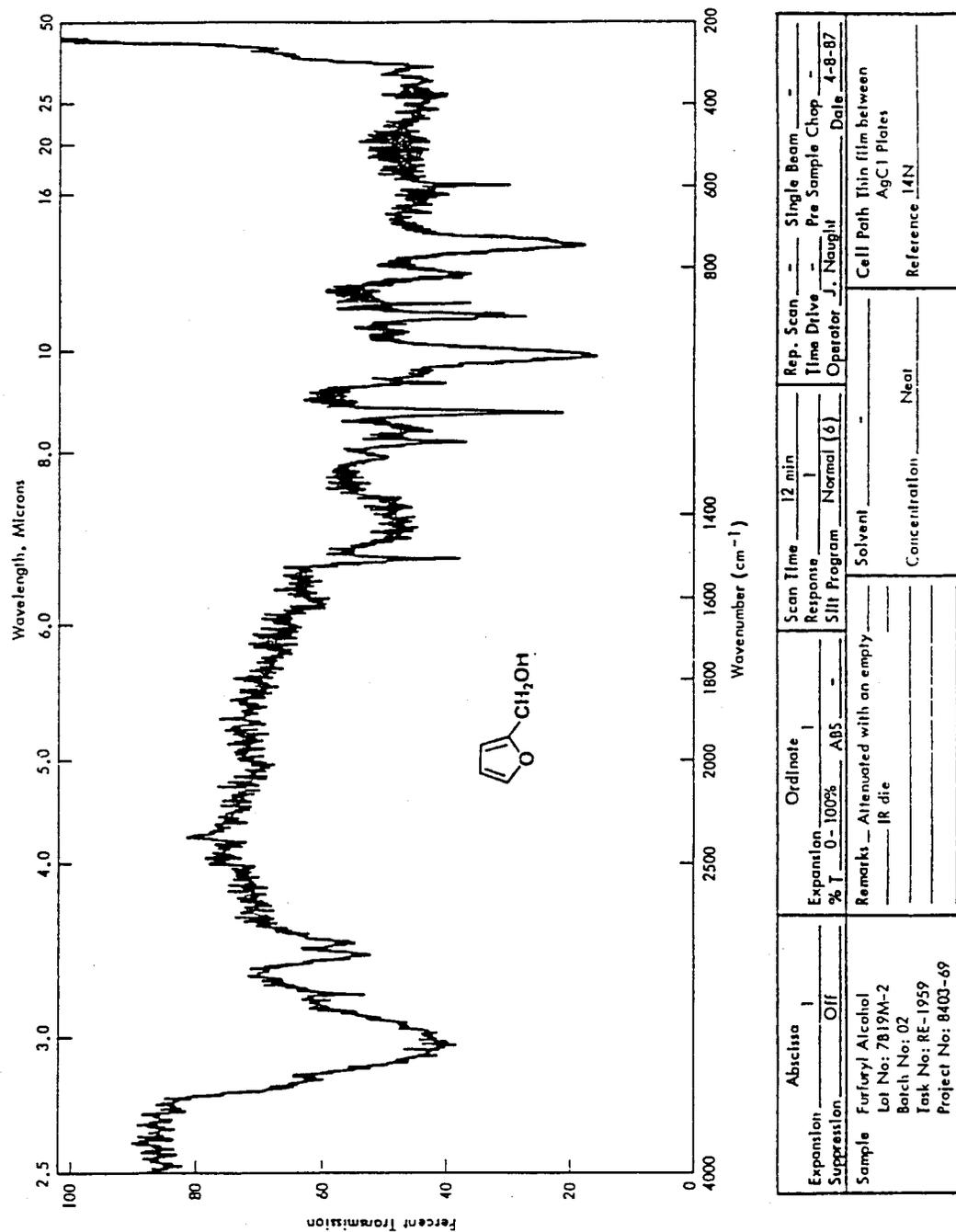


Figure J1
Infrared Absorption Spectrum of Furfuryl Alcohol

Furfuryl Alcohol
 Lot No.: 7B19H-2
 Batch No.: 02
 Project No.: 8403-69
 Task No.: RE-1959

