NTP TECHNICAL REPORT

ON THE

TOXICOLOGY AND CARCINOGENESIS

STUDIES OF

AZT

(CAS NO. 30516-87-1)

AND

AZT/α-INTERFERON A/D

IN B6C3F$_1$ MICE

(GAVAGE STUDIES)

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

February 1999

NTP TR 469

NIH Publication No. 99-3959

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.

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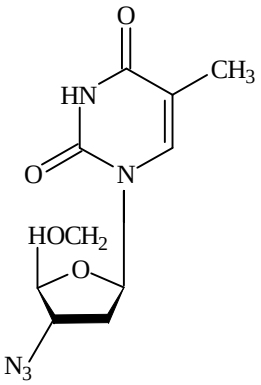
CONTENTS

ABSTRACT



3′-AZIDO-3′-DEOXYTHYMIDINE

CAS No. 30516-87-1

Chemical Formula: $C_{10}H_{13}N_5O_4$ Molecular Weight: 267.24

Synonyms: AZT; 3′-azido-2′,3′-dideoxythymidine; azidodeoxythymidine; azidothymidine; 3′-azidothymidine; 3′-deoxy-3′-azidothymidine; 3′-deoxy-(8CI) (9CI); BW A509U; Compound S; ZDV; zidovudine
Trade name: Retrovir®

3′-Azido-3′-deoxythymidine (AZT) is the most widely used and evaluated chemotherapeutic agent for the treatment of persons with acquired immune deficiency syndrome (AIDS) and persons seropositive for human immunodeficiency virus (HIV). The National Cancer Institute nominated AZT for toxicity and carcinogenicity studies because of the impending large-scale use of AZT in the treatment of adult patients with AIDS or AIDS-related complex. α-Interferon A/D, which displays antiviral activity in mice, is a hybrid molecule composed of the N-terminal portion of human α-interferon A and the C-terminal portion of human α-interferon D. AZT and α-interferon A/D combination studies were conducted because *in vitro* studies of AZT and α-interferon have demonstrated that the combination is more effective in blocking HIV infection than either agent alone. Male and female B6C3F$_1$ mice received AZT (approximately 98% pure) in 0.5% aqueous methylcellulose by gavage for 14 weeks or 2 years. In addition, male and female B6C3F$_1$ mice received α-interferon A or α-interferon A/D by subcutaneous injection for 2 years, and male and female B6C3F$_1$ mice received AZT in 0.5% aqueous methylcellulose by gavage in combination with α-interferon A/D by subcutaneous injection for 2 years. Genetic toxicology studies were conducted in *Salmonella typhimurium*, cultured Chinese hamster ovary cells, mouse bone marrow erythrocytes, and mouse peripheral blood erythrocytes.

14-WEEK AZT STUDY

Groups of 10 male and 10 female mice received AZT in 0.5% methylcellulose by gavage at doses of 0, 50, 100, 200, 800, or 2,000 mg/kg daily for 14 weeks. Additional groups of 10 male and 10 female mice received AZT in 0.5% methylcellulose by gavage at doses of 0, 100, 800, or 2,000 mg/kg daily for 14 weeks and then were held without treatment for an additional 4 weeks before necropsy. One female receiving 100 mg/kg and two females receiving

200 mg/kg died during week 1 as a result of gavage trauma; one female receiving 2,000 mg/kg also died prior to the end of the 14-week dosing period. One female receiving 2,000 mg/kg in the recovery study also died from gavage trauma during week 1. The final mean body weights of dosed mice were similar to those of the vehicle control groups at the end of the dosing period and at the end of the recovery period. Female mice receiving 200, 800, or 2,000 mg/kg gained less weight than the vehicle controls during the 14-week dosing period.

Exposure to AZT was toxic to the bone marrow, resulting in significant changes in the peripheral blood (decreased hematocrit values, erythrocyte counts, and hemoglobin concentrations, and increased mean cell volume and mean cell hemoglobin) and bone marrow (erythroid hypoplasia) characteristic of a dose- and time-dependent, minimal to moderate, poorly regenerative macrocytic anemia. At the end of the 4-week recovery period, the hematology parameters had returned to normal, indicating that the hematotoxicity was reversible.

2-YEAR STUDIES

AZT

Groups of 95 male and 95 female mice received AZT in 0.5% methylcellulose by gavage at daily doses of 0, 30, 60, or 120 mg/kg body weight, administered as two equal doses at least 6 hours apart, 5 days per week for 105 weeks. Each group of 95 animals was composed of a core group of 50 animals for evaluation of carcinogenic response, a group of 30 animals for evaluation of hematology and bone marrow cellularity, and a group of 15 animals from which blood was drawn for determination of plasma AZT concentrations at week 54.

α-Interferon A/D and AZT/α-Interferon A/D Studies

Groups of 80 male and 80 female mice received AZT in 0.5% aqueous methylcellulose by gavage at daily doses of 0, 30, 60, or 120 mg/kg body weight, given in two equal doses, 5 days per week for 105 weeks. Those groups receiving AZT also received subcutaneous injections of 500 or 5,000 U α-interferon A/D three times per week for 105 weeks. Additional groups of 80 male and 80 female mice received subcutaneous injections of the vehicle, 500 U α-interferon A/D, 5,000 U α-interferon A/D, or 5,000 U α-interferon A, three times per week for 105 weeks.

Each group of 80 animals was composed of a core group of 50 animals for evaluation of carcinogenic response and a group of 30 animals for evaluation of hematology and bone marrow cellularity.

Because of the large number of animals involved, the 2-year studies were started in four phases and, for clarity, are presented as follows: the AZT study, the α-interferon A/D study, the AZT/500 U α-interferon A/D study, and the AZT/5,000 U α-interferon A/D study.

Design of the 2-Year AZT, AZT/α-Interferon A/D, and α-Interferon A/D Studies

AZT Dose	AZT Study	AZT/500 U α-Interferon A/D Study	AZT/5,000 U α-Interferon A/D Study	500 or 5,000 U α-Interferon A/D or 5,000 U α-Interferon A Study
Vehicle Control	95 male and 95 female mice[a]	80 male and 80 female mice[b]	80 male and 80 female mice[b]	80 male and 80 female mice[b]
30 mg/kg AZT	95 male and 95 female mice	80 male and 80 female mice	80 male and 80 female mice	None
60 mg/kg AZT	95 male and 95 female mice	80 male and 80 female mice	80 male and 80 female mice	None
120 mg/kg AZT	95 male and 95 female mice	80 male and 80 female mice	80 male and 80 female mice	None

[a] For the AZT study, there were 95 male and 95 female mice; these were divided into 50 males and 50 females in the core groups, 30 males and 30 females in the clinical pathology groups (hematology and bone marrow analyses only), and 15 males and 15 females for plasma AZT concentration determinations.

[b] For the α-interferon A/D study and the AZT/α-interferon A/D studies, there were 80 male and 80 female mice for each study; these were divided into 50 males and 50 females in the core groups and 30 males and 30 females in the clinical pathology groups (hematology and bone marrow analyses only).

Survival and Body Weights

Survival and mean body weights of mice exposed to AZT, α-interferon A, α-interferon A/D, or AZT plus α-interferon A/D were generally similar to those of the vehicle control groups.

Hematology and Bone Marrow Analyses

All groups of male and female mice receiving AZT exhibited changes in peripheral blood and bone marrow characteristic of a dose- and time-dependent, minimal to mild, macrocytic, nonresponsive anemia. In females, these changes were evident throughout the study. In males, the macrocytic anemia had resolved by week 80 in the 30 mg/kg group; at study termination erythrocyte macrocytosis was present only in males receiving 60 or 120 mg/kg AZT or AZT plus α-interferon A/D. There were no treatment-related alterations in hematology or bone marrow parameters in groups that received only α-interferon A or A/D.

Pathology Findings

Incidences of squamous cell carcinoma and squamous cell papilloma or carcinoma (combined) of the vagina occurred with a positive trend and were significantly increased in groups of female mice receiving 60 or 120 mg/kg AZT alone or in combination with α-interferon A/D. Epithelial hyperplasia was observed in all dosed groups of females, and the incidence was significantly increased in the 120 mg/kg AZT group.

Three renal tubule adenomas and one renal tubule carcinoma were observed in male mice receiving 120 mg/kg AZT; the combined incidence in this group exceeded the range in historical controls. A renal tubule adenoma was observed in one male receiving 60 mg AZT/kg and 500 U α-interferon A/D; however, none were observed in other groups. Evaluation of step sections revealed a few more renal tubule hyperplasias but no additional neoplasms.

The incidence of harderian gland adenoma was increased in male mice receiving 120 mg/kg AZT and exceeded the range in historical controls. Harderian gland neoplasms were observed in other groups but did not follow a treatment-related pattern.

Overall Incidences of Vaginal Neoplasms and Hyperplasia of the Vaginal Epithelium in Female Mice in the 2-Year Gavage Studies of AZT and AZT/α-Interferon A/D[a]

	Vehicle Control	30 mg AZT/kg	60 mg AZT/kg	120 mg AZT/kg
AZT alone	2/197 (1%)[b] 1/197	0/49 (0%) 3/49	5/45 (11%) 4/45	11/49 (22%) 11/49
500 U α-Interferon A/D	0/49 (0%) 0/49	0/44 (0%) 4/44	5/48 (10%) 8/48	6/48 (13%) 12/48
5,000 U α-Interferon A/D	1/50 (2%) 1/50	1/48 (2%) 4/48	5/48 (10%) 8/48	4/50 (8%) 15/50

[a] Data are presented as number of vaginal neoplasms/number of animals microscopically examined (first line) and number of vaginal hyperplasias/number of animals microscopically examined (second line)
[b] Combined incidences of controls from the AZT alone study and the AZT/α-interferon A/D studies; incidences in the vehicle control group from the AZT alone study are 0/50 (0%) (neoplasms) and 0/50 (hyperplasia)

Overall Incidence of Harderian Gland Neoplasms in Male Mice in the 2-Year Gavage Studies of AZT and AZT/α-Interferon A/D[a]

	Vehicle Control	30 mg AZT/kg	60 mg AZT/kg	120 mg AZT/kg
AZT alone	13/200 (6%)[b]	5/50 (10%)	2/50 (4%)	10/50 (20%)
500 U α-Interferon A/D	3/50 (6%)	3/50 (6%)	1/50 (2%)	4/50 (8%)
5,000 U α-Interferon A/D	3/50 (6%)	9/50 (18%)	4/50 (8%)	4/50 (8%)

[a] Data are presented as number of harderian gland neoplasms/number of animals necropsied
[b] Combined incidences of controls from the AZT alone study and the AZT/α-interferon A/D studies; incidence in the vehicle control group from the AZT alone study is 3/50 (6%)

Male mice had a pattern of nonneoplastic liver lesions along with silver-staining helical organisms within the liver consistent with an infection with *Helicobacter hepaticus*. An organism compatible with *H. hepaticus* was confirmed by polymerase chain reaction-restriction fragment length polymorphism-based assays. Detection of dose-related differences in neoplasm incidences in these studies was not considered to have been significantly impacted by the infection with *H. hepaticus* or its associated hepatitis.

GENETIC TOXICOLOGY

AZT is mutagenic *in vitro* and *in vivo*. It induced gene mutations in *Salmonella typhimurium* strain TA102, with and without S9; no increases in mutations were noted in the other tested strains of *S. typhimurium*. AZT induced sister chromatid exchanges, but not chromosomal aberrations, in cultured Chinese hamster ovary cells, with and without S9. *In vivo* studies with male mice administered AZT by gavage showed highly significant increases in micronucleated erythrocytes in bone marrow and peripheral blood after exposure periods that ranged from 72 hours to 14 weeks.

CONCLUSIONS

Under the conditions of these 2-year gavage studies there was *equivocal evidence of carcinogenic activity** of AZT in male mice based on increased incidences of renal tubule and harderian gland neoplasms in groups

receiving AZT alone. There was *clear evidence of carcinogenic activity* of AZT in female mice based on increased incidences of squamous cell neoplasms of the vagina in groups that received AZT alone or in combination with α-interferon A/D.

Hematotoxicity occurred in all groups that received AZT.

Treatment with AZT alone and AZT in combination with α-interferon A/D resulted in increased incidences of epithelial hyperplasia of the vagina in all dosed groups of females.

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* Explanation of Levels of Evidence of Carcinogenic Activity is on page 14. A summary of the Technical Reports Review Subcommittee comments and the public discussion on this Technical Report appears on page 16.

Summary of the 2-Year Carcinogenesis and Genetic Toxicology Studies of AZT and AZT/α-Interferon A/D in Mice

	AZT	α-Interferon A/D	AZT/500 U α-Interferon A/D	AZT/5,000 U α-Interferon A/D
Doses	0, 30, 60, or 120 mg AZT/kg body weight in 0.5% methylcellulose by gavage, given 5 days per week in two equal doses of 0, 15, 30, or 60 mg/kg per dose	0, 500, or 5,000 U α-interferon A/D or 5000 U α-interferon A administered subcutaneously three times per week	0, 30, 60, or 120 mg AZT/kg body weight in 0.5% methylcellulose by gavage, given 5 days per week in two equal doses of 0, 15, 30, or 60 mg/kg per dose. Dosed groups also received 500 U α-interferon A/D administered subcutaneously three times per week.	0, 30, 60, or 120 mg AZT/kg body weight in 0.5% methylcellulose by gavage, given 5 days per week in two equal doses of 0, 15, 30, or 60 mg/kg per dose. Dosed groups also received 5,000 U α-interferon A/D administered subcutaneously three times per week.
Body weights	Dosed groups similar to vehicle control groups	Dosed groups generally similar to vehicle control groups	Dosed groups similar to vehicle control groups	Dosed groups similar to vehicle control groups
2-Year survival rates	Males 32/50, 35/50, 29/50, 42/50 Females 34/50, 39/50, 31/50, 31/50	Males 27/50, 28/50, 28/50 Females 25/50, 32/50, 25/50	Males 36/50, 27/50, 38/50, 35/50 Females 33/50, 32/50, 32/50, 24/49	Males 31/50, 35/50, 35/50, 34/50 Females 37/50, 38/50, 36/50, 32/50
Nonneoplastic effects	Females Vagina: epithelial hyperplasia (0/50, 3/49, 2/45, 7/49); atypical hyperplasia (0/50, 0/49, 2/45, 4/49)	None	Females Vagina: epithelial hyperplasia (0/49, 4/44, 6/48, 11/48); atypical hyperplasia (0/49, 0/44, 2/48, 1/48)	Females Vagina: epithelial hyperplasia (1/50, 3/48, 7/48, 12/50); atypical hyperplasia (0/50, 1/48, 1/48, 3/50)
Neoplastic effects	Females Vagina: squamous cell carcinoma (0/50, 0/49, 5/45, 9/49); squamous cell papilloma or carcinoma (0/50, 0/49, 5/45, 11/49)	None	Females Vagina: squamous cell carcinoma (0/49, 0/44, 5/48, 6/48)	Females Vagina: squamous cell carcinoma (0/50, 0/48, 5/48, 4/50)
Uncertain findings	Males Kidney: renal tubule adenoma (0/50, 0/48, 0/49, 3/50); renal tubule carcinoma (0/50, 0/48, 0/49, 1/50) Harderian gland: adenoma (3/50, 2/50, 2/50, 10/50); adenoma or carcinoma (3/50, 5/50, 2/50, 10/50)	None	None	None

Summary of the 2-Year Carcinogenesis and Genetic Toxicology Studies of AZT and AZT/α-Interferon A/D in Mice

		AZT	α-Interferon A/D	AZT/500 U α-Interferon A/D	AZT/5,000 U α-Interferon A/D
Level of evidence of carcinogenic activity	Males	Equivocal evidence			
	Females	Clear evidence			
Genetic toxicology					
Salmonella typhimurium gene mutations:		Positive in strain TA102 with and without S9; negative in strains TA97, TA98, TA100, TA104, and TA1535, with and without S9			
Sister chromatid exchanges					
Cultured Chinese hamster ovary cells *in vitro*:		Positive with and without S9			
Chromosomal aberrations					
Cultured Chinese hamster ovary cells *in vitro*:		Negative with and without S9			
Micronucleated erythrocytes					
Mouse bone marrow *in vivo*:		Positive			
Mouse peripheral blood *in vivo*:		Positive			

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 AZT and AZT/α-interferon A/D on 11 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 the NTP studies:

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

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SUMMARY OF TECHNICAL REPORTS REVIEW SUBCOMMITTEE COMMENTS

On 11 December 1996, the draft Technical Report on the toxicology and carcinogenesis studies of 3′-azido-3′-deoxythymidine (AZT) and AZT/α-interferon A/D 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. R.D. Irwin, NIEHS, introduced the toxicology and carcinogenesis studies of AZT and AZT/α-interferon A/D by discussing the uses of the chemicals and rationale for study, describing the experimental design (including a recovery group of mice to assess reversibility of bone marrow changes), reporting on the lack of survival and body weight effects, and commenting on treatment-related neoplasms and nonneoplastic lesions in mice. The proposed conclusions for the 2-year studies in mice were *equivocal evidence of carcinogenic activity* of AZT in male mice and *clear evidence of carcinogenic activity* of AZT in female mice.

