NTP TECHNICAL REPORT

ON THE

TOXICOLOGY AND CARCINOGENESIS

STUDIES OF

POLYVINYL ALCOHOL

(Molecular Weight ≈24,000)

(CAS NO. 9002-89-5)

IN FEMALE B6C3F$_1$ MICE

(INTRAVAGINAL STUDIES)

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

May 1998

NTP TR 474

NIH Publication No. 98-3964

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

NTP TECHNICAL REPORT

ON THE

TOXICOLOGY AND CARCINOGENESIS

STUDIES OF

POLYVINYL ALCOHOL

(Molecular Weight ≈24,000)

(CAS NO. 9002-89-5)

IN FEMALE B6C3F$_1$ MICE

(INTRAVAGINAL STUDIES)

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

May 1998

NTP TR 474

NIH Publication No. 98-3964

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

CONTRIBUTORS

National Toxicology Program
Evaluated and interpreted results and reported findings

A. Radovsky, D.V.M., Ph.D., Study Scientist
D.A. Bridge, B.S.
J.R. Bucher, Ph.D.
R.E. Chapin, Ph.D.
J.R. Hailey, D.V.M.
J.K. Haseman, Ph.D.
R.R. Maronpot, D.V.M.
G.N. Rao, D.V.M., Ph.D.
J.H. Roycroft, Ph.D.
C.S. Smith, Ph.D.
G.S. Travlos, D.V.M.
D.B. Walters, Ph.D.
K.L. Witt, M.S., Oak Ridge Associated Universities

Arthur D. Little, Inc.
Conducted studies, evaluated pathology findings

J.K. Marquis, Ph.D., Principal Investigator (30-day study)
C.L. Berman, Ph.D., Principal Investigator (2-year study)
M.E.P. Goad, D.V.M., Ph.D.

Experimental Pathology Laboratories, Inc.
Provided pathology quality assurance

J.F. Hardisty, D.V.M., Principal Investigator
C.C. Shackelford, D.V.M., M.S., Ph.D.

Dynamac Corporation
Prepared quality assurance audits

S. Brecher, Ph.D., Principal Investigator

NTP Pathology Working Group
Evaluated slides, prepared pathology report on mice (2 May 1996)

L.L. Lanning, D.V.M., Chairperson
Pathology Associates International
M. Butt, D.V.M.
Pathology Associates International
B.J. Davis, D.V.M., Ph.D.
North Carolina State University
D. Dixon, D.V.M., Ph.D.
National Toxicology Program
J.K. Hailey, D.V.M.
National Toxicology Program
R.A. Herbert, D.V.M., Ph.D.
National Toxicology Program
A. Nyska, D.V.M.
National Toxicology Program
A. Radovsky, D.V.M., Ph.D.
National Toxicology Program
C.C. Shackelford, D.V.M., M.S., Ph.D.
Experimental Pathology Laboratories, Inc.

Analytical Sciences, Inc.
Provided statistical analyses

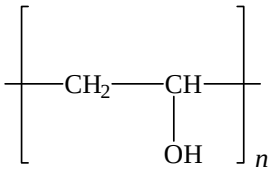
R.W. Morris, M.S., Principal Investigator
S.R. Lloyd, M.S.
N.G. Mintz, B.S.

Biotechnical Services, Inc.
Prepared Technical Report

S.R. Gunnels, M.A., Principal Investigator
J.R. Carlton, B.A.
L.M. Harper, B.S.
A.M. Macri-Hanson, M.A., M.F.A.

CONTENTS

ABSTRACT



POLYVINYL ALCOHOL

CAS No. 9002-89-5

Chemical Formula: $(C_2H_4O)_n$ Molecular Weight: approximately 24,000

Synonyms: Ethenol homopolymer, PVA
Trade names: Akwa Tears, Alcotex, Alvyl, Aracet, Cipoviol, Covol, Elvanol, Ethenol, Gelvatol, Gohsenol, Ivalon, Kuralon, Kurare, Lemol, Liquifilm, Mowiol, Polydesis, Polysizer, Polyvinol, Polyviol, Poval, Resistoflex, Rhodoviol, Sno Tears, Solvar, Sumitex, Vibatex, Vinacol, Vinalak, Vinarol, Vinarole, Vinavilol, Vinol, Vinylon

Polyvinyl alcohol is produced primarily for use in textile sizing, adhesives, polymerization aids, and paper coatings. It is also used in surgical drapes, towels, and gauze sponges; protective gloves; cosmetic formulations; topical ophthalmic preparations; plastic sponge implants for reconstructive surgery; and intravaginal contraceptive foam and film. In addition, polyvinyl alcohol is used with magnesium sulfate to dilate the cervix of women prior to induction of labor. It is estimated that hundreds of thousands of women in the United States use an intravaginal product containing polyvinyl alcohol each year. The Food and Drug Administration nominated low-viscosity polyvinyl alcohol for a 2-year study because of concern about the lack of information about the long-term toxic and carcinogenic effects by the intravaginal route. Female B6C3F$_1$ mice received polyvinyl alcohol (approximately 99% pure) in deionized water by intravaginal administration for 30 days or 2 years.

30-DAY STUDY IN MICE

Three groups of 50 female B6C3F$_1$ mice were used in this intravaginal study. The vehicle control group received only 20 μL of a deionized water vehicle. The other two groups each received 20 μL of 25% polyvinyl alcohol in deionized water. Animals in one dose group were returned to their cages after dosing; animals in the other dose group were restrained in a vertical nose-down position in restraint bags for several minutes after dosing. Animals were dosed daily for 30 consecutive days. All mice survived to the end of the study. The final mean body weights and body weight gains of dosed mice were similar to those of the vehicle control group. Abnormalities noted in the vaginal area after dosing included vaginal plugs, secretions, and swelling. These vaginal changes were minimal to mild and occurred in vehicle controls as well as in dosed mice. Restraint of mice after dosing appeared to eliminate vaginal secretions but increased both the incidence of vaginal irritation

and the severity of vaginal opening swelling. At necropsy, mildly enlarged uterine horns were observed in 10 vehicle control mice, three 25% mice, and seven 25% (restrained) mice. No chemical-related lesions were observed.

2-YEAR STUDY IN MICE

Three groups of 100 female B6C3F$_1$ mice were used in this intravaginal study: an untreated control group, a vehicle control group receiving 20 μL deionized water vehicle only, and a dosed group receiving 20 μL 25% polyvinyl alcohol in deionized water. Animals were dosed 5 days per week, excluding holidays, for 104 to 105 weeks.

Survival, Body Weights, and Clinical Findings

Survival of dosed mice was similar to that of the two control groups. The final mean body weight of vehicle control mice was less than that of the untreated control group. The mean body weights of the dosed mice were less than those of the untreated controls from week 17 until the end of the study. The only clinical finding was vaginal irritation, observed in six mice in the vehicle control group and 11 mice in the dosed group.

Pathology Findings

No neoplasms or nonneoplastic lesions related to chemical treatment were observed. The incidences of reproductive tract nonneoplastic lesions in the dosed group did not differ significantly from those in the vehicle control group; similarly, the incidences of reproductive tract nonneoplastic lesions in the vehicle control group did not differ significantly from those in the untreated control group.

CONCLUSIONS

Under the conditions of this 2-year study, there was *no evidence of carcinogenic activity** of polyvinyl alcohol (molecular weight approximately 24,000) in female B6C3F$_1$ mice administered 20 μL of a 25% solution intravaginally. There were no neoplasms or nonneoplastic lesions considered related to treatment with polyvinyl alcohol.

---

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

Summary of the 2-Year Carcinogenesis Study of Polyvinyl Alcohol in Female B6C3F$_1$ Mice

Doses	Untreated control, vehicle control receiving 20 μL deionized water only, and dosed group receiving 20 μL 25% polyvinyl alcohol in deionized water
Body weights	Vehicle control and dosed groups slightly less than untreated control group
2-Year survival rates	47/100, 51/100, 61/100
Nonneoplastic effects	None
Neoplastic effects	None
Level of evidence of carcinogenic activity	No evidence

EXPLANATION OF LEVELS OF EVIDENCE OF CARCINOGENIC ACTIVITY

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

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

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

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

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

NATIONAL TOXICOLOGY PROGRAM BOARD OF SCIENTIFIC COUNSELORS
TECHNICAL REPORTS REVIEW SUBCOMMITTEE

The members of the Technical Reports Review Subcommittee who evaluated the draft NTP Technical Report on polyvinyl alcohol on 12 December 1996 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 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.

Gary P. Carlson, Ph.D., Chairperson
School of Health Sciences
Purdue University
West Lafayette, IN

Arnold L. Brown, M.D.
University of Wisconsin Medical School
Madison, WI

Thomas L. Goldsworthy, Ph.D.
Department of Experimental Pathology and Toxicology
Chemical Industry Institute of Toxicology
Research Triangle Park, NC

Robert LeBoeuf, Ph.D.
Corporate Professional and Regulatory Services
Human Safety Department
The Procter & Gamble Company
Cincinnati, OH

Janardan K. Reddy, M.D.
Department of Pathology
Northwestern University Medical School
Chicago, IL

Irma Russo, M.D., Principal Reviewer
Fox Chase Cancer Center
Philadelphia, PA

Louise Ryan, Ph.D.
Division of Biostatistics
Dana-Farber Cancer Institute
Boston, MA

Robert E. Taylor, M.D., Ph.D., Principal Reviewer
Department of Pharmacology
Howard University College of Medicine
Washington, DC

Frederick L. Tyson, Ph.D.
St. Mary's Hospital and Medical Center
Cancer Research Institute
Grand Junction, CO

Jerrold M. Ward, D.V.M., Ph.D.*
National Cancer Institute
Frederick, MD

---

* Did not attend

SUMMARY OF TECHNICAL REPORTS REVIEW SUBCOMMITTEE COMMENTS

On 12 December 1996, the draft Technical Report on the toxicology and carcinogenesis studies of polyvinyl alcohol received public review by the National Toxicology Program's Board of Scientific Counselors' Technical Reports Review Subcommittee. The review meeting was held at the National Institute of Environmental Health Sciences, Research Triangle Park, NC.

Dr. A. Radovsky, NIEHS, introduced the toxicology and carcinogenesis studies of polyvinyl alcohol by discussing the uses of the chemical and rationale for study, describing the experimental design, reporting on survival and body weight effects, and commenting on the lack of compound-related neoplasms or nonneoplastic lesions in female mice. The proposed conclusion was *no evidence of carcinogenic activity* in female B6C3F$_1$ mice. No neoplasms or nonneoplastic lesions were considered related to treatment with polyvinyl alcohol.

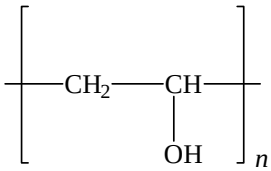
Dr. Russo, a principal reviewer, agreed with the proposed conclusions. She had concerns about the lack of testing in the rat and not having more than one dose. This was in view of studies reporting development of sarcomas at the site of subcutaneous implants of polyvinyl sponges in rats that led the International Agency for Research on Cancer to recommend further studies in animals. Dr. Russo wondered if the chemical could be administered in a sponge or tampon. Dr. Radovsky said the 3′-azido-3′-deoxythymidine (AZT) studies had shown the mouse to be susceptible to developing vaginal neoplasms. She said the possibility of using a pessary or tampon could be considered in a future study.

Dr. Taylor, the second principal reviewer, agreed with the proposed conclusions. He said it would have been of merit to have developed innovative ways to administer higher doses. Dr. Radovsky said the problem with handling of the 25% solution of polyvinyl alcohol was not so much solubility as viscosity. The dose used was the maximum concentration that could be consistently administered with the available dosing equipment.

Dr. W. Allaben, Food and Drug Administration (FDA), said that the FDA was involved in the study design and the agency thought the information needed was obtained in spite of the technical difficulties. Dr. Goldsworthy asked whether Glaxo-Wellcome, in its studies of AZT in rats, observed similar responses with systemic versus intravaginal administration. Dr. Radovsky replied that vaginal neoplasms were induced when AZT was administered by oral gavage or vaginal administration. Dr. Tyson asked whether there was any leakage after intravaginal administration. Dr. Radovsky said there was some, but it was not quantifiable. Dr. H. Matthews, NIEHS, reported that his group studied disposition of radiolabeled polyvinyl alcohol in the rat using measures to avoid ingestion through grooming. He said there was very slight absorption without bioaccumulation after either single or multiple doses.

Dr. Russo moved that the Technical Report on polyvinyl alcohol be accepted with revisions discussed and the conclusions as written for female mice, *no evidence of carcinogenic activity*. Dr. Taylor seconded the motion, which was accepted unanimously with eight votes.

INTRODUCTION



POLYVINYL ALCOHOL

CAS No. 9002-89-5

Chemical Formula: $(C_2H_4O)_n$ Molecular Weight: approximately 24,000

Synonyms: Ethenol homopolymer, PVA
Trade names: Akwa Tears, Alcotex, Alvyl, Aracet, Cipoviol, Covol, Elvanol, Ethenol, Gelvatol, Gohsenol, Ivalon, Kuralon, Kurare, Lemol, Liquifilm, Mowiol, Polydesis, Polysizer, Polyvinol, Polyviol, Poval, Resistoflex, Rhodoviol, Sno Tears, Solvar, Sumitex, Vibatex, Vinacol, Vinalak, Vinarol, Vinarole, Vinavilol, Vinol, Vinylon

CHEMICAL AND PHYSICAL PROPERTIES

Polyvinyl alcohol is a synthetic polymer with a wide range of molecular weights (from less than 15,000 to over 430,000). The physical properties of polyvinyl alcohol polymers are dependent on the molecular weight, degree of hydrolysis, and water content of the polymers (IARC, 1979). The water solubility of polyvinyl alcohol polymer increases as the molecular weight decreases (*Merck Index*, 1976); it is practically insoluble in organic solvents (Lefaux, 1968). The current study is of an aqueous solution of polyvinyl alcohol polymer with a molecular weight of about 24,000. Prior to dissolution, this material is an off-white crystalline solid that is 88% hydrolyzed. It has a pH of 5.9 and a viscosity of 4.82 cps. Its density is 1.006 g/mL and its melting point is 194° C. As a 20% aqueous solution, the polyvinyl alcohol polymer used in this study has a density of 1.07 g/mL.

PRODUCTION, USE, AND HUMAN EXPOSURE

Polyvinyl alcohol is produced by the controlled hydrolysis of polyvinyl acetate. In 1991, 114,000 tons of polyvinyl alcohol was produced in the United States, primarily for use in textile sizing, adhesives, polymerization aids, and paper coatings (*Chemical Economics Handbook*, 1996). The four production grades of polyvinyl alcohol are super-high viscosity (molecular weight 250,000–300,000); high viscosity (molecular weight 170,000–220,000); medium viscosity (molecular weight 120,000–150,000); and low viscosity (molecular weight 25,000–35,000) (*Hawley's*, 1987). The Food and Drug Administration permits the use of polyvinyl alcohol in contact with food (IARC, 1979), and it has been used in grease-resistant coatings for containers such as potato chip bags. Surgical drapes, towels, and gauze sponges made of polyvinyl alcohol which dissolve in hot water have

been developed to simplify hospital waste disposal (Fisher, 1996). Protective gloves composed of polyvinyl alcohol have been used to protect the hands of workers from organic solvents (Lefaux, 1968).

Polyvinyl alcohol is used in many cosmetic formulations such as facial masks, eye shadow and brow products, and lipliners. Concentrations of polyvinyl alcohol in cosmetics are as high as 13% in paste masks (mud packs) (CIR, 1996). Polyvinyl alcohol is also used in topical ophthalmic preparations to increase viscosity. A relatively insoluble form of polyvinyl alcohol is used for plastic sponge implants in reconstructive surgery (Grant, 1974). Polyvinyl alcohol foam spheres have been injected intravascularly for elective embolization of vascular malformations in the brain (Lanman *et al.*, 1988). Pessaries composed of polyvinyl alcohol with incorporated magnesium sulfate have been used in pregnant women for dilatation of the cervix prior to the induction of labor (Johnson *et al.*, 1985). An over-the-counter intravaginal contraceptive foam (Delfen, Ortho Pharmaceutical Corporation) contains less than 1% polyvinyl alcohol. The manufacturer of an over-the-counter soluble intravaginal contraceptive film estimates that over 500,000 women in the United States use their product annually (VCF; Apothecus, Inc., Great Neck, NY); the product is composed of a spermicide, glycerol, and 67% polyvinyl alcohol (molecular weight 25,000).

ABSORPTION, DISTRIBUTION, METABOLISM, AND EXCRETION

In general, synthetic macromolecular polymers such as polyvinyl alcohol are chemically inert and not orally absorbed, but injected polymers could possibly be metabolized (Lefaux, 1968).

Experimental Animals

The distribution of five [^{125}I]-radiolabeled polyvinyl alcohol polymers with molecular weights of 15,000, 70,000, 120,000, 200,000, and 430,000 was determined at up to 30 hours after intravenous administration into 8- to 12-week-old female BALB/cCrSlc mice (Yamaoka *et al.*, 1995). The polymer with a molecular weight of 15,000 had a circulating half-life of 90 minutes compared to 23 hours for the polymer with a molecular weight of 430,000. Almost 80% of the 15,000 molecular weight polymer was excreted by the kidney within 30 minutes after injection.

[^{14}C]-Radiolabeled polyvinyl alcohol with a molecular weight less than or equal to 50,000 was given orally, intravenously, or intravaginally to Fischer 344 rats (Sanders and Matthews, 1990). Following oral administration, greater than 98% of the dose was excreted in the feces within 48 hours and only a trace was detected in the urine. No evidence of polyvinyl alcohol was detected in the tissues. Following intravenous administration, systemic distribution of polyvinyl alcohol was evident with the highest concentrations detected in the liver. Intravenous dosing also resulted in most of the dose being excreted in the urine, thus indicating that the oral dose was not absorbed. Following intravaginal administration of 3 mg/kg polyvinyl alcohol for 1, 3, or 10 days, less than 1% of the dose of polyvinyl alcohol-derived radioactivity was detected in the tissues. The highest concentrations were seen in the liver, but even after 10 doses the concentration in the liver was less than 2 ppm. Polyvinyl alcohol-derived material was slowly cleared, and 0.3 ppm remained in liver tissue 30 days after the last of 10 daily doses.

Twenty-eight consecutive daily doses of 1 mL of 5% polyvinyl alcohol polymers with average molecular weights of 37,000, 133,000, or 185,000 in physiological saline were injected subcutaneously into female Holtzman rats (Hall and Hall, 1963). Using a special stain (Congo red) on histologic tissue sections, the polymers with molecular weights of 133,000 and 185,000, but not the polymer with a molecular weight of 37,000, were found in the liver, spleen, and kidney.

Humans

No specific data on the absorption, distribution, metabolism, or excretion of polyvinyl alcohol in humans were found in the literature.

TOXICITY

In general, macromolecules such as polyvinyl alcohol are considered to have little or no oral or cutaneous toxicity due to their chemical inertness (Lefaux, 1968).

Experimental Animals

Oral LD_{50}s greater than 20 g polyvinyl alcohol/kg body weight for rats and 14.7 g/kg for mice have been reported (Zaitsev *et al.*, 1986).

Polyvinyl alcohol polymers with average molecular weights of 37,000, 133,000, or 185,000 were injected subcutaneously into female Holtzman rats (Hall and Hall, 1963). Twenty-eight consecutive daily doses of 1 mL of 5% polyvinyl alcohol in physiological saline resulted in elevated blood pressure in some rats from each treatment group. The polymer with a molecular weight of 133,000 was associated with widespread cardiovascular lesions, severe polydipsia, severe glomerulonephritis, and enlargement of the heart, kidney, liver, and spleen. The polymer with a molecular weight of 185,000 was associated with renal glomerular swelling and enlargement of the heart, kidney, liver, and spleen. The polymer with a molecular weight of 37,000 was not associated with lesions. The authors concluded that the pathologic effects following subcutaneous injections of polyvinyl alcohol in rats, particularly in the kidney and in production of the nephrotic syndrome, were dependent on the molecular weight rather than on the chemical structure of the polymer.

Intraocular injection of a 1.4% solution of polyvinyl alcohol (unspecified molecular weight) in isotonic saline was made into the eyes of rabbits by the subconjunctival, intracameral (into the anterior chamber), and intravitreal routes (Krishna and Mitchell, 1965). Eyes were examined grossly and microscopically, and intraocular pressures were measured for 6 weeks after injection. Polyvinyl alcohol injections were concluded to be nonirritating. Solid subconjunctival implants of polyvinyl alcohol produced inflammation and fibroblastic proliferation in rabbit eyes (Anderson and Shea, 1961). Five-week dermal toxicity tests with undiluted polyvinyl alcohol and 13-week studies with a peel-off facial mask containing 13% polyvinyl alcohol were conducted in rats by the Cosmetic, Toiletry and Fragrance Association. No significant toxic effects were noted in clinical pathology or clinical or necropsy observations (CIR, 1996).

Humans

Intravascularly injected polyvinyl alcohol foam spheres for elective embolization of vascular malformations resulted in inflammation and necrosis of the blood vessels in which they lodged, but this property was considered efficacious in this application (Lanman *et al.*, 1988). Foamed polyvinyl alcohol has been used in reconstructive surgery for over 40 years for conditions such as rectal prolapse and repair of large hernias without reported toxic effects (Hulman and Kirkham, 1990). Three-week dermal irritation tests using topical formulations containing 13% polyvinyl alcohol resulted in classification of polyvinyl alcohol as a "mild material" for dermal use (CIR, 1996). Sixteen human volunteers used a topical ophthalmic solution containing 1.4% polyvinyl alcohol in saline three times daily on alternate days in a 6-day study of tear replacement solutions without experiencing any ocular discomfort (Fassihi and Naidoo, 1989).

REPRODUCTIVE AND DEVELOPMENTAL TOXICITY

No data on the reproductive or developmental toxicity of polyvinyl alcohol by any route of administration in experimental animals or humans were found in the literature.

CARCINOGENICITY

Experimental Animals

Subcutaneously implanted polyvinyl alcohol sponges in rats have been associated with the appearance of local sarcomas in some studies (Oppenheimer *et al.*, 1955; Dasler and Milliser, 1963; Walter and Chiaramonte, 1965) but not in others (Russell *et al.*, 1959). Dukes and Mitchley (1962) and Roe *et al.* (1967) reported that substantially more local sarcomas resulted from the subcutaneous implantation of 2-mm-thick versus 5-mm-thick polyvinyl alcohol sponges in rats. This suggests that the physical form and the thickness of the polyvinyl alcohol implant may be important in carcinogenicity just as molecular weight is thought to be important in the toxicity of polyvinyl alcohol. No neoplasms were noted at the site of subcutaneous implantation of polyvinyl alcohol powder in a group of 25 Bethesda black rats in a 2-year study (Hueper, 1959). The International Agency for Research on Cancer (IARC, 1979) reviewed these and other data and concluded that further studies were needed before an evaluation of the carcinogenicity of polyvinyl alcohol in animals could be made.

Humans

Implantation of polyvinyl alcohol sponge as a breast prosthesis has been associated with fibrosis (Hamit, 1957). Biopsy of a polyvinyl alcohol foam sponge implanted 20 years earlier for rectal prolapse showed extensive fibrosis around the implant (Hulman and Kirkham, 1990). IARC (1979) concluded that available data were not adequate to determine the possible carcinogenicity of polyvinyl alcohol in humans.

GENETIC TOXICITY

There is only one published report concerning the mutagenicity of polyvinyl alcohol, and the authors concluded that the results of their *in vitro* and *in vivo* investigations were negative (Shibuya *et al.*, 1985). Three assays, the *Salmonella* assay (employing strains TA98, TA100, and TA1537, with and without induced rat liver S9 activation enzymes), the Chinese hamster V79 cell chromosomal aberrations test without S9, and a female mouse bone marrow micronucleus test, were used in the study. Independent evaluation of the results is precluded because no data were presented for polyvinyl alcohol from the latter two assays, and there were some departures from standard protocols in these tests.

STUDY RATIONALE

It is estimated that hundreds of thousands of women in the United States use an intravaginal product containing polyvinyl alcohol each year. The Food and Drug Administration nominated low-viscosity polyvinyl alcohol for a 2-year study because of concern about the lack of information about the long-term toxic and carcinogenic effects by the intravaginal route.

MATERIALS AND METHODS

PROCUREMENT AND CHARACTERIZATION OF POLYVINYL ALCOHOL

Polyvinyl alcohol was obtained from Marubeni America Corporation (New York, NY) in one lot (N082889). Identity, purity, and stability analyses were conducted by the analytical chemistry laboratory, Midwest Research Institute (Kansas City, MO) (Appendix B). Reports on analyses performed in support of the polyvinyl alcohol studies are on file at the National Institute of Environmental Health Sciences.

The chemical, an off-white crystalline solid, was identified as polyvinyl alcohol by infrared, ultraviolet/visible, and nuclear magnetic resonance spectroscopy. Purity of lot N082889 was determined by elemental analyses, United States Pharmacopeia (USP) analyses, and high-performance liquid chromatography. Results of elemental analyses were slightly high for carbon and slightly low for hydrogen when compared with the theoretical values for polyvinyl alcohol. All results of USP analyses indicated that lot N082889 met the USP specifications for polyvinyl alcohol. High-performance liquid chromatography revealed a major peak and three impurities with a combined area of 1.1% relative to the major peak area. The overall purity was determined to be approximately 99%.