Instrument: Varian VXR-300 FT-NMR Spectrometer
 Nucleus: Proton
 Solvent: Deuterated chloroform
 Internal Reference: Chloroform
 Sample Temperature: Ambient
 Operator: D. Timmons
 Date: 3/30/87

Assignments (δ ppm)	J	Integration	
		Observed	Theoretical
(a) 2.35		1.08	1
(b) 4.57		2.06	2
(c) 6.27		1.92	1
(d) 6.33	$J_{d-c}=3.2$ Hz		1
	$J_{d-e}=1.8$ Hz		
(e) 7.39	$J_{e-c}=0.9$ Hz	0.94	1

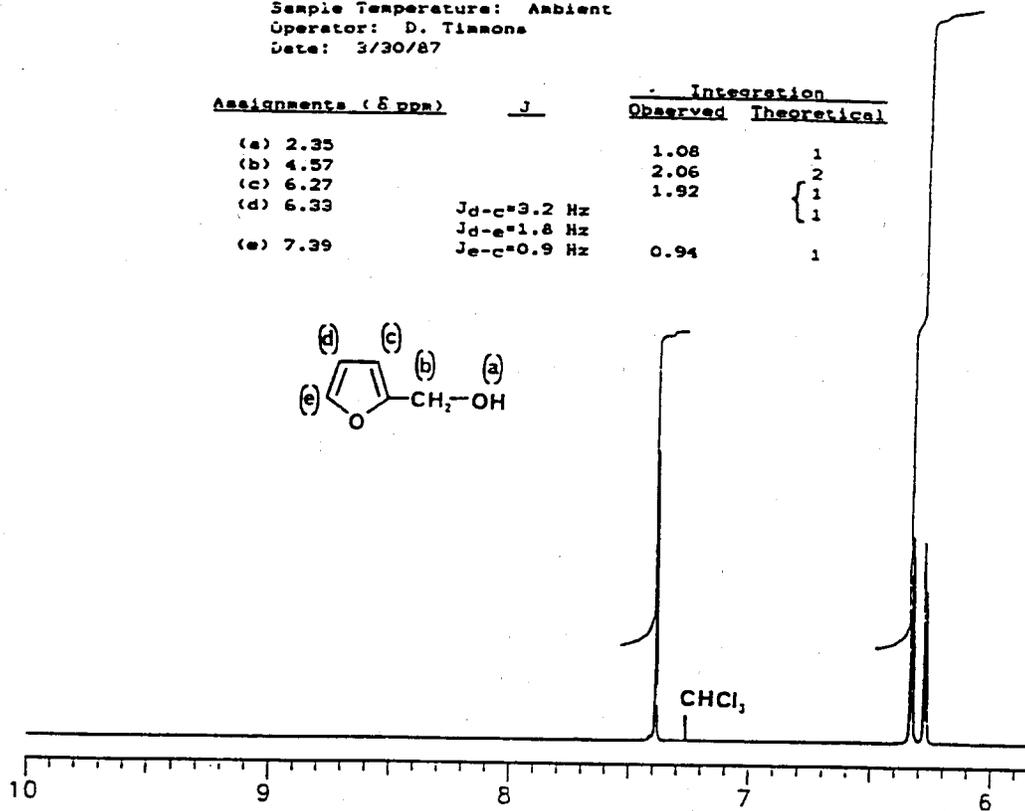


FIGURE J2
 Nuclear Magnetic Resonance Spectrum of Furfuryl Alcohol

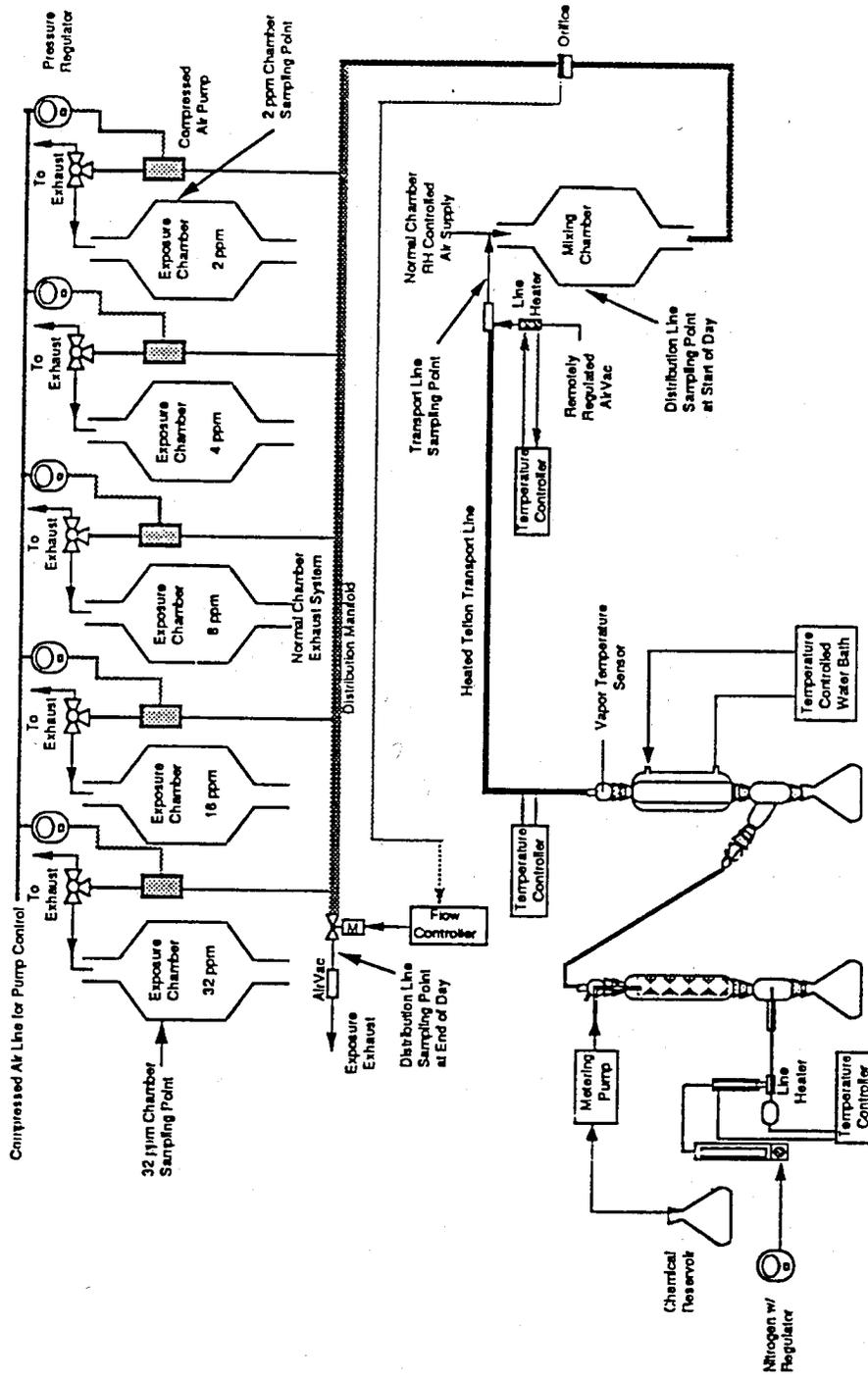


Figure J3a
 Schematic of the Generation and Delivery System
 in the 16-Day and 14-Week Studies