Dr. LeBoeuf, a principal reviewer, agreed with the proposed conclusions. He noted the presence of *Helicobacter hepaticus* as a potential confounding factor for interpretation of liver lesions, but agreed that in this case it would not have an impact on the level of evidence for males or females.

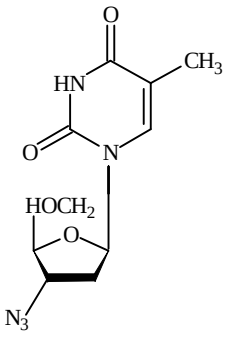
Dr. Reddy, the second principal reviewer, agreed with the proposed conclusions. He asked why the studies were not also conducted in rats and whether there were any case reports indicating an increase in vaginal neoplasms in human females. Dr. Irwin responded that Burroughs Wellcome had conducted asatisfactory study in rats. Dr. K.M. Ayers, Glaxo Wellcome, reported that the findings have been cited in the *Physicians Desk Reference* since about 1990. Dr. Irwin said there are no reports in the literature of genital neoplasms associated with the use of AZT in human females. Dr. Reddy said that, nonetheless, the findings could raise concerns because of the genital papillomas and warts reported in human papilloma virus infected HIV-positive men and women.

Dr. Tyson, the third principal reviewer, agreed with the proposed conclusions. He asked about the rationale for the strain of mice used and thought it would have been of interest to have used a strain of immunocompromised mice. Dr. Tyson commented that useful insights might have been gained from looking for molecular markers found in human vaginal tumors, such as activated oncogenes or certain papilloma viruses. Dr. Irwin said that with the complexity of the study, it was preferred to use the $B6C3F_1$ model for which there was a large historical database.

Dr. Goldsworthy asked whether higher incidences of hepatoblastoma in mice might be associated with *H. hepaticus*. Dr. J.R. Hailey, NIEHS, said that NTP had seen hepatoblastomas more frequently in recent studies as part of what seems to be a progression of that lesion.

Dr. LeBoeuf moved that the Technical Report on AZT and AZT/α-interferon A/D be accepted with the revisions discussed and the conclusions as written for male mice, *equivocal evidence of carcinogenic activity*, and for female mice, *clear evidence of carcinogenic activity*. Dr. Reddy seconded the motion, which was accepted unanimously with eight votes.

INTRODUCTION



3′-AZIDO-3′-DEOXYTHYMIDINE

CAS No. 30516-87-1

Chemical Formula: $C_{10}H_{13}N_5O_4$ Molecular Weight: 267.24

Synonyms: AZT; 3′-azido-2′,3′-dideoxythymidine; azidodeoxythymidine; azidothymidine; 3′-azidothymidine; 3′-deoxy-3′-azidothymidine; 3′-deoxy-(8CI) (9CI); BW A509U; Compound S; ZDV; zidovudine
Trade name: Retrovir®

CHEMICAL AND PHYSICAL PROPERTIES

AZT

3′-Azido-3′-deoxythymidine (AZT) is a dideoxy-nucleoside of thymine and structural analogue of 2′-deoxythymidine (dT), and is the most widely used and evaluated chemotherapeutic agent for the treatment of persons with acquired immune deficiency syndrome (AIDS) and persons seropositive for human immunodeficiency virus (HIV). AZT is a white to off-white, odorless, crystalline solid which is moderately soluble in water (20 mg/mL) and alcohol (71 mg/mL) at 25 C. The oral solution of AZT, which contains 50 mg per 5 mL, is colorless to pale yellow and has a pH of 3 to 4. When reconstituted with water for injection, AZT solutions containing 10 mg AZT/mL have a pH of approximately 5.5 (AHFS, 1997).

Interferon

Interferon is the general name given to a family of cytokines best known for their immunomodulatory function and in particular, their unique ability to interfere with viral replication. Four groups of interferons (α, β, γ, and ω) have been identified in humans and other mammalian species based on cell of origin, antigenic differences, and amino acid sequence homology. Most recently, classification of the various types of interferons has been based on nucleotide sequence homology within coding sequences. Based on structural and functional similarities, α-, β-, and ω-interferons are often collectively referred to as Type I interferons, whereas γ-interferon is referred to as Type II interferon (reviewed in De Maeyer and De Maeyer-Guignard, 1998).

In humans, α-interferon is encoded by a family of approximately 18 nonallelic genes located on the short arm of chromosome 9. The primary translation products of these genes contain 189 amino acids from which a 23-amino-acid N-terminal leader sequence is cleaved posttranslationally to yield a family of α-interferon proteins containing 165 or 166 amino acids. Also present at this locus on chromosome 9 is the single-copy human β-interferon gene, the primary translation product of which is similarly processed to a 166-amino-acid protein that is glycosylated at an asparagine residue (De Maeyer and De Maeyer-Guignard, 1998). The human ω-interferon gene family consists of one functional gene that encodes ω_1-interferon and four pseudogenes (Hauptmann and Swetly, 1985; Adolf *et al.*, 1991). Mature ω_1-interferon contains 170 or 172 amino acids and, like β-interferon, is glycosylated at a single asparagine residue. However, unlike other type I interferons, ω_1-interferon is heterogeneous at its N-terminal end due to the existence of two signal peptidase cleavage sites (Adolf *et al.*, 1991).

The human α-interferon proteins exhibit approximately 80% to 85% sequence homology with one another, while β- and ω_1-interferon are approximately 30% to 40% homologous with α-interferon. By contrast, the mature 166-amino-acid γ-interferon exhibits no obvious sequence homology to α-, β-, or ω_1-interferon, and the single-copy human γ-interferon gene is located at a different genetic locus.

PRODUCTION, USE, AND HUMAN EXPOSURE

AZT

AZT was first synthesized by Horwitz *et al.* (1964), and it was subsequently reported to inhibit HIV replication *in vitro* at concentrations ranging from 50 to 500 nmol/L by Mitsuya *et al.* (1985). Clinical activity for the treatment of AIDS was first reported by Yarchoan *et al.* (1986), and the drug has been commercially developed by Burroughs Wellcome Company (Research Triangle Park, NC). AZT was approved by the Food and Drug Administration for the treatment of adult patients with AIDS or advanced AIDS-related complex in March 1987 (Anonymous, 1987).

AZT is available in capsules or syrup for oral administration and in formulations suitable for intravenous infusion. A typical therapeutic regimen involving oral administration consists of 100 mg AZT every 4 hours, which, for a 60-kg individual, equates to 10 mg/kg per day (AHFS, 1997).

Interferon

α-, β-, and ω-Interferons are induced in many different types of cells, but γ-interferon is produced only by activated T-lymphocytes and natural killer (NK) cells (Capon *et al.*, 1985). Although the steps involved in the induction of interferon synthesis are not well understood, in most responses the synthesis of Type I interferons is coordinately induced, and the resulting "interferon" is a mixture of α, β, and ω subforms. However, cell- and tissue-selective induction of individual subforms is also observed.

The antiproliferative, antiviral, and immunomodulatory activities of the interferons have stimulated interest in the use of these agents for the treatment of a number of disorders including neoplastic as well as viral and microbial diseases. The constitutive level of interferons in normal blood is very low, although synthesis of α-, β-, and ω-interferons is induced by exposure to numerous infectious agents including bacteria, *Rickettsia*, *Mycoplasma*, protozoa, and viruses, as well as by double-stranded RNA and the synthetic polyribonucleotide poly (rI:rC). Due to the therapeutic potential of the interferons, the coding sequences of several human interferon genes have been cloned in bacteria, and this has provided a high-volume source of pure recombinant human interferons (Pestka *et al.*, 1987). Bacterial clones of several hybrid human interferons have also been prepared and evaluated for antiviral activity. Although interferons exhibit strong species specificity in their activity, a few of the human hybrids were found to induce antiviral activity in mice (Pestka, 1983; Pestka *et al.*, 1987). In the studies presented in this Technical Report, a hybrid recombinant human interferon that induces substantial antiviral activity in mice was used. This hybrid is designated $rHIFN_\alpha$ A/D (BglII) and it is obtained from a clone containing the 5′ end of the α-interferon A coding sequence ligated to the α-interferon D coding sequence from which the 5′ end had been cut. The presence of a BglII restriction endonuclease site in the

coding sequences of α-interferon A and α-interferon D genes allowed the two individual sequences to be cleaved and the corresponding pieces ligated to form the hybrid coding sequence. Thus, the first 62 amino acids of $rHIFN_{\alpha}$ A/D are from the N-terminal portion of human α-interferon A, and amino acids 64 to 166 are from human α-interferon D (Pestka, 1983; Horisberger and Di Marco, 1995).

ABSORPTION, DISTRIBUTION, METABOLISM, AND EXCRETION

AZT

Following oral administration AZT is rapidly absorbed, and after oral or intravenous administration it is rapidly distributed (Table 1). Elimination is also rapid, with essentially all parent drug and its metabolites being completely excreted within 24 hours. However, there are significant interspecies differences in the extent to which the parent compound is metabolized (Table 2). In humans and monkeys, the majority of an administered dose is converted to the 5′-O-glucuronide (GAZT) and eliminated in urine along with unmetabolized parent drug and a minor metabolite, 3′-amino-2′,3′-dideoxythymidine (AMT), formed by reduction of the 3′-azido group of AZT. However, in rats and other rodents, the majority of absorbed AZT is eliminated in urine as the parent compound with relatively little conversion to the glucuronide or to AMT (Table 2). GAMT, the glucuronide of AMT, has been reported to be a minor urinary metabolite in monkeys and a minor biliary metabolite in humans, but GAMT has not been identified in rats (de Miranda *et al.*, 1990).

TABLE 1
AZT Pharmacokinetic Parameters[a]

Species	Route	Dose	C_{max} (µg/mL)	T_{max}	$t_{½}$	Reference
Human	oral	400 mg	1.9	0.93 ± 0.42 hrs	1.0 ± 0.8 hrs	Child *et al.*, 1991
	oral	200 mg	1.07 ± 0.3	0.65 ± 0.2 hrs	1.0 ± 0.5 hrs	Singlas *et al.*, 1989
	oral	200 mg	1.07 ± 0.3	0.6 ± 0.2 hrs	1.0 ± 0.4 hrs	Taburet *et al.*, 1990
	intravenous	2.5 mg/kg	1.31 ± 0.3		1.2 ± 0.03 hrs	Stagg *et al.*, 1992
Monkey, rhesus	subcutaneous	33.3 mg/kg	8.9 ± 1.4	0.7 ± 0.3 hrs	0.8 ± 0.1 hrs	Cretton *et al.*, 1991a
Rat, F344	intravenous	40 mg/kg			0.47 ± 0.03 hrs	Wientjes and Au, 1992
Rat, Sprague-Dawley	intravenous	10 mg/kg 50 mg/kg 100 mg/kg 250 mg/kg			0.76 ± 0.35 hrs 1.31 ± 1.05 hrs 2.03 ± 1.67 hrs 1.58 ± 0.81 hrs	Patel *et al.*, 1989
Mouse, $B6C3F_1$	oral	15 mg/kg 30 mg/kg 60 mg/kg	9.1 ± 1.5 18.9 ± 0.5 40.3 ± 7.2	18.3 ± 2.9 min 21.7 ± 7.6 min 15.0 ± 5.0 min	18.5 min 16.5 min 21.9 min	Trang *et al.*, 1993
Mouse, NIH-Swiss	intravenous	250 mg/kg			0.78 hrs	Doshi *et al.*, 1989

[a] When available, data are presented as mean ± standard deviation.

TABLE 2
AZT Metabolites[a]

Species	Urinary Metabolites (% Dose)				Bile (B) or Fecal (F) Metabolites (% Dose)			Reference
	AZT	GAZT	AMT	GAMT	GAZT	AMT	GAMT	
Human	13	86						Good *et al.*, 1990
Human	16.7 ± 2.1	74.7 ± 6.5	2.0 ± 0.5				Trace (B)	Stagg *et al.*, 1992
Human	8.1 ± 2.4	61.5 ± 3.4						Singlas *et al.*, 1989
Monkey, rhesus	26.8 ± 5.2	59.6 ± 5.3	1.4 ± 0.6	0.4 ± 0.3				Cretton *et al.*, 1991a
Rat, Long Evans	87.7	6.1	0.9		5.1 (B)	15 (F)		de Miranda *et al.*, 1990
Rat, Sprague-Dawley	79.0 ± 5.7	0.8 ± 0.7						Mays *et al.*, 1991

[a] When available, data are presented as mean ± standard deviation.

In suspensions of freshly isolated rat hepatocytes, AZT is extensively converted to GAZT with AMT and GAMT formed in lesser amounts. AMT is not a substrate for UDPGT, which indicates that GAMT is formed by reduction of the 3′-azido group of GAZT rather than by glucuronidation of AMT (Cretton *et al.*, 1991b). In microsomes prepared from human liver, the rate of AMT formation is proportional to cytochrome P_{450} content and it is enhanced up to five-fold by the addition of NADPH, FAD, and FMN. AMT formation is abolished by prior incubation with carbon monoxide (Placidi *et al.*, 1993). Somewhat different results were obtained by Nicolas *et al.* (1995) in cultured hepatocytes from rats, dogs, monkeys, and humans. In these systems, AZT is converted primarily to GAZT by hepatocytes from humans (63%-73%) and monkeys (63%-73%), whereas unchanged parent is predominant in rat (86%-90%) or dog (95%) hepatocyte cultures. AMT is a minor metabolite in cultured hepatocytes from all species and GAMT is not detected in cultured hepatocytes.