Stability studies of the bulk chemical were performed by the analytical chemistry laboratory using high-performance liquid chromatography. These studies indicated that polyvinyl alcohol was stable as a bulk chemical for 2 weeks when stored protected from light at temperatures up to 60° C. To ensure stability, the bulk chemical was stored at room temperature protected from light.

Stability was monitored during the 30-day and 2-year studies by high-performance liquid chromatography. No degradation of the bulk chemical was detected.

PREPARATION AND ANALYSIS OF DOSE FORMULATIONS

The dose formulation was prepared twice during the 30-day study and approximately every 4 weeks during the 2-year study by mixing polyvinyl alcohol with heated, charcoal-filtered, deionized water to give the required concentration (Table B1). Stability studies of the dose formulation were performed by the analytical chemistry laboratory using high-performance liquid chromatography. The stability of the dose formulation was confirmed for at least 4 weeks when stored at room temperature protected from light and for 3 weeks when stored open to air and light.

Periodic analyses of the dose formulations of polyvinyl alcohol were conducted at the study laboratory using high-performance liquid chromatography. During the 2-year study, the dose formulations were analyzed every 4 to 8 weeks (Table B2). All dose formulations analyzed and used during the 2-year study were within 10% of the target concentration; all animal room samples were also within 10% of the target concentration.

30-DAY STUDY

The 30-day study was conducted to evaluate the cumulative toxic effects of repeated exposure to polyvinyl alcohol and to determine the appropriate doses to be used in the 2-year study.

Female B6C3F$_1$ mice were obtained from Taconic Farms (Germantown, NY). On receipt, the mice were 4 weeks old. Animals were quarantined for 11 days and were 6 weeks old on the first day of the study. There were three groups of 50 females in this intravaginal study. The vehicle control group received only 20 μL of deionized water. The other two groups each received 20 μL of a 25% solution of polyvinyl alcohol in deionized water, resulting in an average dose of 250 mg polyvinyl alcohol/kg body

weight at the start of the study when mice averaged 20 g in weight and 213 mg/kg at the end of the study. The dose volume was delivered by an Eppendorf repeater pipette with a 0.5 mL Combitip inserted approximately 1 mm into the vaginal opening. Animals in one dosed group were returned to their cages after dosing; animals in the other dosed group were restrained in a vertical nose-down position in restraint bags for several minutes after dosing. Animals were dosed daily for 30 consecutive days. Feed and water were available *ad libitum*. The animals were housed individually. Clinical findings were recorded weekly. The animals were weighed initially, weekly, and at the end of the study. Details of the study design and animal maintenance are summarized in Table 1. Histopathologic examinations were performed on all mice, but were limited to the uterus and vagina.

2-YEAR STUDY

Study Design

There were three groups of 100 female mice in this intravaginal study: an untreated control group, a vehicle control group receiving 20 μL of deionized water vehicle, and a dosed group receiving 20 μL of 25% polyvinyl alcohol in deionized water, which resulted in doses of 250 mg/kg in mice at the beginning of the study and 83 mg/kg when mice weighed 60 g. The dose volume was delivered by an Eppendorf repeater pipette with a 0.5 mL Combitip inserted approximately 1 mm into the vaginal opening.

Source and Specification of Animals

Female B6C3F$_1$ mice were obtained from Taconic Farms (Germantown, NY) for use in the 2-year study. Mice were quarantined for 12 days before the beginning of the study. Ten mice were randomly selected for parasite evaluation and gross observation of disease. Mice were 6 to 7 weeks old at the beginning of the study. The health of the animals was monitored during the study according to the protocols of the NTP Sentinel Animal Program (Appendix D).

Animal Maintenance

The animals were housed individually. Feed and water were available *ad libitum*. Cages and racks were rotated once every 2 weeks. Further details of animal maintenance are given in Table 1. Information on feed composition and contaminants is provided in Appendix C.

Clinical Examinations and Pathology

All animals were observed twice daily. Body weights were recorded initially, weekly for the first 13 weeks, monthly thereafter, and at study termination; clinical findings were recorded monthly.

A complete necropsy and microscopic examination were performed on all 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 (i.e., adrenal gland, kidney, ovary), samples from each organ were examined. Tissues examined microscopically are listed in Table 1.

Microscopic evaluations were completed by the study laboratory pathologist, and the pathology data were entered into the Toxicology Data Management System. The slides, paraffin blocks, and residual wet tissues were sent to the NTP Archives for inventory, slide/block match, and wet tissue audit. The slides, individual animal data records, and pathology tables were evaluated by an independent quality assessment laboratory. The individual animal records and tables were compared for accuracy, the slide and tissue counts were verified, and the histotechnique was evaluated. For the 2-year study, a quality assessment pathologist reviewed the clitoral gland, liver, ovary, glandular stomach, thyroid gland, uterus, and vagina.

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 pathologist, 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 Intravaginal Studies of Polyvinyl Alcohol

30-Day Study	2-Year Study
Study Laboratory Arthur D. Little, Inc. (Cambridge, MA)	Arthur D. Little, Inc. (Cambridge, MA)
Strain and Species B6C3F$_1$ mice	B6C3F$_1$ mice
Animal Source Taconic Farms (Germantown, NY)	Taconic Farms (Germantown, NY)
Time Held Before Studies 11 days	12 days
Average Age When Studies Began 6 weeks	6-7 weeks
Date of First Dose 17 December 1991	18 February 1992
Duration of Dosing 7 days per week for 30 consecutive days	5 days per week, excluding holidays, for 104 to 105 weeks
Date of Last Dose 15 January 1992	16 February 1994
Necropsy Dates 16 January 1992	15-17 February 1994
Average Age at Necropsy 11 weeks	111-112 weeks
Size of Study Groups 50 females	100 females
Method of Distribution Animals were distributed randomly into groups of approximately equal initial mean body weights.	Same as 30-day study
Animals per Cage 1	1
Method of Animal Identification Tail tattoo	Same as 30-day study
Diet NIH-07 open formula pelleted diet (Zeigler Brothers, Inc., Gardners, PA), available *ad libitum*, changed once per week	Same as 30-day study
Water Tap water (Cambridge municipal supply) via clear glass bottles with plastic Teflon-lined caps and stainless steel sipper tubes, available *ad libitum*, changed twice per week	Same as 30-day study
Cages Polycarbonate (Allentown Caging, Allentown, NJ), changed once per week	Same as 30-day study

TABLE 1
Experimental Design and Materials and Methods in the Intravaginal Studies of Polyvinyl Alcohol

30-Day Study	2-Year Study
Bedding Heat-treated hardwood chips (Northeastern Products, Warrensburg, NY), changed once per week	Same as 30-day study
Cage Filters Reemay spun-bonded polyester (Allentown Caging, Allentown, NJ), changed once every 2 weeks	Same as 30-day study, except changed once per week
Racks Stainless steel (Allentown Caging, Allentown, NJ), changed once every 2 weeks	Same as 30-day study, except changed once per week
Animal Room Environment Temperature: 13°-24° C Relative humidity: 32%-70% Room fluorescent light: 12 hours/day Room air changes: 10-15/hour	Temperature: 16°-28° C Relative humidity: 23%-78% Room fluorescent light: 12 hours/day Room air changes: 10-15/hour
Doses Vehicle control group receiving 20 μL of deionized water vehicle only and two dosed groups receiving 20 μL of 25% polyvinyl alcohol in deionized water (250 mg/kg). The dose volume was delivered by an Eppendorf repeater pipette with a 0.5 mL Combitip inserted approximately 1 mm into the vaginal opening. Animals in one dosed group were returned to their cages after dosing; animals in the other dosed group were restrained in a vertical nose-down position in restraint bags for several minutes after dosing.	Untreated control, vehicle control receiving 20 μL of deionized water vehicle only, and dosed group receiving 20 μL of 25% polyvinyl alcohol in deionized water (250 mg/kg in 20 g mice; 83 mg/kg in 60 g mice). The dose volume was delivered by an Eppendorf repeater pipette with a 0.5 mL Combitip inserted approximately 1 mm into the vaginal opening.
Type and Frequency of Observation 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 13 weeks, monthly thereafter, and at the end of the studies; clinical findings were recorded monthly.
Method of Sacrifice CO_2 asphyxiation	Same as 30-day study
Necropsy Necropsy performed on all animals.	Necropsy performed on all animals
Histopathology Histopathologic examination was performed on all mice, but was limited to the uterus and vagina.	Complete histopathology was performed on all mice. In addition to gross lesions and tissue masses, the following tissues were examined: adrenal gland, bone with marrow, brain, clitoral gland, esophagus, gallbladder, heart and aorta, large intestine (cecum, colon, rectum), small intestine (duodenum, jejunum, ileum), kidney, liver, lungs and bronchi, mammary gland, nose, ovary, pancreas, pancreatic islets, pituitary gland, salivary gland, skin, spinal cord with sciatic nerve, spleen, stomach (forestomach and glandular), thymus, thyroid gland, trachea, urinary bladder, uterus, and vagina.

STATISTICAL METHODS

Survival Analyses

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

Calculation of Incidence

The incidences of neoplasms and nonneoplastic lesions as presented in Tables A1 and A4 are given as the number of animals bearing such lesions at a specific anatomic site and the number of animals with that site examined microscopically. For calculation of statistical significance, the incidences of most neoplasms (Tables A3a, A3b, and A3c) and all nonneoplastic lesions are given as the numbers of animals affected at each site examined microscopically. However, when macroscopic examination was required to detect neoplasms in certain tissues (e.g., harderian gland, intestine, mammary gland, and skin) before microscopic evaluation, or when neoplasms had multiple potential sites of occurrence (e.g., leukemia or lymphoma), the denominators consist of the number of animals on which a necropsy was performed. Tables A3a, A3b, and A3c also give the survival-adjusted neoplasm rate for each group and each site-specific neoplasm, i.e., the Kaplan-Meier estimate of the neoplasm incidence that would have been observed at the end of the study in the absence of mortality from all other competing risks (Kaplan and Meier, 1958).

Analysis of Neoplasm Incidences

The majority of neoplasms in this study were considered to be incidental to the cause of death or not rapidly lethal. Thus, the primary statistical method used was logistic regression analysis, which assumed that the diagnosed neoplasms were discovered as the result of death from an unrelated cause and thus did not affect the risk of death. In this approach, neoplasm prevalence was modeled as a logistic function of chemical exposure and time. Both linear and quadratic terms in time were incorporated initially, and the quadratic term was eliminated if the fit of the model was not significantly enhanced. The neoplasm incidences of dosed and control groups were compared on the basis of the likelihood score test for the regression coefficient of dose. This method of adjusting for intercurrent mortality is the prevalence analysis of Dinse and Lagakos (1983), further described and illustrated by Dinse and Haseman (1986). When neoplasms are incidental, this comparison of the time-specific neoplasm prevalences also provides a comparison of the time-specific neoplasm incidences (McKnight and Crowley, 1984).

In addition to logistic regression, other methods of statistical analysis were used, and the results of these tests are summarized in the appendixes. These methods include the life table test (Cox, 1972; Tarone, 1975), appropriate for rapidly lethal neoplasms, and the Fisher exact test (Armitage, 1971; Gart *et al.*, 1979), a procedure based on the overall proportion of neoplasm-bearing animals.

Tests of significance included pairwise comparisons of the dosed group with each group of controls. Continuity-corrected tests were used in the analysis of neoplasm incidence, and reported P values are one sided. The procedures described in the preceding paragraphs were also used to evaluate selected nonneoplastic lesions. For further discussion of these statistical methods, refer to Haseman (1984).

Analysis of Nonneoplastic Lesion Incidences

Because all nonneoplastic lesions in this study were considered to be incidental to the cause of death or not rapidly lethal, the primary statistical analysis used was a logistic regression analysis in which nonneoplastic lesion prevalence was modeled as a logistic function of chemical exposure and time.

Analysis of Continuous Variables

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

QUALITY ASSURANCE METHODS

The 2-year study was conducted in compliance with Food and Drug Administration Good Laboratory Practice Regulations (21 CFR, Part 58). In addition, as records from the 2-year study were submitted to the NTP Archives, this study was audited retrospectively by an independent quality assurance contractor. Separate audits covering completeness and accuracy of the pathology data, pathology specimens, final pathology tables, and a draft of this NTP Technical Report were conducted. 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, so all comments had been resolved or were otherwise addressed during the preparation of this Technical Report.

RESULTS

MICE

30-DAY STUDY

All mice survived to the end of the study (Table 2). The final mean body weights and body weight gains of the dosed groups were similar to those of the vehicle control group. Abnormalities noted in the vaginal area after dosing included vaginal plugs, secretions, and swelling. These vaginal changes were minimal to mild and occurred in vehicle controls as well as in dosed mice. Restraint of mice after dosing appeared to eliminate vaginal secretions but increased both the incidence of vaginal irritation and the severity of vaginal opening swelling. At necropsy, mildly enlarged uterine horns were observed in 10 vehicle control mice, in three 25% mice, and in seven 25% (restrained) mice. No chemical-related lesions were observed.

TABLE 2
Survival and Body Weights of Mice in the 30-Day Intravaginal Study of Polyvinyl Alcohol

Dose (%)	Survival[a]	Mean Body Weight[b] (g)			Final Weight Relative to Controls (%)
		Initial	Final	Change	
Female					
0	50/50	19.8 ± 0.1	23.0 ± 0.2	3.3 ± 0.2	
25	50/50	20.0 ± 0.1	23.2 ± 0.2	3.2 ± 0.2	101
25 (restrained)	50/50	19.9 ± 0.2	23.4 ± 0.2	3.5 ± 0.2	102

[a] Number of animals surviving at 30 days/number initially in group
[b] Weights and weight changes are given as mean ± standard error. Differences from the control group were not significant by Dunnett's test.

Dose Selection Rationale: A one-species study was considered adequate to indicate possible toxicity or carcinogenicity from intravaginal polyvinyl alcohol administration. The mouse rather than the rat was chosen as the most appropriate rodent species because it was felt that retention time of the dissolved polyvinyl alcohol might be better in the smaller vagina of the mouse. An untreated control group in addition to a vehicle control group was used in the 2-year study in order to determine whether there were effects from intravaginal dosing alone because this dosing route had not been used previously. The 30-day study established that 0.02 mL (20 μL) of a 25% aqueous solution of polyvinyl alcohol (molecular weight approximately 24,000) was the maximum dose volume and concentration that could be administered based on the viscosity of the material and the size of the vagina in 6- to 7-week-old mice. There was no evidence of adverse effects from this maximum dose volume and concentration in the 30-day study. Administration of 20 μL of a 25% solution resulted in an average dose of 250 mg/kg at the start of the study when the average weight of the mice was 20 g and an average dose of 83 mg/kg on week 85 when the average weight of the mice was 60 g.

2-YEAR STUDY

Survival

Estimates of 2-year survival probabilities for female mice are shown in Table 3 and in the Kaplan-Meier survival curves (Figure 1). Survival of dosed mice was similar to that of the untreated control and vehicle control groups.

TABLE 3
Survival of Female Mice in the 2-Year Intravaginal Study of Polyvinyl Alcohol

	Untreated Control	Vehicle Control	25%
Animals initially in study	100	100	100
Accidental deaths[a]	10	4	5
Moribund	19	25	13
Natural deaths	24	20	21
Animals surviving to study termination	47	51	61
Percent probability of survival at end of study[b]	53	53	64
Mean survival (days)[c]	645	674	676
Survival analysis[d]			P=0.142N
Survival analysis[e]			P=0.158N

[a] Censored from survival analyses
[b] Kaplan-Meier determinations
[c] Mean of all deaths (uncensored, censored, and terminal sacrifice)
[d] The result of the life table pairwise comparison (Cox, 1972) with the untreated control group. Lower mortality in the dosed group is indicated by **N**.
[e] The result of the life table pairwise comparison (Cox, 1972) with the vehicle control group. Lower mortality in the dosed group is indicated by **N**.

Body Weights and Clinical Findings

The final mean body weight of vehicle control mice was less than that of the untreated control group (Figure 2 and Table 4). The mean body weights of the dosed mice were less than those of the untreated controls from week 17 until the end of the study. The only clinical finding was vaginal irritation, observed in six mice in the vehicle control group and 11 mice in the dosed group.

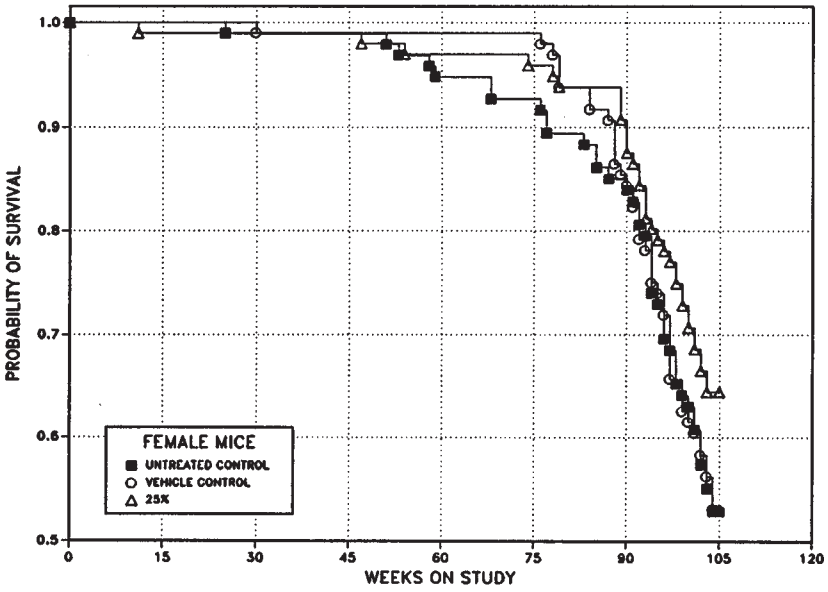


FIGURE 1
Kaplan-Meier Survival Curves for Female Mice Administered Polyvinyl Alcohol Intravaginally for 2 Years

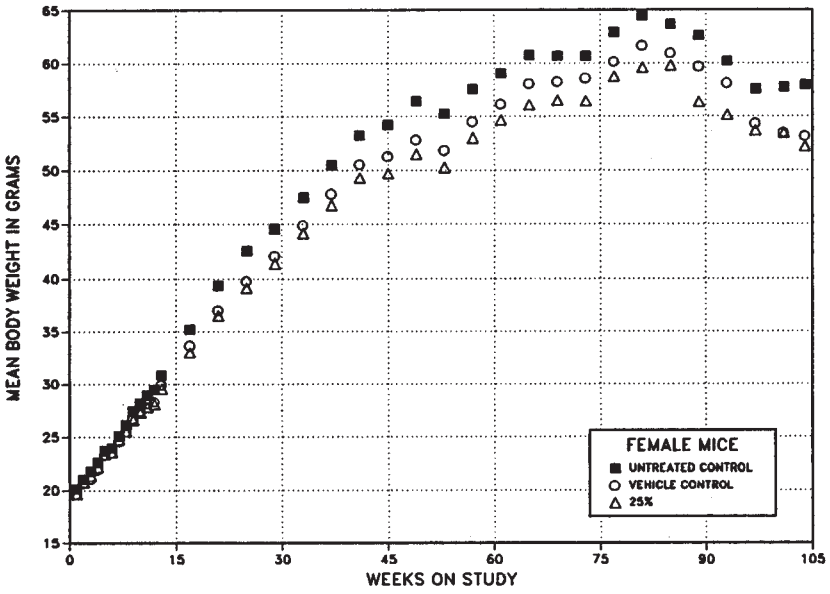


FIGURE 2
Growth Curves for Female Mice Administered Polyvinyl Alcohol Intravaginally for 2 Years

TABLE 4
Mean Body Weights and Survival of Female Mice in the 2-Year Intravaginal Study of Polyvinyl Alcohol

Weeks on Study	Untreated Control		Vehicle Control			25%		
	Av. Wt. (g)	No. of Survivors	Av. Wt. (g)	Wt. (% of untreated controls)	No. of Survivors	Av. Wt. (g)	Wt. (% of untreated controls)	No. of Survivors
1	20.2	100	19.6	97	100	19.7	98	100
2	21.1	100	20.7	98	100	20.8	99	100
3	21.8	100	21.1	97	100	21.4	98	100
4	22.7	100	22.0	97	100	22.2	98	100
5	23.7	100	23.3	98	100	23.4	99	100
6	24.0	100	23.5	98	100	23.6	98	100
7	25.1	100	24.6	98	100	24.8	99	100
8	26.1	100	25.5	98	100	25.5	98	100
9	27.4	100	26.7	97	100	26.6	97	100
10	28.2	100	27.4	97	100	27.3	97	100
11	28.9	99	28.2	98	100	27.8	96	100
12	29.5	99	28.3	96	100	28.1	95	99
13	30.9	99	29.9	97	100	29.6	96	99
17	35.2	98	33.7	96	100	33.1	94	98
21	39.4	98	37.0	94	100	36.5	93	98
25	42.6	97	39.8	93	100	39.1	92	98
29	44.6	96	42.1	94	100	41.4	93	98
33	47.5	96	44.9	95	99	44.2	93	98
37	50.5	96	47.8	95	99	46.8	93	98
41	53.3	96	50.5	95	99	49.3	93	98
45	54.3	96	51.3	95	99	49.7	92	98
49	56.4	96	52.8	94	96	51.5	91	96
53	55.2	94	51.8	94	96	50.3	91	96
57	57.6	93	54.5	95	96	53.0	92	96
61	59.1	91	56.2	95	96	54.7	93	95
65	60.8	90	58.1	96	96	56.1	92	95
69	60.7	88	58.3	96	95	56.5	93	95
73	60.7	87	58.6	97	95	56.5	93	94
77	62.9	84	60.1	96	94	58.8	94	92
81	64.5	82	61.7	96	90	59.6	92	90
85	63.7	80	61.0	96	88	59.8	94	90
89	62.6	77	59.7	95	83	56.4	90	90
93	60.2	73	58.1	97	76	55.2	92	80
97	57.6	63	54.3	94	69	53.7	93	74
101	57.8	57	53.5	93	59	53.5	93	66
104	58.0	47	53.2	92	52	52.2	90	61
Mean for weeks								
1-13	25.4		24.7	97		24.7	97	
14-52	47.1		44.4	94		43.5	92	
53-104	60.1		57.1	95		55.5	92	

Pathology and Statistical Analyses

This section describes the statistically significant or biologically noteworthy changes in the incidences of nonneoplastic lesions of the reproductive tract (clitoral gland, ovary, uterus, and vagina) and other organs. There were no neoplasms that were considered possibly related to polyvinyl alcohol. Summaries of the incidences of neoplasms and nonneoplastic lesions, individual animal tumor diagnoses, and statistical analyses of primary neoplasms that occurred with an incidence of at least 5% in at least one animal group are presented in Appendix A.

Reproductive Tract: There were no neoplasms observed in the reproductive tract of mice that were considered related to polyvinyl alcohol treatment. The incidences and severities of nonneoplastic lesions of the reproductive tract of mice in the dosed group were similar to those in the vehicle control and untreated control groups (Tables 5 and A4). None of the reproductive tract nonneoplastic lesions were related to chemical treatment.

TABLE 5
Incidences of Selected Nonneoplastic Lesions of the Reproductive Tract of Female Mice in the 2-Year Intravaginal Study of Polyvinyl Alcohol

	Untreated Control		Vehicle Control		25%	
Clitoral gland[a]	89		81		83	
Atrophy[b]	29	(1.8)[c]	26	(1.6)	18	(1.8)
Hyperplasia	4	(1.8)	8	(2.0)	10	(1.5)
Chronic inflammation	2	(4.0)	1	(4.0)	0	
Ovary	95		97		97	
Cyst	13	(2.2)	13	(2.7)	15	(2.4)
Lymphoid hyperplasia	0		1	(3.0)	0	
Tubulostromal hyperplasia	0		0		1	(3.0)
Acute or chronic inflammation	1	(4.0)	2	(4.0)	2	(4.0)
Thrombosis	2	(4.0)	2	(3.5)	1	(3.0)
Uterus	100		100		100	
Hydrometra	7	(3.9)	2	(4.0)	2	(3.0)
Chronic inflammation	3	(2.7)	1	(3.0)	0	
Endometrial angiectasis	1	(2.0)	1	(3.0)	0	
Endometrial cystic hyperplasia	90	(2.9)	97	(3.1)	98	(3.0)
Vagina	97		99		99	
Acute, chronic, or epithelial inflammation	0		5	(2.6)	1	(3.0)
Epithelial hyperplasia	0		1	(3.0)	0	

[a] Number of animals with organ examined microscopically
[b] Number of animals with lesion. Incidences in the 25% group were not significantly different from those in the vehicle control group; incidences in the vehicle control group were not significantly different from those in the untreated control group.
[c] Average severity grade of lesions in affected animals: 1=minimal, 2=mild, 3=moderate, 4=marked

Other Organs: Incidences of chronic inflammation of the pancreas (untreated control, 18/97; vehicle control, 40/95; 25%, 36/98) and thymic atrophy (66/98, 82/93, 79/99) in the vehicle control and dosed groups were greater than those in the untreated control group (Table A4). Neither of these increased incidences of nonneoplastic lesions were considered related to chemical treatment, but because they occurred in intravaginally dosed mice, they may have been associated with the dosing method.