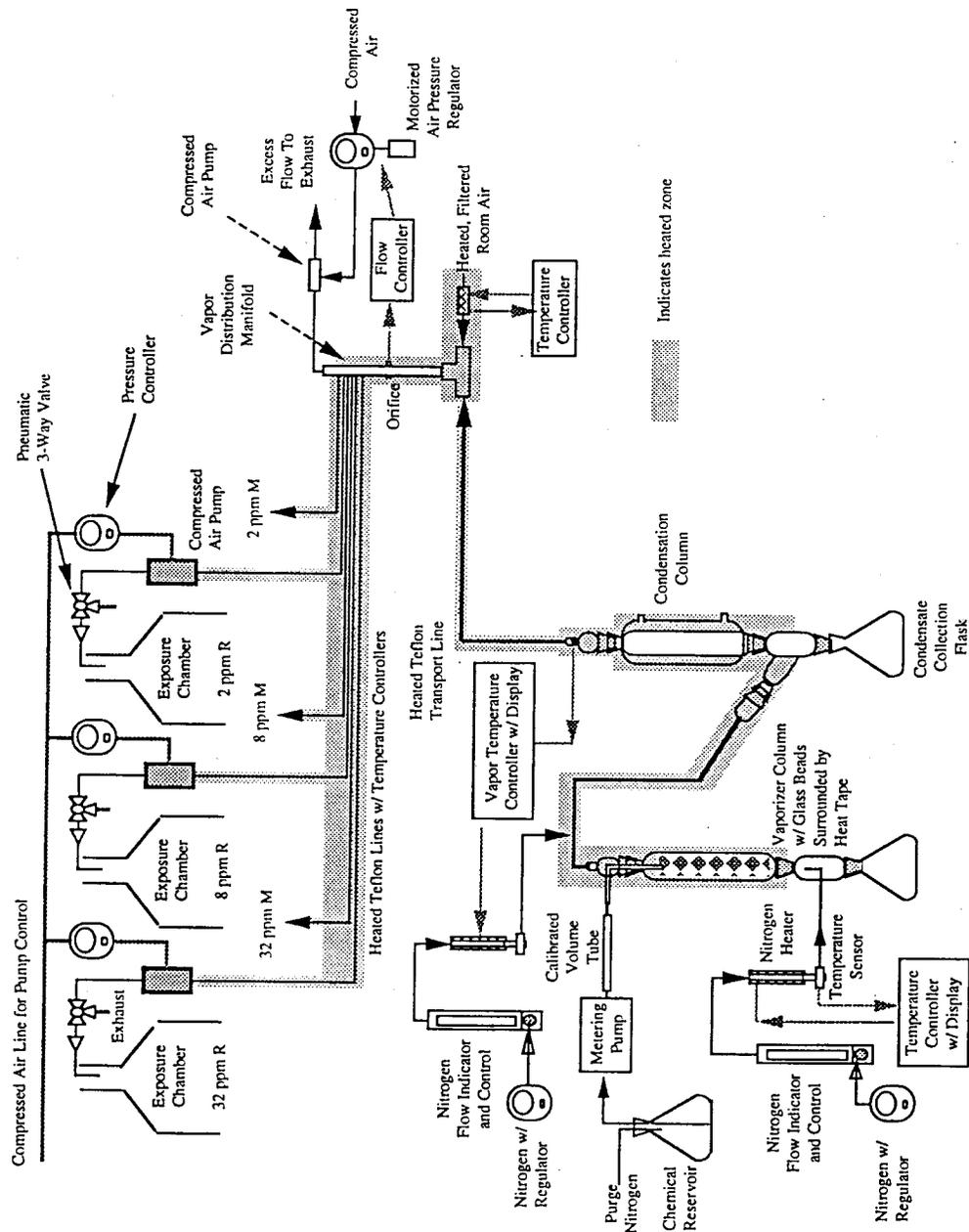


FIGURE J3B
Schematic of the Generation and Delivery System
in the 2-Year Studies

TABLE J1
Summary of Chamber Concentrations in the 16-Day Inhalation Studies of Furfuryl Alcohol