Interferon

The disposition and pharmacokinetics of recombinant human interferons have been evaluated in several species. Following intravenous administration to humans, dogs, monkeys, rats, and mice, interferons are rapidly cleared from blood regardless of the type, subtype, or species of origin (Greig *et al.*, 1988; Greischel *et al.*, 1988; Lave *et al.*, 1995). However, in homologous species or in nonhomologous species in which a particular type or subtype of interferon exhibits biological activity, clearance is slower due to interaction with cells in the blood (Johns *et al.*, 1990). Distribution to tissues also occurs rapidly, with the greatest concentration of material present in the liver and kidneys 30 to 60 minutes after administration (Rosenberg *et al.*, 1985; Greig *et al.*, 1988; Wills, 1990; Kerry *et al.*, 1993). The primary route of excretion is via the kidney, where interferons are filtered through the glomerulus, reabsorbed, and degraded by tubular epithelial cells (Bocci *et al.*, 1982; Rosenberg *et al.*, 1985). Since the products of interferon degradation are amino acids which reenter the blood and are reused, very few degradation products are excreted in urine.

PHARMACOLOGY

AZT

The antiviral activity of AZT depends on its conversion to a nucleotide triphosphate (3′-azido-2′,3′-dideoxythymidine triphosphate; AZTTP). AZT enters mammalian cells by nonfacilitated diffusion (Zimmerman *et al.*, 1987) and it is then phosphorylated in successive reactions catalyzed by thymidine

kinase, thymidylate kinase, and nucleoside diphosphokinase. The resulting nucleoside triphosphate, AZTTP, is a substrate for HIV reverse transcriptase and a competitive inhibitor of dTTP. Because the 3′ position of AZT is blocked with an azido group, incorporation of AZTTP into a growing polynucleotide chain (e.g., cDNA) terminates elongation at that position. Thus AZT intervenes at a relatively early stage of the viral replication cycle. AZTTP is also a substrate for cellular DNA polymerases; however, the K_i and K_m of AZTTP for HIV reverse transcriptase are lower than for cellular DNA polymerases. Accordingly, AZTTP inhibits viral replication at doses lower than those at which it is an efficient substrate for the cellular DNA polymerases (Furman *et al.*, 1986; Ono, 1989; Huang *et al.*, 1990; Parker *et al.*, 1991).

Interferon

Although α-, β-, and ω-interferons are induced in many different types of cells, they all bind to the same (Type I) receptor on target cells. In contrast, γ-interferon is produced only by activated T lymphocytes and NK cells, and it acts via a different (Type II) receptor on target cells (Capon *et al.*, 1985; De Maeyer and De Maeyer-Guignard, 1998). Type I interferons act locally as autocrine or paracrine mediators and represent a first line of defense that is active against invading organisms prior to any significant response by the immune system (γ-interferon is not produced until T cells have been activated by antigen exposure, and γ-interferon is involved primarily in activation of immune reactions).

The antiviral activity of α-, β-, or ω-interferon is initiated by and requires binding of these Type I interferons to the Type I receptor on target cells; productive receptor occupancy results in activation of the JAK-STAT signal transduction pathway and leads to the transcription of genes whose promoters contain interferon response sequences (Müller *et al.*, 1994; David, 1995; Hwang *et al.*, 1995). The products of these genes are responsible for the observed antiviral activity of Type I interferons. Details of this process and the identity and function of its various molecular components are being actively investigated, and the subject has recently been reviewed (Schindler and Darnell, 1995).

TOXICITY

AZT

Exposure to AZT results in myelosuppression and anemia in humans and experimental animals. In humans, this toxicity limits the useful therapeutic dose range of AZT (Fischl, 1989; Pluda *et al.*, 1991; Balzarini, 1994). The primary target of AZT toxicity is the hematopoietic system of the bone marrow; *in vitro* coculture studies have demonstrated that AZT is cytotoxic to human and murine hematopoietic progenitor cells including colony forming units CFU-GEMM, CFU-GM, CFU-E, and CFU-Meg (Sommadossi *et al.*, 1987; Dainiak *et al.*, 1988; Gallicchio *et al.*, 1989). In cultures of human bone marrow cells, the extent of incorporation of AZTTP into cellular DNA and the growth inhibition of human clonal peripheral blood mononuclear cells have been correlated (Sommadossi and Carlisle, 1987; Sommadossi *et al.*, 1989). In human erythroid K-562 leukemia cells induced to differentiate by butyric acid treatment, AZT selectively reduced the steady-state level of globin mRNA (Weidner and Sommadossi, 1990). Neither the kinetics of induction nor the steady-state mRNA levels of other components of the heme biosynthetic pathway were altered, including erythroid-specific isozymes of aminolevulinate synthase and porphobilinogen deaminase (Fowler *et al.*, 1995). These results suggest a specific effect on transcription of the globin gene in erythroid cells.

Another prominent dose-limiting toxicity observed primarily in patients undergoing long-term AZT therapy is a toxic mitochondrial myopathy (Dalakas *et al.*, 1990). Clinical symptoms include myalgia, muscle weakness, and elevated levels of creatinine kinase in serum. These symptoms correlate with the presence in muscle biopsies of abnormal mitochondria containing paracrystalline inclusions. Human muscle myotubes grown in tissue culture exposed to AZT for 9 days exhibited increased numbers of mitochondria as well as enlarged mitochondria with abnormal cristae and electron-dense deposits in the matrix (Lamperth *et al.*, 1991).

Biochemically and morphologically similar changes are present in rats exposed to AZT, which exhibit enlarged mitochondria with disorganized or absent cristae in skeletal and cardiac muscle (Lamperth

et al., 1991; Lewis *et al.*, 1992). These changes correlate with impaired function of the electron-transport chain in skeletal muscle mitochondria (Lamperth *et al.*, 1991). In Sprague-Dawley rats administered 1 mg/mL AZT in drinking water for 35 days, decreases in mitochondrial DNA, RNA, and protein synthesis were observed in skeletal muscle mitochondria (Lewis *et al.*, 1992). AZTTP is an inhibitor and alternate substrate for mitochondrial DNA polymerase γ from both skeletal and cardiac muscle (Simpson *et al.*, 1989; Lewis *et al.*, 1994), and therefore it is likely that AZT is acting as an inhibitor and chain terminator, disrupting mitochondrial DNA synthesis.

Interferon

Humans administered type I interferons often experience a variety of toxic responses (Fent and Zbinden, 1988). The most frequently described are flu-like symptoms including fever, tachycardia, headache, myalgia, fatigue, and often nausea and vomiting. Leukopenia, neutropenia, and particularly with α-interferon, thrombocytopenia and elevated amino peptidase and transaminase levels in serum are also frequently observed. These effects are typically dose related and readily reverse upon discontinuation of treatment (Spiegel, 1987).

Pure animal interferons are generally unavailable and this has limited the types of toxicology studies that have been done. More effort has been directed at cloning human interferon genes. For this reason, the toxicology of the recombinant human hybrid interferon α-interferon A/D, which is active in mice and is available in pure form, has been evaluated in a few relevant studies. Rosenthal *et al*. (1990) administered 0, 1,000, 10,000, or 100,000 U α-interferon A/D per day intraperitoneally to female C57Bl/6N mice for 10 days. Spleen weights were significantly increased at all doses, and thymus weights were decreased in the groups receiving 10,000 or 100,000 U. Many of the observed responses were similar to those observed in humans undergoing interferon therapy, including anemia, leukopenia, thrombocytopenia, and elevation of serum transaminase activity. Dunn and Crnic (1993) administered daily intraperitoneal injections of 1,600 U α-interferon A/D per g body weight to Balb/c mice and observed a depression in open field spontaneous motor activity and in swimming performance but no decrease in grip strength in treated animals.

GENETIC TOXICITY

AZT was reported to be weakly positive in the mouse lymphoma cell mutagenicity test (Ayers, 1988; Olin and Kastrup, 1995) and to induce transformation in cultured mammalian cells (Olin and Kastrup, 1995). Results of *in vitro* cytogenetic assays with mammalian cells showed that AZT induced sister chromatid exchanges, chromosomal aberrations, and micronuclei in human lymphocytes and chromosomal aberrations and sister chromatid exchanges in cultured Chinese hamster ovary cells (Cid and Larripa, 1994). In these experiments, human lymphocytes appeared to be somewhat more sensitive to the genotoxic effects of AZT than were cultured Chinese hamster ovary cells (effective dose concentrations were lower in experiments with human lymphocytes).

In vivo, AZT has been shown to be an effective inducer of micronucleated erythrocytes in mice and rats administered AZT in various combinations of routes and exposure durations (Oleson and Getman, 1990; Phillips *et al.*, 1991). Increases in micronucleus frequencies of 6 to 27 times the concurrent control frequency were noted in peripheral blood and bone marrow erythrocytes of mice after multiple treatments with 100 to 2,000 mg/kg AZT per day for periods of 72 hours, 96 hours, or 90 days; no increase in the frequency of micronucleated erythrocytes was noted in mice after 90 days of treatment with a lower dose of 25 mg/kg AZT (Phillips *et al.*, 1991). In apparent contrast to these positive results, negative results were reported in an *in vivo* bone marrow micronucleus test with male mice (Motimaya *et al.*, 1994); in this test, AZT was administered as a single intraperitoneal injection at doses ranging from about 14 to 29 mg/kg and bone marrow was harvested 36 or 48 hours after treatment (optimum harvest time is generally accepted to be 24 hours after treatment). The doses used in this experiment approximated the average daily total dose prescribed for humans, but used only a single treatment compared to the long-term chronic administrations employed in humans. The data reported by Motimaya *et al*. (1994), taken together with the Phillips *et al*. (1991) data, indicate that low doses of AZT may not induce damage detected as micronucleated erythrocytes in mice, but that multiple treatments with higher doses are extremely effective in inducing this type of genetic damage.

The relevance of these data to human genetic hazard is supported by the results of investigations performed by Shafik *et al*. (1991), who reported significantly increased frequencies of chromosomal aberrations (> 8%) in lymphocytes of AIDS patients receiving AZT therapy compared to AIDS patients not receiving AZT. The frequency of chromosomal aberrations (0.5%) in the group not receiving AZT was comparable to the baseline frequency determined in a healthy adult population (Bender *et al.*, 1988). The AZT-treated group had received the standard dosage of 1,200 mg AZT per day for at least 4 weeks prior to this investigation. These data strongly suggest that at therapeutic doses, AZT can induce chromosomal damage in humans.

STUDY RATIONALE

The National Cancer Institute nominated AZT for toxicity and carcinogenicity studies in 1986 because of the impending large-scale use of AZT in the treatment of adult patients with AIDS or AIDS-related complex. A number of *in vitro* studies in human cells (reviewed in Poli *et al.*, 1994) have shown that α- and β-interferon interfere with the replication of HIV at numerous steps during the viral life cycle. α-Interferon has also shown antineoplastic activity against AIDS-related Kaposi's sarcoma (Lane, 1989; Lane *et al.*, 1990). Moreover, *in vitro* studies of α-interferon and AZT have demonstrated that the combination is more effective in blocking HIV infection than either agent alone (Dubreuil *et al.*, 1990). Based on these findings, several clinical trials involving AZT and α-interferon combination therapy have been conducted. The present study was initiated to examine the potential risks associated with long-term exposure to AZT and how this might be influenced by coadministration of α-interferon. This study was conducted in male and female mice because of the more extensive database on the effects of AZT and interferons in mice and because the use of mice would minimize the quantity of AZT needed. Two separate recombinant interferons were selected: the hybrid discussed previously ($rHIFN_{\alpha}$ A/D), which is active in mice, and $rHIFN_{\alpha}$ 2A, a pure recombinant human interferon α subtype that exhibits no antiviral activity in mice.

MATERIALS AND METHODS

PROCUREMENT AND CHARACTERIZATION

AZT

3′-Azido-3′-deoxythymidine (AZT) was obtained from the Burroughs Wellcome Company (Research Triangle Park, NC) in three lots (809796, 80/0557-130-B, and 86/5082-184). Lot 809796 was used during the 14-week study and 2-year AZT and AZT/α-interferon A/D studies, and lots 80/0557-130-B and 86/5082-184 were used during the 2-year AZT and AZT/α-interferon A/D studies. Identity, purity, and stability analyses were conducted by the analytical chemistry laboratory, Midwest Research Institute (Kansas City, MO) (Appendix O). Reports on analyses performed in support of the AZT and AZT/α-interferon A/D studies are on file at the National Institute of Environmental Health Sciences (NIEHS).

All lots of the chemical, a white to slightly off-white fine powder, were identified as AZT by infrared spectroscopy. Lots 809796 and 80/0557-130-B were also identified by ultraviolet/visible and nuclear magnetic resonance spectroscopy and by melting point range. For lot 809796, the optical rotation value was consistent with values determined by the study laboratory, and an additional determination of the optical rotation value for lot 809796 indicated a value consistent with that reported by the supplier. For lot 80/0557-130-B, the optical rotation value was consistent with the results from the second determination for lot 809796. For lot 80/0557-130-B, the partition coefficient between octanol and pH 7.4 phosphate buffer was determined to be 0.05 at room temperature, and the maximum solubility in water at 25° C was determined to be 22.8 mg/mL. The purities of lots 809796 and 80/0557-130-B were determined using elemental analyses, Karl Fischer water analysis, functional group titration, thin-layer chromatography, and high-performance liquid chromatography. For lot 809796, elemental analyses for carbon, hydrogen, and nitrogen were in agreement with the theoretical values for AZT. Karl Fischer water analysis indicated 0.10% ± 0.03% water. Functional group titration indicated a purity of 101.4% ± 0.5%. Thin-layer chromatography by one system indicated a major spot and a trace impurity; thin-layer chromatography by another system indicated a major spot and a minor impurity. High-performance liquid chromatography indicated one major peak and two impurities with a combined area of 1.8% relative to the major peak area. One of these impurities was identified as thymine from an ultraviolet spectrum, and the thymine content was estimated to be 0.80% ± 0.01% with high-performance liquid chromatography. The overall purity of lot 809796 was determined to be approximately 98%.

For lot 80/0557-130-B, elemental analyses for carbon, hydrogen, and nitrogen were in agreement with the theoretical values for AZT. Karl Fischer water analysis indicated 0.04% ± 0.01% water. Functional group titration indicated a purity of 102.1% ± 0.5%. Thin-layer chromatography by two systems indicated a major spot and a trace impurity. High-performance liquid chromatography indicated one major peak and two impurities with a combined area of 1.6% relative to the major peak area. Major peak comparisons of lot 80/0557-130-B with lot 809796 indicated a purity of 100.3% ± 0.9% for lot 80/0557-130-B relative to lot 809796. The overall purity of lot 80/0557-130-B was determined to be approximately 98%.

The purity of lot 86/5082-184 relative to that of lot 80/0557-130-B was determined by the study laboratory with high-performance liquid chromatography. The purity of lot 86/5082-184 relative to lot 80/0557-130-B was determined to be approximately 102%.