DISCUSSION AND CONCLUSIONS

It is estimated that hundreds of thousands of women in the United States use a vaginal contraceptive film (VCF) each year (Apothecus, Inc.). VCF is composed of 67% polyvinyl alcohol along with a spermicide and is designed to rapidly dissolve in the vagina. The average dose of polyvinyl alcohol from a single use of intravaginal VCF in a 55-kg woman is 3 mg/kg. In the present 30-day and 2-year studies, daily doses of intravaginal polyvinyl alcohol solution in female mice ranged from 83 to 250 mg/kg. There were no significant differences in survival, body weights, clinical findings, or neoplasms or nonneoplastic lesions between vehicle control and dosed mice in the current study.

The NTP historical database at present does not list any agents for which the vagina was a target for neoplasm induction. However, current studies of AZT in mice indicate that the mouse is susceptible to neoplasm induction at this site (NTP, 1998). The 18 studies in the historical database in which either the uterus or cervix was the site of neoplasm induction were equally distributed between mice and rats. In the current study there was no evidence of neoplasm induction in the reproductive tract or other organs of mice administered a daily intravaginal dose of 20 μL of a 25% solution of polyvinyl alcohol (molecular weight approximately 24,000) for 2 years. Nonneoplastic lesions of the reproductive tract in dosed mice were few in number and did not differ in severity or incidence from those in the vehicle control group.

In addition to concern about the reproductive tract, systemic absorption studies in rats suggested that the liver and kidneys might also be exposed to polyvinyl alcohol after intravaginal administration (Hall and Hall, 1963; Sanders and Matthews, 1990). In the current study, incidences of neoplasms and nonneoplastic lesions of the liver in dosed mice were not significantly greater than those in the vehicle control mice. Incidences of atrophy, clear cell foci, and glycogen depletion of the liver were greater in vehicle control and dosed mice than in untreated control mice, but these lesions commonly occur spontaneously and their biologic significance is unknown. In rats, subcutaneous injection of polyvinyl alcohol (molecular weight 35,000 to 240,000) has been used to create a condition of benign glomerulopathy with thickening of the glomerular basement membrane but without alteration of the glomerular filtration rate (Sterzel *et al.*, 1983; Mauer *et al.*, 1985). In the current study with intravaginally administered polyvinyl alcohol in mice, no differences between the kidneys of untreated controls, vehicle controls, and dosed mice were detected by light microscopy.

Incidences of chronic inflammation of the pancreas and of thymic atrophy in untreated controls were less than those in either vehicle control or dosed mice. Both are common spontaneous lesions. Body weights of untreated controls were greater than those of either vehicle control or dosed mice throughout most of the study, perhaps indicative of an effect associated with intravaginal dosing.

CONCLUSIONS

Under the conditions of this 2-year study, there was *no evidence of carcinogenic activity** of polyvinyl alcohol (molecular weight approximately 24,000) in female B6C3F$_1$ mice administered 20 μL of a 25% solution intravaginally. There were no neoplasms or nonneoplastic lesions considered related to treatment with polyvinyl alcohol.

---

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

REFERENCES

Anderson, D.L., and Shea, M. (1961). Tissue response to polyvinyl alcohol implants in rabbits. *Am. J. Ophthalmol.* **51**, 1200-1203.

Armitage, P. (1971). *Statistical Methods in Medical Research*, pp. 362-365. John Wiley and Sons, New York.

Boorman, G.A., Montgomery, C.A., Jr., Eustis, S.L., Wolfe, M.J., McConnell, E.E., and Hardisty, J.F. (1985). Quality assurance in pathology for rodent carcinogenicity studies. In *Handbook of Carcinogen Testing* (H.A. Milman and E.K. Weisburger, Eds.), pp. 345-357. Noyes Publications, Park Ridge, NJ.

Chemical Economics Handbook (1996). Product Review Polyvinyl Alcohol. 580.1810C. SRI International.

Cobler, J., Long, M., and Owens, E. (1968). Analytical chemistry of vinyl film-forming polymers. *Sci. Technol. Polym. Films*, 702-812. Interscience Publishers, New York.

Code of Federal Regulations (CFR) **21**, Part 58.

Cosmetic Ingredient Review (CIR) (1996). Final Report. Polyvinyl Alcohol. Expert Panel of the Cosmetic Ingredient Review, Washington, DC.

Cox, D.R. (1972). Regression models and life-tables. *J. R. Stat. Soc.* **B34**, 187-220.

Dasler, W., and Milliser, R.V. (1963). Induction of tumors in rats by subcutaneous implants of surgical sponges. *Experientia* **19**, 424-426.

Dinse, G.E., and Haseman, J.K. (1986). Logistic regression analysis of incidental-tumor data from animal carcinogenicity experiments. *Fundam. Appl. Toxicol.* **6**, 44-52.

Dinse, G.E., and Lagakos, S.W. (1983). Regression analysis of tumour prevalence data. *Appl. Statist.* **32**, 236-248.

Dukes, C.E., and Mitchley, B.C.V. (1962). Polyvinyl sponge implants: Experimental and clinical observations. *Br. J. Plast. Surg.* **16**, 225-235.

Dunnett, C.W. (1955). A multiple comparison procedure for comparing several treatments with a control. *J. Am. Stat. Assoc.* **50**, 1096-1121.

Fassihi, A.R., and Naidoo, N.T. (1989). Irritation associated with tear-replacement ophthalmic drops. A pharmaceutical and subjective investigation. *S. Afr. Med. J.* **75**, 233-235.

Fisher, B.E. (1996). Dissolving medical waste. *Environ. Health Perspect.* **104**, 708-710.

Gart, J.J., Chu, K.C., and Tarone, R.E. (1979). Statistical issues in interpretation of chronic bioassay tests for carcinogenicity. *JNCI* **62**, 957-974.

Grant, W.M. (1974). *Toxicology of the Eye*, 2nd ed., pp. 849-850. Charles C. Thomas, Springfield, IL.

Hall, C.E., and Hall, O. (1963). Polyvinyl alcohol nephrosis: Relationship of degree of polymerization to pathophysiologic effects. *Proc. Soc. Exp. Biol. Med.* **112**, 86-91.

Hamit, H.F. (1957). Implantation of plastics in the breast. Complications in a case. *Arch. Surg.* **75**, 224-229.

Haseman, J.K. (1984). Statistical issues in the design, analysis and interpretation of animal carcinogenicity studies. *Environ. Health Perspect.* **58**, 385-392.

Hawley's Condensed Chemical Dictionary (1987). 11th ed. (N.I. Sax and R.J. Lewis, Sr., Eds.), p. 945. Van Nostrand Reinhold, New York.

Hollander, M., and Wolfe, D.A. (1973). *Nonparametric Statistical Methods*, pp. 120-123. John Wiley and Sons, New York.

Hueper, W.C. (1959). Carcinogenic studies on water-soluble and insoluble macromolecules. *Arch. Pathol.* **67**, 589-617.

Hulman, G., and Kirkham, J.S. (1990). Ivalon (polyvinyl alcohol) sponge presenting as an extrarectal mass. *Histopathology* **16**, 502-504.

International Agency for Research on Cancer (IARC) (1979). IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans. Vinyl Acetate, Polyvinyl Acetate and Polyvinyl Alcohol, Vol. 19. IARC, Lyon, France.

Johnson, I.R., Macpherson, M.B.A., Welch, C.C., and Filshie, G.M. (1985). A comparison of Lamicel and prostaglandin E_2 vaginal gel for cervical ripening before induction of labor. *Am. J. Obstet. Gynecol.* **151**, 604-607.

Kaplan, E.L., and Meier, P. (1958). Nonparametric estimation from incomplete observations. *J. Am. Stat. Assoc.* **53**, 457-481.

Krishna, N., and Mitchell, B. (1965). Polyvinyl alcohol as an ophthalmic vehicle. Effect on ocular structures. *Am. J. Ophthalmol.* **59**, 860-864.

Lanman, T.H., Martin, N.A., and Vinters, H.V. (1988). The pathology of encephalic arteriovenous malformations treated by prior embolotherapy. *Neuroradiology* **30**, 1-10.

Lefaux, R. (1968). *Practical Toxicology of Plastics* (P.P. Hopf, Ed.), pp. 19-20, 48-60, 200, 282-284. CRC Press, Cleveland, OH.

McConnell, E.E., Solleveld, H.A., Swenberg, J.A., and Boorman, G.A. (1986). Guidelines for combining neoplasms for evaluation of rodent carcinogenesis studies. *JNCI* **76**, 283-289.

McKnight, B., and Crowley, J. (1984). Tests for differences in tumor incidence based on animal carcinogenesis experiments. *J. Am. Stat. Assoc.* **79**, 639-648.

Maronpot, R.R., and Boorman, G.A. (1982). Interpretation of rodent hepatocellular proliferative alterations and hepatocellular tumors in chemical safety assessment. *Toxicol. Pathol.* **10**, 71-80.

Mauer, S.M., Steffes, M.W., and Brown, D.M. (1985). Effects of mesangial localization of polyvinyl alcohols on glomerular basement membrane thickness. *Kidney Int.* **27**, 751-755.

The Merck Index (1976). 9th ed. (M. Windholz, Ed.), p. 706. Merck and Company, Rahway, NJ.

The Merck Index (1989). 11th ed. (S. Budavari, Ed.), p. 1208. Merck and Company, Rahway, NJ.

National Cancer Institute (NCI) (1976). Guidelines for Carcinogen Bioassay in Small Rodents. Technical Report Series No. 1. NIH Publication No. 76-801. U.S. Department of Health, Education, and Welfare, Public Health Service, National Institutes of Health, Bethesda, MD.

National Institutes of Health (NIH) (1978). Open Formula Rat and Mouse Ration (NIH-07). Specification NIH-11-1335. U.S. Department of Health, Education, and Welfare, Public Health Service, National Institutes of Health, Bethesda, MD.

National Toxicology Program (NTP) (1998). Toxicology and Carcinogenesis Studies of AZT (CAS No. 30516-87-1) and AZT/α-Interferon A/D in $B6C3F_1$ Mice (Gavage Studies). Technical Report Series No. 469. NIH Publication No. 98-3959. U.S. Department of Health and Human Services, Public Health Service, National Institutes of Health, Research Triangle Park, NC. (in press)

Oppenheimer, B.S., Oppenheimer, E.T., Danishefsky, I., Stout, A.P., and Eirich, F.R. (1955). Further studies of polymers as carcinogenic agents in animals. *Cancer Res.* **15**, 333-340.

Roe, F.J.C., Dukes, C.E., and Mitchley, B.C.V. (1967). Sarcomas at the site of implantation of a polyvinyl plastic sponge: Incidence reduced by use of thin implants. *Biochem. Pharmacol.* **16**, 647-650.

Russell, F.E., Simmers, M.H., Hirst, A.E., and Pudenz, R.H. (1959). Tumors associated with embedded polymers. *J. Natl. Cancer Inst.* **23**, 305-311.

Sanders, J.M., and Matthews, H.B. (1990). Vaginal absorption of polyvinyl alcohol in Fischer 344 rats. *Hum. Exp. Toxicol.* **9**, 71-77.

Shibuya, T., Tanaka, N., Katoh, M., Matsuda, Y.T., and Morita, K. (1985). Mutagenicity testing of ST-film with the Ames test, chromosome test *in vitro* and micronucleus test in female mice. *J. Toxicol. Sci.* **10**, 135-141.

Sterzel, R.B., Eisenbach, G.M., Seiler, M.W., and Hoyer, J.R. (1983). Uptake of polyvinyl alcohol by macrophages in the glomerular mesangium of rats. Histologic and functional studies. *Am. J. Pathol.* **111**, 247-257.

Tarone, R.E. (1975). Tests for trend in life table analysis. *Biometrika* **62**, 679-682.

Walter, J.B., and Chiaramonte, L.G. (1965). The tissue responses of the rat to implanted ivalon, etheron, and polyfoam plastic sponges. *Br. J. Surg.* **52**, 49-54.

Williams, D.A. (1971). A test for differences between treatment means when several dose levels are compared with a zero dose control. *Biometrics* **27**, 103-117.

Williams, D.A. (1972). The comparison of several dose levels with a zero dose control. *Biometrics* **28**, 519-531.

Yamaoka, T., Tabata, Y., and Ikada, Y. (1995). Comparison of body distribution of poly(vinyl alcohol) with other water-soluble polymers after intravenous administration. *J. Pharm. Pharmacol.* **47**, 479-486.

Zaitsev, N.A. and Skachkova, I.N. and Sechenov, I.M. (1986). Substantiation of hygienic standards for some polymeric compounds in water with the use of gradual standardization. *Gig. Sanit.* **10**, 75-76.

APPENDIX A
SUMMARY OF LESIONS IN FEMALE MICE IN THE 2-YEAR INTRAVAGINAL STUDY OF POLYVINYL ALCOHOL

TABLE A1
Summary of the Incidence of Neoplasms in Female Mice in the 2-Year Intravaginal Study of Polyvinyl Alcohol[a]

	Untreated Control	Vehicle Control	25%
Disposition Summary			
Animals initially in study	100	100	100
Early deaths			
Accidental deaths	10	4	5
Moribund	19	25	13
Natural deaths	24	20	21
Survivors			
Terminal sacrifice	47	51	61
Animals examined microscopically	100	100	100
Alimentary System			
Gallbladder	(76)	(87)	(79)
Hepatocholangiocarcinoma, metastatic, liver			1 (1%)
Intestine small, duodenum	(88)	(90)	(92)
Polyp adenomatous	1 (1%)	1 (1%)	
Intestine small, jejunum	(89)	(90)	(91)
Squamous cell carcinoma, metastatic, stomach, forestomach	1 (1%)		
Intestine small, ileum	(88)	(90)	(92)
Liver	(99)	(99)	(100)
Hepatocellular carcinoma	11 (11%)	18 (18%)	20 (20%)
Hepatocellular adenoma	25 (25%)	43 (43%)	36 (36%)
Hepatocellular adenoma, multiple	30 (30%)	13 (13%)	19 (19%)
Hepatocholangiocarcinoma			2 (2%)
Histiocytic sarcoma	4 (4%)	2 (2%)	1 (1%)
Serosa, fibrosarcoma, metastatic, skeletal muscle	1 (1%)		
Mesentery	(33)	(25)	(36)
Carcinoma, metastatic, islets, pancreatic		1 (4%)	
Hepatocholangiocarcinoma, metastatic, liver			2 (6%)
Histiocytic sarcoma	1 (3%)		
Rhabdomyosarcoma, metastatic, skeletal muscle	1 (3%)		
Sarcoma	1 (3%)		
Squamous cell carcinoma, metastatic, stomach, forestomach	1 (3%)		
Yolk sac carcinoma, metastatic, ovary			1 (3%)
Pancreas	(97)	(95)	(98)
Adenoma	1 (1%)		
Carcinoma		1 (1%)	
Fibrosarcoma, metastatic, skeletal muscle	1 (1%)		
Hepatocholangiocarcinoma, metastatic, liver			1 (1%)
Squamous cell carcinoma, metastatic, stomach, forestomach	1 (1%)		
Salivary glands	(99)	(97)	(100)
Stomach, forestomach	(94)	(93)	(97)
Squamous cell carcinoma	1 (1%)		
Squamous cell papilloma	2 (2%)		
Stomach, glandular	(93)	(93)	(96)
Leiomyosarcoma			1 (1%)
Cardiovascular System			
Heart	(100)	(99)	(100)
Hemangiosarcoma	1 (1%)		
Hepatocellular carcinoma, metastatic, liver	1 (1%)		

TABLE A1
Summary of the Incidence of Neoplasms in Female Mice in the 2-Year Intravaginal Study of Polyvinyl Alcohol

	Untreated Control	Vehicle Control	25%
Endocrine System			
Adrenal cortex	(100)	(94)	(97)
Carcinoma, metastatic, islets, pancreatic		1 (1%)	
Hepatocellular carcinoma, metastatic, liver		1 (1%)	
Histiocytic sarcoma	1 (1%)		
Squamous cell carcinoma, metastatic, stomach, forestomach	1 (1%)		
Capsule, adenoma		1 (1%)	
Capsule, carcinoma			1 (1%)
Adrenal medulla	(99)	(94)	(92)
Hepatocholangiocarcinoma, metastatic, liver			1 (1%)
Pheochromocytoma benign		2 (2%)	
Islets, pancreatic	(97)	(94)	(97)
Adenoma		3 (3%)	1 (1%)
Hepatocholangiocarcinoma, metastatic, liver			1 (1%)
Parathyroid gland	(59)	(59)	(69)
Adenoma			1 (1%)
Pituitary gland	(88)	(86)	(84)
Pars distalis, adenoma	13 (15%)	9 (10%)	10 (12%)
Pars intermedia, adenoma	1 (1%)		
Thyroid gland	(100)	(96)	(100)
C-cell, adenoma		1 (1%)	
Follicular cell, adenoma	8 (8%)	9 (9%)	11 (11%)
Follicular cell, carcinoma		1 (1%)	
General Body System			
Tissue NOS	(1)		
Squamous cell carcinoma, metastatic, stomach, forestomach	1 (100%)		
Genital System			
Ovary	(95)	(97)	(97)
Cystadenoma	6 (6%)	5 (5%)	3 (3%)
Granulosa cell tumor benign	1 (1%)	2 (2%)	
Hemangiosarcoma	1 (1%)		
Hepatocellular carcinoma, metastatic, liver	1 (1%)	1 (1%)	
Hepatocholangiocarcinoma, metastatic, liver			1 (1%)
Histiocytic sarcoma	3 (3%)	1 (1%)	
Liposarcoma		1 (1%)	
Luteoma	1 (1%)		2 (2%)
Squamous cell carcinoma, metastatic, stomach, forestomach	1 (1%)		
Teratoma benign			1 (1%)
Yolk sac carcinoma			2 (2%)
Uterus	(100)	(100)	(100)
Carcinoma			1 (1%)
Deciduoma NOS			1 (1%)
Granular cell tumor benign	1 (1%)	1 (1%)	
Hamartoma	1 (1%)		
Hepatocellular carcinoma, metastatic, liver	1 (1%)		
Histiocytic sarcoma	4 (4%)	2 (2%)	1 (1%)
Leiomyoma		1 (1%)	
Polyp stromal		1 (1%)	3 (3%)
Sarcoma stromal		2 (2%)	
Squamous cell carcinoma, metastatic, stomach, forestomach	1 (1%)		
Serosa, fibrosarcoma, metastatic, skeletal muscle	1 (1%)		
Vagina	(97)	(99)	(99)
Histiocytic sarcoma			1 (1%)

TABLE A1
Summary of the Incidence of Neoplasms in Female Mice in the 2-Year Intravaginal Study of Polyvinyl Alcohol

	Untreated Control	Vehicle Control	25%
Hematopoietic System			
Bone marrow	(100)	(98)	(100)
Histiocytic sarcoma		1 (1%)	
Lymph node	(15)	(21)	(21)
Liposarcoma		1 (5%)	
Plasma cell tumor benign			1 (5%)
Squamous cell carcinoma, metastatic, stomach, forestomach	1 (7%)		
Iliac, histiocytic sarcoma	1 (7%)	1 (5%)	
Inguinal, fibrosarcoma, metastatic, skeletal muscle	1 (7%)		
Mediastinal, fibrosarcoma, metastatic, skeletal muscle	1 (7%)		
Mediastinal, histiocytic sarcoma	1 (7%)		
Mediastinal, sarcoma, metastatic, uncertain primary site		1 (5%)	
Renal, histiocytic sarcoma	1 (7%)	1 (5%)	
Lymph node, mandibular	(92)	(94)	(93)
Plasma cell tumor benign			1 (1%)
Lymph node, mesenteric	(90)	(93)	(93)
Fibrosarcoma, metastatic, skeletal muscle	1 (1%)		
Hepatocellular carcinoma, metastatic, liver	1 (1%)	1 (1%)	
Hepatocholangiocarcinoma, metastatic, liver			1 (1%)
Histiocytic sarcoma	4 (4%)		
Rhabdomyosarcoma, metastatic, skeletal muscle	1 (1%)		
Sarcoma, metastatic, uncertain primary site		1 (1%)	
Squamous cell carcinoma, metastatic, stomach, forestomach	1 (1%)		
Spleen	(98)	(96)	(98)
Fibrosarcoma, metastatic, skeletal muscle	1 (1%)		
Histiocytic sarcoma	2 (2%)		
Sarcoma, metastatic, uncertain primary site		1 (1%)	
Thymus	(98)	(93)	(99)
Alveolar/bronchiolar carcinoma, metastatic, lung	1 (1%)		
Fibrosarcoma, metastatic, skin		1 (1%)	
Fibrosarcoma, metastatic, skeletal muscle	1 (1%)		
Hepatocellular carcinoma, metastatic, liver	1 (1%)		
Hepatocholangiocarcinoma, metastatic, liver			1 (1%)
Thymoma benign	1 (1%)		1 (1%)
Integumentary System			
Mammary gland	(93)	(92)	(91)
Adenoma	1 (1%)		
Carcinoma			1 (1%)
Skin	(98)	(98)	(100)
Fibrosarcoma	1 (1%)		
Sarcoma	1 (1%)		
Subcutaneous tissue, fibrosarcoma	1 (1%)	2 (2%)	
Subcutaneous tissue, fibrous histiocytoma	1 (1%)		
Subcutaneous tissue, pinna, fibrosarcoma			1 (1%)
Musculoskeletal System			
Bone	(100)	(100)	(100)
Pelvis, sarcoma			1 (1%)
Skeletal muscle	(9)	(10)	(8)
Fibrosarcoma, metastatic, skeletal muscle	1 (11%)		
Hepatocholangiocarcinoma, metastatic, liver			1 (13%)
Rhabdomyosarcoma	2 (22%)	2 (20%)	2 (25%)
Sarcoma			1 (13%)
Squamous cell carcinoma, metastatic, stomach, forestomach	1 (11%)		

TABLE A1
Summary of the Incidence of Neoplasms in Female Mice in the 2-Year Intravaginal Study of Polyvinyl Alcohol

	Untreated Control	Vehicle Control	25%
Nervous System			
Brain	(100)	(99)	(100)
Respiratory System			
Lung	(100)	(98)	(100)
Alveolar/bronchiolar adenoma	6 (6%)	7 (7%)	8 (8%)
Alveolar/bronchiolar carcinoma	3 (3%)	3 (3%)	5 (5%)
Carcinoma, metastatic, harderian gland	1 (1%)		
Fibrosarcoma, metastatic, skin		1 (1%)	
Hepatocellular carcinoma, metastatic, liver	4 (4%)	2 (2%)	
Hepatocholangiocarcinoma, metastatic, liver			2 (2%)
Histiocytic sarcoma	2 (2%)	1 (1%)	
Osteosarcoma, metastatic, tissue NOS	1 (1%)		
Sarcoma, metastatic, uncertain primary site		1 (1%)	1 (1%)
Yolk sac carcinoma, metastatic, ovary			1 (1%)
Nose	(100)	(100)	(100)
Carcinoma		1 (1%)	
Special Senses System			
Harderian gland	(5)	(11)	(6)
Adenoma	4 (80%)	9 (82%)	4 (67%)
Carcinoma	1 (20%)	2 (18%)	1 (17%)
Zymbal's gland		(3)	
Carcinoma		1 (33%)	
Urinary System			
Kidney	(100)	(98)	(100)
Adenoma		1 (1%)	
Histiocytic sarcoma	1 (1%)		
Urinary bladder	(96)	(96)	(98)
Histiocytic sarcoma		1 (1%)	
Systemic Lesions			
Multiple organs[b]	(100)	(100)	(100)
Histiocytic sarcoma	4 (4%)	2 (2%)	1 (1%)
Lymphoma malignant	13 (13%)	14 (14%)	18 (18%)
Neoplasm Summary			
Total animals with primary neoplasms[c]	78	82	88
Total primary neoplasms	145	160	161
Total animals with benign neoplasms	67	72	69
Total benign neoplasms	103	109	102
Total animals with malignant neoplasms	38	40	51
Total malignant neoplasms	42	51	58
Total animals with metastatic neoplasms	11	7	4
Total metastatic neoplasms	33	13	15
Total animals with malignant neoplasms of uncertain primary site		2	1
Total animals with uncertain neoplasms—benign or malignant			1
Total uncertain neoplasms			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 A2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Intravaginal Study of Polyvinyl Alcohol: Untreated Control