Target Concentration (ppm)	Total Number of Readings	Average Concentration ^a (ppm)
Rat Chambers		
16	144	15.5 ± 1.0
31	142	30.0 ± 1.8
63	141	61.4 ± 3.9
125	141	119 ± 9.0
250	21	229 ± 7.3
Mouse Chambers		
16	146	15.5 ± 1.0
31	143	30.2 ± 1.7
63	141	61.8 ± 3.8
125	141	120 ± 9.1
250	34	226 ± 33

^a Mean ± standard deviation

TABLE J2
Summary of Chamber Concentrations in the 14-Week Inhalation Studies of Furfuryl Alcohol

Target Concentration (ppm)	Total Number of Readings	Average Concentration ^a (ppm)
Rat Chambers		
2	743	2.0 ± 0.10
4	742	4.0 ± 0.21
8	737	8.1 ± 0.38
16	735	16.1 ± 0.77
32	739	32.2 ± 1.43
Mouse Chambers		
2	754	2.0 ± 0.10
4	753	4.0 ± 0.20
8	749	8.1 ± 0.38
16	746	16.1 ± 0.72
32	750	32.2 ± 1.41

^a Mean ± standard deviation

TABLE J3
Summary of Chamber Concentrations in the 2-Year Inhalation Studies of Furfuryl Alcohol

Target Concentration (ppm)	Total Number of Readings	Average Concentration ^a (ppm)
Rat Chambers		
2	4,769	2.01 ± 0.11
8	4,759	8.02 ± 0.43
32	4,786	32.3 ± 1.93
Mouse Chambers		
2	5,161	1.99 ± 0.12
8	5,194	8.01 ± 0.45
32	5,198	31.9 ± 2.07

^a Mean ± standard deviation

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

TABLE K1	Ingredients of NIH-07 Rat and Mouse Ration	242
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TABLE K1
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 K2
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
<i>d</i> - α -Tocopheryl acetate	20,000 IU	
Choline	560.0 g	Choline chloride
Folic acid	2.2 g	
Niacin	30.0 g	
<i>d</i> -Pantothenic acid	18.0 g	<i>d</i> -Calcium pantothenate
Riboflavin	3.4 g	
Thiamine	10.0 g	Thiamine mononitrate
B ₁₂	4,000 μ g	
Pyridoxine	1.7 g	Pyridoxine hydrochloride
Biotin	140.0 mg	<i>d</i> -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 K3
Nutrient Composition of NIH-07 Rat and Mouse Ration