Accelerated stability studies of lot 809796 of the bulk chemical were performed by the analytical chemistry laboratory using high-performance liquid chromatography. These studies indicated that AZT was stable as a bulk chemical for at least 2 weeks when stored protected from light at temperatures up to 60° C. To ensure stability, the bulk chemical was stored in the original container (double plastic bags inside a metal can) in the dark at room temperature

(approximately 22° C) for 2 months after receipt before the 14-week study began and at approximately −20° C thereafter. Stability was monitored during the 14-week and 2-year studies using high-performance liquid chromatography. No degradation of the bulk chemical was detected.

Methylcellulose

Methylcellulose was obtained from Fisher Scientific Company (Pittsburgh, PA) in one lot (876672), which was used during the 14-week study, the 2-year AZT study, and the 2-year AZT/α-interferon A/D studies. Identity, purity, and stability analyses were conducted by the analytical chemistry laboratory.

The chemical, a white powder, was identified as methylcellulose by infrared, ultraviolet/visible, and nuclear magnetic resonance spectroscopy. No melting point was observed up to 300° C; the sample decomposed at 250° to 300° C. The purity of lot 876672 was determined by elemental analyses, Karl Fischer water analysis, functional group titration, and high-performance liquid chromatography. The methoxy group content was estimated from the nuclear magnetic resonance spectrum. United States Pharmacopeia (USP) XXI analyses for the identification, apparent viscosity, weight loss on drying, residue on ignition, arsenic content, heavy metal content, and percent methoxy content were also performed. Elemental analyses for carbon and hydrogen were in agreement with the theoretical values for methylcellulose based on 1.8 degrees of substitution and corrected for 1.94% water (indicated by Karl Fischer water analysis). In addition, elemental analyses indicated 0.058% sodium. Functional group titration indicated 30.62% ± 0.08% methoxy group content; this value is consistent with the theoretical value, assuming 1.8 degrees of substitution (30.4%), and with the estimate of the methoxy group content from the nuclear magnetic spectrum (31.7%). The complete battery of USP tests for methylcellulose indicated the following results: the chemical was identified as methylcellulose; the apparent viscosity was 3,749 to 4,060 cP; the weight loss on drying was 1.9% ± 0.3%; the residue on ignition was less than 0.3%; the tests for arsenic and heavy metals were passed; and the methoxy group content was 30.3% ± 0.2% for lot 876672 and 28.3% ± 0.0% for the USP reference material. The chemical met the USP specifications for methylcellulose for all analyses. High-performance liquid chromatography indicated one major peak and no impurities with areas greater than or equal to 0.1% relative to the major peak area. Cumulative analytical data indicated that lot 876672 of methylcellulose was suitable for use as a dosing vehicle.

Accelerated stability studies of the bulk chemical were performed by the analytical chemistry laboratory using gas chromatography (USP XXI method). These studies indicated that methylcellulose was stable as a bulk chemical for 3 weeks when stored protected from light at temperatures up to 60° C. To ensure stability, the bulk chemical was stored in the original containers in the dark at room temperature. Stability was monitored by Galbraith Laboratories, Inc. (Knoxville, TN), during the 14-week and 2-year studies using gas chromatography to determine methoxy group content. Results of duplicate analyses were all within the required range of 27.5% to 31.5% methoxy group content. No degradation of the bulk chemical was detected.

α-Interferon A/D and α-Interferon A

α-Interferon A/D and α-interferon A were obtained from Hoffman-La Roche (Nutley, NJ). α-Interferon A/D was obtained in one lot (1084), which was used during the 2-year α-interferon A/D and AZT/α-interferon A/D studies. α-Interferon A was obtained in one lot (019116), which was used during the 2-year α-interferon A/D study. Antiviral activity assays were conducted by the study laboratory.

Information from the manufacturer indicated a protein concentration of 2.8 mg/mL and a bulk activity of 1.5×10^8 U/mL for lot 1084 of α-interferon A/D and a protein concentration of 5.47 mg/mL and a bulk activity of 1.095×10^9 U/mL for lot 019116 of α-interferon A. The bulk chemical was stored in the original containers (plastic bottles) at approximately −20° C from receipt until 2 weeks before the 2-year studies began and at −140° or −180° C in the vapor phase of a liquid nitrogen cryopreservation vat thereafter. Each lot of the α-interferon A/D and α-interferon A bulk chemicals was evaluated by determining the ability to confer protection against viral challenge using the viral cytopathic effect assay (Table O1). Prior to the beginning of the studies, the antiviral activities (titers) of α-interferon A/D and α-interferon A were determined along with that of an international standard α_2-interferon obtained from the National Institute of Allergy and Infectious Diseases.

Complete details of the procedures used and the results are on file at NIEHS.

PREPARATION AND ANALYSIS OF DOSE FORMULATIONS

AZT

The dosing vehicle was prepared by mixing methylcellulose with heated deionized water and then diluting with water to form a 0.5% solution, which was allowed to cool. AZT was then mixed with the dosing vehicle until a homogeneous suspension was obtained to give the required concentrations (Table O2). The dose formulations were stored at room temperature (at the beginning of the 14-week study) or refrigerated at approximately 5° C in amber glass bottles in the dark for up to 20 days. Homogeneity studies of a 200 mg/g solution of lot 809796 were performed by the analytical chemistry laboratory using high- performance liquid chromatography. Stability studies of a 2 mg/g solution were also performed using high-performance liquid chromatography. Homogeneity was confirmed, and the stability of the solution was confirmed for 3 weeks at room temperature when stored in the dark and for 3 hours when open to air and light.

The periodic analyses of the dose formulations of AZT were conducted at the study laboratory using high-performance liquid chromatography. During all studies, the formulations were analyzed every 4 to 8 weeks (Tables O3 and O4). All of the dose formulations analyzed and used during the 14-week and 2-year studies were within 10% of the target concentrations. All of the animal room samples were also within 10% of the target concentrations.

α-Interferon A/D and α-Interferon A

The dosing vehicle was prepared by aseptically mixing sterile C57Bl/6 mouse serum (Harlan Sprague-Dawley, Inc., Indianapolis, IN) in Earle's Balanced Salt Solution (Grand Island Biologicals Co.) to achieve a 10% solution, which was adjusted to a pH of approximately 7.2. Based on titers determined for the bulk chemicals, dose formulations were prepared by dilution of the stock solution. Therefore, the same amount (quantity of pure recombinant protein) of α-interferon A/D or α-interferon A was administered to the animals throughout the 2-year studies. α-Interferon A/D and α-interferon A were thawed at room temperature, and serial dilutions were prepared in the vehicle under sterile conditions using sterile pipettes and a calibrated Matrix Electropette (Table O2). The dose formulations were stored in sterile, Teflon®-capped, brown glass dosing vials at 4° C. Samples for antiviral activity assays were stored at −140° C or cryopreserved in liquid nitrogen. Sterility of the dose preparations was monitored with a 2-week incubation in both Sabouraud's broth and thioglycollate broth at 37° C followed by a visual examination for microbial growth. Stability of α-interferon A/D and α-interferon A dose formulations had been previously established for 42 days.

Periodic analyses of the antiviral activity of the dose formulations of α-interferon A/D and α-interferon A were conducted at the study laboratory using the same methods as for the bulk chemicals. Those assays demonstrated that interferon dose formulations used in the studies retained antiviral activity under normal dosing conditions. However, the differences between the titers of dose formulations determined by the cytopathic effect assay (observed) and the titers expected from making known dilutions of the calibrated laboratory standards (theoretical) were consistently greater than 10%. Because of this variability and the demonstrated stability of antiviral activity under dosing conditions, routine analysis of interferon dose formulations by the cytopathic effect assay was discontinued in October 1991. The long-term stability of laboratory standards from which dose formulations were prepared was confirmed with the cytopathic effect assay in March 1993.

14-WEEK STUDY

The 14-week study was conducted to evaluate the cumulative toxic effects of repeated exposure to AZT and to determine the appropriate doses to be used in the 2-year studies. A recovery group was included to evaluate the reversibility of toxicity in male and female mice allowed a 4-week recovery period after the 14-week dosing period ended.

Male and female $B6C3F_1$ mice were obtained from Simonsen Laboratories, Inc. (Gilroy, CA). At the time of receipt, the mice were 4 weeks old. Animals were quarantined for 11 days and were approximately 6 weeks old on the first day of the study. Before the

study began, five male and five female mice were randomly selected for parasite evaluation and gross observation for evidence of disease. At the end of the study, serologic analyses were performed on five male and three female 50 mg/kg mice using the protocols of the NTP Sentinel Animal Program (Appendix Q).

Groups of 10 male and 10 female mice received AZT in 0.5% methylcellulose by gavage at doses of 0, 50, 100, 200, 800, or 2,000 mg/kg, daily for 14 weeks. Additional groups of 10 male and 10 female mice received AZT in 0.5% methylcellulose by gavage at doses of 0, 100, 800, or 2,000 mg/kg, daily for 14 weeks, and then were held without treatment for an additional 4 weeks before necropsy. All doses were administered twice daily (one half the total daily dose) except on days of neurobehavioral evaluations. Feed and water were available *ad libitum*. Mice were housed individually. Clinical findings were recorded weekly for mice. The animals were weighed initially and then weekly throughout the study. Details of the study design and animal maintenance are summarized in Table 4.

On days 5 and 23 and at the end of the 14-week dosing period for core study mice and on day 89 and at the end of the holding period for recovery group mice, blood was collected from the retroorbital sinus of all animals for hematology analyses. Bone marrow analyses were performed on 0, 100, 800, and 2,000 mg/kg core study mice at the end of the dosing period and on recovery group mice at the end of the holding period. Blood for hematology determinations was placed in tubes containing EDTA as an anticoagulant. Erythrocyte, platelet, and leukocyte counts, hematocrit values, hemoglobin concentration, mean cell volume, mean cell hemoglobin, and mean cell hemoglobin concentration were determined using an Ortho ELT-8 (Ortho Instruments, Westwood, MA) or a Technicon H·1 (Technicon Corporation, Tarrytown, NY) hematology analyzer. Differential leukocyte counts, reticulocyte and nucleated erythrocyte counts, and morphologic evaluation of blood cells were determined by light microscopic evaluation of blood films. Bone marrow suspensions were produced by flushing the femurs with Modified Hanks Balanced Salt Solution (HBSS) containing EDTA and albumin supplements. Total nucleated cell counts were determined using a Technicon H·1. The suspensions were further diluted with HBSS and centrifuged. Cells were stained with Wright-Giemsa and evaluated with oil-immersion light microscopy. At least 500 cells per slide were differentially identified and counted. The hematology and bone marrow parameters measured are listed in Table 4.

Neurobehavioral evaluations were conducted prior to the beginning of the study and on days 44 and 88 for core study mice and on day 116 (females) or 117 (males) for recovery group mice. Mice in the 0, 100, 800, and 2,000 mg/kg groups were subjected to the following behavioral tests: 1) a functional observational battery which included the assessment of home cage behaviors, handling behaviors, physiological measures, open field behavior, reflex responses, and the measurement of forelimb and hindlimb grip strength; 2) motor activity; 3) thermal sensitivity; and 4) startle response.

The sequence of neurobehavioral evaluations was such that the least interactive test was conducted first with the most manipulative procedures being performed last. For functional observations, animals were first rated on posture, presence or absence of tonic or clonic convulsions, vocalizations, and palpebral closure. Animals were then removed from the cage and various handling measures were recorded, including general observation, ease of removal from the cage, ease of handling, lacrimation, palpebral closure, fur appearance, piloerection, and salivation. Then the animals were weighed and their body temperatures were recorded. Animals were placed individually in an open field for 3 minutes. During this time animals were observed for the number of rears (supported and unsupported), presence or absence of tonic or clonic convulsions, gait and gait score, mobility score, arousal level, presence or absence of stereotyped behavior, and number of fecal boli or urine pools. Observations were recorded for the following responses or reflexes: approach, touch, click, tail pinch (including the presence or absence of vocalizations to tail pinch), pupil, righting, and landing footsplay. Forelimb and hindlimb grip strengths were measured using strain gauges (Chatillion Force Measurement Co., Greensboro, NC).

Measurement of motor activity was performed using Opto-Varimax Mini activity monitors (Columbus Instruments International Corporation, Columbus, OH). Animal motor activity was monitored for 10 minutes, after which time a score was recorded for ambulatory behavior and for other behaviors (e.g.,

grooming). The time it took each animal to remove its tail from a 55° C water bath (tail-flick response) was recorded to determine thermal sensitivity. Animals were exposed to an acoustic stimulus and an air puff stimulus to determine startle response in terms of reactivity and excitability. The latency to respond, peak threshold, and time of the peak were recorded using a Responder-X Startle Monitor (Columbus Instruments International Corporation, Columbus, OH).

At the end of the 14-week dosing period, samples were collected for sperm motility evaluations from core study and recovery group male mice receiving 0, 100, 800, or 2,000 mg/kg. For recovery group females, vaginal samples were collected at the end of the 14-week dosing period and again at the end of the 4-week recovery period for vaginal cytology evaluations. The parameters evaluated are listed in Table 4. Methods used were those described in the NTP's sperm morphology and vaginal cytology evaluations protocol (NTP, 1987). For 12 consecutive days prior to the end of dosing and again prior to the end of the recovery period, the vaginal vaults of the females were moistened with saline, if necessary, and samples of vaginal fluid and cells were stained. Relative numbers of leukocytes, nucleated epithelial cells, and large squamous epithelial cells were determined and used to ascertain estrous cycle stage (i.e., diestrus, proestrus, estrus, and metestrus). Male animals were evaluated for sperm count and motility. The left testis and left epididymis were isolated and weighed. The tail of the epididymis (cauda epididymis) was then removed from the epididymal body (corpus epididymis) and weighed. Modified Tyrode's buffer was applied to slides and a small incision was made at the distal border of the cauda epididymis. The sperm effluxing from the incision were dispersed in the buffer on the slides, and the numbers of motile and nonmotile spermatozoa were counted for five fields per slide by two observers. Following completion of sperm motility estimates, each left cauda epididymis was placed in buffered saline solution. Caudae were finely minced, and the tissue was incubated in the saline solution and then heat fixed at 65° C. Sperm density was then determined microscopically with the aid of a hemacytometer. To quantify spermatogenesis, the testicular spermatid head count was determined by removing the tunica albuginea and homogenizing the left testis in phosphate-buffered saline containing 10% dimethyl sulfoxide. Homogenization-resistant spermatid nuclei were counted with a hemacytometer.

A necropsy was performed on all animals. The heart, left and right kidneys, liver, lung, right testis, and thymus were weighed. Tissues for microscopic examination were fixed and preserved in 10% neutral buffered formalin, processed and trimmed, embedded in paraffin, sectioned to a thickness of 5 to 6 µm, and stained with hematoxylin and eosin. Sections of brain, spinal cord, and sciatic nerve from all mice were also stained with Luxol fast blue and Holmes silver. A complete histopathologic examination was performed on all mice. Table 4 lists the tissues and organs routinely examined.