Number of Days on Study	0 6 7	1 1 0	1 6 8	1 7 5	3 5 0	3 5 7	3 6 5	4 0 0	4 1 0	4 4 1	4 7 3	4 7 6	4 8 3	5 1 1	5 2 9	5 3 0	5 3 8	5 3 9	5 8 1	5 9 2	5 9 5	5 9 5	6 0 6	6 2 5	6 3 4
Carcass ID Number	0 7 6	0 1 9	0 9 6	0 2 8	0 3 0	0 7 3	0 7 1	0 0 5	0 8 4	0 2 1	0 7 4	0 1 6	0 5 6	0 5 0	0 5 1	0 7 8	0 0 8	0 4 1	0 4 9	0 5 5	0 0 7	0 3 9	0 3 3	0 8 7	0 0 1
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder	+	+	A	+	+	A	+	A	A	A	I	+	A	A	+	I	A	+	+	+	A	A	A	+	A
Intestine large, colon	+	+	+	+	+	A	+	+	+	A	+	+	A	+	+	A	A	+	+	+	+	A	A	+	+
Intestine large, rectum	+	+	A	+	+	A	+	+	A	A	+	+	A	+	+	A	A	+	+	+	+	A	A	+	+
Intestine large, cecum	+	+	A	+	+	A	+	+	A	A	+	+	A	A	+	A	A	+	+	+	+	A	A	+	+
Intestine small, duodenum	+	+	A	+	+	A	+	+	A	A	+	+	A	A	+	A	A	+	+	+	+	A	A	+	+
Polyp adenomatous																				X					
Intestine small, jejunum	+	+	A	+	+	A	+	+	+	A	+	+	A	A	+	A	A	+	+	+	+	A	A	+	+
Squamous cell carcinoma, metastatic, stomach, forestomach									X																
Intestine small, ileum	+	+	A	+	+	A	+	+	A	A	+	+	A	A	+	A	A	+	+	+	+	A	A	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+
Hepatocellular carcinoma																	X								
Hepatocellular adenoma							X										X			X				X	X
Hepatocellular adenoma, multiple																									
Histiocytic sarcoma																					X				
Serosa, fibrosarcoma, metastatic, skeletal muscle																									
Mesentery							+		+		+		+		+				+						
Histiocytic sarcoma																									
Rhabdomyosarcoma, metastatic, skeletal muscle																									
Sarcoma																									
Squamous cell carcinoma, metastatic, stomach, forestomach									X																
Pancreas	+	+	+	+	+	A	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	A	+	+
Adenoma																									
Fibrosarcoma, metastatic, skeletal muscle																									
Squamous cell carcinoma, metastatic, stomach, forestomach									X																
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	A	+	+	+	A	+	+	+	A	+	+	A	+	+	+	+	A	+	+	+
Squamous cell carcinoma									X																
Squamous cell papilloma																									
Stomach, glandular	+	+	+	+	+	A	+	+	+	A	+	+	+	A	+	+	A	+	+	+	+	A	A	+	+
Cardiovascular System																									
Blood vessel																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																									
Hepatocellular carcinoma, metastatic, liver																	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 Female Mice in the 2-Year Intravaginal Study of Polyvinyl Alcohol: Untreated Control

Number of Days on Study	6 4 0	6 4 3	6 4 6	6 5 2	6 5 5	6 5 5	6 5 7	6 5 7	6 5 9	6 6 6	6 6 8	6 6 8	6 7 5	6 8 2	6 8 2	6 8 6	6 9 0	6 9 6	7 0 3	7 0 4	7 0 4	7 0 9	7 1 1	7 1 4	7 1 8
Carcass ID Number	0 2 6	0 1 5	0 6 0	0 6 6	0 1 3	0 6 5	0 1 0	0 9 2	0 0 3	0 7 0	0 2 3	0 9 4	0 9 3	0 6 9	0 8 8	0 8 5	0 5 8	0 3 8	0 8 3	0 8 0	0 9 8	0 2 9	0 5 4	0 2 4	0 0 2
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder	+	I	+	+	+	I	A	A	+	A	A	A	+	+	+	+	+	+	A	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	A
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	A
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	A
Polyp adenomatous																									
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	A
Squamous cell carcinoma, metastatic, stomach, forestomach																									
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	A
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular carcinoma		X				X					X							X							
Hepatocellular adenoma	X										X	X							X			X	X	X	
Hepatocellular adenoma, multiple							X			X			X		X	X				X					
Histiocytic sarcoma								X	X												X				
Serosa, fibrosarcoma, metastatic, skeletal muscle																						X			
Mesentery			+		+	+	+			+			+	+		+	+			+	+			+	+
Histiocytic sarcoma																					X				
Rhabdomyosarcoma, metastatic, skeletal muscle																									
Sarcoma																X									
Squamous cell carcinoma, metastatic, stomach, forestomach																									
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Fibrosarcoma, metastatic, skeletal muscle																						X			
Squamous cell carcinoma, metastatic, stomach, forestomach																									
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+
Squamous cell carcinoma																									
Squamous cell papilloma										X															
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+
Cardiovascular System																									
Blood vessel																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																									
Hepatocellular carcinoma, metastatic, liver																									

TABLE A2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Intravaginal Study of Polyvinyl Alcohol: Untreated Control

	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7
Number of Days on Study	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	3	3	3	3	3
	1	5	5	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	0	0	0	0	0
	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Carcass ID Number	2	4	6	0	1	1	2	3	4	4	4	4	5	6	7	7	7	8	9	9	1	1	2	3	3
	7	2	1	9	7	8	5	5	0	5	6	7	9	2	2	5	7	1	1	9	1	2	2	2	6
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Polyp adenomatous																									
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell carcinoma, metastatic, stomach, forestomach																									
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular carcinoma		X																		X	X				
Hepatocellular adenoma	X	X				X		X		X												X			
Hepatocellular adenoma, multiple			X				X		X				X	X	X	X	X	X	X		X		X	X	
Histiocytic sarcoma																									
Serosa, fibrosarcoma, metastatic, skeletal muscle																									
Mesentery											+		+	+	+		+	+			+	+			
Histiocytic sarcoma																									
Rhabdomyosarcoma, metastatic, skeletal muscle														X											
Sarcoma																									
Squamous cell carcinoma, metastatic, stomach, forestomach																									
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																X									
Fibrosarcoma, metastatic, skeletal muscle																									
Squamous cell carcinoma, metastatic, stomach, forestomach																									
Salivary glands	+	+	I	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell carcinoma																									
Squamous cell papilloma																			X						
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cardiovascular System																									
Blood vessel																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																									
Hepatocellular carcinoma, metastatic, liver																									

TABLE A2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Intravaginal Study of Polyvinyl Alcohol: Untreated Control

Number of Days on Study	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	
Carcass ID Number	0 3 7	0 4 3	0 4 8	0 5 3	0 5 7	0 6 4	0 6 7	0 6 8	0 8 2	0 8 6	0 8 9	0 9 5	0 0 4	0 1 4	0 2 0	0 3 1	0 3 4	0 4 4	0 5 2	0 5 6	0 6 3	0 7 9	0 9 0	0 9 7	1 0 0	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	100
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	+	I	+	+	+	+	+	+	I	+	+	+	+	+	76
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	92
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	89
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	88
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	88
Polyp adenomatous																										1
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	89
Squamous cell carcinoma, metastatic, stomach, forestomach																										1
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	88
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	99
Hepatocellular carcinoma			X															X				X				11
Hepatocellular adenoma							X					X	X				X			X		X			X	25
Hepatocellular adenoma, multiple		X	X	X	X			X	X	X					X	X		X	X							30
Histiocytic sarcoma																										4
Serosa, fibrosarcoma, metastatic, skeletal muscle																										1
Mesentery										+	+				+		+	+					+			33
Histiocytic sarcoma																										1
Rhabdomyosarcoma, metastatic, skeletal muscle																										1
Sarcoma																										1
Squamous cell carcinoma, metastatic, stomach, forestomach																										1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	97
Adenoma																										1
Fibrosarcoma, metastatic, skeletal muscle																										1
Squamous cell carcinoma, metastatic, stomach, forestomach																										1
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	99
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	94
Squamous cell carcinoma																										1
Squamous cell papilloma																										2
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	93
Cardiovascular System																										
Blood vessel				+																						1
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	100
Hemangiosarcoma				X																						1
Hepatocellular carcinoma, metastatic, liver																										1

TABLE A2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Intravaginal Study of Polyvinyl Alcohol: Untreated Control

Number of Days on Study	0 6 7	1 1 0	1 6 8	1 7 5	3 5 0	3 5 7	3 6 5	4 0 0	4 1 0	4 4 1	4 7 3	4 7 6	4 8 3	5 1 1	5 2 9	5 3 0	5 3 8	5 3 9	5 8 1	5 9 2	5 9 5	5 9 5	6 0 6	6 2 5	6 3 4
Carcass ID Number	0 7 6	0 1 9	0 9 6	0 2 8	0 3 0	0 7 3	0 7 1	0 0 5	0 8 4	0 2 1	0 7 4	0 1 6	0 0 6	0 5 0	0 5 1	0 7 8	0 0 8	0 4 1	0 4 9	0 5 5	0 0 7	0 3 9	0 3 3	0 8 7	0 0 1
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																									
Squamous cell carcinoma, metastatic, stomach, forestomach									X																
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islets, pancreatic	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+
Parathyroid gland	+	+	I	I	I	+	+	+	+	I	+	I	I	I	I	+	I	I	+	+	I	+	I	I	I
Pituitary gland	+	+	+	+	+	A	M	I	+	+	M	+	+	+	M	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma																									
Pars intermedia, adenoma																									
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell, adenoma																									
General Body System																									
Tissue NOS									+																
Squamous cell carcinoma, metastatic, stomach, forestomach									X																
Genital System																									
Clitoral gland	+	+	+	+	+	+	+	I	+	+	+	+	+	M	+	I	+	+	+	+	+	I	+	+	+
Ovary	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+
Cystadenoma															X										
Granulosa cell tumor benign																									
Hemangiosarcoma																				X					
Hepatocellular carcinoma, metastatic, liver																X									
Histiocytic sarcoma																					X				
Luteoma																									
Squamous cell carcinoma, metastatic, stomach, forestomach									X																
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Granular cell tumor benign																									
Hamartoma																									
Hepatocellular carcinoma, metastatic, liver																X									
Histiocytic sarcoma																					X				
Squamous cell carcinoma, metastatic, stomach, forestomach									X																
Serosa, fibrosarcoma, metastatic, skeletal muscle																									
Vagina	+	+	+	+	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node								+	+						+										
Squamous cell carcinoma, metastatic, stomach, forestomach									X																
Iliac, histiocytic sarcoma																									
Inguinal, fibrosarcoma, metastatic, skeletal muscle																									
Mediastinal, fibrosarcoma, metastatic, skeletal muscle																									
Mediastinal, histiocytic sarcoma																									
Renal, histiocytic sarcoma																									

TABLE A2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Intravaginal Study of Polyvinyl Alcohol: Untreated Control

Number of Days on Study	6 4 0	6 4 3	6 4 6	6 5 2	6 5 5	6 5 5	6 5 7	6 5 7	6 5 9	6 6 6	6 6 8	6 6 8	6 7 5	6 8 2	6 8 2	6 8 6	6 9 0	6 9 6	7 0 3	7 0 4	7 0 4	7 0 9	7 1 1	7 1 4	7 1 8
Carcass ID Number	0 2 6	0 1 5	0 6 0	0 6 6	0 1 3	0 6 5	0 1 0	0 9 2	0 0 3	0 7 0	0 2 3	0 9 4	0 9 3	0 6 9	0 8 8	0 8 5	0 5 8	0 3 8	0 8 3	0 8 0	0 9 8	0 2 9	0 5 4	0 2 4	0 0 2
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																					X				
Squamous cell carcinoma, metastatic, stomach, forestomach																									
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	I	+	+	+	+	+	+	+	+
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid gland	+	+	+	+	+	+	+	I	I	+	+	+	+	+	I	I	+	+	I	I	I	+	I	+	+
Pituitary gland	+	+	+	+	+	+	+	M	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	I	+
Pars distalis, adenoma							X							X			X								
Pars intermedia, adenoma																									
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell, adenoma																X									
General Body System																									
Tissue NOS																									
Squamous cell carcinoma, metastatic, stomach, forestomach																									
Genital System																									
Clitoral gland	I	+	+	+	+	+	+	+	+	I	I	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Ovary	+	+	+	+	+	+	+	+	+	+	I	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cystadenoma																		X					X		
Granulosa cell tumor benign																									
Hemangiosarcoma																									
Hepatocellular carcinoma, metastatic, liver																									
Histiocytic sarcoma								X	X																
Luteoma																									
Squamous cell carcinoma, metastatic, stomach, forestomach																									
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Granular cell tumor benign																									
Hamartoma																									
Hepatocellular carcinoma, metastatic, liver																									
Histiocytic sarcoma								X	X												X				
Squamous cell carcinoma, metastatic, stomach, forestomach																									
Serosa, fibrosarcoma, metastatic, skeletal muscle																						X			
Vagina	+		+	+	+	+	+	+	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node				+						+						+			+		+	+		+	
Squamous cell carcinoma, metastatic, stomach, forestomach																									
Iliac, histiocytic sarcoma																					X				
Inguinal, fibrosarcoma, metastatic, skeletal muscle																						X			
Mediastinal, fibrosarcoma, metastatic, skeletal muscle																						X			
Mediastinal, histiocytic sarcoma																					X				
Renal, histiocytic sarcoma																					X				

TABLE A2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Intravaginal Study of Polyvinyl Alcohol: Untreated Control

Number of Days on Study	721	725	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	730	730	730	730	730
Carcass ID Number	02717	04422	06161	00219	01117	01418	02325	03435	04140	04445	04646	04747	05049	05662	07222	07725	07737	08041	09111	09919	01111	01212	02223	03236
Endocrine System																								
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																								
Squamous cell carcinoma, metastatic, stomach, forestomach																								
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid gland	+	I	I	+	I	+	+	+	+	I	+	+	+	+	+	+	I	I	I	I	+	+	I	I	I
Pituitary gland	+	+	+	+	+	+	+	M	+	+	+	M	+	+	+	+	+	+	+	+	M	+	+	+	M
Pars distalis, adenoma			X	X															X						
Pars intermedia, adenoma																									
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell, adenoma								X	X		X						X								
General Body System																								
Tissue NOS																								
Squamous cell carcinoma, metastatic, stomach, forestomach																								
Genital System																								
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	I
Ovary	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cystadenoma															X										
Granulosa cell tumor benign												X													
Hemangiosarcoma																									
Hepatocellular carcinoma, metastatic, liver																									
Histiocytic sarcoma																									
Luteoma																									
Squamous cell carcinoma, metastatic, stomach, forestomach																									
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Granular cell tumor benign																									
Hamartoma														X											
Hepatocellular carcinoma, metastatic, liver																									
Histiocytic sarcoma																									
Squamous cell carcinoma, metastatic, stomach, forestomach																									
Serosa, fibrosarcoma, metastatic, skeletal muscle																									
Vagina	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node	+				+				+																
Squamous cell carcinoma, metastatic, stomach, forestomach																									
Iliac, histiocytic sarcoma																									
Inguinal, fibrosarcoma, metastatic, skeletal muscle																									
Mediastinal, fibrosarcoma, metastatic, skeletal muscle																									
Mediastinal, histiocytic sarcoma																									
Renal, histiocytic sarcoma																									

TABLE A2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Intravaginal Study of Polyvinyl Alcohol: Untreated Control

Number of Days on Study	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	
Carcass ID Number	0 3 7	0 4 3	0 4 8	0 5 3	0 5 7	0 6 4	0 6 7	0 6 8	0 8 2	0 8 6	0 8 9	0 9 5	0 0 4	0 1 4	0 2 0	0 3 1	0 3 4	0 4 4	0 5 2	0 5 6	0 6 3	0 7 9	0 9 0	0 9 7	1 0 0	Total Tissues/ Tumors
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	100
Histiocytic sarcoma																										1
Squamous cell carcinoma, metastatic, stomach, forestomach																										1
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	99
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	97
Parathyroid gland	+	+	+	+	+	I	+	+	+	I	+	I	I	+	+	+	I	+	+	+	+	I	+	I	I	59
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	88
Pars distalis, adenoma	X						X			X					X	X						X			X	13
Pars intermedia, adenoma																					X					1
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	100
Follicular cell, adenoma	X		X																						X	8
General Body System																										
Tissue NOS																										1
Squamous cell carcinoma, metastatic, stomach, forestomach																										1
Genital System																										
Clitoral gland	+	+	+	+	+	+	+	M	+	I	+	+	+	+	+	+	I	+	+	+	+	+	+	+	+	89
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	I	+	+	+	+	+	+	+	+	+	+	+	95
Cystadenoma																								X	X	6
Granulosa cell tumor benign																										1
Hemangiosarcoma																										1
Hepatocellular carcinoma, metastatic, liver																										1
Histiocytic sarcoma																										3
Luteoma												X														1
Squamous cell carcinoma, metastatic, stomach, forestomach																										1
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	100
Granular cell tumor benign			X																							1
Hamartoma																										1
Hepatocellular carcinoma, metastatic, liver																										1
Histiocytic sarcoma																										4
Squamous cell carcinoma, metastatic, stomach, forestomach																										1
Serosa, fibrosarcoma, metastatic, skeletal muscle																										1
Vagina	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	97
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	100
Lymph node													+									+				15
Squamous cell carcinoma, metastatic, stomach, forestomach																										1
Iliac, histiocytic sarcoma																										1
Inguinal, fibrosarcoma, metastatic, skeletal muscle																										1
Mediastinal, fibrosarcoma, metastatic, skeletal muscle																										1
Mediastinal, histiocytic sarcoma																										1
Renal, histiocytic sarcoma																										1

TABLE A2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Intravaginal Study of Polyvinyl Alcohol: Untreated Control

Number of Days on Study	0 6 7	1 1 0	1 6 8	1 7 5	3 5 0	3 5 7	3 6 5	4 0 0	4 1 0	4 4 1	4 7 3	4 7 6	4 8 3	5 1 1	5 2 9	5 3 0	5 3 8	5 3 9	5 8 1	5 9 2	5 9 5	5 9 5	6 0 6	6 2 5	6 3 4
Carcass ID Number	0 7 6	0 1 9	0 9 6	0 2 8	0 3 0	0 7 3	0 7 1	0 0 5	0 8 4	0 2 1	0 7 4	0 1 6	0 0 6	0 5 0	0 5 1	0 7 8	0 0 8	0 4 1	0 4 9	0 5 5	0 0 7	0 3 9	0 3 3	0 8 7	0 0 1
Hematopoietic System (continued)																									
Lymph node, mandibular	+	+	+	I	+	+	M	+	+	+	+	I	+	+	+	+	+	+	I	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	A	+	+	+	A	+	+	A	A	+	+	+	+	+	+	+	A	A	I	+
Fibrosarcoma, metastatic, skeletal muscle																									
Hepatocellular carcinoma, metastatic, liver																									
Histiocytic sarcoma																					X				
Rhabdomyosarcoma, metastatic, skeletal muscle																									
Squamous cell carcinoma, metastatic, stomach, forestomach									X																
Spleen	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+
Fibrosarcoma, metastatic, skeletal muscle																									
Histiocytic sarcoma																									
Thymus	+	+	+	+	+	+	+	I	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar carcinoma, metastatic, lung											X														
Fibrosarcoma, metastatic, skeletal muscle																									
Hepatocellular carcinoma, metastatic, liver																	X								
Thymoma benign																									
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+
Adenoma																									
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+
Fibrosarcoma																									
Sarcoma																									
Subcutaneous tissue, fibrosarcoma																									
Subcutaneous tissue, fibrous histiocytoma																									
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skeletal muscle									+			+								+					
Fibrosarcoma, metastatic, skeletal muscle																									
Rhabdomyosarcoma																									
Squamous cell carcinoma, metastatic, stomach, forestomach									X																
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Peripheral nerve												+								+					
Spinal cord												+													
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																									
Alveolar/bronchiolar carcinoma											X														
Carcinoma, metastatic, harderian gland																									
Hepatocellular carcinoma, metastatic, liver																	X								
Histiocytic sarcoma																					X				
Osteosarcoma, metastatic, tissue NOS																									
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

TABLE A2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Intravaginal Study of Polyvinyl Alcohol: Untreated Control

Number of Days on Study	6 4 0	6 4 3	6 4 6	6 5 2	6 5 5	6 5 5	6 5 7	6 5 7	6 5 9	6 6 6	6 6 8	6 6 8	6 7 5	6 8 2	6 8 2	6 8 6	6 9 0	6 9 6	7 0 3	7 0 4	7 0 4	7 0 9	7 1 1	7 1 4	7 1 8
Carcass ID Number	0 2 6	0 1 5	0 6 0	0 6 6	0 1 3	0 6 5	0 1 0	0 9 2	0 0 3	0 7 0	0 2 3	0 9 4	0 9 3	0 6 9	0 8 8	0 8 5	0 5 8	0 3 8	0 8 3	0 8 0	0 9 8	0 2 9	0 5 4	0 2 4	0 0 2
Hematopoietic System (continued)																									
Lymph node, mandibular	+	+	+	+	+	I	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	I	+	+	+
Lymph node, mesenteric	+	+	+	+	+	I	+	+	+	+	+	+	+	+	I	+	+	+	+	+	+	+	+	+	I
Fibrosarcoma, metastatic, skeletal muscle																						X			
Hepatocellular carcinoma, metastatic, liver																									
Histiocytic sarcoma								X	X												X				
Rhabdomyosarcoma, metastatic, skeletal muscle																									
Squamous cell carcinoma, metastatic, stomach, forestomach																									
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrosarcoma, metastatic, skeletal muscle																						X			
Histiocytic sarcoma								X													X				
Thymus	+	I	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar carcinoma, metastatic, lung																									
Fibrosarcoma, metastatic, skeletal muscle																						X			
Hepatocellular carcinoma, metastatic, liver																									
Thymoma benign																									
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma											X														
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+
Fibrosarcoma																							X		
Sarcoma																									
Subcutaneous tissue, fibrosarcoma																			X						
Subcutaneous tissue, fibrous histiocytoma																									
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skeletal muscle				+																+	+	+			
Fibrosarcoma, metastatic, skeletal muscle																					X				
Rhabdomyosarcoma																									
Squamous cell carcinoma, metastatic, stomach, forestomach																									
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Peripheral nerve																							+		
Spinal cord																							+		
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma		X		X																					
Alveolar/bronchiolar carcinoma													X												
Carcinoma, metastatic, harderian gland			X																						
Hepatocellular carcinoma, metastatic, liver		X				X																			
Histiocytic sarcoma									X																
Osteosarcoma, metastatic, tissue NOS																									
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

TABLE A2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Intravaginal Study of Polyvinyl Alcohol: Untreated Control

Number of Days on Study	721	725	725	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	730	730	730	730	730
Carcass ID Number	02 7	04 2	06 1	09 9	01 7	11 8	23 5	35 5	40 0	44 5	44 6	46 7	47 9	50 9	66 2	70 2	77 5	77 7	78 1	90 1	99 9	01 1	11 2	12 2	23 2	33 2	36 6
Hematopoietic System (continued)																											
Lymph node, mandibular	+	+	I	+	+	+	+	+	+	+	+	I	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrosarcoma, metastatic, skeletal muscle																											
Hepatocellular carcinoma, metastatic, liver																											
Histiocytic sarcoma																											
Rhabdomyosarcoma, metastatic, skeletal muscle														X													
Squamous cell carcinoma, metastatic, stomach, forestomach																											
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrosarcoma, metastatic, skeletal muscle																											
Histiocytic sarcoma																											
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar carcinoma, metastatic, lung																											
Fibrosarcoma, metastatic, skeletal muscle																											
Hepatocellular carcinoma, metastatic, liver																											
Thymoma benign																		X									
Integumentary System																											
Mammary gland	I	+	I	+	I	I	+	+	+	+	+	+	I	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																											
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrosarcoma																											
Sarcoma																											
Subcutaneous tissue, fibrosarcoma																											
Subcutaneous tissue, fibrous histiocytoma																											
Musculoskeletal System																											
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skeletal muscle														+									+				
Fibrosarcoma, metastatic, skeletal muscle																											
Rhabdomyosarcoma														X									X				
Squamous cell carcinoma, metastatic, stomach, forestomach																											
Nervous System																											
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Peripheral nerve																											
Spinal cord																											
Respiratory System																											
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma				X				X																X			
Alveolar/bronchiolar carcinoma			X																								
Carcinoma, metastatic, harderian gland																											
Hepatocellular carcinoma, metastatic, liver		X																									
Histiocytic sarcoma																											
Osteosarcoma, metastatic, tissue NOS	X																										
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

TABLE A2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Intravaginal Study of Polyvinyl Alcohol: Untreated Control