Nutrient	Mean \pm Standard Deviation	Range	Number of Samples
Protein (% by weight)	23.35 \pm 0.52	22.2) 24.3	24
Crude fat (% by weight)	5.38 \pm 0.18	5.10) 5.90	24
Crude fiber (% by weight)	3.24 \pm 0.35	2.60) 4.30	24
Ash (% by weight)	6.37 \pm 0.23	5.94) 6.81	24
Amino Acids (% of total diet)			
Arginine	1.273 \pm 0.083	1.100) 1.390	12
Cystine	0.307 \pm 0.068	0.181) 0.400	12
Glycine	1.152 \pm 0.051	1.060) 1.220	12
Histidine	0.581 \pm 0.029	0.531) 0.630	12
Isoleucine	0.913 \pm 0.034	0.867) 0.965	12
Leucine	1.969 \pm 0.053	1.850) 2.040	12
Lysine	1.269 \pm 0.050	1.200) 1.370	12
Methionine	0.436 \pm 0.104	0.306) 0.699	12
Phenylalanine	0.999 \pm 0.114	0.665) 1.110	12
Threonine	0.899 \pm 0.059	0.824) 0.985	12
Tryptophan	0.216 \pm 0.146	0.107) 0.671	12
Tyrosine	0.690 \pm 0.091	0.564) 0.794	12
Valine	1.079 \pm 0.057	0.962) 1.170	12
Essential Fatty Acids (% of total diet)			
Linoleic	2.389 \pm 0.223	1.830) 2.570	11
Linolenic	0.273 \pm 0.034	0.210) 0.320	11
Vitamins			
Vitamin A (IU/kg)	6,602 \pm 572	5,730) 8,800	24
Vitamin D (IU/kg)	4,450 \pm 1,382	3,000) 6,300	4
α -Tocopherol (ppm)	35.24 \pm 8.58	22.5) 48.9	12
Thiamine (ppm)	16.58 \pm 2.32	13.0) 22.0	24
Thiamine (ppm)	17.13 \pm 2.03	14.0) 22.0	23
Riboflavin (ppm)	7.78 \pm 0.899	6.10) 9.00	12
Niacin (ppm)	98.73 \pm 23.21	65.0) 150.0	12
Pantothenic acid (ppm)	32.94 \pm 8.92	23.0) 59.2	12
Pyridoxine (ppm)	9.28 \pm 2.49	5.60) 14.0	12
Folic acid (ppm)	2.56 \pm 0.70	1.80) 3.70	12
Biotin (ppm)	0.265 \pm 0.046	0.190) 0.354	12
Vitamin B ₁₂ (ppb)	41.6 \pm 18.6	10.6) 65.0	12
Choline (ppm)	2,955 \pm 382	2,300) 3,430	11
Minerals			
Calcium (%)	1.13 \pm 0.04	1.06) 1.20	24
Phosphorus (%)	0.91 \pm 0.05	0.76) 1.00	24
Potassium (%)	0.886 \pm 0.059	0.772) 0.971	10
Chloride (%)	0.531 \pm 0.082	0.380) 0.635	10
Sodium (%)	0.316 \pm 0.031	0.258) 0.370	12
Magnesium (%)	0.165 \pm 0.010	0.148) 0.180	12
Sulfur (%)	0.266 \pm 0.060	0.208) 0.420	11
Iron (ppm)	348.0 \pm 83.7	255.0) 523.0	12
Manganese (ppm)	93.27 \pm 5.62	81.7) 102.0	12
Zinc (ppm)	59.42 \pm 9.73	46.1) 81.6	12
Copper (ppm)	11.63 \pm 2.46	8.09) 15.4	12
Iodine (ppm)	3.49 \pm 1.14	1.52) 5.83	11
Chromium (ppm)	1.57 \pm 0.53	0.60) 2.09	12
Cobalt (ppm)	0.81 \pm 0.27	0.49) 1.23	8

TABLE K4
Contaminant Levels in NIH-07 Rat and Mouse Ration^a

	Mean ± Standard Deviation ^b	Range	Number of Samples
Contaminants			
Arsenic (ppm)	0.54 ± 0.11	0.30) 0.70	24
Cadmium (ppm)	0.09 ± 0.07	0.04) 0.20	24
Lead (ppm)	0.33 ± 0.13	0.20) 0.70	24
Mercury (ppm) ^c	0.02 ± 0.0	0.02) 0.03	24
Selenium (ppm)	0.36 ± 0.08	0.10) 0.50	24
Aflatoxins (ppb)	<5.0		24
Nitrate nitrogen (ppm) ^d	6.88 ± 2.86	2.90) 14.0	24
Nitrite nitrogen (ppm) ^d	0.60 ± 0.87	0.10) 3.50	24
BHA (ppm) ^e	2.29 ± 4.20	1.00) 20.0	24
BHT (ppm) ^e	1.54 ± 1.02	1.0) 5.0	24
Aerobic plate count (CFU/g)	95,150 ± 164,754	7,200) 710,000	24
Coliform (MPN/g)	4 ± 4	3) 23	24
<i>Escherichia coli</i> (MPN/g)	<3		24
<i>Salmonella</i> (MPN/g)	Negative		24
Total nitrosoamines (ppb) ^f	10.82 ± 4.49	4.7) 23.0	24
<i>N</i> -Nitrosodimethylamine (ppb) ^f	8.56 ± 4.53	2.9) 21.0	24
<i>N</i> -Nitrosopyrrolidine (ppb) ^f	2.26 ± 1.20	1.0) 6.0	24
Pesticides (ppm)			
α-BHC	<0.01		24
β-BHC	<0.02		24
γ-BHC	<0.01		24
δ-BHC	<0.01		24
Heptachlor	<0.01		24
Aldrin	<0.01		24
Heptachlor epoxide	<0.01		24
DDE	<0.01		24
DDD	<0.01		24
DDT	<0.01		24
HCB	<0.01		24
Mirex	<0.01		24
Methoxychlor	<0.05		24
Dieldrin	<0.01		24
Endrin	<0.01		24
Telodrin	<0.01		24
Chlordane	<0.05		24
Toxaphene	<0.10		24
Estimated PCBs	<0.20		24
Ronnel	<0.01		24
Ethion	<0.02		24
Trithion	<0.05		24
Diazinon	<0.10		24
Methyl parathion	<0.02		24
Ethyl parathion	<0.02		24
Malathion	0.13 ± 0.13	0.05) 0.53	24
Endosulfan I	<0.01		24
Endosulfan II	<0.01		24
Endosulfan sulfate	<0.03		24