2-YEAR STUDIES

Study Design

Because of the large number of animals involved, the 2-year studies were started in four phases: the AZT study, the α-interferon A/D study, the AZT/500 U α-interferon A/D study, and the AZT/5,000 U α-interferon A/D study. Table 3 shows a matrix of the overall study design.

For the AZT study, groups of 95 male and 95 female mice received AZT in 0.5% aqueous methylcellulose by gavage at daily doses of 0, 30, 60, or 120 mg/kg body weight, administered as two equal doses (one in the morning and one in the afternoon, at least 6 hours apart), 5 days per week for 105 weeks. Each group of 95 mice was composed of the following: 1) a core group of 50 mice for evaluation of carcinogenic response, 2) a group of 30 mice for clinical pathology analyses, and 3) a group of 15 mice from which blood was collected at week 54 after the first daily dose was administered for determinations of plasma AZT concentrations. At the end of the study, up to 10 mice from each study core group were evaluated for alterations in hematology and bone marrow parameters, and up to 23 mice were evaluated for plasma AZT concentrations. The clinical pathology groups were further divided into three groups of 10 mice each. Blood for hematology determinations was collected from each group of 10 mice at two time points, 6 months apart. After the second collection, mice in that group were euthanized with CO_2, and bone marrow samples were collected for determination of marrow cellularity. Therefore, hematology

parameters were evaluated at six time points during the study (weeks 14, 27, 40, 54, 66, and 80), and bone marrow was evaluated at three time points during the study (weeks 54, 66, and 80).

For the α-interferon A/D study, groups of 80 male and 80 female mice received subcutaneous injections of 0, 500 or 5,000 U α-interferon A/D, or 5,000 U α-interferon A, three times per week, for 105 weeks.

For the AZT/α-interferon A/D studies, groups of 80 male and 80 female mice received AZT in 0.5% aqueous methylcellulose by gavage at daily doses of 0, 30, 60, or 120 mg/kg body weight, administered as two equal doses (one in the morning and one in the afternoon, at least 6 hours apart), 5 days per week for 105 weeks. The dosed groups also received subcutaneous injections of 500 or 5,000 U α-interferon A/D three times per week. For the α-interferon A/D study and the AZT/α-interferon A/D studies, each group of 80 mice was composed of the following: 1) a core group of 50 mice for evaluation of carcinogenic response and 2) a group of 30 mice for clinical pathology analyses. At the end of the study, up to 10 mice from each core group were evaluated for alterations in hematology and bone marrow parameters. The clinical pathology groups were further divided into three groups of 10 mice each. Blood for hematology determinations was collected from each group of 10 mice at two timepoints, approximately 9 months apart. After the second collection, mice were euthanized with CO_2, and bone marrow samples were collected for determination of marrow cellularity. Therefore, hematology parameters were evaluated at six time points during the study (weeks 14, 27, 40, 54, 65 or 66, and 79), and bone marrow was evaluated at three time points during the study (weeks 54, 65 or 66, and 79).

TABLE 3
Design of the 2-Year AZT, AZT/α-Interferon A/D, and α-Interferon A/D Studies

AZT Dose	AZT Study	AZT/500 U α-Interferon A/D Study	AZT/5,000 U α-Interferon A/D Study	500 or 5,000 U α-Interferon A/D or 5,000 U α-Interferon A Study
Vehicle Control	95 male and 95 female mice[a]	80 male and 80 female mice[b]	80 male and 80 female mice[b]	80 male and 80 female mice[b]
30 mg/kg AZT	95 male and 95 female mice	80 male and 80 female mice	80 male and 80 female mice	None
60 mg/kg AZT	95 male and 95 female mice	80 male and 80 female mice	80 male and 80 female mice	None
120 mg/kg AZT	95 male and 95 female mice	80 male and 80 female mice	80 male and 80 female mice	None

[a] For the AZT study, there were 95 male and 95 female mice; these were divided into 50 males and 50 females in the core groups, 30 males and 30 females in the clinical pathology groups (hematology and bone marrow analyses only), and 15 males and 15 females for plasma AZT concentration determinations.

[b] For the α-interferon A/D study and the AZT/α-interferon A/D studies, there were 80 male and 80 female mice for each study; these were divided into 50 males and 50 females in the core groups and 30 males and 30 females in the clinical pathology groups (hematology and bone marrow analyses only).

Source and Specification of Animals

Male and female $B6C3F_1$ mice were obtained from Simonsen Laboratories, Inc. (Gilroy, CA) for use in the 2-year studies. Mice were quarantined for 17 to 20 days before the beginning of the studies. Up to five male and five female mice per study design group were randomly selected for parasite evaluation and gross observation of disease. Mice were approximately 7 to 8 weeks old at the beginning of the studies. Throughout the studies, serology samples

were collected periodically from up to five male and five female sentinel mice from the core study and clinical pathology groups, and occasionally from mice in the dosed groups in each study. The health of the animals was monitored during the studies according to the protocols of the NTP Sentinel Animal Program (Appendix Q). Because mouse hepatitis virus was detected in dosed and sentinel mice, additional (naive) sentinels were obtained and monitored during the AZT study; no antibody titers to mouse hepatitis virus were detected in sera from the naive sentinels.

Animal Maintenance

Mice were housed five per cage during the quarantine period and individually during the studies. Feed and water were available *ad libitum*. Cages and racks were rotated every 2 weeks, cage filters were changed once every 2 weeks, and bedding was changed once per week. Further details of animal maintenance are given in Table 4. Information on feed composition and contaminants is provided in Appendix P.

Clinical Examinations and Pathology

All animals were observed twice daily. Clinical findings were recorded at the beginning of the studies and monthly thereafter. Body weights were recorded at the beginning of the studies, approximately weekly for the first 13 weeks, monthly thereafter, and at the end of the studies.

Blood was collected from the retroorbital sinus for hematology analyses. Methodologies were similar to those described for the 14-week study. A Technicon H·1 hematology analyzer was used for hematology determinations. Whole blood films were stained with new methylene blue for reticulocyte counts. Bone marrow suspensions were produced by flushing the femurs with HBSS containing EDTA, gentamicin, and albumin supplements. The parameters measured are listed in Table 4.

At week 54 of the 2-year AZT study, blood was collected from the retroorbital sinus of as many as 15 male and 15 female mice per group designated for the determination of plasma concentrations of AZT. Three animals per group were examined at each of five time points (15, 30, 60, 90, or 120 minutes after dosing). On the last day of the 2-year AZT study, blood was collected from the retroorbital sinus of 18 male and 18 female mice from each core study dosed group at six time points (5, 15, 30, 60, 90, or 120 minutes after dosing), with three animals per group evaluated at each time point. Mice designated for the determination of plasma concentrations of AZT were fasted overnight prior to dosing and received only one of the two equal doses of AZT on the day blood was collected. Blood was also collected from five males and five females from the 30, 60, and 120 mg/kg core groups before any doses were administered on the last day of the study. Blood was placed in tubes containing EDTA as the anticoagulant, the tubes were centrifuged, and the plasma was removed. The plasma was stored at approximately −20° C until analysis. Plasma samples were analyzed using high-performance liquid chromatography for the analysis of concentrations of AZT. The mean plasma concentrations of AZT and standard deviations were calculated.

A complete necropsy was performed on all mice and microscopic examination was performed on all core study mice. At necropsy, all organs and tissues were examined for grossly visible lesions, and all major tissues were fixed and preserved in 10% neutral buffered formalin, processed and trimmed, embedded in paraffin, sectioned to a thickness of 5 to 6 µm, and stained with hematoxylin and eosin for microscopic examination. For all paired organs (e.g., adrenal gland, kidney, ovary), samples from each organ were examined. Tissues examined microscopically are listed in Table 4.

Microscopic evaluations were completed by the study laboratory pathologist, and the pathology data were entered into the Toxicology Data Management System. The microscopic 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 AZT study, a quality assessment pathologist evaluated slides from all tumors and all potential target organs, which included the adrenal gland, bone marrow, harderian gland, kidney, and liver of male mice and the bone marrow, kidney, liver, and vagina of female mice. For the 2-year α-interferon A/D study, a quality assessment pathologist evaluated slides from all tumors and all potential target organs, which included the kidney and liver of male mice and the kidney,

liver, spleen, thyroid gland, uterus, and vagina of female mice. For the 2-year AZT/500 U α-interferon A/D study, a quality assessment pathologist evaluated slides from all tumors and all potential target organs, which included the adrenal gland, kidney, and liver of male mice and the adrenal gland, bone marrow, kidney, liver, spleen, uterus, and vagina of female mice. For the 2-year AZT/5,000 U α-interferon A/D study, a quality assessment pathologist evaluated slides from all tumors and all potential target organs, which included the adrenal gland, bone marrow, harderian gland, kidney, liver, lymph node, preputial gland, stomach (glandular), thyroid gland, and tooth of male mice and the adrenal gland, bone marrow, kidney, liver, pituitary gland, spleen, stomach (forestomach and glandular), thyroid gland, and vagina of female mice.

The quality assessment report and the reviewed slides were submitted to the NTP Pathology Working Group (PWG) chairperson, who reviewed the selected tissues and addressed any inconsistencies in the diagnoses made by the laboratory and quality assessment pathologists. Representative histopathology slides containing examples of lesions related to chemical administration, examples of disagreements in diagnoses between the laboratory and quality assessment pathologists, or lesions of general interest were presented by the chairperson to the PWG for review. The PWG consisted of the quality assessment pathologist and other pathologists experienced in rodent toxicologic pathology. This group examined the tissues without any knowledge of dose groups or previously rendered diagnoses. When the PWG consensus differed from the opinion of the laboratory pathologist, the diagnosis was changed. Final diagnoses for reviewed lesions represent a consensus between the laboratory pathologist, reviewing pathologist(s), and the PWG. Details of these review procedures have been described, in part, by Maronpot and Boorman (1982) and Boorman *et al*. (1985). For subsequent analyses of the pathology data, the decision of whether to evaluate the diagnosed lesions for each tissue type separately or combined was generally based on the guidelines of McConnell *et al*. (1986).

TABLE 4
Experimental Design and Materials and Methods in the Gavage Studies of AZT and AZT/α-Interferon A/D

14-Week Study	2-Year Studies
Study Laboratory Southern Research Institute (Birmingham, AL)	Southern Research Institute (Birmingham, AL)
Strain and Species $B6C3F_1$ mice	$B6C3F_1$ mice
Animal Source Simonsen Laboratories, Inc. (Gilroy, CA)	Simonsen Laboratories, Inc. (Gilroy, CA)
Time Held Before Studies 11 days	17–20 days
Average Age When Studies Began 6 weeks	7–8 weeks
Date of First Dose 10 April 1989 (males) or 3 April 1989 (females)	AZT: 9 July 1990 α-Interferon A/D: 5 September 1990 AZT/500 U α-Interferon A/D: 8 October 1990 AZT/5,000 U α-Interferon A/D: 14 January 1991 All studies: Dosing of groups designated for clinical pathology analyses and determination of plasma AZT concentrations began 5–7 days after core study dosing began.
Duration of Dosing 93 days (core study); 92 days (recovery group)	105 weeks
Date of Last Dose 11 July 1989 (males) or 4 July 1989 (females) (core study); 10 July 1989 (males) or 3 July 1989 (females) (recovery group)	AZT: 8 July 1992 (males) or 10 July 1992 (females) α-Interferon A/D: 2 September 1992 AZT/500 U α-Interferon A/D: 8 October 1992 (males) or 6 October 1992 (females) AZT/5,000 U α-Interferon A/D: 12 January 1993 (males) or 14 January 1993 (females)
Necropsy Dates 12 July 1989 (males) or 5 July 1989 (females) (core study); 8 August 1989 (males) or 1 August 1989 (females) (recovery group)	AZT: 6–8 July 1992 (males) or 8–10 July 1992 (females) α-Interferon A/D: 1–3 September 1992 (males) or 2–4 September 1992 (females) AZT/500 U α-Interferon A/D: 7–9 October 1992 (males) or 5–7 October 1992 (females) AZT/5,000 U α-Interferon A/D: 11–13 January 1993 (males) or 12–15 January 1993 (females)
Average Age at Necropsy 20 weeks (core study); 23 weeks (recovery group)	112 weeks
Size of Study Groups 10 males and 10 females	50 males and 50 females (core groups) 30 males and 30 females (clinical pathology groups) 15 males and 15 females (plasma AZT determination groups)

TABLE 4
Experimental Design and Materials and Methods in the Gavage Studies of AZT and AZT/α-Interferon A/D

14-Week Study	2-Year Studies
Method of Distribution Animals were distributed randomly into groups of approximately equal initial mean body weights.	Same as 14-week study
Animals per Cage 1	1
Method of Animal Identification Tail tattoo; mice were later identified by ear punch because the skin of the tails became dark and made it difficult to read the tattoos.	Microchip implant
Diet NIH-07 open formula pelleted diet (Zeigler Brothers, Inc., Gardners, PA), available *ad libitum*	Same as 14-week study
Water Tap water (Birmingham municipal supply) via automatic watering system (Edstrom Industries, Inc., Waterford, WI), available *ad libitum*	Same as 14-week study
Cages Solid-bottom polycarbonate (Lab Products, Inc., Maywood, NJ), rotated every 2 weeks	Same as 14-week study
Bedding Sani-Chips® heat-treated hardwood chips (P.J. Murphy Forest Products, Montville, NJ), changed once per week	Same as 14-week study
Cage Filters Reemay® spun-bonded polyester (Andico, Birmingham, AL), changed once every 2 weeks	Same as 14-week study
Racks Stainless steel (Lab Products, Inc., Maywood, NJ), rotated once every 2 weeks	Same as 14-week study
Animal Room Environment Temperature: 20.4°–24.1° C (males); 20.6°–24.5° C (females) Relative humidity: 37%–83% (males); 38%–81% (females) Fluorescent light: 12 hours/day Room air changes: at least 10/hour	AZT: Temperature: 17.9°–27.8° C Relative humidity: 27%–83% Fluorescent light: 12 hours/day Room air changes: at least 10/hour α-Interferon A/D: Temperature: 17.0°–25.9° C Relative humidity: 22%–87% Fluorescent light: 12 hours/day Room air changes: at least 10/hour AZT/500 U α-Interferon A/D: Temperature: 12.8°–24.4° C Relative humidity: 18%–89% Fluorescent light: 12 hours/day Room air changes: at least 10/hour AZT/5,000 U α-Interferon A/D: Temperature: 14.8°–24.3° C Relative humidity: 15%–89% Fluorescent light: 12 hours/day Room air changes: at least 10/hour

Experimental Design and Materials and Methods in the Gavage Studies of AZT and AZT/α-Interferon A/D

14-Week Study	2-Year Studies
Doses 0, 50, 100, 200, 800, or 2,000 mg/kg body weight in 0.5% methylcellulose by gavage at a volume of 20 mL/kg body weight, given 7 days per week in two equal doses of 0, 25, 50, 100, 400, or 1,000 mg/kg per dose, except on days of neurobehavioral testing (core study); 0, 100, 800, or 2,000 mg/kg body weight in 0.5% methylcellulose by gavage at a volume of 20 mL/kg body weight, given 7 days per week in two equal doses of 0, 50, 400, or 1,000 mg/kg per dose, except on days of neurobehavioral testing (recovery group)	AZT: Daily doses of 0, 30, 60, or 120 mg AZT/kg body weight in 0.5% methylcellulose by gavage at a volume of 10 mL/kg body weight, given 5 days per week in two equal doses α-Interferon A/D: 0, 500, or 5,000 U α-interferon A/D, or 5,000 U α-interferon A at a volume of 0.5 mL/dose, administered subcutaneously three times per week AZT/500 U α-Interferon A/D: Daily doses of 0, 30, 60, or 120 mg AZT/kg body weight in 0.5% methylcellulose by gavage at a volume of 10 mL/kg body weight, given 5 days per week in two equal doses. Dosed groups also received 500 U α-interferon A/D at a volume of 0.5 mL/dose, administered subcutaneously three times per week. AZT/5,000 U α-Interferon A/D: Daily doses of 0, 30, 60, or 120 mg AZT/kg body weight in 0.5% methylcellulose by gavage at a volume of 10 mL/kg body weight, given 5 days per week in two equal doses. Dosed groups also received 5,000 U α-interferon A/D at a volume of 0.5 mL/dose, administered subcutaneously three times per week.
Type and Frequency of Observation Observed twice daily; animals were weighed initially and then weekly throughout the study; clinical findings were recorded weekly. Feed consumption was measured weekly.	Observed twice daily; animals were weighed initially, weekly for approximately 13 weeks, monthly thereafter, and at the end of the studies; clinical findings were recorded at the beginning of the studies and monthly thereafter.
Method of Sacrifice CO_2 asphyxiation	CO_2 asphyxiation
Necropsy Necropsy was performed on all animals. Organs weighed were the heart, left and right kidneys, liver, lung, right testis, and thymus.	Necropsy was performed on all animals.