Number of Days on Study	730	730	730	730	730	730	730	730	730	730	730	730	730	731	731	731	731	731	731	731	731	731	731	731	731	731	
Carcass ID Number	03 37	04 33	04 38	05 53	05 57	06 04	06 67	06 68	08 02	08 86	08 89	09 05	09 04	01 44	02 00	03 01	03 34	04 42	05 22	05 56	06 63	07 99	09 07	09 70	10 00		Total Tissues/ Tumors
Hematopoietic System (continued)																											
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	92
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	90
Fibrosarcoma, metastatic, skeletal muscle																											1
Hepatocellular carcinoma, metastatic, liver			X																								1
Histiocytic sarcoma																											4
Rhabdomyosarcoma, metastatic, skeletal muscle																											1
Squamous cell carcinoma, metastatic, stomach, forestomach																											1
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	98
Fibrosarcoma, metastatic, skeletal muscle																											1
Histiocytic sarcoma																											2
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	98
Alveolar/bronchiolar carcinoma, metastatic, lung																											1
Fibrosarcoma, metastatic, skeletal muscle																											1
Hepatocellular carcinoma, metastatic, liver																											1
Thymoma benign																											1
Integumentary System																											
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	I	+	+		93
Adenoma																											1
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		98
Fibrosarcoma																											1
Sarcoma																		X									1
Subcutaneous tissue, fibrosarcoma																											1
Subcutaneous tissue, fibrous histiocytoma													X														1
Musculoskeletal System																											
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	100
Skeletal muscle																											9
Fibrosarcoma, metastatic, skeletal muscle																											1
Rhabdomyosarcoma																											2
Squamous cell carcinoma, metastatic, stomach, forestomach																											1
Nervous System																											
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	100
Peripheral nerve																											3
Spinal cord																											2
Respiratory System																											
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	100
Alveolar/bronchiolar adenoma																						X					6
Alveolar/bronchiolar carcinoma																											3
Carcinoma, metastatic, harderian gland																											1
Hepatocellular carcinoma, metastatic, liver																											4
Histiocytic sarcoma																											2
Osteosarcoma, metastatic, tissue NOS																											1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	100
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	100

TABLE A2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Intravaginal Study of Polyvinyl Alcohol: Untreated Control

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

TABLE A2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Intravaginal Study of Polyvinyl Alcohol: Untreated Control

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

TABLE A2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Intravaginal Study of Polyvinyl Alcohol: Untreated Control

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

TABLE A2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Intravaginal Study of Polyvinyl Alcohol: Untreated Control

Number of Days on Study	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	
Carcass ID Number	0 3 7	0 4 3	0 4 8	0 5 3	0 5 7	0 6 4	0 6 7	0 6 8	0 8 2	0 8 6	0 8 9	0 9 5	0 0 4	0 1 4	0 2 0	0 3 1	0 3 4	0 4 4	0 5 2	0 5 6	0 6 3	0 7 9	0 9 0	0 9 7	1 0 0	Total Tissues/ Tumors	
Special Senses System																											
Eye																										4	
Harderian gland																							+			5	
Adenoma																							X			4	
Carcinoma																										1	
Urinary System																											
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	100	
Histiocytic sarcoma																										1	
Urinary bladder	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	96	
Systemic Lesions																											
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	100	
Histiocytic sarcoma																										4	
Lymphoma malignant								X					X								X	X				13	

TABLE A2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Intravaginal Study of Polyvinyl Alcohol: Vehicle Control

Number of Days on Study	2 0 5	3 1 3	3 1 4	3 1 4	4 6 2	5 3 2	5 4 2	5 4 8	5 4 8	5 4 8	5 8 8	5 8 8	6 0 9	6 1 1	6 1 1	6 1 1	6 1 3	6 2 0	6 2 7	6 3 4	6 3 7	6 3 9	6 4 0	6 4 3	6 4 6
Carcass ID Number	1 3 5	1 0 9	1 7 7	1 8 3	1 1 8	1 8 2	1 8 6	1 8 5	1 8 9	1 9 3	1 0 7	6 7	1 2 7	4 8	1 5 1	1 5 4	1 0 6	1 4 4	1 3 0	1 6 6	1 4 3	1 4 0	3 4	7 5	1 7
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder	+	A	A	+	A	+	+	+	+	+	A	A	A	+	+	+	A	+	+	+	+	A	+	+	+
Intestine large, colon	+	+	A	+	+	A	+	+	+	+	A	A	A	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	A	A	A	A	+	+	+	+	A	A	A	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	A	A	+	A	+	+	+	+	A	A	A	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	A	A	A	A	+	+	+	+	A	A	A	+	+	+	+	+	+	+	+	+	+	+	+
Polyp adenomatous																									
Intestine small, jejunum	+	+	A	A	A	A	+	+	+	+	A	A	A	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	A	A	A	A	+	+	+	+	A	A	A	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular carcinoma										X			X				X		X						
Hepatocellular adenoma																X	X					X	X	X	
Hepatocellular adenoma, multiple																									
Histiocytic sarcoma											X										X				
Mesentery								+						+		+				+		+			
Carcinoma, metastatic, islets, pancreatic																									
Pancreas	+	+	+	+	+	+	+	I	+	+	+	A	A	+	+	+	+	+	+	+	+	A	+	+	+
Carcinoma																									
Salivary glands	+	+	+	+	+	+	+	+	+	+	M	A	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	A	A	A	+	+	+	+	+	A	A	A	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	A	A	A	+	+	+	+	+	A	A	A	+	+	+	+	+	+	+	+	+	+	+	+
Cardiovascular System																									
Heart	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	I	+	+	+	A	A	+	+	+	+	+	+	+	+	+	M	+	+
Carcinoma, metastatic, islets, pancreatic																									
Hepatocellular carcinoma, metastatic, liver																			X						
Capsule, adenoma																									
Adrenal medulla	+	+	+	+	+	+	+	I	+	+	+	A	A	+	+	+	+	+	+	+	+	+	M	+	+
Pheochromocytoma benign																									
Islets, pancreatic	+	+	A	+	+	+	+	I	+	+	+	A	A	+	+	+	+	+	+	+	+	A	+	+	+
Adenoma											X														
Parathyroid gland	+	I	A	I	I	I	+	I	+	+	+	A	+	+	+	I	+	+	+	I	+	+	+	+	+
Pituitary gland	+	+	+	+	M	+	+	I	M	+	+	A	A	+	+	+	+	+	+	+	+	+	M	+	+
Pars distalis, adenoma																		X						X	X
Thyroid gland	+	+	A	I	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+
C-cell, adenoma																									
Follicular cell, adenoma																				X					
Follicular cell, carcinoma																									
General Body System																									
None																									

TABLE A2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Intravaginal Study of Polyvinyl Alcohol: Vehicle Control

Number of Days on Study	654	655	658	661	668	671	775	775	775	775	779	779	900	900	900	904	905	111	111	117	121	122	122	128	129
Carcass ID Number	110	160	103	288	333	374	111	112	197	200	201	169	204	232	259	295	313	222	272	205	157	168	198	288	308
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder	+	+	+	+	+	A	+	+	+	+	+	A	+	+	+	+	+	+	+	+	A	+	A	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	A	+	+	A	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	A	+	+	A	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	A	+	+	A	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	A	A	+	+	A	+	+	+	+	+	+	+	+	+	+
Polyp adenomatous																									
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	A	A	+	+	A	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	A	A	+	+	A	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular carcinoma				X	X								X			X								X	
Hepatocellular adenoma		X		X						X			X		X	X	X	X	X						X
Hepatocellular adenoma, multiple	X										X	X												X	
Histiocytic sarcoma																									
Mesentery				+	+				+			+		+					+	+					+
Carcinoma, metastatic, islets, pancreatic				X																					
Pancreas	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma				X																					
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+
Cardiovascular System																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, islets, pancreatic				X																					
Hepatocellular carcinoma, metastatic, liver																									
Capsule, adenoma																									
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma benign																									
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Parathyroid gland	+	+	I	I	+	I	+	I	+	+	+	A	+	+	I	I	+	I	I	+	I	I	+	I	I
Pituitary gland	M	+	+	M	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	I	+	+	+	+
Pars distalis, adenoma															X				X						
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+
C-cell, adenoma																									
Follicular cell, adenoma																X	X								X
Follicular cell, carcinoma																									
General Body System																									
None																									

TABLE A2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Intravaginal Study of Polyvinyl Alcohol: Vehicle Control

Number of Days on Study	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	730	730	730	730	730	730	730
Carcass ID Number	119	138	142	145	153	158	161	165	171	178	181	184	187	190	191	192	194	196	102	114	123	124	129	131	136
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder	+	+	+	+	+	I	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Polyp adenomatous																									
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular carcinoma											X										X		X		
Hepatocellular adenoma			X	X		X	X	X	X	X	X			X			X	X		X			X	X	
Hepatocellular adenoma, multiple					X								X		X						X				
Histiocytic sarcoma																									
Mesentery							+		+	+	+			+								+			
Carcinoma, metastatic, islets, pancreatic																									
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma																									
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cardiovascular System																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+
Carcinoma, metastatic, islets, pancreatic																									
Hepatocellular carcinoma, metastatic, liver																									
Capsule, adenoma																									
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+
Pheochromocytoma benign									X																
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma			X																						
Parathyroid gland	+	+	I	+	+	I	I	+	+	+	I	+	I	I	+	+	+	+	+	+	+	+	+	+	+
Pituitary gland	I	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+
Pars distalis, adenoma									X																
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C-cell, adenoma																									
Follicular cell, adenoma	X			X			X				X									X					
Follicular cell, carcinoma																									
General Body System																									
None																									

TABLE A2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Intravaginal Study of Polyvinyl Alcohol: Vehicle Control

Number of Days on Study	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	
Carcass ID Number	1 3 7	1 3 9	1 4 1	1 4 6	1 4 7	1 4 9	1 5 0	1 5 5	1 6 2	1 6 3	1 6 8	1 7 6	1 7 9	1 8 0	1 1 5	1 2 0	1 2 1	1 2 5	1 2 6	1 5 2	1 5 6	1 6 4	1 7 0	1 7 3	1 9 9	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	100
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	87
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	93
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	91
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	92
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	90
Polyp adenomatous																X										1
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	90
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	90
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	99
Hepatocellular carcinoma					X						X			X					X		X				X	18
Hepatocellular adenoma		X	X		X			X	X	X	X			X	X		X	X			X		X		X	43
Hepatocellular adenoma, multiple							X					X	X									X		X		13
Histiocytic sarcoma																										2
Mesentery							+			+					+		+		+			+				25
Carcinoma, metastatic, islets, Pancreatic																										1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	95
Carcinoma																										1
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	97
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	93
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	93
Cardiovascular System																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	99
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	94
Carcinoma, metastatic, islets, pancreatic																										1
Hepatocellular carcinoma, metastatic, liver																										1
Capsule, adenoma															X											1
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	94
Pheochromocytoma benign	X																									2
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	94
Adenoma																							X			3
Parathyroid gland	I	+	+	+	I	+	I	I	+	+	+	I	I	+	+	I	I	+	+	I	+	I	I	I	I	59
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	M	86
Pars distalis, adenoma	X																X	X								9
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	96
C-cell, adenoma																			X							1
Follicular cell, adenoma																										9
Follicular cell, carcinoma								X																		1
General Body System																										
None																										

TABLE A2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Intravaginal Study of Polyvinyl Alcohol: Vehicle Control

Number of Days on Study	2 0 5	3 1 3	3 1 4	3 1 4	4 6 2	5 3 2	5 4 2	5 4 8	5 4 8	5 4 8	5 8 8	5 8 8	6 0 9	6 1 1	6 1 1	6 1 1	6 1 3	6 2 0	6 2 7	6 3 4	6 3 7	6 3 9	6 4 0	6 4 3	6 4 6
Carcass ID Number	1 3 5	1 0 9	1 7 7	1 8 3	1 1 8	1 8 2	1 8 6	1 8 5	1 8 9	1 9 3	1 0 7	1 6 7	1 2 7	1 4 8	1 5 1	1 5 4	1 0 6	1 4 4	1 3 0	1 6 6	1 4 3	1 4 0	1 3 4	1 7 5	1 1 7
Genital System																									
Clitoral gland	+	I	I	I	I	+	+	+	+	+	+	A	I	+	I	I	+	+	+	+	+	+	I	+	+
Ovary	+	+	+	+	+	+	+	+	+	+	+	A	A	+	+	+	+	+	+	+	+	+	+	+	+
Cystadenoma																									
Granulosa cell tumor benign																									
Hepatocellular carcinoma, metastatic, liver																			X						
Histiocytic sarcoma											X														
Liposarcoma																									
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Granular cell tumor benign																									
Histiocytic sarcoma											X										X				
Leiomyoma																									
Polyp stromal																									
Sarcoma stromal																									
Vagina	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma											X														
Lymph node	+						+									+			+		+			+	
Liposarcoma																									
Iliac, histiocytic sarcoma																					X				
Mediastinal, sarcoma, metastatic, uncertain primary site																									
Renal, histiocytic sarcoma																					X				
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	M	A	A	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	I	A	+	+	+	+	I	+	+	A	A	A	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular carcinoma, metastatic, liver																									
Sarcoma, metastatic, uncertain primary site																									
Spleen	+	+	A	+	+	+	+	+	+	+	+	A	A	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma, metastatic, uncertain primary site																									
Thymus	+	+	+	+	+	+	+	I	M	+	A	A	A	+	+	+	+	+	+	+	+	+	+	+	+
Fibrosarcoma, metastatic, skin																									
Integumentary System																									
Mammary gland	+	+	+	+	I	I	+	+	I	+	+	A	+	+	+	I	+	+	+	+	+	+	+	+	+
Skin	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+
Subcutaneous tissue, fibrosarcoma																									
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skeletal muscle										+					+	+				+					
Rhabdomyosarcoma										X															
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Peripheral nerve															+					+					
Spinal cord																				+					

TABLE A2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Intravaginal Study of Polyvinyl Alcohol: Vehicle Control

Number of Days on Study	654	654	658	661	668	671	775	775	775	775	779	779	790	900	900	904	905	911	911	917	921	922	922	928	929
Carcass ID Number	110	160	203	288	333	374	111	112	197	200	201	169	204	232	259	295	313	222	270	205	257	196	188	288	208
Genital System																									
Clitoral gland	+	+	+	+	+	+	+	I	I	+	+	I	+	+	+	+	+	+	+	+	+	+	+	+	+
Ovary	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+
Cystadenoma																			X						
Granulosa cell tumor benign																									
Hepatocellular carcinoma, metastatic, liver																									
Histiocytic sarcoma																									
Liposarcoma														X											
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Granular cell tumor benign																									
Histiocytic sarcoma																									
Leiomyoma																									
Polyp stromal																									
Sarcoma stromal																									
Vagina	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																									
Lymph node								+			+			+				+						+	
Liposarcoma														X											
Iliac, histiocytic sarcoma																									
Mediastinal, sarcoma, metastatic, uncertain primary site																									
Renal, histiocytic sarcoma																									
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular carcinoma, metastatic, liver																									
Sarcoma, metastatic, uncertain primary site																									
Spleen	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma, metastatic, uncertain primary site																									
Thymus	+	+	+	+	+	+	+	+	+	+	+	A	+	I	+	+	+	+	+	+	+	+	+	+	+
Fibrosarcoma, metastatic, skin																X									
Integumentary System																									
Mammary gland	+	+	+	+	I	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+
Skin	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+
Subcutaneous tissue, fibrosarcoma										X						X									
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skeletal muscle			+							+						+		+			+				
Rhabdomyosarcoma																X									
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+
Peripheral nerve			+															+							
Spinal cord	+																	+							

TABLE A2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Intravaginal Study of Polyvinyl Alcohol: Vehicle Control

Number of Days on Study	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	730	730	730	730	730	730	730
Carcass ID Number	11 19	11 38	11 42	11 45	11 53	11 58	11 61	11 65	11 71	11 78	11 81	11 84	11 87	11 90	11 91	11 92	11 94	11 96	11 02	11 14	11 23	11 24	11 29	11 31	11 36
Genital System																										
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	I	I	+	+	+	I	I	+	+	+	+	+	+	I
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cystadenoma																							X		
Granulosa cell tumor benign																									
Hepatocellular carcinoma, metastatic, liver																									
Histiocytic sarcoma																									
Liposarcoma																									
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Granular cell tumor benign																							X		
Histiocytic sarcoma																									
Leiomyoma																									
Polyp stromal																						X			
Sarcoma stromal								X								X									
Vagina	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																									
Lymph node	+																+		+						
Liposarcoma																									
Iliac, histiocytic sarcoma																									
Mediastinal, sarcoma, metastatic, uncertain primary site																									
Renal, histiocytic sarcoma																									
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	I	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular carcinoma, metastatic, liver																									
Sarcoma, metastatic, uncertain primary site																									
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma, metastatic, uncertain primary site																									
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrosarcoma, metastatic, skin																									
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Subcutaneous tissue, fibrosarcoma																									
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skeletal muscle									+																
Rhabdomyosarcoma																									
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Peripheral nerve																									
Spinal cord																									

TABLE A2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Intravaginal Study of Polyvinyl Alcohol: Vehicle Control

Number of Days on Study	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	731	731	731	731	731	731	731	731	731	731	
Carcass ID Number	13 37	13 39	14 41	14 46	14 47	14 49	15 00	15 05	16 02	16 03	16 08	17 06	17 09	18 00	11 05	12 01	12 05	12 06	15 02	15 06	16 04	17 00	17 03	19 09	Total Tissues/ Tumors
Genital System																										
Clitoral gland	+	+	+	+	+	+	+	+	+	I	+	+	+	+	+	+	+	+	+	+	+	+	I	+	81
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	97
Cystadenoma			X						X									X							5
Granulosa cell tumor benign														X										X	2
Hepatocellular carcinoma, metastatic, liver																									1
Histiocytic sarcoma																									1
Liposarcoma																									1
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	100
Granular cell tumor benign																									1
Histiocytic sarcoma																									2
Leiomyoma													X												1
Polyp stromal																									1
Sarcoma stromal																									2
Vagina	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	99
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	I	+	+	+	+	+	+	+	+	+	+	+	+	+	+	98
Histiocytic sarcoma																									1
Lymph node				+	+		+	+		+								+			+				21
Liposarcoma																									1
Iliac, histiocytic sarcoma																									1
Mediastinal, sarcoma, metastatic, uncertain primary site										X															1
Renal, histiocytic sarcoma																									1
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	I	+	+	+	+	+	94
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	93
Hepatocellular carcinoma, metastatic, liver																								X	1
Sarcoma, metastatic, uncertain primary site										X															1
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	96
Sarcoma, metastatic, uncertain primary site										X															1
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	93
Fibrosarcoma, metastatic, skin																									1
Integumentary System																										
Mammary gland	+	+	+	+	+	+	I	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	92
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	98
Subcutaneous tissue, fibrosarcoma																									2
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	100
Skeletal muscle																									10
Rhabdomyosarcoma																									2
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	99
Peripheral nerve																									4
Spinal cord																									3

TABLE A2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Intravaginal Study of Polyvinyl Alcohol: Vehicle Control

Number of Days on Study	2 0 5	3 1 3	3 1 4	3 1 4	4 6 2	5 3 2	5 4 2	5 4 8	5 4 8	5 4 8	5 8 8	5 8 8	6 0 9	6 1 1	6 1 1	6 1 1	6 1 3	6 2 0	6 2 7	6 3 4	6 3 7	6 3 9	6 4 0	6 4 3	6 4 6
Carcass ID Number	1 3 5	1 0 9	1 7 7	1 8 3	1 1 8	1 8 2	1 8 6	1 8 5	1 8 9	1 9 3	1 0 7	1 6 7	1 2 7	1 4 8	1 5 1	1 5 4	1 0 6	1 4 4	1 3 0	1 6 6	1 4 3	1 4 0	1 3 4	1 7 5	1 1 7
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	A	A	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma															X										
Alveolar/bronchiolar carcinoma									X																
Fibrosarcoma, metastatic, skin																									
Hepatocellular carcinoma, metastatic, liver																			X						
Histiocytic sarcoma											X														
Sarcoma, metastatic, uncertain primary site																									
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma												X													
Pleura																									
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Eye																		+				+			
Harderian gland																		+				+			
Adenoma																									
Carcinoma																		X				X			
Zymbal's gland																									
Carcinoma																									
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	A	A	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Urinary bladder	+	+	A	+	+	M	+	I	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																					X				
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma											X										X				
Lymphoma malignant																			X				X		

TABLE A2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Intravaginal Study of Polyvinyl Alcohol: Vehicle Control

Number of Days on Study	654	654	658	661	668	671	675	675	675	675	675	679	690	690	690	694	705	711	711	717	721	722	722	728	729
Carcass ID Number	11100	16000	10303	12828	13323	17374	11111	11112	19027	20020	10201	16609	10404	13232	15929	19595	11913	12222	17205	10557	15716	19988	18808	10208
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma													X								X	X			
Alveolar/bronchiolar carcinoma																									
Fibrosarcoma, metastatic, skin																X									
Hepatocellular carcinoma, metastatic, liver																									
Histiocytic sarcoma																									
Sarcoma, metastatic, uncertain primary site												X													
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma																									
Pleura																									
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Eye					+			+					+												
Harderian gland					+		+	+					+												
Adenoma					X		X	X					X												
Carcinoma																									
Zymbal's gland																									
Carcinoma																									
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma													X												
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																									
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																									
Lymphoma malignant	X				X																X			X	

TABLE A2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Intravaginal Study of Polyvinyl Alcohol: Vehicle Control

Number of Days on Study	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	730	730	730	730	730	730	730
Carcass ID Number	11019	11038	11042	11045	11053	11058	11061	11065	11071	11078	11081	11084	11087	11090	11091	11092	11094	11096	11102	11104	11123	11124	11129	11131	11136
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																										
Alveolar/bronchiolar carcinoma																					X					
Fibrosarcoma, metastatic, skin																										
Hepatocellular carcinoma, metastatic, liver																										
Histiocytic sarcoma																										
Sarcoma, metastatic, uncertain primary site																										
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma																										
Pleura																										
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																										
Eye						+																				
Harderian gland		+				+			+																	
Adenoma		X				X			X																	
Carcinoma																										
Zymbal's gland								+																		
Carcinoma																										
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																										
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																										
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																										
Lymphoma malignant						X		X											X					X		

TABLE A2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Intravaginal Study of Polyvinyl Alcohol: Vehicle Control

Number of Days on Study	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	731	731	731	731	731	731	731	731	731	731	
Carcass ID Number	13 7	13 9	14 1	14 6	14 7	14 9	15 0	15 5	16 2	16 3	16 8	17 6	17 9	18 0	11 5	12 0	12 1	12 5	12 6	15 2	15 6	16 4	17 0	17 3	19 9	Total Tissues/ Tumors
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	98
Alveolar/bronchiolar adenoma	X																	X				X				7
Alveolar/bronchiolar carcinoma				X																						3
Fibrosarcoma, metastatic, skin																										1
Hepatocellular carcinoma, metastatic, liver					X																					2
Histiocytic sarcoma																										1
Sarcoma, metastatic, uncertain primary site																										1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	100
Carcinoma																										1
Pleura																					+					1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	100
Special Senses System																										
Eye																										6
Harderian gland							+													+						11
Adenoma							X													X						9
Carcinoma																										2
Zymbal's gland			+									+														3
Carcinoma			X																							1
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	98
Adenoma																										1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	96
Histiocytic sarcoma																										1
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	100
Histiocytic sarcoma																										2
Lymphoma malignant	X						X											X			X					14

TABLE A2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Intravaginal Study of Polyvinyl Alcohol: 25%

Number of Days on Study	07 12	11 12	13 13	32 34	37 22	50 44	50 07	51 14	54 22	55 33	61 19	62 00	62 00	62 04	62 24	62 27	63 34	63 37	63 38	64 00	64 06	64 06	64 06	65 11	65 18	66 01
Carcass ID Number	25 58	24 10	22 18	23 09	23 08	22 82	23 38	28 85	22 29	23 36	22 81	23 01	26 04	21 43	29 11	24 41	22 12	29 94	27 00	24 13	23 16	26 63	24 14	26 19	26 69	23 30
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder	+	+	A	+	+	A	+	I	+	+	+	+	+	I	A	A	A	A	+	+	+	+	A	A	+	
Hepatocholangiocarcinoma, metastatic, liver													X													
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	A	A	+	+	+	+	+	+	+	
Intestine large, rectum	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	A	A	A	+	+	+	+	+	+	+	
Intestine large, cecum	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	A	A	A	+	+	+	+	+	+	+	
Intestine small, duodenum	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	A	A	+	+	+	+	A	+	+	
Intestine small, jejunum	+	+	A	+	+	A	+	+	+	+	+	+	+	+	+	+	A	A	+	+	+	+	A	+	+	
Intestine small, ileum	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	A	A	+	+	+	+	A	+	+	
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Hepatocellular carcinoma							X				X			X					X			X			
Hepatocellular adenoma								X	X	X			X							X			X	X	X
Hepatocellular adenoma, multiple																										
Hepatocholangiocarcinoma										X			X													
Histiocytic sarcoma																										
Mesentery					+			+		+		+	+			+		+	+					+		
Hepatocholangiocarcinoma, metastatic, liver										X			X													
Yolk sac carcinoma, metastatic, ovary					X																					
Oral mucosa																										
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	I	A	+	+	+	+	+	+	+	
Hepatocholangiocarcinoma, metastatic, liver													X													
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	A	+	+	+	+	A	+	+	
Stomach, glandular	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	A	A	+	+	+	+	A	+	+	
Leiomyosarcoma				X																						
Cardiovascular System																										
Blood vessel													+													
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Endocrine System																										
Adrenal cortex	+	+	+	I	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Capsule, carcinoma																										
Adrenal medulla	+	+	+	I	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Hepatocholangiocarcinoma, metastatic, liver										X																
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	I	A	+	+	+	+	+	+	+	
Adenoma																										
Hepatocholangiocarcinoma, metastatic, liver													X													
Parathyroid gland	+	+	I	+	+	+	I	+	I	+	+	+	+	I	+	+	I	+	I	+	+	+	+	+	+	
Adenoma																										
Pituitary gland	+	+	+	+	M	+	M	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	
Pars distalis, adenoma																	X	X		X						
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Follicular cell, adenoma																		X								
General Body System																										
None																										