^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 All values except for the lots milled September, November, and December 1991 were less than the detection limit. The detection limit is given as the mean.

^d Sources of contamination: alfalfa, grains, and fish meal

^e Sources of contamination: soy oil and fish meal

^f All values were corrected for percent recovery.

APPENDIX L

SENTINEL ANIMAL PROGRAM

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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 14-week and 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

14-Week Study

ELISA

PVM (pneumonia virus of mice)

Study termination

RCV/SDA (rat coronavirus/
sialodacryoadenitis virus)

Study termination

Sendai

Study termination

Hemagglutination Inhibition

H-1 (Toolan's H-1 virus)

Study termination

KRV (Kilham rat virus)

Study termination

2-Year Study

ELISA

Mycoplasma arthritidis

Study termination

Mycoplasma pulmonis

Study termination

PVM

6, 12, and 18 months, study termination

RCV/SDA

6, 12, and 18 months, study termination

Sendai

6, 12, and 18 months, study termination

Immunofluorescence Assay

PVM

18 months

Sendai

18 months

Hemagglutination Inhibition

H-1

6, 12, and 18 months, study termination

KRV

6, 12, and 18 months, study termination

Method and Test**Time of Analysis****MICE****14-Week Study**

ELISA

Ectromelia virus	Study termination
GDVII (mouse encephalomyelitis virus)	Study termination
MVM (minute virus of mice)	Study termination
Mouse adenoma virus	Study termination
MHV (mouse hepatitis virus)	Study termination
PVM	Study termination
Reovirus 3	Study termination
Sendai	Study termination

Immunofluorescence Assay

EDIM (epizootic diarrhea of infant mice)	Study termination
LCM (lymphocytic choriomeningitis virus)	Study termination

Hemagglutination Inhibition

K (papovavirus)	Study termination
Polyoma virus	Study termination

2-Year Study

ELISA

Ectromelia virus	6, 12, and 18 months, study termination
EDIM	6, 12, and 18 months, study termination
GDVII	6, 12, and 18 months, study termination
LCM	6, 12, and 18 months, study termination
Mouse adenoma virus-FL	6, 12, and 18 months, study termination
MHV	6, 12, and 18 months, study termination
<i>M. arthritidis</i>	Study termination
<i>M. pulmonis</i>	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

EDIM	12 and 18 months, study termination
------	-------------------------------------

Hemagglutination Inhibition

K	6, 12, and 18 months, study termination
MVM	6, 12, and 18 months, study termination
Polyoma virus	6, 12, and 18 months, study termination

RESULTS

One rat was positive for *M. arthritidis* at the end of the 2-year study. Further evaluation of the sample positive for *M. arthritidis* by immunoblot and Western blot procedures indicated that the positive titer may have been due to cross reaction with antibodies of nonpathogenic *Mycoplasma* or other agents. Only one sample was positive and there were no clinical findings or histopathologic changes of *M. arthritidis* infection in the animal with a positive titer. Accordingly, the *M. arthritidis*-positive titer was considered a false positive.