TABLE 4
Experimental Design and Materials and Methods in the Gavage Studies of AZT and AZT/α-Interferon A/D

	14-Week Study	2-Year Studies
Clinical Pathology	On days 5 and 23 and at the end of the 14-week dosing period (core study) and on day 89 and at the end of the holding period (recovery group), blood was collected from the retroorbital sinus of all animals for hematology analyses. Bone marrow analyses were performed on 0, 100, 800, and 2,000 mg/kg core study mice at the end of the dosing period and on recovery group mice at the end of the holding period. ***Hematology:*** hematocrit; hemoglobin concentration; erythrocyte, reticulocyte, and nucleated erythrocyte counts; mean cell volume; mean cell hemoglobin; mean cell hemoglobin concentration; platelet count; and leukocyte count and differentials ***Bone Marrow Analyses:*** total femoral count, M:E ratio, rubriblasts, prorubricytes, rubricytes, metarubricytes, myeloblasts, promyelocytes, myelocytes (basophilic, eosinophilic, and neutrophilic), metamyelocytes (basophilic, eosinophilic, and neutrophilic), bands (basophilic, eosinophilic, and neutrophilic), segments (basophilic, eosinophilic, and neutrophilic), lymphocytes, macrophages, monocytes, megakaryo cells, plasma cells, mitotic figures, fat cells, mast cells, smudge cells, osteoblasts, osteoclasts, and other bone marrow cells	Blood was collected from the retroorbital sinus of up to 10 mice per clinical pathology group at 14, 27, and 40 weeks for hematology determinations. Blood was also collected from the retroorbital sinus of up to 10 mice per clinical pathology group at 54, 65 or 66, and 79 or 80 weeks and from up to 10 core study mice per group at study termination for hematology determinations. Bone marrow analyses were performed on up to 10 mice per clinical pathology group at 54, 65 or 66, and 79 or 80 weeks and up to 10 core study mice per group at study termination. ***Hematology:*** hematocrit; hemoglobin concentration; erythrocyte, reticulocyte, and nucleated erythrocyte counts; mean cell volume; mean cell hemoglobin; mean cell hemoglobin concentration; platelet count; and leukocyte count and differentials ***Bone Marrow Analyses:*** total femoral count, M:E ratio, rubriblasts, prorubricytes, rubricytes, metarubricytes, myeloblasts, promyelocytes, myelocytes (basophilic, eosinophilic, and neutrophilic), metamyelocytes (basophilic, eosinophilic, and neutrophilic), bands (basophilic, eosinophilic, and neutrophilic), neutrophilic hypersegments, segments (basophilic, eosinophilic, and neutrophilic), lymphocytes, macrophages, monocytes, megakaryo cells, plasma cells, mitotic figures, fat cells, mast cells, smudge cells, osteoblasts, osteoclasts, and other bone marrow cells
Histopathology	Complete histopathology was performed on all animals. In addition to gross lesions and tissue masses, the following tissues were examined: adrenal gland, brain, clitoral gland, esophagus, femur and marrow, gallbladder, heart and aorta, large intestine (cecum, colon, rectum), small intestine (duodenum, jejunum, ileum), kidney, liver, lung, lymph nodes (mandibular, mesenteric), mammary gland, nose, ovary, pancreas, parathyroid gland, pituitary gland, preputial gland, prostate gland, salivary gland, seminal vesicle, skin, spinal cord, spleen, testes and epididymis, thigh muscle, thymus, thyroid gland, trachea, urinary bladder, uterus, and vagina (from animals used in vaginal cytology evaluations).	Complete histopathology was performed on all core study animals. In addition to gross lesions and tissue masses, the following tissues were examined: adrenal gland, brain, clitoral gland, esophagus, femur and marrow, gallbladder, heart and aorta, kidney, large intestine (cecum, colon, rectum), small intestine (duodenum, jejunum, ileum), liver, lungs and bronchi, lymph nodes (mandibular, mesenteric), mammary gland, thigh muscle, nose, ovary, pancreas, parathyroid gland, pituitary gland, preputial gland, prostate gland, salivary gland, seminal vesicle, spleen, stomach (forestomach and glandular stomach), testes and epididymis, thymus, thyroid gland, trachea, urinary bladder, uterus, and vagina.
Sperm Motility and Vaginal Cytology	At the end of the 14-week dosing period, samples were collected for sperm motility evaluations from core study and recovery group male mice receiving 0, 100, 800, or 2,000 mg/kg. The following parameters were evaluated: sperm count and motility; epididymal spermatozoal data; and left cauda, left epididymis, and left testis weights. For recovery group females, vaginal samples were collected up to 12 consecutive days prior to the end of the 14-week dosing period and again before the end of the 4-week recovery period for vaginal cytology evaluations. The parameters evaluated were relative frequency of estrous stages and estrous cycle length.	None

TABLE 4
Experimental Design and Materials and Methods in the Gavage Studies of AZT and AZT/α-Interferon A/D

14-Week Study	2-Year Studies
Neurobehavioral Studies Neurobehavioral evaluations were conducted prior to the beginning of the study and on days 44 and 88 for core study mice and on day 117 (males) or 116 (females) for recovery group mice. All mice in the 0, 100, 800, and 2,000 mg/kg groups were subjected to the following behavioral tests: 1) a functional observational battery which included the assessment of home cage behaviors, handling behaviors, physiological measures, open field behavior, reflex responses, and the measurement of forelimb and hindlimb grip strength; 2) motor activity; 3) thermal sensitivity; and 4) startle response.	None
Determinations of AZT in Plasma None	At week 54 of the 2-year AZT study, blood was collected from the retroorbital sinus of as many as 15 male and 15 female anesthetized mice from each group designated for the determination of plasma concentrations of AZT at five time points (15, 30, 60, 90, or 120 minutes after the first daily dose of AZT was administered); three mice from each group of 15 were evaluated at each time point. On the last day of the 2-year AZT study, blood was collected from the retroorbital sinus of 18 male and 18 female anesthetized mice from each core study dosed group at six time points (5, 15, 30, 60, 90, or 120 minutes after the first daily dose of AZT was administered); three mice from each group were evaluated at each time point. Additionally, on the last day of the study, blood was collected from five male and five female mice in the dosed core study groups before the first daily dose was administered. The mean plasma concentrations of AZT and standard deviations were calculated.

STATISTICAL METHODS

Survival Analyses

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

Calculation of Incidence

The incidences of neoplasms or nonneoplastic lesions are presented in Tables A1, A4, B1, B4, C1, C3, D1, D4, E1, E3, F1, F3, G1, G3, H1, and H3 as the numbers of animals bearing such lesions at a specific anatomic site and the numbers of animals with that site examined microscopically. For calculation of statistical significance, the incidences of most neoplasms (Tables A2, B2, C2, D2, E2, F2, G2, and H2) 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 A2, B2, C2, D2, E2, F2, G2, and H2 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 these studies 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 exposed 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 and the Cochran-Armitage trend test (Armitage, 1971; Gart *et al.*, 1979), procedures based on the overall proportion of neoplasm-bearing animals.

Tests of significance included pairwise comparisons of each dosed group with controls and a test for an overall dose-related trend. 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

Two approaches were employed to assess the significance of pairwise comparisons between dosed and control groups in the analysis of continuous variables. Organ and body weight data, which have approximately normal distributions, were analyzed with the parametric multiple comparison procedures of Dunnett (1955) and Williams (1971, 1972). Hematology, bone marrow, spermatid, epididymal spermatozoal,

and neurobehavioral data, which have typically skewed distributions, were analyzed using the nonparametric multiple comparison methods of Shirley (1977) and Dunn (1964). Jonckheere's test (Jonckheere, 1954) was used to assess the significance of the dose-related trends and to determine whether a trend-sensitive test (Williams' or Shirley's test) was more appropriate for pairwise comparisons than a test that does not assume a monotonic dose-related trend (Dunnett's or Dunn's test). Prior to statistical analysis, extreme values identified by the outlier test of Dixon and Massey (1951) were examined by NTP personnel, and implausible values were eliminated from the analysis. Average severity values were analyzed for significance with the Mann-Whitney U test (Hollander and Wolfe, 1973). Because vaginal cytology data are proportions (the proportion of the observation period that an animal was in a given estrous stage), an arcsine transformation was used to bring the data into closer conformance with a normality assumption. Treatment effects were investigated by applying a multivariate analysis of variance (Morrison, 1976) to the transformed data to test for simultaneous equality of measurements across dose levels.

Historical Control Data

Although the concurrent control group is always the first and most appropriate control group used for evaluation, historical control data can be helpful in the overall assessment of neoplasm incidence in certain instances. Consequently, neoplasm incidences from the NTP historical control database which is updated yearly are included in the NTP reports for neoplasms appearing to show compound-related effects. Because there are no methylcellulose gavage studies in the NTP historical control database, historical data from water gavage studies were used for comparison. Likewise, there are no subcutaneous studies in the NTP historical control database, so feed studies were used for comparison in that portion of the current studies.

QUALITY ASSURANCE METHODS

The 14-week and 2-year studies were conducted in compliance with Food and Drug Administration Good Laboratory Practice Regulations (21 CFR, Part 58). In addition, as records from the 2-year studies were submitted to the NTP Archives, these studies were audited retrospectively by an independent quality assurance contractor. Separate audits covered completeness and accuracy of the pathology data, pathology specimens, final pathology tables, and a draft of this NTP Technical Report. Audit procedures and findings are presented in the reports and are on file at NIEHS. The audit findings were reviewed and assessed by NTP staff, and all comments were resolved or otherwise addressed during the preparation of this Technical Report.

GENETIC TOXICOLOGY

The genetic toxicity of AZT was assessed by testing the ability of the chemical to induce mutations in various strains of *Salmonella typhimurium*, sister chromatid exchanges and chromosomal aberrations in cultured Chinese hamster ovary cells, and increases in the frequency of micronucleated erythrocytes in bone marrow and peripheral blood of mice. The protocols for these studies and the results are given in Appendix I.

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

There is a strong correlation between a chemical's potential electrophilicity (structural alert to DNA reactivity), mutagenicity in *Salmonella*, and carcinogenicity in rodents. The combination of electrophilicity and *Salmonella* mutagenicity is highly correlated with the induction of carcinogenicity in rats and mice and/or at multiple tissue sites (Ashby and Tennant, 1991). Other *in vitro* genetic toxicity tests correlate less well with rodent carcinogenicity (Tennant *et al.*, 1987; Zeiger *et al.*, 1990), although these other tests can provide information on the types of DNA and chromosome effects that can be induced by the chemical being investigated. Data from NTP studies show that a positive response in *Salmonella* is the most predictive *in vitro* test for rodent carcinogenicity (89% of the *Salmonella* mutagens are rodent carcino-

gens), and that there is no complementarity among the *in vitro* genetic toxicity tests. That is, no battery of tests that included the *Salmonella* test improved the predictivity of the *Salmonella* test alone.

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

RESULTS

MICE

14-WEEK AZT STUDY

In the 14-week study, one female receiving 100 mg/kg and two females receiving 200 mg/kg died during week 1 as a result of gavage trauma; one female receiving 2,000 mg/kg also died prior to the end of the 14-week dosing period (Table 5). One female in the 2,000 mg/kg group in the 14-week gavage with 4-week recovery study died during week 1 due to gavage trauma (Table 6). Females receiving 200, 800, or 2,000 mg/kg gained less weight than the vehicle controls during the 14-week dosing period. The final mean body weights of dosed mice were similar to those of the vehicle control groups at the end of the 14-week dosing period and at the end of the 4-week recovery period.

TABLE 5
Survival and Body Weights of Mice in the 14-Week Gavage Study of AZT

Dose (mg/kg)	Survival[a]	Mean Body Weight[b] (g)			Final Weight Relative to Controls (%)
		Initial	Final	Change	
Male					
0	10/10	23.0 ± 0.4	33.1 ± 0.5	10.1 ± 0.6	
50	10/10	23.0 ± 0.3	33.9 ± 0.6	10.9 ± 0.5	102
100	10/10	22.8 ± 0.4	35.5 ± 1.0	12.7 ± 0.9*	107
200	10/10	23.4 ± 0.5	34.6 ± 0.9	11.3 ± 0.5	105
800	10/10	23.3 ± 0.4	34.0 ± 0.7	10.7 ± 0.7	103
2,000	10/10	23.1 ± 0.4	32.4 ± 0.6	9.3 ± 0.3	98
Female					
0	10/10	19.0 ± 0.9	28.9 ± 1.3	10.0 ± 1.2	
50	10/10	19.3 ± 0.5	28.6 ± 0.5	9.3 ± 0.5	99
100	9/10[c]	18.8 ± 0.7	27.6 ± 0.4	8.1 ± 0.4	95
200	8/10[c]	18.6 ± 0.9	27.2 ± 0.7	7.3 ± 0.5*	94
800	10/10	19.6 ± 0.3	26.3 ± 0.6	6.7 ± 0.5*	91
2,000	9/10[d]	19.1 ± 0.2	26.8 ± 1.0	7.8 ± 0.9*	93

* Significantly different ($P \leq 0.05$) from the vehicle control group by Williams' or Dunnett's test
[a] Number of animals surviving at 14 weeks/number initially in group
[b] Weights and weight changes are given as mean ± standard error.
[c] Week of death: 1 (gavage trauma)
[d] Week of death: 9

TABLE 6
Survival and Body Weights of Mice in the 14-Week Gavage with 4-Week Recovery Study of AZT

Dose (mg/kg)	Survival[a]	Mean Body Weight[b] (g)			Final Weight Relative to Controls (%)
		Initial	Final	Change	
Male					
0	10/10	23.4 ± 0.4	37.2 ± 1.0	13.7 ± 0.8	
100	10/10	23.2 ± 0.3	38.8 ± 0.7	15.6 ± 0.5	104
800	10/10	23.7 ± 0.4	38.3 ± 1.4	14.6 ± 1.3	103
2,000	10/10	22.9 ± 0.4	36.1 ± 1.3	13.3 ± 1.0	97
Female					
0	10/10	19.9 ± 0.3	30.8 ± 1.4	10.9 ± 1.1	
100	10/10	19.7 ± 0.3	32.3 ± 0.5	12.6 ± 0.4	105
800	10/10	20.0 ± 0.2	32.8 ± 1.1	12.8 ± 1.0	106
2,000	9/10[c]	19.6 ± 0.2	30.1 ± 0.9	10.4 ± 0.8	98

[a] Number of animals surviving at 17 weeks/number initially in group
[b] Weights and weight changes are given as mean ± standard error. Differences from the vehicle control groups were not significant by Dunnett's test.
[c] Week of death: 1 (gavage trauma)

Clinical findings during the 14-week study included a chemical-related darkening of the skin on the tail, feet, and muzzle beginning around week 6. Darkened skin was also observed in dosed mice following the 4-week recovery period, but it was limited to the tail and was less severe than that observed in dosed mice at the end of the 14-week dosing period.