TABLE A2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Intravaginal Study of Polyvinyl Alcohol: 25%

Number of Days on Study	6 6 8	6 7 5	6 8 2	6 8 6	6 8 8	6 9 0	6 9 6	6 9 7	7 0 1	7 0 4	7 0 8	7 1 4	7 2 1	7 2 1	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9
Carcass ID Number	2 1 0	2 6 7	2 0 9	2 5 7	2 8 9	2 4 2	2 4 4	2 3 3	2 6 1	2 8 8	2 7 1	2 2 8	2 4 5	2 9 5	2 0 4	2 0 7	2 1 5	2 1 9	2 2 6	2 2 7	2 3 2	2 4 6	2 4 8	2 4 9	2 5 5
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	I	+	+	+	+	+
Gallbladder	+	+	+	+	A	+	+	A	A	A	+	A	A	+	+	+	+	+	+	+	+	+	+	I	+
Hepatocholangiocarcinoma, metastatic, liver																									
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	A	+	+	+	A	A	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	A	+	+	+	A	A	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	+	A	+	+	+	A	A	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular carcinoma								X				X						X		X				X	X
Hepatocellular adenoma				X	X		X	X			X		X					X				X	X		X
Hepatocellular adenoma, multiple						X			X	X		X			X	X	X		X	X					
Hepatocholangiocarcinoma																									
Histiocytic sarcoma																					X				
Mesentery				+				+	+	+	+		+						+	+			+	+	
Hepatocholangiocarcinoma, metastatic, liver																									
Yolk sac carcinoma, metastatic, ovary																									
Oral mucosa																									
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocholangiocarcinoma, metastatic, liver																									
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leiomyosarcoma																									
Cardiovascular System																									
Blood vessel																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal cortex	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Capsule, carcinoma																									
Adrenal medulla	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocholangiocarcinoma, metastatic, liver																									
Islets, pancreatic	+	+	I	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Hepatocholangiocarcinoma, metastatic, liver																									
Parathyroid gland	+	+	I	I	+	I	+	+	I	+	+	I	I	I	+	I	+	+	+	+	+	+	+	+	+
Adenoma																									
Pituitary gland	M	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma														X		X						X			
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell, adenoma						X								X											
General Body System																									
None																									

TABLE A2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Intravaginal Study of Polyvinyl Alcohol: 25%

Number of Days on Study	729	729	729	729	729	729	729	729	729	729	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730
Carcass ID Number	25 6	26 5	27 5	27 6	27 7	29 2	29 3	29 7	29 9	30 0	30 3	30 5	31 2	31 7	32 0	32 1	32 4	32 5	33 4	33 7	34 7	35 0	35 1	35 4	35 9
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder	+	+	+	+	+	+	+	+	+	+	I	+	+	+	+	+	+	I	+	+	+	+	+	+	+
Hepatocholangiocarcinoma, metastatic, liver																									
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular carcinoma		X		X								X													
Hepatocellular adenoma	X	X	X								X	X				X	X	X	X					X	
Hepatocellular adenoma, multiple							X			X					X										X
Hepatocholangiocarcinoma																									
Histiocytic sarcoma																									
Mesentery					+		+	+	+	+	+	+			+	+	+								
Hepatocholangiocarcinoma, metastatic, liver																									
Yolk sac carcinoma, metastatic, ovary																									
Oral mucosa																									
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocholangiocarcinoma, metastatic, liver																									
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leiomyosarcoma																									
Cardiovascular System																									
Blood vessel													+												
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Capsule, carcinoma																	X								
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	I	+	I	+	+	+	+	+	+	+	+	+	+
Hepatocholangiocarcinoma, metastatic, liver																									
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Hepatocholangiocarcinoma, metastatic, liver																									
Parathyroid gland	+	I	+	I	+	+	+	I	I	+	+	+	I	+	I	I	+	+	+	+	I	+	+	I	+
Adenoma																			X						
Pituitary gland	+	+	+	+	M	+	+	+	+	I	+	+	+	M	I	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma				X													X								
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell, adenoma				X																		X		X	
General Body System																									
None																									

TABLE A2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Intravaginal Study of Polyvinyl Alcohol: 25%

Number of Days on Study	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	
Carcass ID Number	2 6 0	2 6 2	2 6 6	2 6 8	2 7 2	2 7 8	2 8 3	2 8 4	2 9 0	2 0 2	2 0 6	2 1 1	2 1 3	2 3 1	2 3 5	2 5 2	2 5 3	2 7 3	2 7 4	2 7 9	2 8 0	2 8 6	2 8 7	2 9 6	2 9 8	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	99
Gallbladder	+	+	+	+	+	+	+	+	I	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	I	79
Hepatocholangiocarcinoma, metastatic, liver																										1
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	97
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	96
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	96
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	92
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	91
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	92
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	100
Hepatocellular carcinoma	X		X		X			X	X	X																20
Hepatocellular adenoma	X		X			X									X				X				X	X	X	36
Hepatocellular adenoma, multiple				X	X			X	X	X						X										19
Hepatocholangiocarcinoma																										2
Histiocytic sarcoma																										1
Mesentery				+		+						+		+		+				+			+			36
Hepatocholangiocarcinoma, metastatic, liver																										2
Yolk sac carcinoma, metastatic, ovary																										1
Oral mucosa						+																				1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	98
Hepatocholangiocarcinoma, metastatic, liver																										1
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	100
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	97
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	96
Leiomyosarcoma																										1
Cardiovascular System																										
Blood vessel																										2
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	100
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	97
Capsule, carcinoma																										1
Adrenal medulla	+	+	+	I	+	+	+	+	M	+	+	+	+	+	I	+	+	+	+	+	+	+	+	+	I	92
Hepatocholangiocarcinoma, metastatic, liver																										1
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	97
Adenoma																							X			1
Hepatocholangiocarcinoma, metastatic, liver																										1
Parathyroid gland	I	+	I	+	I	+	I	+	+	+	+	I	+	+	+	I	+	I	+	+	+	+	+	+	I	69
Adenoma																										1
Pituitary gland	M	+	+	+	+	+	+	+	M	+	+	+	+	+	M	+	+	+	+	I	+	I	I	+	M	84
Pars distalis, adenoma				X																				X		10
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	100
Follicular cell, adenoma				X	X											X				X	X					11
General Body System																										
None																										

TABLE A2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Intravaginal Study of Polyvinyl Alcohol: 25%

Number of Days on Study	07 12	11 12	31 13	32 14	37 12	50 14	50 17	51 14	54 12	55 13	61 19	62 00	62 00	62 14	62 14	62 17	63 14	63 17	63 18	64 10	64 16	64 16	65 11	65 18	66 01
Carcass ID Number	25 18	24 10	21 18	23 19	30 18	08 12	33 18	38 15	22 19	33 16	38 11	06 01	61 04	19 13	94 11	42 11	29 12	94 14	70 10	41 13	41 16	16 13	61 14	63 19	33 10
Genital System																									
Clitoral gland	+	I	+	+	+	+	+	I	+	+	+	+	+	+	+	I	A	+	I	+	I	I	+	I	+
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+
Cystadenoma																									
Hepatocholangiocarcinoma, metastatic, liver										X															
Luteoma																								X	
Teratoma benign																									
Yolk sac carcinoma					X																				
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma																			X						
Deciduoma NOS																									
Histiocytic sarcoma																									
Polyp stromal												X													
Vagina	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																									
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node															+	+				+				+	
Plasma cell tumor benign																								X	
Lymph node, mandibular	+	+	+	+	+	I	+	+	+	+	+	I	+	+	+	+	I	+	+	+	+	+	+	+	+
Plasma cell tumor benign																									
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	M	+	+	+	+	+	+	+
Hepatocholangiocarcinoma, metastatic, liver													X												
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+
Thymus	+	+	+	+	+	I	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocholangiocarcinoma, metastatic, liver													X												
Thymoma benign																									
Integumentary System																									
Mammary gland	I	+	+	+	+	+	+	+	+	+	+	+	I	+	+	I	+	+	+	I	+	+	+	+	+
Carcinoma																								X	
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Subcutaneous tissue, pinna, fibrosarcoma																									
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pelvis, sarcoma									X																
Skeletal muscle								+	+	+		+		+						+					
Hepatocholangiocarcinoma, metastatic, liver										X															
Rhabdomyosarcoma																									
Sarcoma									X																
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Peripheral nerve								+				+		+						+					
Spinal cord								+				+		+						+					

TABLE A2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Intravaginal Study of Polyvinyl Alcohol: 25%

Number of Days on Study	668	675	682	686	688	690	699	697	701	704	708	711	721	721	729	729	729	729	729	729	729	729	729	729
Carcass ID Number	210	267	209	257	289	242	244	233	261	288	281	218	245	295	204	207	215	219	226	227	232	246	248	249	255
Genital System																									
Clitoral gland	+	+	+	+	I	I	+	+	+	+	+	+	+	+	+	+	+	I	+	+	+	+	I	+	+
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cystadenoma						X																			
Hepatocholangiocarcinoma, metastatic, liver																									
Luteoma																									
Teratoma benign																									
Yolk sac carcinoma																									
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma																									
Deciduoma NOS																									
Histiocytic sarcoma																					X				
Polyp stromal																									
Vagina	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																					X				
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node			+				+						+			+	+								
Plasma cell tumor benign																									
Lymph node, mandibular	+	+	+	+	+	+	+	I	+	+	+	+	+	I	+	+	+	+	+	+	+	+	+	+	+
Plasma cell tumor benign											X														
Lymph node, mesenteric	+	+	+	A	+	+	+	I	+	+	I	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocholangiocarcinoma, metastatic, liver																									
Spleen	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocholangiocarcinoma, metastatic, liver																									
Thymoma benign																									
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	I	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma																									
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Subcutaneous tissue, pinna, fibrosarcoma																									
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pelvis, sarcoma																									
Skeletal muscle																									
Hepatocholangiocarcinoma, metastatic, liver																									
Rhabdomyosarcoma																									
Sarcoma																									
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Peripheral nerve																									
Spinal cord																									

TABLE A2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Intravaginal Study of Polyvinyl Alcohol: 25%

Number of Days on Study	729	729	729	729	729	729	729	729	729	729	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730
Carcass ID Number	25606	26505	27505	27606	27707	27902	27903	27907	27909	28000	28003	28005	28012	28017	28020	28021	28024	28025	28034	28037	28047	28050	28051	28054	28059
Genital System																									
Clitoral gland	+	+	+	+	+	+	+	I	+	I	+	+	+	+	+	+	+	+	+	+	+	+	+	I	+
Ovary	+	+	I	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+
Cystadenoma																									
Hepatocholangiocarcinoma, metastatic, liver																									
Luteoma																		X							
Teratoma benign																	X								
Yolk sac carcinoma																									
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma																									
Deciduoma NOS																									
Histiocytic sarcoma																									
Polyp stromal	X																								
Vagina	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																									
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node		+			+			+		+									+				+		
Plasma cell tumor benign																									
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Plasma cell tumor benign																									
Lymph node, mesenteric	+	+	+	+	I	+	I	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocholangiocarcinoma, metastatic, liver																									
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocholangiocarcinoma, metastatic, liver																									
Thymoma benign																									
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	I	+	+	+	+	+	+	+	+	+	+	+	+	+	I
Carcinoma																									
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Subcutaneous tissue, pinna, fibrosarcoma																						X			
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pelvis, sarcoma																									
Skeletal muscle																			+						
Hepatocholangiocarcinoma, metastatic, liver																									
Rhabdomyosarcoma																			X						
Sarcoma																									
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Peripheral nerve																									
Spinal cord																									

TABLE A2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Intravaginal Study of Polyvinyl Alcohol: 25%

Number of Days on Study	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	
Carcass ID Number	2 6 0	2 6 2	2 6 6	2 6 8	2 7 2	2 7 8	2 8 3	2 8 4	2 9 0	2 0 2	2 0 6	2 1 1	2 1 3	2 3 1	2 3 5	2 5 2	2 5 3	2 7 3	2 7 4	2 7 9	2 8 0	2 8 6	2 8 7	2 9 6	2 9 8	Total Tissues/ Tumors
Genital System																										
Clitoral gland	+	+	+	+	+	+	+	I	+	+	+	+	+	I	+	+	+	+	+	+	+	+	+	+	+	83
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	97
Cystadenoma												X		X												3
Hepatocholangiocarcinoma, metastatic, liver																										1
Luteoma																										2
Teratoma benign																										1
Yolk sac carcinoma																	X									2
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	100
Carcinoma																										1
Deciduoma NOS																						X				1
Histiocytic sarcoma																										1
Polyp stromal		X																								3
Vagina	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	99
Histiocytic sarcoma																										1
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	100
Lymph node					+									+		+				+			+	+		21
Plasma cell tumor benign																										1
Lymph node, mandibular	+	+	+	+	+	+	+	I	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	I	+	93
Plasma cell tumor benign																										1
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	93
Hepatocholangiocarcinoma, metastatic, liver																										1
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	98
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	99
Hepatocholangiocarcinoma, metastatic, liver																										1
Thymoma benign																			X							1
Integumentary System																										
Mammary gland	I	I	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	91
Carcinoma																										1
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	100
Subcutaneous tissue, pinna, fibrosarcoma																										1
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	100
Pelvis, sarcoma																										1
Skeletal muscle														+												8
Hepatocholangiocarcinoma, metastatic, liver																										1
Rhabdomyosarcoma														X												2
Sarcoma																										1
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	100
Peripheral nerve																										4
Spinal cord																										4

TABLE A2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Intravaginal Study of Polyvinyl Alcohol: 25%

Number of Days on Study	072	112	313	324	372	504	507	514	542	553	619	620	620	624	624	627	634	637	638	640	646	646	651	658	661
Carcass ID Number	258	240	218	239	208	282	238	285	229	236	281	201	264	213	291	241	222	294	270	243	216	263	214	269	230
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma			X						X																
Alveolar/bronchiolar carcinoma																									
Hepatocholangiocarcinoma, metastatic, liver										X			X												
Sarcoma, metastatic, uncertain primary site											X														
Yolk sac carcinoma, metastatic, ovary					X																				
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Eye																					+				
Harderian gland																					+				
Adenoma																									
Carcinoma																					X				
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	I	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																									
Lymphoma malignant															X	X	X								

TABLE A2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Intravaginal Study of Polyvinyl Alcohol: 25%

Number of Days on Study	668	675	682	688	688	690	696	697	701	704	708	714	721	721	729	729	729	729	729	729	729	729	729	729
Carcass ID Number	210	267	209	257	289	242	244	233	261	288	271	284	245	495	204	207	215	219	226	227	232	246	248	249	255
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																							X		
Alveolar/bronchiolar carcinoma		X															X				X				
Hepatocholangiocarcinoma, metastatic, liver																									
Sarcoma, metastatic, uncertain primary site																									
Yolk sac carcinoma, metastatic, ovary																									
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Eye						+																			
Harderian gland						+																			
Adenoma						X																			
Carcinoma																									
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																					X				
Lymphoma malignant			X				X						X												X

TABLE A2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Intravaginal Study of Polyvinyl Alcohol: 25%

Number of Days on Study	729	729	729	729	729	729	729	729	729	729	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730
Carcass ID Number	25 6	26 5	27 5	27 6	27 7	29 2	29 3	29 7	29 9	30 0	30 3	30 5	31 2	31 7	32 0	32 1	32 4	32 5	33 4	33 7	34 7	35 0	35 1	35 4	35 9	
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Alveolar/bronchiolar adenoma																	X	X					X			
Alveolar/bronchiolar carcinoma																										
Hepatocholangiocarcinoma, metastatic, liver																										
Sarcoma, metastatic, uncertain primary site																										
Yolk sac carcinoma, metastatic, ovary																										
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Special Senses System																										
Eye																										
Harderian gland																										
Adenoma																										
Carcinoma																										
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Histiocytic sarcoma																										
Lymphoma malignant		X			X			X		X	X	X		X									X			

TABLE A2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Intravaginal Study of Polyvinyl Alcohol: 25%

Number of Days on Study	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	
Carcass ID Number	2 6 0	2 6 2	2 6 6	2 6 8	2 7 2	2 7 8	2 8 3	2 8 4	2 9 0	2 0 2	2 0 6	2 1 1	2 1 3	2 3 1	2 3 5	2 5 2	2 5 3	2 7 3	2 7 4	2 7 9	2 8 0	2 8 6	2 8 7	2 9 6	2 9 8	Total Tissues/ Tumors
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	100
Alveolar/bronchiolar adenoma		X																					X			8
Alveolar/bronchiolar carcinoma																				X		X				5
Hepatocholangiocarcinoma, metastatic, liver																										2
Sarcoma, metastatic, uncertain primary site																										1
Yolk sac carcinoma, metastatic, ovary																										1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	100
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	100
Special Senses System																										
Eye	+																									3
Harderian gland	+											+				+		+								6
Adenoma												X				X		X								4
Carcinoma																										1
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	100
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	98
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	100
Histiocytic sarcoma																										1
Lymphoma malignant						X								X										X		18

TABLE A3a
Statistical Analysis of Primary Neoplasms in Female Mice in the 2-Year Intravaginal Study of Polyvinyl Alcohol: Untreated Control vs. Vehicle Control

	Untreated Control	Vehicle Control
Harderian Gland: Adenoma		
Overall rate[a]	4/100 (4%)	9/100 (9%)
Adjusted rate[b]	7.1%	15.0%
Terminal rate[c]	2/47 (4%)	5/51 (10%)
First incidence (days)	640	668
Life table test[d]		P=0.160
Logistic regression test[d]		P=0.152
Fisher exact test[d]		P=0.125
Harderian Gland: Adenoma or Carcinoma		
Overall rate	5/100 (5%)	11/100 (11%)
Adjusted rate	8.3%	17.1%
Terminal rate	2/47 (4%)	5/51 (10%)
First incidence (days)	640	620
Life table test		P=0.130
Logistic regression test		P=0.115
Fisher exact test		P=0.096
Liver: Hepatocellular Adenoma		
Overall rate	55/99 (56%)	56/99 (57%)
Adjusted rate	80.3%	80.5%
Terminal rate	34/47 (72%)	38/51 (75%)
First incidence (days)	365	611
Life table test		P=0.384N
Logistic regression test		P=0.355N
Fisher exact test		P=0.500
Liver: Hepatocellular Carcinoma		
Overall rate	11/99 (11%)	18/99 (18%)
Adjusted rate	18.6%	27.5%
Terminal rate	5/47 (11%)	9/51 (18%)
First incidence (days)	538	548
Life table test		P=0.175
Logistic regression test		P=0.143
Fisher exact test		P=0.114
Liver: Hepatocellular Adenoma or Carcinoma		
Overall rate	59/99 (60%)	61/99 (62%)
Adjusted rate	82.6%	82.9%
Terminal rate	35/47 (74%)	39/51 (76%)
First incidence (days)	365	548
Life table test		P=0.421N
Logistic regression test		P=0.402N
Fisher exact test		P=0.442
Lung: Alveolar/bronchiolar Adenoma		
Overall rate	6/100 (6%)	7/98 (7%)
Adjusted rate	11.0%	11.8%
Terminal rate	4/47 (9%)	3/51 (6%)
First incidence (days)	643	611
Life table test		P=0.558
Logistic regression test		P=0.542
Fisher exact test		P=0.485

TABLE A3a
Statistical Analysis of Primary Neoplasms in Female Mice in the 2-Year Intravaginal Study of Polyvinyl Alcohol: Untreated Control vs. Vehicle Control

	Untreated Control	Vehicle Control
Lung: Alveolar/bronchiolar Adenoma or Carcinoma		
Overall rate	9/100 (9%)	10/98 (10%)
Adjusted rate	15.2%	16.4%
Terminal rate	4/47 (9%)	5/51 (10%)
First incidence (days)	473	548
Life table test		P=0.571
Logistic regression test		P=0.525
Fisher exact test		P=0.481
Ovary: Cystadenoma		
Overall rate	6/95 (6%)	5/97 (5%)
Adjusted rate	11.1%	9.4%
Terminal rate	3/45 (7%)	4/51 (8%)
First incidence (days)	529	711
Life table test		P=0.428N
Logistic regression test		P=0.437N
Fisher exact test		P=0.486N
Pituitary Gland (Pars Distalis): Adenoma		
Overall rate	13/88 (15%)	9/86 (10%)
Adjusted rate	26.2%	14.9%
Terminal rate	9/43 (21%)	4/47 (9%)
First incidence (days)	657	620
Life table test		P=0.196N
Logistic regression test		P=0.210N
Fisher exact test		P=0.266N
Thyroid Gland (Follicular Cell): Adenoma		
Overall rate	8/100 (8%)	9/96 (9%)
Adjusted rate	16.3%	15.8%
Terminal rate	7/47 (15%)	6/51 (12%)
First incidence (days)	686	634
Life table test		P=0.566
Logistic regression test		P=0.555
Fisher exact test		P=0.464
Thyroid Gland (Follicular Cell): Adenoma or Carcinoma		
Overall rate	8/100 (8%)	10/96 (10%)
Adjusted rate	16.3%	17.6%
Terminal rate	7/47 (15%)	7/51 (14%)
First incidence (days)	686	634
Life table test		P=0.469
Logistic regression test		P=0.456
Fisher exact test		P=0.368
All Organs: Malignant Lymphoma		
Overall rate	13/100 (13%)	14/100 (14%)
Adjusted rate	23.1%	23.0%
Terminal rate	7/47 (15%)	8/51 (16%)
First incidence (days)	652	627
Life table test		P=0.578N
Logistic regression test		P=0.580
Fisher exact test		P=0.500

TABLE A3a
Statistical Analysis of Primary Neoplasms in Female Mice in the 2-Year Intravaginal Study of Polyvinyl Alcohol: Untreated Control vs. Vehicle Control

	Untreated Control	Vehicle Control
All Organs: Benign Neoplasms		
Overall rate	67/100 (67%)	72/100 (72%)
Adjusted rate	90.3%	92.1%
Terminal rate	40/47 (85%)	45/51 (88%)
First incidence (days)	365	588
Life table test		P=0.533N
Logistic regression test		P=0.540N
Fisher exact test		P=0.270
All Organs: Malignant Neoplasms		
Overall rate	39/100 (39%)	42/100 (42%)
Adjusted rate	52.7%	55.9%
Terminal rate	14/47 (30%)	21/51 (41%)
First incidence (days)	410	548
Life table test		P=0.545N
Logistic regression test		P=0.557
Fisher exact test		P=0.387
All Organs: Benign or Malignant Neoplasms		
Overall rate	78/100 (78%)	82/100 (82%)
Adjusted rate	93.9%	96.4%
Terminal rate	42/47 (89%)	48/51 (94%)
First incidence (days)	365	548
Life table test		P=0.449N
Logistic regression test		P=0.464N
Fisher exact test		P=0.298

[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] Kaplan-Meier estimated neoplasm incidence at the end of the study after adjustment for intercurrent mortality
[c] Observed incidence at terminal kill
[d] Beneath the vehicle control group incidence are the P values corresponding to pairwise comparisons between the untreated control group and the vehicle control group. The life table test regards neoplasms in animals dying prior to terminal kill as being (directly or indirectly) the cause of death. The logistic regression test regards these lesions as nonfatal. The Fisher exact test compares directly the overall incidence rates. For all tests, a lower incidence in the vehicle control group is indicated by **N**.