At the end of the 14-week dosing period, the absolute heart weight and the absolute and relative thymus weights of males receiving 50 mg/kg, the absolute left and right kidney weights of males receiving 200 mg/kg, and the absolute and relative liver weights of males receiving 50 or 200 mg/kg were significantly greater than those of the vehicle control group (Table J1). The absolute right testis weight of males receiving 2,000 mg/kg and the absolute thymus weight of females receiving 2,000 mg/kg were significantly lower than those of the vehicle control groups. At the end of the recovery period, the absolute heart weight of males receiving 800 mg/kg was significantly greater than that of the vehicle control group.

The hematology and bone marrow data for mice in the 14-week study are listed in Table K1. In general, a dose- and time-dependent, minimal to moderate, macrocytic, nonresponsive anemia occurred in male and female mice; these findings are consistent with the AZT-induced hematotoxicity reported previously for mice (Thompson *et al.*, 1991). On day 5, decreased erythrocyte counts occurred in 800 mg/kg female and 2,000 mg/kg male and female mice. By day 23, erythrocyte counts were decreased in males administered 100 mg/kg or greater and in all dosed groups of females; at study termination, decreased erythrocyte counts occurred in all dosed groups. Decreased hematocrit values and hemoglobin concentrations also occurred in various dosed groups at all time points. There was no indication of an erythropoietic response to the anemia, based on the lack of increased reticulocyte numbers; in fact, reticulocyte counts were decreased in 200 mg/kg or greater male and female mice on day 5 and in the 100 mg/kg or greater female and 800 mg/kg or greater male mice at week 14. The erythrocytes were macrocytic, evidenced by increased mean cell volume and mean cell hemoglobin in all dosed groups on day 23 and at study termination; a macrocytosis, without an increase of reticulocyte counts, would be consistent with an effective erythropoiesis. An erythroid hypoplasia in the bone marrow, evidenced by decreased total femur counts and erythroid precursor (rubricyte and metarubri-

cyte) numbers and increased M:E ratios, occurred in males administered 800 mg/kg or greater and in females receiving 100 mg/kg or greater; the bone marrow results support the decreased reticulocyte counts in the peripheral blood. Bone marrow lymphocyte (2,000 mg/kg males and 100 mg/kg or greater females), metamyelocyte, band, segmented neutrophil, and monocyte counts (100 mg/kg and greater females) also decreased; these decreases also would have contributed to the decreased total femur counts. Increased platelet counts occurred on day 23 in males administed 800 mg/kg or greater and in females receiving 100 mg/kg or greater, and in 2,000 mg/kg males at week 14. Increased platelet counts were not associated with increased numbers of megakaryocytes in the bone marrow and would be consistent with evidence in humans that increased platelet counts are related to enhanced platelet survival (Panzer *et al.*, 1989). The data from the recovery portion of the 14-week study indicate that AZT-induced hematotoxicity is reversible. At the end of the 4-week recovery period the macrocytic anemia had ameliorated. Additionally, platelet and bone marrow variable counts of dosed animals returned to control values.

There were no consistent treatment-related effects on reproductive (Table L1) or neurobehavioral parameters (Table M1) evaluated during the 14-week study.

At the end of the 14-week dosing period, bone marrow atrophy in males receiving 2,000 mg/kg and females receiving 800 or 2,000 mg/kg and splenic hematopoietic cell proliferation in males and females receiving 200, 800, or 2,000 mg/kg were considered chemical related. No chemical-related lesions were observed at the end of the recovery period.

Dose Selection Rationale: The only significant toxic response associated with AZT treatment was a poorly regenerative, normochromic, macrocytic anemia which increased in severity with increasing dose concentration but was present to some extent in animals at each dose concentration. A no-effect level was not achieved in the 14-week study, and because of the potentially cumulative nature of bone marrow toxicity in the presence of daily exposure to AZT, it was considered desirable to include a dose below 50 mg/kg in the 2-year study. At doses of 200 mg/kg and greater the severity of anemia was considered to be potentially life threatening in a 2-year study, whereas the response at 100 mg/kg was similar to that observed at 50 mg/kg and was considered somewhat low for the high dose in a 2-year study. Therefore, total daily doses selected for the 2-year AZT study were 30, 60, and 120 mg/kg to be administered by gavage as twice-daily doses of 15, 30, and 60 mg/kg.

2-YEAR AZT STUDY

Survival

Estimates of 2-year survival probabilities for male and female mice are shown in Table 7 and in the Kaplan-Meier survival curves (Figure 1). Males receiving 120 mg/kg had a significantly greater probability of survival than the vehicle control group; survival of all other groups of dosed mice was similar to that of the vehicle control groups.

Body Weights and Clinical Findings

Mean body weights of dosed groups of mice were similar to those of the vehicle control groups throughout the study (Tables 8 and 9; Figure 2). There were no chemical-related clinical findings.

Hematology and Bone Marrow Analyses

The hematology and bone marrow data for mice in the 2-year study of AZT are listed in Table K2. In general, a dose- and time-dependent, minimal to mild, macrocytic, nonresponsive anemia occurred in all dosed mice; these findings were consistent with the AZT-induced hematotoxicity reported for mice in the 14-week study. At week 80, macrocytic anemia was resolved in 30 mg/kg males; at study termination, only erythrocytic macrocytosis occurred in 60 and 120 mg/kg males. Macrocytic anemia was observed in all dosed groups of female mice throughout the study.

TABLE 7
Survival of Mice in the 2-Year Gavage Study of AZT

	Vehicle Control	30 mg/kg	60 mg/kg	120 mg/kg
Male				
Animals initially in study	50	50	50	50
Accidental deaths[a]	0	0	3	0
Moribund	6	9	9	4
Natural deaths	12	6	9	4
Animals surviving to study termination	32	35	29	42
Percent probability of survival at end of study[b]	64	70	62	84
Mean survival (days)[c]	684	679	647	710
Survival analysis[d]	P = 0.054N	P = 0.674N	P = 0.905	P = 0.044N
Female				
Animals initially in study	50	50	50	50
Accidental deaths[a]	0	0	3	1
Moribund	5	5	9	7
Natural deaths	11	6	7	11
Animals surviving to study termination	34	39[e]	31	31
Percent probability of survival at end of study	68	78	66	63
Mean survival (days)	689	707	648	687
Survival analysis	P = 0.499	P = 0.360N	P = 0.971	P = 0.874

[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 trend test (Tarone, 1975) is in the vehicle control column, and the results of the life table pairwise comparisons (Cox, 1972) with the vehicle controls are in the dosed group columns. A negative trend or lower mortality in a dosed group is indicated by **N**.
[e] Includes one animal that died during the last week of the study

FIGURE 1
Kaplan-Meier Survival Curves for Male and Female Mice Administered AZT in Methylcellulose by Gavage for 2 Years

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

Weeks on Study	Vehicle Control		30 mg/kg			60 mg/kg			120 mg/kg		
	Av. Wt. (g)	No. of Survivors	Av. Wt. (g)	Wt. (% of controls)	No. of Survivors	Av. Wt. (g)	Wt. (% of controls)	No. of Survivors	Av. Wt. (g)	Wt. (% of controls)	No. of Survivors
1	25.6	50	25.5	100	50	25.6	100	49	25.4	99	50
2	27.0	50	27.1	100	50	27.2	101	49	27.1	100	50
3	28.0	50	27.9	100	50	27.9	100	49	27.7	99	50
4	29.2	50	28.9	99	50	29.3	100	49	29.0	99	50
5	29.7	50	29.4	99	50	29.7	100	49	29.4	99	50
6	30.6	50	30.5	100	50	30.8	101	49	30.3	99	50
7	31.5	50	31.4	100	50	31.7	101	49	31.3	99	50
8	32.4	50	32.2	99	50	32.5	100	49	32.1	99	50
9	32.9	50	32.7	99	50	33.0	100	49	32.8	100	50
10	33.4	50	33.2	99	50	33.3	100	49	33.1	99	50
11	33.8	50	34.1	101	50	34.5	102	49	33.8	100	50
12	35.4	50	35.5	100	50	35.7	101	49	35.1	99	50
13	34.0	50	34.0	100	50	34.3	101	49	33.6	99	50
17	39.0	50	39.0	100	50	39.2	101	49	38.7	99	50
21	42.1	50	41.6	99	50	42.6	101	49	41.4	98	50
25	44.2	50	44.1	100	50	44.4	101	49	43.7	99	50
30	46.4	50	45.9	99	50	46.1	99	49	45.4	98	50
33	46.8	50	46.8	100	50	47.3	101	49	46.5	99	50
37	47.9	50	47.7	100	50	48.0	100	48	47.7	100	50
41	49.1	50	48.7	99	49	49.3	100	48	48.8	99	50
45	48.9	50	48.8	100	49	49.0	100	47	48.8	100	50
49	49.3	49	48.7	99	49	49.4	100	47	49.3	100	50
53	50.2	49	49.5	99	47	50.0	100	47	50.1	100	50
57	49.8	49	49.5	99	47	49.5	99	46	50.0	100	50
61	49.5	49	49.3	100	47	49.0	99	45	49.5	100	50
65	50.1	48	49.6	99	47	49.4	99	45	50.3	100	50
69	50.0	47	49.7	99	46	48.7	97	44	49.8	100	50
73	50.2	47	49.9	99	45	48.8	97	42	49.8	99	50
77	49.9	47	49.8	100	45	48.7	98	42	49.8	100	49
81	49.2	47	49.2	100	45	47.7	97	41	49.7	101	47
85	48.9	43	48.6	99	43	47.5	97	39	49.8	102	46
89	48.2	41	47.5	99	43	46.1	96	38	49.3	102	45
93	47.4	38	46.3	98	41	45.3	96	35	48.6	103	45
97	46.2	38	45.8	99	38	44.4	96	33	47.3	102	45
101	45.3	34	45.0	99	38	44.2	98	31	47.5	105	42
Mean for weeks											
1-13	31.0		31.0	100		31.2	101		30.8	99	
14-52	46.0		45.7	99		46.1	100		45.6	99	
53-101	48.8		48.4	99		47.6	98		49.3	101	

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

Weeks on Study	Vehicle Control		30 mg/kg			60 mg/kg			120 mg/kg		
	Av. Wt. (g)	No. of Survivors	Av. Wt. (g)	Wt. (% of controls)	No. of Survivors	Av. Wt. (g)	Wt. (% of controls)	No. of Survivors	Av. Wt. (g)	Wt. (% of controls)	No. of Survivors
1	20.4	50	20.2	99	50	20.7	102	49	20.6	101	49
2	22.2	50	22.0	99	50	22.1	100	49	22.3	101	49
3	23.0	50	23.3	101	50	23.4	102	49	23.4	102	49
4	23.9	50	24.2	101	50	24.3	102	49	24.2	101	49
5	24.8	50	24.8	100	50	25.2	102	49	25.2	102	49
6	25.7	50	26.0	101	50	26.5	103	49	26.4	103	49
7	26.6	50	26.9	101	50	27.2	102	49	27.4	103	49
8	27.1	50	27.4	101	50	27.5	102	49	27.8	103	49
9	27.9	50	28.3	101	50	28.4	102	49	28.7	103	49
10	28.2	50	28.8	102	50	29.1	103	49	29.1	103	49
11	28.6	50	29.6	104	50	29.8	104	49	30.0	105	49
12	29.1	50	30.2	104	50	30.5	105	49	30.2	104	49
13	29.5	50	30.0	102	50	30.3	103	48	30.3	103	49
17	34.0	50	34.6	102	50	34.6	102	48	34.7	102	49
21	37.1	50	38.0	102	50	37.9	102	48	37.5	101	49
25	39.8	50	40.1	101	50	40.3	101	48	40.2	101	49
29	42.1	50	42.7	101	50	42.6	101	48	42.4	101	49
33	44.1	50	44.5	101	50	44.5	101	47	44.8	102	49
37	46.4	50	47.2	102	50	46.7	101	47	47.5	102	49
41	48.6	50	49.0	101	50	48.8	100	47	49.2	101	49
45	50.2	50	51.2	102	50	50.7	101	45	50.8	101	49
49	51.7	50	52.8	102	50	52.2	101	45	52.2	101	49
53	53.2	50	54.6	103	50	54.0	102	45	54.2	102	49
57	54.2	49	55.3	102	50	54.3	100	45	54.6	101	49
61	54.3	48	55.6	102	50	54.0	99	45	55.6	102	49
65	55.1	48	56.4	102	50	54.8	100	45	56.3	102	49
69	55.2	47	57.1	103	50	54.8	99	45	56.0	101	48
73	56.1	47	57.6	103	50	55.4	99	44	57.0	102	47
77	57.3	45	57.6	101	48	56.1	98	43	57.5	100	47
81	58.0	45	57.8	100	48	56.1	97	42	58.3	101	46
85	57.7	45	56.7	98	47	55.6	96	41	58.0	101	46
89	57.0	42	57.3	101	45	57.5	101	38	57.9	102	43
93	55.8	41	56.5	101	43	57.0	102	38	57.4	103	42
97	55.2	39	55.2	100	41	55.5	101	36	55.3	100	41
101	53.8	37	55.4	103	39	55.5	103	33	55.1	102	37
Mean for weeks											
1-13	25.9		26.3	102		26.5	102		26.6	103	
14-52	43.8		44.5	102		44.3	101		44.4	101	
53-101	55.6		56.4	101		55.4	100		56.4	101	

FIGURE 2
Growth Curves for Male and Female Mice
Administered AZT in Methylcellulose by Gavage for 2 Years

Determinations of AZT Concentrations in Plasma

Mean plasma concentrations of AZT were determined at week 54 and at the end of the study and are presented in Table N1. At week 54, peak plasma concentrations of all dosed groups of males and 30 and 60 mg/kg females occurred at the earliest time point evaluated (15 minutes), with peak concentrations in females approximately twice the corresponding values in males. In females receiving 120 mg/kg, the peak plasma concentration occurred at 30 minutes; however, there was significant variation of the three individual values at this time point as reflected by the large standard deviation. In males and females, peak concentrations increased in a dose-proportional manner at week 54.