TABLE A3b
Statistical Analysis of Primary Neoplasms in Female Mice in the 2-Year Intravaginal Study of Polyvinyl Alcohol: Untreated Control vs. 25%

	Untreated Control	25%
Harderian Gland: Adenoma or Carcinoma		
Overall rate[a]	5/100 (5%)	5/100 (5%)
Adjusted rate[b]	8.3%	7.4%
Terminal rate[c]	2/47 (4%)	3/61 (5%)
First incidence (days)	640	646
Life table test[d]		P=0.507N
Logistic regression test[d]		P=0.583N
Fisher exact test[d]		P=0.626N
Liver: Hepatocellular Adenoma		
Overall rate	55/99 (56%)	55/100 (55%)
Adjusted rate	80.3%	69.2%
Terminal rate	34/47 (72%)	37/61 (61%)
First incidence (days)	365	514
Life table test		P=0.081N
Logistic regression test		P=0.239N
Fisher exact test		P=0.525N
Liver: Hepatocellular Carcinoma		
Overall rate	11/99 (11%)	20/100 (20%)
Adjusted rate	18.6%	28.0%
Terminal rate	5/47 (11%)	13/61 (21%)
First incidence (days)	538	507
Life table test		P=0.181
Logistic regression test		P=0.088
Fisher exact test		P=0.062
Liver: Hepatocellular Adenoma or Carcinoma		
Overall rate	59/99 (60%)	62/100 (62%)
Adjusted rate	82.6%	73.4%
Terminal rate	35/47 (74%)	39/61 (64%)
First incidence (days)	365	507
Life table test		P=0.143N
Logistic regression test		P=0.416N
Fisher exact test		P=0.420
Lung: Alveolar/bronchiolar Adenoma		
Overall rate	6/100 (6%)	8/100 (8%)
Adjusted rate	11.0%	11.7%
Terminal rate	4/47 (9%)	6/61 (10%)
First incidence (days)	643	313
Life table test		P=0.548
Logistic regression test		P=0.410
Fisher exact test		P=0.391
Lung: Alveolar/bronchiolar Carcinoma		
Overall rate	3/100 (3%)	5/100 (5%)
Adjusted rate	4.7%	7.8%
Terminal rate	0/47 (0%)	4/61 (7%)
First incidence (days)	473	675
Life table test		P=0.474
Logistic regression test		P=0.383
Fisher exact test		P=0.360

TABLE A3b
Statistical Analysis of Primary Neoplasms in Female Mice in the 2-Year Intravaginal Study of Polyvinyl Alcohol: Untreated Control vs. 25%

	Untreated Control	25%
Lung: Alveolar/bronchiolar Adenoma or Carcinoma		
Overall rate	9/100 (9%)	13/100 (13%)
Adjusted rate	15.2%	19.3%
Terminal rate	4/47 (9%)	10/61 (16%)
First incidence (days)	473	313
Life table test		P=0.434
Logistic regression test		P=0.274
Fisher exact test		P=0.249
Ovary: Cystadenoma		
Overall rate	6/95 (6%)	3/97 (3%)
Adjusted rate	11.1%	4.8%
Terminal rate	3/45 (7%)	2/59 (3%)
First incidence (days)	529	690
Life table test		P=0.157N
Logistic regression test		P=0.204N
Fisher exact test		P=0.238N
Pituitary Gland (Pars Distalis): Adenoma		
Overall rate	13/88 (15%)	10/84 (12%)
Adjusted rate	26.2%	16.5%
Terminal rate	9/43 (21%)	6/50 (12%)
First incidence (days)	657	634
Life table test		P=0.206N
Logistic regression test		P=0.293N
Fisher exact test		P=0.372N
Thyroid Gland (Follicular Cell): Adenoma		
Overall rate	8/100 (8%)	11/100 (11%)
Adjusted rate	16.3%	16.7%
Terminal rate	7/47 (15%)	8/61 (13%)
First incidence (days)	686	637
Life table test		P=0.528
Logistic regression test		P=0.445
Fisher exact test		P=0.315
All Organs: Malignant Lymphoma		
Overall rate	13/100 (13%)	18/100 (18%)
Adjusted rate	23.1%	25.8%
Terminal rate	7/47 (15%)	12/61 (20%)
First incidence (days)	652	624
Life table test		P=0.451
Logistic regression test		P=0.324
Fisher exact test		P=0.217
All Organs: Benign Neoplasms		
Overall rate	67/100 (67%)	69/100 (69%)
Adjusted rate	90.3%	81.9%
Terminal rate	40/47 (85%)	46/61 (75%)
First incidence (days)	365	313
Life table test		P=0.076N
Logistic regression test		P=0.332N
Fisher exact test		P=0.440

TABLE A3b
Statistical Analysis of Primary Neoplasms in Female Mice in the 2-Year Intravaginal Study of Polyvinyl Alcohol: Untreated Control vs. 25%

	Untreated Control	25%
All Organs: Malignant Neoplasms		
Overall rate	39/100 (39%)	51/100 (51%)
Adjusted rate	52.7%	60.9%
Terminal rate	14/47 (30%)	30/61 (49%)
First incidence (days)	410	324
Life table test		P=0.393
Logistic regression test		P=0.088
Fisher exact test		P=0.059
All Organs: Benign or Malignant Neoplasms		
Overall rate	78/100 (78%)	88/100 (88%)
Adjusted rate	93.9%	91.6%
Terminal rate	42/47 (89%)	53/61 (87%)
First incidence (days)	365	313
Life table test		P=0.257N
Logistic regression test		P=0.135
Fisher exact test		P=0.045

[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] Kaplan-Meier estimated neoplasm incidence at the end of the study after adjustment for intercurrent mortality
[c] Observed incidence at terminal kill
[d] Beneath the dosed group incidence are the P values corresponding to pairwise comparisons between the untreated control group and the dosed group. The life table test regards neoplasms in animals dying prior to terminal kill as being (directly or indirectly) the cause of death. The logistic regression test regards these lesions as nonfatal. The Fisher exact test compares directly the overall incidence rates. For all tests, a lower incidence in the dosed group is indicated by **N**.

TABLE A3c
Statistical Analysis of Primary Neoplasms in Female Mice in the 2-Year Intravaginal Study of Polyvinyl Alcohol: Vehicle Control vs. 25%

	Vehicle Control	25%
Harderian Gland: Adenoma		
Overall rate[a]	9/100 (9%)	4/100 (4%)
Adjusted rate[b]	15.0%	6.3%
Terminal rate[c]	5/51 (10%)	3/61 (5%)
First incidence (days)	668	690
Life table test[d]		P=0.081N
Logistic regression test[d]		P=0.107N
Fisher exact test[d]		P=0.125N
Harderian Gland: Adenoma or Carcinoma		
Overall rate	11/100 (11%)	5/100 (5%)
Adjusted rate	17.1%	7.4%
Terminal rate	5/51 (10%)	3/61 (5%)
First incidence (days)	620	646
Life table test		P=0.063N
Logistic regression test		P=0.091N
Fisher exact test		P=0.096N
Liver: Hepatocellular Adenoma		
Overall rate	56/99 (57%)	55/100 (55%)
Adjusted rate	80.5%	69.2%
Terminal rate	38/51 (75%)	37/61 (61%)
First incidence (days)	611	514
Life table test		P=0.147N
Logistic regression test		P=0.373N
Fisher exact test		P=0.468N
Liver: Hepatocellular Carcinoma		
Overall rate	18/99 (18%)	20/100 (20%)
Adjusted rate	27.5%	28.0%
Terminal rate	9/51 (18%)	13/61 (21%)
First incidence (days)	548	507
Life table test		P=0.533N
Logistic regression test		P=0.452
Fisher exact test		P=0.442
Liver: Hepatocellular Adenoma or Carcinoma		
Overall rate	61/99 (62%)	62/100 (62%)
Adjusted rate	82.9%	73.4%
Terminal rate	39/51 (76%)	39/61 (64%)
First incidence (days)	548	507
Life table test		P=0.213N
Logistic regression test		P=0.535N
Fisher exact test		P=0.536
Lung: Alveolar/bronchiolar Adenoma		
Overall rate	7/98 (7%)	8/100 (8%)
Adjusted rate	11.8%	11.7%
Terminal rate	3/51 (6%)	6/61 (10%)
First incidence (days)	611	313
Life table test		P=0.603
Logistic regression test		P=0.516
Fisher exact test		P=0.516

TABLE A3c
Statistical Analysis of Primary Neoplasms in Female Mice in the 2-Year Intravaginal Study of Polyvinyl Alcohol: Vehicle Control vs. 25%

	Vehicle Control	25%
Lung: Alveolar/bronchiolar Carcinoma		
Overall rate	3/98 (3%)	5/100 (5%)
Adjusted rate	5.0%	7.8%
Terminal rate	2/51 (4%)	4/61 (7%)
First incidence (days)	548	675
Life table test		P=0.437
Logistic regression test		P=0.377
Fisher exact test		P=0.372
Lung: Alveolar/bronchiolar Adenoma or Carcinoma		
Overall rate	10/98 (10%)	13/100 (13%)
Adjusted rate	16.4%	19.3%
Terminal rate	5/51 (10%)	10/61 (16%)
First incidence (days)	548	313
Life table test		P=0.461
Logistic regression test		P=0.349
Fisher exact test		P=0.348
Ovary: Cystadenoma		
Overall rate	5/97 (5%)	3/97 (3%)
Adjusted rate	9.4%	4.8%
Terminal rate	4/51 (8%)	2/59 (3%)
First incidence (days)	711	690
Life table test		P=0.290N
Logistic regression test		P=0.320N
Fisher exact test		P=0.360N
Pituitary Gland (Pars Distalis): Adenoma		
Overall rate	9/86 (10%)	10/84 (12%)
Adjusted rate	14.9%	16.5%
Terminal rate	4/47 (9%)	6/50 (12%)
First incidence (days)	620	634
Life table test		P=0.559
Logistic regression test		P=0.478
Fisher exact test		P=0.478
Thyroid Gland (Follicular Cell): Adenoma		
Overall rate	9/96 (9%)	11/100 (11%)
Adjusted rate	15.8%	16.7%
Terminal rate	6/51 (12%)	8/61 (13%)
First incidence (days)	634	637
Life table test		P=0.549
Logistic regression test		P=0.472
Fisher exact test		P=0.445
Thyroid Gland (Follicular Cell): Adenoma or Carcinoma		
Overall rate	10/96 (10%)	11/100 (11%)
Adjusted rate	17.6%	16.7%
Terminal rate	7/51 (14%)	8/61 (13%)
First incidence (days)	634	637
Life table test		P=0.535N
Logistic regression test		P=0.571
Fisher exact test		P=0.540

TABLE A3c
Statistical Analysis of Primary Neoplasms in Female Mice in the 2-Year Intravaginal Study of Polyvinyl Alcohol: Vehicle Control vs. 25%

	Vehicle Control	25%
All Organs: Malignant Lymphoma		
Overall rate	14/100 (14%)	18/100 (18%)
Adjusted rate	23.0%	25.8%
Terminal rate	8/51 (16%)	12/61 (20%)
First incidence (days)	627	624
Life table test		P=0.447
Logistic regression test		P=0.316
Fisher exact test		P=0.282
All Organs: Benign Neoplasms		
Overall rate	72/100 (72%)	69/100 (69%)
Adjusted rate	92.1%	81.9%
Terminal rate	45/51 (88%)	46/61 (75%)
First incidence (days)	588	313
Life table test		P=0.070N
Logistic regression test		P=0.292N
Fisher exact test		P=0.378N
All Organs: Malignant Neoplasms		
Overall rate	42/100 (42%)	51/100 (51%)
Adjusted rate	55.9%	60.9%
Terminal rate	21/51 (41%)	30/61 (49%)
First incidence (days)	548	324
Life table test		P=0.397
Logistic regression test		P=0.089
Fisher exact test		P=0.128
All Organs: Benign or Malignant Neoplasms		
Overall rate	82/100 (82%)	88/100 (88%)
Adjusted rate	96.4%	91.6%
Terminal rate	48/51 (94%)	53/61 (87%)
First incidence (days)	548	313
Life table test		P=0.314N
Logistic regression test		P=0.141
Fisher exact test		P=0.161

[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] Kaplan-Meier estimated neoplasm incidence at the end of the study after adjustment for intercurrent mortality
[c] Observed incidence at terminal kill
[d] Beneath the dosed group incidence are the P values corresponding to pairwise comparisons between the vehicle control group and the dosed group. The life table test regards neoplasms in animals dying prior to terminal kill as being (directly or indirectly) the cause of death. The logistic regression test regards these lesions as nonfatal. The Fisher exact test compares directly the overall incidence rates. For all tests, a lower incidence in the dosed group is indicated by **N**.

TABLE A4
Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 2-Year Intravaginal Study of Polyvinyl Alcohol[a]

	Untreated Control	Vehicle Control	25%
Disposition Summary			
Animals initially in study	100	100	100
Early deaths			
Accidental deaths	10	4	5
Moribund	19	25	13
Natural deaths	24	20	21
Survivors			
Terminal sacrifice	47	51	61
Animals examined microscopically	100	100	100
Alimentary System			
Esophagus	(100)	(100)	(99)
Periesophageal tissue, inflammation, chronic			1 (1%)
Gallbladder	(76)	(87)	(79)
Hyperplasia	1 (1%)		
Intestine large, colon	(92)	(93)	(97)
Inflammation, chronic		1 (1%)	1 (1%)
Lymphoid tissue, hyperplasia	1 (1%)		
Serosa, inflammation, chronic	1 (1%)		
Intestine large, rectum	(89)	(91)	(96)
Inflammation, chronic		1 (1%)	1 (1%)
Serosa, inflammation, chronic	1 (1%)		
Intestine large, cecum	(88)	(92)	(96)
Inflammation, chronic		1 (1%)	
Serosa, inflammation, chronic	1 (1%)		
Intestine small, duodenum	(88)	(90)	(92)
Inflammation, chronic		1 (1%)	
Epithelium, hyperplasia	2 (2%)		1 (1%)
Serosa, inflammation, chronic	1 (1%)		
Intestine small, jejunum	(89)	(90)	(91)
Inflammation, chronic		1 (1%)	
Epithelium, hyperplasia		1 (1%)	
Peyer's patch, hyperplasia	2 (2%)		
Serosa, inflammation, chronic	1 (1%)		
Intestine small, ileum	(88)	(90)	(92)
Inflammation, chronic		1 (1%)	
Epithelium, hyperplasia		1 (1%)	
Peyer's patch, hyperplasia, lymphoid	1 (1%)		
Serosa, inflammation, chronic	1 (1%)		
Liver	(99)	(99)	(100)
Atrophy	1 (1%)	10 (10%)	2 (2%)
Basophilic focus	2 (2%)	1 (1%)	
Clear cell focus	1 (1%)	10 (10%)	6 (6%)
Depletion glycogen	20 (20%)	37 (37%)	30 (30%)
Eosinophilic focus	2 (2%)	3 (3%)	2 (2%)
Fibrosis	1 (1%)	2 (2%)	
Hematopoietic cell proliferation	23 (23%)	35 (35%)	25 (25%)
Infarct	1 (1%)		1 (1%)
Inflammation	3 (3%)	2 (2%)	1 (1%)
Necrosis	3 (3%)	5 (5%)	4 (4%)
Pigmentation, hemosiderin	1 (1%)	2 (2%)	
Vacuolization cytoplasmic	38 (38%)	43 (43%)	39 (39%)
Centrilobular, dilatation	1 (1%)		
Centrilobular, inflammation, chronic	1 (1%)		
Serosa, inflammation, chronic		1 (1%)	

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

TABLE A4
Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 2-Year Intravaginal Study of Polyvinyl Alcohol

	Untreated Control	Vehicle Control	25%
Alimentary System (continued)			
Mesentery	(33)	(25)	(36)
Inflammation, chronic	3 (9%)	1 (4%)	
Necrosis	27 (82%)	23 (92%)	31 (86%)
Pancreas	(97)	(95)	(98)
Atrophy	11 (11%)	8 (8%)	6 (6%)
Hyperplasia	1 (1%)		
Hyperplasia, lymphoid		1 (1%)	
Inflammation, chronic	18 (19%)	40 (42%)	36 (37%)
Necrosis	1 (1%)		
Vacuolization cytoplasmic	1 (1%)		
Acinus, atrophy			1 (1%)
Duct, cyst		1 (1%)	
Duct, dilatation			1 (1%)
Salivary glands	(99)	(97)	(100)
Atrophy	6 (6%)	6 (6%)	5 (5%)
Inflammation, chronic	52 (53%)	61 (63%)	58 (58%)
Stomach, forestomach	(94)	(93)	(97)
Inflammation			1 (1%)
Epithelium, hyperplasia	1 (1%)		3 (3%)
Serosa, inflammation, chronic		1 (1%)	
Stomach, glandular	(93)	(93)	(96)
Ectopic liver		1 (1%)	
Hemorrhage	1 (1%)		
Inflammation, chronic	1 (1%)		1 (1%)
Epithelium, atrophy		1 (1%)	
Epithelium, hyperplasia		1 (1%)	1 (1%)
Epithelium, metaplasia, squamous		1 (1%)	
Epithelium, mineralization		1 (1%)	
Serosa, inflammation, chronic		1 (1%)	
Cardiovascular System			
Blood vessel	(1)		(2)
Aorta, degeneration	1 (100%)		
Aorta, metaplasia, osseous			1 (50%)
Heart	(100)	(99)	(100)
Cardiomyopathy	2 (2%)	4 (4%)	6 (6%)
Degeneration	83 (83%)	92 (93%)	90 (90%)
Inflammation, chronic	1 (1%)	1 (1%)	1 (1%)
Mineralization		1 (1%)	
Thrombosis		1 (1%)	
Epicardium, hyperplasia, lymphoid		1 (1%)	
Epicardium, mineralization		1 (1%)	
Valve, thrombosis	1 (1%)		3 (3%)
Endocrine System			
Adrenal cortex	(100)	(94)	(97)
Accessory adrenal cortical nodule	1 (1%)	4 (4%)	1 (1%)
Angiectasis		2 (2%)	
Atrophy	1 (1%)		
Hematopoietic cell proliferation		1 (1%)	
Hemorrhage	1 (1%)		
Vacuolization cytoplasmic		1 (1%)	
Capsule, hyperplasia	4 (4%)	5 (5%)	7 (7%)
Capsule, inflammation, chronic	2 (2%)		

TABLE A4
Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 2-Year Intravaginal Study of Polyvinyl Alcohol

	Untreated Control	Vehicle Control	25%
Endocrine System (continued)			
Adrenal cortex (continued)	(100)	(94)	(97)
Zona glomerulosa, atrophy		1 (1%)	
Zona glomerulosa, hyperplasia	11 (11%)	9 (10%)	17 (18%)
Zona reticularis, hematopoietic cell proliferation			1 (1%)
Zona reticularis, hyperplasia	6 (6%)	4 (4%)	3 (3%)
Adrenal medulla	(99)	(94)	(92)
Hemorrhage			1 (1%)
Islets, pancreatic	(97)	(94)	(97)
Atrophy	2 (2%)		2 (2%)
Hyperplasia	70 (72%)	80 (85%)	78 (80%)
Infiltration cellular, lymphocyte		1 (1%)	
Necrosis	1 (1%)		
Parathyroid gland	(59)	(59)	(69)
Cyst		1 (2%)	
Hyperplasia	2 (3%)		1 (1%)
Infiltration cellular, lymphocyte		1 (2%)	
Inflammation, chronic			1 (1%)
Pituitary gland	(88)	(86)	(84)
Atrophy	1 (1%)		
Hemorrhage	2 (2%)	1 (1%)	
Pigmentation, hemosiderin	1 (1%)		
Pars distalis, angiectasis	1 (1%)		
Pars distalis, hyperplasia	27 (31%)	28 (33%)	29 (35%)
Pars intermedia, angiectasis			1 (1%)
Pars intermedia, hyperplasia		1 (1%)	
Thyroid gland	(100)	(96)	(100)
Inflammation, chronic			1 (1%)
Follicular cell, cyst			1 (1%)
Follicular cell, hyperplasia	57 (57%)	57 (59%)	58 (58%)
General Body System			
None			
Genital System			
Clitoral gland	(89)	(81)	(83)
Atrophy	29 (33%)	26 (32%)	18 (22%)
Hyperplasia	4 (4%)	8 (10%)	10 (12%)
Inflammation, chronic	2 (2%)	1 (1%)	
Ovary	(95)	(97)	(97)
Angiectasis	1 (1%)	1 (1%)	
Atrophy	1 (1%)		
Cyst	13 (14%)	13 (13%)	15 (15%)
Hemorrhage	2 (2%)	1 (1%)	2 (2%)
Hyperplasia, lymphoid		1 (1%)	
Hyperplasia, tubulostromal			1 (1%)
Inflammation, acute	1 (1%)		
Inflammation, chronic		2 (2%)	2 (2%)
Necrosis	1 (1%)	2 (2%)	4 (4%)
Thrombosis	2 (2%)	2 (2%)	1 (1%)
Periovarian tissue, inflammation, chronic	2 (2%)		

TABLE A4
Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 2-Year Intravaginal Study of Polyvinyl Alcohol

	Untreated Control	Vehicle Control	25%
Genital System (continued)			
Uterus	(100)	(100)	(100)
Amyloid deposition	1 (1%)		
Diestrus		1 (1%)	
Hemorrhage	2 (2%)		1 (1%)
Hydrometra	7 (7%)	2 (2%)	2 (2%)
Inflammation	2 (2%)		
Inflammation, chronic active	1 (1%)	1 (1%)	
Endometrium, angiectasis	1 (1%)	1 (1%)	
Endometrium, hemorrhage	1 (1%)		
Endometrium, hyperplasia, cystic	90 (90%)	97 (97%)	98 (98%)
Serosa, inflammation, chronic	2 (2%)		
Vagina	(97)	(99)	(99)
Diestrus		1 (1%)	
Inflammation, acute		2 (2%)	
Inflammation, chronic		2 (2%)	1 (1%)
Epithelium, hyperplasia		1 (1%)	
Epithelium, inflammation, chronic		1 (1%)	
Hematopoietic System			
Bone marrow	(100)	(98)	(100)
Amyloid deposition	1 (1%)		
Depletion cellular	1 (1%)		
Hyperplasia	12 (12%)	16 (16%)	11 (11%)
Infiltration cellular, histiocyte			1 (1%)
Myelofibrosis	19 (19%)	19 (19%)	26 (26%)
Pigmentation, hemosiderin		1 (1%)	
Lymph node	(15)	(21)	(21)
Ectasia		1 (5%)	
Hyperplasia	2 (13%)	3 (14%)	
Infiltration cellular, plasma cell		1 (5%)	
Bronchial, hemorrhage	1 (7%)		
Iliac, hemorrhage, chronic			1 (5%)
Iliac, hyperplasia		1 (5%)	3 (14%)
Iliac, inflammation, acute		1 (5%)	
Mediastinal, hemorrhage	1 (7%)		
Mediastinal, hyperplasia	1 (7%)	3 (14%)	4 (19%)
Renal, hemorrhage	1 (7%)		
Renal, hyperplasia			1 (5%)
Renal, inflammation, acute		1 (5%)	
Lymph node, mandibular	(92)	(94)	(93)
Atrophy	12 (13%)	6 (6%)	12 (13%)
Hemorrhage		1 (1%)	
Hyperplasia	16 (17%)	18 (19%)	10 (11%)
Hyperplasia, lymphoid	1 (1%)		
Infiltration cellular, histiocyte			1 (1%)
Necrosis	2 (2%)		
Pigmentation, hemosiderin	2 (2%)	2 (2%)	3 (3%)
Lymph node, mesenteric	(90)	(93)	(93)
Atrophy	12 (13%)	14 (15%)	10 (11%)
Hemorrhage	1 (1%)		
Hyperplasia	7 (8%)	6 (6%)	6 (6%)
Inflammation, chronic	2 (2%)	2 (2%)	2 (2%)
Necrosis	1 (1%)		1 (1%)
Pigmentation, hemosiderin			1 (1%)

TABLE A4
Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 2-Year Intravaginal Study of Polyvinyl Alcohol

	Untreated Control	Vehicle Control	25%
Hematopoietic System (continued)			
Spleen	(98)	(96)	(98)
Fibrosis			1 (1%)
Hematopoietic cell proliferation	52 (53%)	56 (58%)	59 (60%)
Inflammation, chronic			1 (1%)
Necrosis	2 (2%)		
Pigmentation, hemosiderin	41 (42%)	49 (51%)	46 (47%)
Thrombosis	1 (1%)		
Capsule, inflammation, chronic		1 (1%)	
Lymphoid follicle, atrophy	8 (8%)	1 (1%)	4 (4%)
Lymphoid follicle, hyperplasia	52 (53%)	65 (68%)	64 (65%)
Red pulp, atrophy	7 (7%)	1 (1%)	3 (3%)
Thymus	(98)	(93)	(99)
Atrophy	66 (67%)	82 (88%)	79 (80%)
Hemorrhage	2 (2%)		
Hyperplasia, lymphoid		1 (1%)	
Inflammation, chronic		1 (1%)	1 (1%)
Necrosis	1 (1%)		
Integumentary System			
Mammary gland	(93)	(92)	(91)
Atrophy			1 (1%)
Hyperplasia	8 (9%)	5 (5%)	7 (8%)
Inflammation, chronic		1 (1%)	
Skin	(98)	(98)	(100)
Edema	1 (1%)	2 (2%)	
Inflammation, chronic	1 (1%)	4 (4%)	
Epidermis, hyperplasia			1 (1%)
Hair follicle, atrophy	2 (2%)	2 (2%)	1 (1%)
Subcutaneous tissue, inflammation, chronic			1 (1%)
Vulva, inflammation, chronic			1 (1%)
Vulva, ulcer	1 (1%)		
Musculoskeletal System			
Bone	(100)	(100)	(100)
Hyperostosis	1 (1%)		2 (2%)
Osteoporosis	1 (1%)		1 (1%)
Skeletal muscle	(9)	(10)	(8)
Degeneration		1 (10%)	
Inflammation, chronic	3 (33%)		
Metaplasia, osseous		1 (10%)	
Nervous System			
Brain	(100)	(99)	(100)
Hydrocephalus	2 (2%)	3 (3%)	2 (2%)
Infiltration cellular, lymphocyte			1 (1%)
Inflammation, chronic	1 (1%)	1 (1%)	
Choroid plexus, hyperplasia			1 (1%)
Meninges, infiltration cellular, lymphocyte		1 (1%)	
Thalamus, mineralization	46 (46%)	53 (54%)	33 (33%)
Peripheral nerve	(3)	(4)	(4)
Inflammation, chronic	1 (33%)		

TABLE A4
Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 2-Year Intravaginal Study of Polyvinyl Alcohol

	Untreated Control	Vehicle Control	25%
Respiratory System			
Lung	(100)	(98)	(100)
Edema	9 (9%)	9 (9%)	3 (3%)
Hemorrhage	8 (8%)	3 (3%)	2 (2%)
Infiltration cellular	1 (1%)		
Inflammation, acute	7 (7%)		1 (1%)
Inflammation, chronic	9 (9%)	17 (17%)	16 (16%)
Pigmentation, hemosiderin		1 (1%)	
Thrombosis		1 (1%)	1 (1%)
Alveolar epithelium, hyperplasia	1 (1%)		1 (1%)
Bronchus, inflammation, chronic		1 (1%)	
Nose	(100)	(100)	(100)
Hemorrhage	1 (1%)		1 (1%)
Respiratory epithelium, inflammation	22 (22%)	15 (15%)	22 (22%)
Trachea	(100)	(100)	(100)
Peritracheal tissue, inflammation, chronic			1 (1%)
Special Senses System			
Eye	(4)	(6)	(3)
Atrophy	1 (25%)		
Cataract		2 (33%)	
Cornea, inflammation, chronic	3 (75%)	4 (67%)	3 (100%)
Urinary System			
Kidney	(100)	(98)	(100)
Congestion			1 (1%)
Hydronephrosis	1 (1%)	3 (3%)	2 (2%)
Inflammation	1 (1%)	1 (1%)	2 (2%)
Metaplasia, osseous	1 (1%)		
Mineralization	1 (1%)		
Nephropathy	88 (88%)	90 (92%)	93 (93%)
Glomerulus, amyloid deposition	1 (1%)		1 (1%)
Urinary bladder	(96)	(96)	(98)
Atrophy			1 (1%)
Degeneration		1 (1%)	
Inflammation, chronic		2 (2%)	3 (3%)
Serosa, inflammation, chronic	1 (1%)		

APPENDIX B
CHEMICAL CHARACTERIZATION AND DOSE FORMULATION STUDIES

CHEMICAL CHARACTERIZATION AND DOSE FORMULATION STUDIES

PROCUREMENT AND CHARACTERIZATION OF POLYVINYL ALCOHOL

Polyvinyl alcohol was obtained from Marubeni America Corporation (New York, NY) in one lot (N082889), which was used during the 30-day 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 polyvinyl alcohol studies are on file at the National Institute of Environmental Health Sciences.

The chemical, an off-white crystalline solid, was identified as polyvinyl alcohol by infrared, ultraviolet/visible, and nuclear magnetic resonance spectroscopy. The infrared spectrum was consistent with the literature spectrum (Cobler *et al.*, 1968), and the infrared, ultraviolet/visible, and nuclear magnetic resonance spectra were consistent with the structure of polyvinyl alcohol. The infrared and nuclear magnetic resonance spectra are presented in Figures B1 and B2. The melting point of 193.7° C, at which decomposition also occurred, was consistent with a literature reference (*Merck Index*, 1989). A density of 1.0064 ± 0.0011 g/mL was determined for lot N082889. The molecular weight was determined with high-performance liquid chromatography (HPLC) with the following system: TSK-GEL® G3000 PWXL column with refractive index detection and a solvent system of 0.1 M sodium nitrate. The flow rate was 0.8 mL/minute. Polyvinyl alcohol internal standards of molecular weights 15,000, 22,000, and 49,000 were also analyzed. The molecular weight of lot N082889 was determined to be approximately 24,000.

The purity of lot N082889 was determined by elemental analyses, United States Pharmacopeia (USP) Method XXII analyses (weight loss on drying, degree of hydrolysis, pH, viscosity, residue on ignition, water-insoluble substances), and HPLC. HPLC was performed with the system described for the molecular weight determination.

Results of elemental analyses were slightly high for carbon and slightly low for hydrogen when compared with the theoretical values for polyvinyl alcohol. The USP analyses for polyvinyl alcohol indicated the following results: weight loss on drying, 4.2% ± 0.1%; degree of hydrolysis, 88.3% ± 0.1%; pH, 5.9 ± 0.1; viscosity, 4.82 cps; residue on ignition, 0.75% ± 0.04%; water-insoluble substances, 0.09%. These results indicate that lot N082889 met the USP XXII specifications for polyvinyl alcohol. HPLC indicated one major peak and three impurities with a combined area of 1.1% relative to the major peak area. The overall purity was determined to be approximately 99%.

Accelerated stability studies of the bulk chemical were performed by the analytical chemistry laboratory. HPLC was performed using the system described above. These studies indicated that polyvinyl alcohol was stable as a bulk chemical for 2 weeks when stored protected from light at temperatures up to 60° C. To ensure stability, the bulk chemical was stored at room temperature, protected from light, in sealed containers in a vented cabinet. Stability was monitored during the 30-day and 2-year studies with HPLC. No degradation of the bulk chemical was detected.

PREPARATION AND ANALYSIS OF DOSE FORMULATIONS

The dose formulations were prepared by mixing polyvinyl alcohol with heated, charcoal-filtered, deionized water (Millipore Corporation, Bedford, MA) to give the required concentration (Table B1). The dose formulations were stored at room temperature, protected from light, in sealed containers for up to 5 weeks (30-day study) or 4 weeks (2-year study).

The analytical chemistry laboratory determined density, viscosity, and syringeability values of 5%, 10%, 15%, and 20% polyvinyl alcohol formulations. Viscosity was determined with Ubbelohde and Routine Opaque viscometers. Syringeability was tested with different sizes of gavage needles and catheters. Density ranged from 1.011 g/mL for the 5% solution to 1.066 g/mL for the 20% solution; viscosity ranged from 6.16 cP for the 5% solution to 540.8 cP for the 20% solution. The syringeability of up to a 15% solution through a 5.5-inch catheter was verified.

Stability studies of a 15% (150 mg/mL) polyvinyl alcohol dose formulation were also performed by the analytical chemistry laboratory using HPLC with the same system as for the bulk stability analyses but with a solvent system of Milli-Q water. The stability of the dose formulation was confirmed for 4 weeks when stored at room temperature protected from light and for 3 weeks when stored open to air and light. Additional stability analyses of the dose formulation were performed by the study laboratory with HPLC. The 25% dose formulation was determined to be stable for at least 97 days when stored at room temperature, sealed and protected from light, and for 3 hours under simulated dosing conditions (open to air and light).

For the 30-day study, doses were prepared once and analyzed by HPLC. The dose formulation (25.46%) was within 2% of the target concentration of 25%. An animal room sample from the 30-day study was also analyzed and was determined to be 26.59% (6.4% greater than the target concentration).

Periodic analyses of the dose formulations in the 2-year study of polyvinyl alcohol were conducted at the study laboratory using HPLC. The formulations were analyzed every 4 to 8 weeks (Table B2). All dose formulations analyzed and used during the 2-year studies were within 10% of the target concentration, with no value greater than 105% of the target concentration; all animal room samples were also within 10% of the target concentration, with no value greater than 104% of the target concentration.

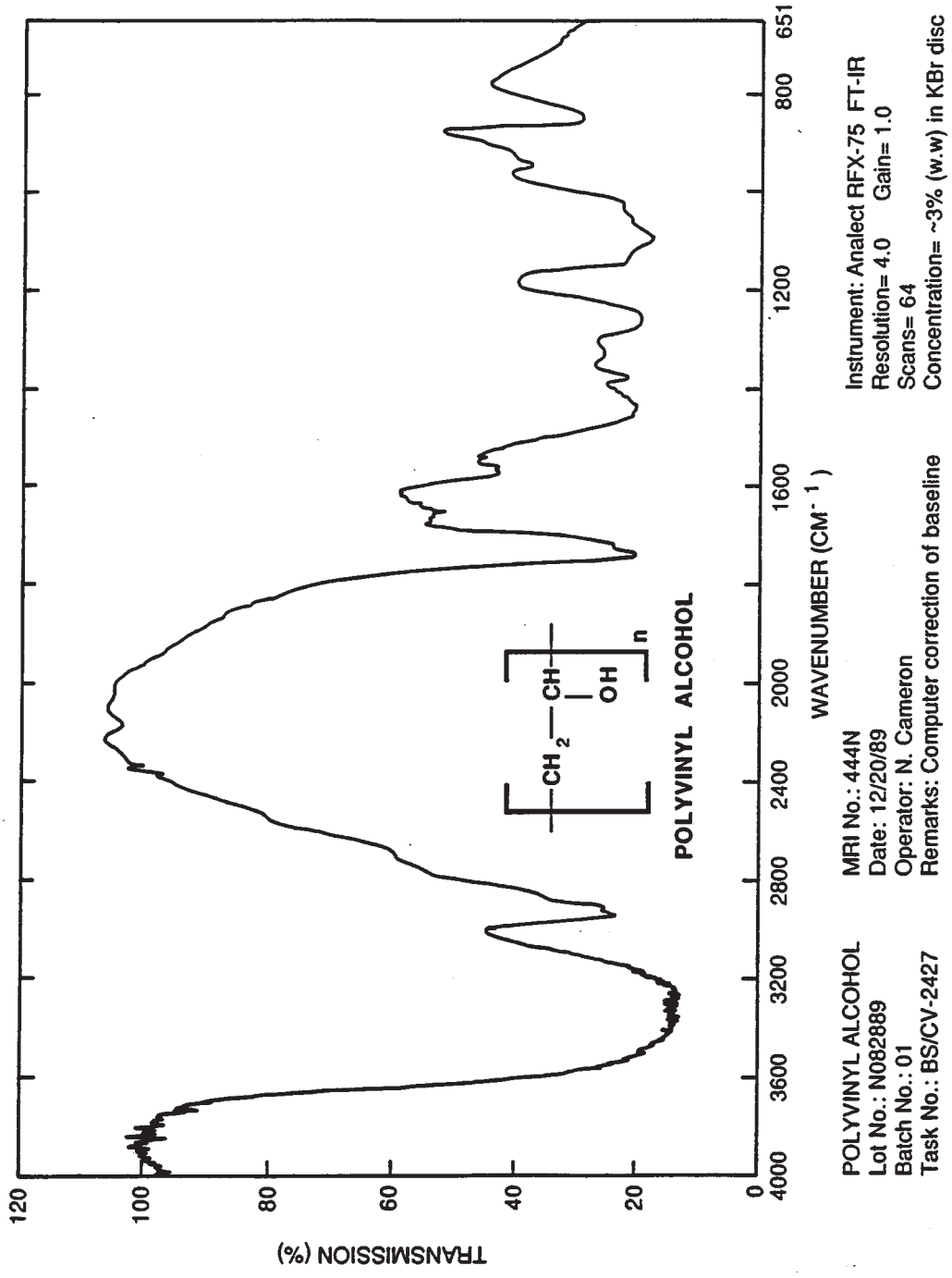


FIGURE B1
Infrared Absorption Spectrum of Polyvinyl Alcohol

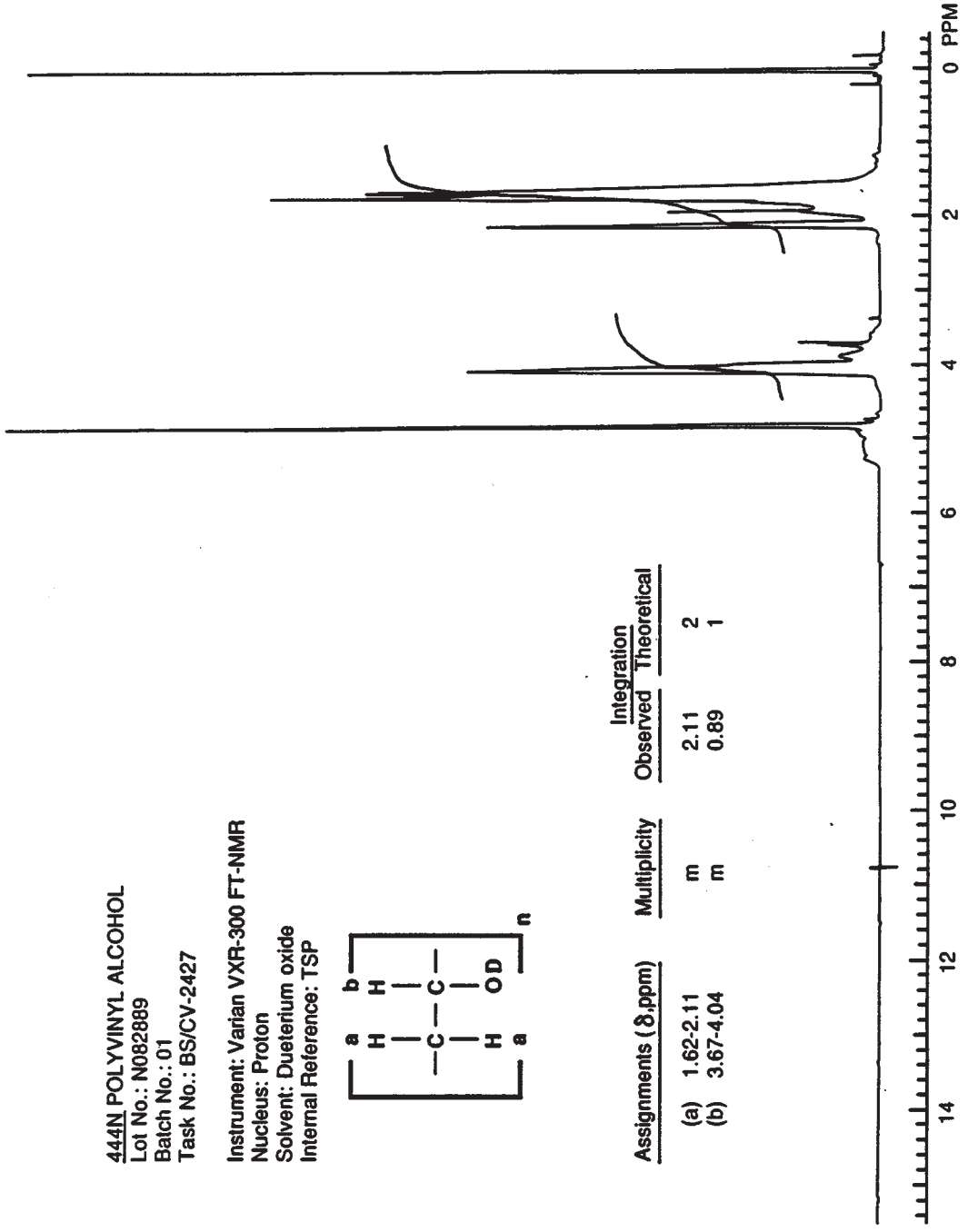


FIGURE B2
Nuclear Magnetic Resonance Spectrum of Polyvinyl Alcohol

TABLE B1
Preparation and Storage of Dose Formulations in the Intravaginal Studies of Polyvinyl Alcohol

30-Day Study	2-Year Study
Preparation Polyvinyl alcohol was stirred for 60 to 90 minutes with a magnetic stir bar in deionized water in a sealed bottle in a heated water bath (75°-85° C).	Same as 30-day study; water bath at 85° C.
Chemical Lot Number N082889	N082889
Maximum Storage Time 5 weeks	4 weeks
Storage Conditions Stored in sealed containers at room temperature protected from light	Same as 30-day study
Study Laboratory Arthur D. Little, Inc. (Cambridge, MA)	Arthur D. Little, Inc. (Cambridge, MA)
Analytical Chemistry Laboratory Midwest Research Institute (Kansas City, MO)	Midwest Research Institute (Kansas City, MO)

TABLE B2
Results of Analyses of Dose Formulations Administered to Female Mice in the 2-Year Intravaginal Study of Polyvinyl Alcohol

Date Prepared	Date Analyzed	Target Concentration (%)	Determined Concentration[a] (%)	Difference from Target (%)
13 February 1992	13 February 1992	25	25.36	+1
	16 March 1992[b]	25	25.06	0
7 April 1992	8 April 1992	25	24.98	0
7 May 1992	7 May 1992	25	25.72	+3
3 June 1992	3 June 1992	25	26.23	+5
28 July 1992	28 July 1992	25	25.67	+3
	29 September 1992[b]	25	25.01	0
23 September 1992	29 September 1992	25	24.59	−2
18 November 1992	19 November 1992	25	25.10	0
14 January 1993	14 January 1993	25	24.48	−2
	1 March 1993[b]	25	25.51	+2
9 March 1993	10 March 1993	25	24.09	−4
5 May 1993	5 May 1993	25	26.14	+5
29 June 1993	30 June 1993	25	26.00	+4
	27 August 1993[b]	25	26.06	+4
26 August 1993	27 August 1993	25	25.76	+3
20 October 1993	22 October 1993	25	24.25	−3
14 December 1993	15 December 1993	25	25.02	0
	23 January 1994[b]	25	25.50	+2

[a] Results of duplicate analyses
[b] Animal room sample

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

TABLE C1
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 C2
Vitamins and Minerals in NIH-07 Rat and Mouse Ration[a]

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

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

TABLE C3
Nutrient Composition of NIH-07 Rat and Mouse Ration

Nutrient	Mean ± Standard Deviation	Range	Number of Samples
Protein (% by weight)	23.33 ± 0.47	22.2 – 24.2	26
Crude fat (% by weight)	5.38 ± 0.17	5.10 – 5.90	26
Crude fiber (% by weight)	3.20 ± 0.33	2.60 – 4.30	26
Ash (% by weight)	6.36 ± 0.22	5.94 – 6.81	26
Amino Acids (% of total diet)			
Arginine	1.280 ± 0.083	1.110 – 1.390	11
Cystine	0.308 ± 0.071	0.181 – 0.400	11
Glycine	1.158 ± 0.048	1.060 – 1.220	11
Histidine	0.584 ± 0.027	0.531 – 0.630	11
Isoleucine	0.917 ± 0.033	0.867 – 0.965	11
Leucine	1.975 ± 0.051	1.850 – 2.040	11
Lysine	1.274 ± 0.049	1.200 – 1.370	11
Methionine	0.437 ± 0.109	0.306 – 0.699	11
Phenylalanine	0.999 ± 0.120	0.665 – 1.110	11
Threonine	0.904 ± 0.058	0.824 – 0.985	11
Tryptophan	0.218 ± 0.153	0.107 – 0.671	11
Tyrosine	0.685 ± 0.094	0.564 – 0.794	11
Valine	1.086 ± 0.055	0.962 – 1.170	11
Essential Fatty Acids (% of total diet)			
Linoleic	2.407 ± 0.227	1.830 – 2.570	10
Linolenic	0.259 ± 0.065	0.100 – 0.320	10
Vitamins			
Vitamin A (IU/kg)	6,635 ± 544	5,940 – 8,800	26
Vitamin D (IU/kg)	4,450 ± 1382	3,000 – 6,300	4
α-Tocopherol (ppm)	35.43 ± 8.98	22.5 – 48.9	11
Thiamine (ppm)	16.52 ± 2.26	13.0 – 22.0	25
Riboflavin (ppm)	7.83 ± 0.923	6.10 – 9.00	11
Niacin (ppm)	99.22 ± 24.27	65.0 – 150.0	11
Pantothenic acid (ppm)	30.55 ± 3.52	23.0 – 34.6	11
Pyridoxine (ppm)	9.11 ± 2.53	5.60 – 14.0	11
Folic acid (ppm)	2.46 ± 0.63	1.80 – 3.70	11
Biotin (ppm)	0.268 ± 0.047	0.190 – 0.354	11
Vitamin B_{12} (ppb)	40.5 ± 19.1	10.6 – 65.0	11
Choline (ppm)	2,991 ± 382	2,300 – 3,430	10
Minerals			
Calcium (%)	1.13 ± 0.04	1.06 – 1.20	26
Phosphorus (%)	0.90 ± 0.05	0.760 – 1.00	26
Potassium (%)	0.886 ± 0.063	0.772 – 0.971	9
Chloride (%)	0.529 ± 0.087	0.380 – 0.635	9
Sodium (%)	0.316 ± 0.033	0.258 – 0.371	11
Magnesium (%)	0.166 ± 0.010	0.148 – 0.181	11
Sulfur (%)	0.272 ± 0.059	0.208 – 0.420	10
Iron (ppm)	350.5 ± 87.3	255.0 – 523.0	11
Manganese (ppm)	92.48 ± 5.14	81.7 – 99.4	11
Zinc (ppm)	59.33 ± 10.2	46.1 – 81.6	11
Copper (ppm)	11.81 ± 2.50	8.09 – 15.4	11
Iodine (ppm)	3.54 ± 1.19	1.52 – 5.83	10
Chromium (ppm)	1.66 ± 0.46	0.85 – 2.09	11
Cobalt (ppm)	0.76 ± 0.23	0.49 – 1.15	7

TABLE C4
Contaminant Levels in NIH-07 Rat and Mouse Ration[a]

	Mean ± Standard Deviation[b]	Range	Number of Samples
Contaminants			
Arsenic (ppm)	0.54 ± 0.14	0.10 – 0.70	26
Cadmium (ppm)	0.09 ± 0.07	0.04 – 0.20	26
Lead (ppm)	0.31 ± 0.12	0.20 – 0.70	26
Mercury (ppm)	0.02	0.02 – 0.03	26
Selenium (ppm)	0.36 ± 0.08	0.10 – 0.50	26
Aflatoxins (ppb)	<5.0		26
Nitrate nitrogen (ppm)[c]	7.00 ± 2.79	2.90 – 14.0	26
Nitrite nitrogen (ppm)[c]	0.70 ± 0.93	0.10 – 3.50	26
BHA (ppm)[d]	2.19 ± 4.04	1.00 – 20.0	26
BHT (ppm)[d]	1.58 ± 0.99	1.0 – 5.00	26
Aerobic plate count (CFU/g)	101,400 ± 157,227	7,200 – 710,000	26
Coliform (MPN/g)	4 ± 3.9	3 – 23	26
Escherichia coli (MPN/g)	<3		26
Salmonella (MPN/g)	Negative		26
Total nitrosoamines (ppb)[e]	10.97 ± 4.39	4.70 – 23.00	26
N-Nitrosodimethylamine (ppb)[e]	8.72 ± 4.44	2.90 – 21.0	26
N-Nitrosopyrrolidine (ppb)[e]	2.26 ± 1.14	1.00 – 6.00	26
Pesticides (ppm)			
α-BHC	<0.01		26
β-BHC	<0.02		26
γ-BHC	<0.01		26
δ-BHC	<0.01		26
Heptachlor	<0.01		26
Aldrin	<0.01		26
Heptachlor epoxide	<0.01		26
DDE	<0.01		26
DDD	<0.01		26
DDT	<0.01		26
HCB	<0.01		26
Mirex	<0.01		26
Methoxychlor	<0.05		26
Dieldrin	<0.01		26
Endrin	<0.01		26
Telodrin	<0.01		26
Chlordane	<0.05		26
Toxaphene	<0.10		26
Estimated PCBs	<0.20		26
Ronnel	<0.01		26
Ethion	<0.02		26
Trithion	<0.05		26
Diazinon	<0.10		26
Methyl parathion	<0.02		26
Ethyl parathion	<0.02		26
Malathion	0.13 ± 0.13	0.05 – 0.53	26
Endosulfan I	<0.01		26
Endosulfan II	<0.01		26
Endosulfan sulfate	<0.03		26

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

APPENDIX D
SENTINEL ANIMAL PROGRAM

SENTINEL ANIMAL PROGRAM

METHODS

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

Serum samples were collected from randomly selected mice during the 2-year study. 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
ELISA	
Ectromelia virus	6, 12, 18, and 24 months
EDIM (epizootic diarrhea of infant mice)	6, 12, and 24 months
GDVII (mouse encephalomyelitis virus)	6, 12, 18, and 24 months
LCM (lymphocytic choriomeningitis virus)	6, 12, 18, and 24 months
Mouse adenoma virus-FL	6, 12, 18, and 24 months
MHV (mouse hepatitis virus)	6, 12, 18, and 24 months
Mycoplasma arthritidis	24 months
Mycoplasma pulmonis	24 months
PVM (pneumonia virus of mice)	6, 12, 18, and 24 months
Reovirus 3	6, 12, 18, and 24 months
Sendai	6, 12, 18, and 24 months
Immunofluorescence Assay	
Ectromelia virus	18 months
EDIM	18 and 24 months
GDVII	18 months
LCM	24 months
Hemagglutination Inhibition	
K (papovavirus)	6, 12, 18, and 24 months
MVM (minute virus of mice)	6, 12, 18, and 24 months
Polyoma virus	6, 12, 18, and 24 months

RESULTS

One sample was positive for *M. arthritidis* at 24 months. 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 the positive titer. Accordingly, the *M. arthritidis*-positive titer was considered to be false positive. One sample was positive for EDIM antibodies by ELISA, but this result could not be confirmed by immunofluorescence assay due to insufficient serum.