At the end of the study, peak plasma AZT concentrations exhibited considerably more variation, with peak concentrations occurring 5 to 30 minutes after dosing. In general, peak values of females were similar to those of males.

Pathology and Statistical Analysis

This section describes the statistically significant or biologically noteworthy changes in the incidences of neoplasms and/or nonneoplastic lesions of the vagina, kidney, harderian gland, liver, adrenal gland, and bone marrow. Summaries of the incidences of neoplasms and nonneoplastic lesions, statistical analyses of primary neoplasms that occurred with an incidence of at least 5% in at least one animal group, and historical incidences for the neoplasms mentioned in this section are presented in Appendix A for male mice and Appendix B for female mice.

Vagina: The incidences of squamous cell carcinoma and squamous cell papilloma or carcinoma (combined) occurred with a positive trend and were significantly increased in groups of female mice receiving 60 or 120 mg/kg (Tables 10 and B2). Epithelial hyperplasia was observed in all dosed groups of females but not in the vehicle controls; the incidence was significantly increased in the 120 mg/kg group (Tables 10 and B4).

Squamous cell carcinomas were typically keratinizing proliferations of anaplastic cells that usually protruded into the lumen and infiltrated into the submucosa and smooth muscle of the vagina (Plate 1). Squamous cell papillomas protruded but did not invade underlying tissue (Plate 2). The proliferating cells of the papillomas were uniform in size and shape, and their arrangement was more ordered and consistent than that of the carcinomas. Epithelial hyperplasia was a focal to multifocal nodular thickening of the basal and middle layers of epithelium (Plate 3). Atypical hyperplasia consisted of focal to multifocal thickening of epithelial cells that were somewhat variable in size and shape (Plate 4).

TABLE 10
Incidences of Neoplasms and Nonneoplastic Lesions of the Vagina in Female Mice in the 2-Year Gavage Study of AZT

	Vehicle Control	30 mg/kg	60 mg/kg	120 mg/kg
Number Examined Microscopically	50	49	45	49
Epithelium, Hyperplasia[a]	0	3 (1.0)[b]	2 (2.0)	7** (2.3)
Epithelium, Hyperplasia, Atypical	0	0	2 (3.0)	4 (2.3)
Squamous Cell Papilloma				
Overall rate[c]	0/50 (0%)	0/49 (0%)	0/45 (0%)	2/49 (4%)
Squamous Cell Carcinoma				
Overall rate	0/50 (0%)	0/49 (0%)	5/45 (11%)	9/49 (18%)
Adjusted rate[d]	0.0%	0.0%	12.8%	26.8%
Terminal rate[e]	0/34 (0%)	0/39 (0%)	1/30 (3%)	7/31 (23%)
First incidence (days)	—[g]	—	493	695
Logistic regression test[f]	P < 0.001	—	P = 0.028	P = 0.002
Squamous Cell Papilloma or Squamous Cell Carcinoma				
Overall rate	0/50 (0%)	0/49 (0%)	5/45 (11%)	11/49 (22%)
Adjusted rate	0.0%	0.0%	12.8%	32.9%
Terminal rate	0/34 (0%)	0/39 (0%)	1/30 (3%)	9/31 (29%)
First incidence (days)	—	—	493	695
Logistic regression test	P < 0.001	—	P = 0.028	P < 0.001

** Significantly different (P≤0.01) from the vehicle control group by the logistic regression test
[a] Number of animals with lesion
[b] Average severity grade of lesions in affected animals: 1 = minimal, 2 = mild, 3 = moderate, 4 = marked
[c] Number of neoplasm-bearing animals/number of animals microscopically examined
[d] Kaplan-Meier estimated neoplasm incidence at the end of the study after adjustment for intercurrent mortality
[e] Observed incidence at terminal kill
[f] Beneath the vehicle control incidence are the P values associated with the trend test. Beneath the dosed group incidence are the P values corresponding to pairwise comparisons between the vehicle controls and that dosed group. The logistic regression test regards neoplasms in animals dying prior to terminal kill as nonfatal.
[g] Not applicable; no neoplasms in animal group

Kidney: During histological examination of the standard kidney sections, three renal tubule adenomas and one renal tubule carcinoma were observed in 120 mg/kg males and one renal tubule hyperplasia was observed in a 30 mg/kg male (Tables 11, A1, A2, and A4). The incidences of adenoma and of adenoma or carcinoma (combined) exceeded the range in historical controls (Table A3a). Evaluation of step sections did not reveal any additional neoplasms; however, five additional renal tubule hyperplasias were observed in 60 mg/kg males and six additional hyperplasias were observed in 120 mg/kg males.

Renal tubule adenomas consisted of multiple disorganized layers of epithelium forming solid or tubular structures that compressed adjacent tissue. The renal tubule carcinoma was larger and had more structural disorganization and cellular anaplasia than

TABLE 11
Incidences of Neoplasms and Nonneoplastic Lesions of the Kidney in Male Mice in the 2-Year Gavage Study of AZT

	Vehicle Control	30 mg/kg	60 mg/kg	120 mg/kg
Single Sections (Standard Evaluation)				
Number Examined Microscopically	50	48	49	50
Renal Tubule Hyperplasia, Focal[a]	0	1 (2.0)[b]	0	0
Renal Tubule Adenoma[c]				
Overall rate[d]	0/50 (0%)	0/48 (0%)	0/49 (0%)	3/50 (6%)
Renal Tubule Carcinoma				
Overall rate	0/50 (0%)	0/48 (0%)	0/49 (0%)	1/50 (2%)
Renal Tubule Adenoma or Carcinoma[e]				
Overall rate	0/50 (0%)	0/48 (0%)	0/49 (0%)	4/50 (8%)
Adjusted rate[f]	0.0%	0.0%	0.0%	9.5%
Terminal rate[g]	0/32 (0%)	0/35 (0%)	0/29 (0%)	4/42 (10%)
First incidence (days)	—[i]	—	—	729 (T)
Logistic regression test[h]	P = 0.007	—	—	P = 0.103
Step Sections (Extended Evaluation)				
Number Examined Microscopically	50	—[j]	50	50
Renal Tubule Hyperplasia	0		5* (1.0)	6* (1.0)
Single and Step Sections (Combined)				
Number Examined Microscopically	50	48	50	50
Renal Tubule Hyperplasia	0	1 (2.0)	5* (1.0)	6* (1.0)

(T)Terminal sacrifice
* Significantly different ($P \leq 0.05$) from the vehicle control group by the logistic regression test
[a] Number of animals with lesion
[b] Average severity grade of lesions in affected animals: 1 = minimal, 2 = mild, 3 = moderate, 4 = marked
[c] Historical incidence for 2-year NTP gavage studies with water vehicle control groups: 0/365
[d] Number of neoplasm-bearing animals/number of animals microscopically examined
[e] Historical incidence (mean ± standard deviation): 2/365 (0.6% ± 1.5%); range, 0%-4%
[f] Kaplan-Meier estimated neoplasm incidence at the end of the study after adjustment for intercurrent mortality
[g] Observed incidence at terminal kill
[h] Beneath the vehicle control incidence are the P values associated with the trend test. Beneath the dosed group incidence are the P values corresponding to pairwise comparisons between the vehicle controls and that dosed group. The logistic regression test regards neoplasms in animals dying prior to terminal kill as nonfatal.
[i] Not applicable; no neoplasms in animal group
[j] Not examined at this dose level

the adenomas. Renal tubule hyperplasia consisted of tubules with stratified epithelium rather than the normal single layer of epithelium.

Harderian Gland: The incidence of harderian gland adenoma was increased in 120 mg/kg males and exceeded the range in historical controls (Tables 12, A2, and A3b). Carcinomas occurred in three male mice receiving 30 mg/kg, but none were observed in vehicle controls or other dosed groups. The incidences of harderian gland neoplasms were not increased in groups of female mice (Tables 12, B1, and B2). Hyperplasia was present in one male receiving 30 mg/kg (Table A4). Harderian gland adenomas were papillary, acinar, or cystic formations of slightly pleomorphic epithelial cells that compressed adjacent tissue.

TABLE 12
Incidences of Neoplasms of the Harderian Gland in Mice in the 2-Year Gavage Study of AZT

	Vehicle Control	30 mg/kg	60 mg/kg	120 mg/kg
Male				
Adenoma[a]				
Overall rate[b]	3/50 (6%)	2/50 (4%)	2/50 (4%)	10/50 (20%)
Adjusted rate[c]	9.4%	5.7%	6.3%	23.1%
Terminal rate[d]	3/32 (9%)	2/35 (6%)	1/29 (3%)	9/42 (21%)
First incidence (days)	729 (T)	729 (T)	667	612
Logistic regression test[e]	P = 0.009	P = 0.459N	P = 0.546N	P = 0.059
Carcinoma				
Overall rate	0/50 (0%)	3/50 (6%)	0/50 (0%)	0/50 (0%)
Adenoma or Carcinoma				
Overall rate	3/50 (6%)	5/50 (10%)	2/50 (4%)	10/50 (20%)
Adjusted rate	9.4%	13.3%	6.3%	23.1%
Terminal rate	3/32 (9%)	4/35 (11%)	1/29 (3%)	9/42 (13%)
First incidence (days)	729 (T)	458	667	612
Logistic regression test	P = 0.027	P = 0.355	P = 0.546N	P = 0.059
Female				
Adenoma				
Overall rate	4/50 (8%)	2/50 (4%)	0/50 (0%)	1/50 (2%)
Carcinoma				
Overall rate	1/50 (2%)	0/50 (0%)	1/50 (2%)	1/50 (2%)
Adenoma or Carcinoma				
Overall rate	5/50 (10%)	2/50 (4%)	1/50 (2%)	2/50 (4%)

(T)Terminal sacrifice
[a] Historical incidence for 2-year NTP gavage studies with water vehicle control groups (mean ± standard deviation): 18/365 (4.9% ± 3.5%); range, 2%-10%
[b] Number of neoplasm-bearing animals/number of animals necropsied
[c] Kaplan-Meier estimated neoplasm incidence at the end of the study after adjustment for intercurrent mortality
[d] Observed incidence at terminal kill
[e] Beneath the vehicle control incidence are the P values associated with the trend test. Beneath the dosed group incidence are the P values corresponding to pairwise comparisons between the vehicle controls and that dosed group. The logistic regression test regards neoplasms in animals dying prior to terminal kill as nonfatal. A lower incidence in a dosed group is indicated by **N**.

Liver: The incidence of hepatoblastoma was increased in males receiving 60 mg/kg, but not in the 30 or 120 mg/kg groups (Tables 13 and A2). Hepatoblastomas are uncommon neoplasms, which occur spontaneously or may be chemically induced in the liver of several strains of mice including $B6C3F_1$ (Turusov *et al.*, 1973; Nonoyama *et al.*, 1988). It is considered a malignant neoplasm and in NTP studies, its metastatic potential appears similar to that of hepatocellular carcinomas. Hepatoblastomas are easily diagnosed because of their distinctive morphology on H&E-stained sections. They almost always occur within an existing proliferative lesion, most often within a hepatocellular carcinoma. In NTP studies, the diagnosis of hepatoblastoma is made whenever this distinctive lesion is observed. To avoid duplicate diagnoses, a separate diagnosis for the lesion within which the hepatoblastoma occurs is not made.

The cell of origin of the hepatoblastoma has not been clearly defined in rodents or humans, but may be a very primordial cell (Abenoza *et al.*, 1987; Nonoyama *et al.*, 1988; Van Eyken *et al.*, 1990). To fully appreciate the significance of a potentially chemical-related increase in neoplasms, the NTP generally performs statistical analyses on benign and malignant neoplasms of like histogenesis both independently and in combination. Although the biology is not fully understood, hepatoblastoma is considered to be part of the spectrum of neoplastic liver lesions that occur both spontaneously and as a result of chemical treatment. Therefore, the NTP considers the combinations of hepatocellular carcinoma plus hepatoblastoma and hepatocellular adenoma and carcinoma plus hepatoblastoma the most important for analyses of the carcinogenic potential of an agent on the liver. In this study of AZT, the incidences of all malignant hepatocellular neoplasms (carcinomas and hepatoblastomas) and all hepatocellular neoplasms (adenomas, carcinomas, and hepatoblastomas) were not different between vehicle control and treated groups. Therefore, the slight increase in the incidence of hepatoblastoma in the 60 mg/kg group was not considered related to administration of AZT.

The incidence of hepatocellular adenoma, hepatocellular carcinoma, or hepatoblastoma (combined) was significantly greater in females receiving 120 mg/kg than in the vehicle control group (Tables 13 and B2). The increase was primarily of benign neoplasms (adenomas), and potentially preneoplastic foci of alteration were not different between the vehicle control and 120 mg/kg group (Table B4). An increase was not observed in male mice in this study, and there is no evidence of increases in liver neoplasms observed in the companion studies in which similar amounts of AZT were administered. This marginal increase of a very common neoplasm type was not considered related to administration of AZT.

Relatively high incidences of chronic inflammation and hepatocyte karyomegaly occurred in all groups of male mice; these lesions were usually observed together in the same liver (Tables 13 and A4). Chronic inflammation was characterized by oval cell hyperplasia, minimal to mild mononuclear inflammatory cell infiltrates, and, in more severe lesions, nodular regenerative hepatocellular hyperplasia. These changes were generally mild to moderate in severity and observed throughout the liver (usually not within proliferative lesions), but they appeared most pronounced in the portal regions. Similar lesions were observed in very few females, and the severity was also less than that observed in many males (Tables 13 and B4). Liver sections from only one of five male mice with liver lesions appeared positive for bacterial organisms consistent with *Helicobacter* when examined using Steiner's modification of the Warthin-Starry silver stain (Appendix R).

TABLE 13
Incidences of Neoplasms and Nonneoplastic Lesions of the Liver in Mice in the 2-Year Gavage Study of AZT

	Vehicle Control		30 mg/kg		60 mg/kg		120 mg/kg	
Male								
Number Examined Microscopically	50		50		50		50	
Chronic Inflammation[a]	17	(1.9)[b]	24	(1.9)	24	(1.8)	16	(2.1)
Hepatocyte, Karyomegaly	7	(2.3)	10	(2.3)	15*	(2.3)	5	(1.8)
Hepatocellular Adenoma	25		23		23		26	
Hepatocellular Carcinoma	21		26		22		19	
Hepatoblastoma	1		2		6*		2	
Hepatocellular Adenoma, Hepatocellular Carcinoma, or Hepatoblastoma	36		39		36		39	
Female								
Number Examined Microscopically	50		50		50		50	
Chronic Inflammation	1	(2.0)	2	(1.0)	2	(1.0)	1	(2.0)
Hepatocyte, Karyomegaly	1	(2.0)	1	(2.0)	0		0	
Necrosis, Focal	3	(2.7)	3	(2.7)	2	(1.5)	10*	(2.5)
Hepatocellular Adenoma[c]	20		18		17		28	
Hepatocellular Carcinoma[d]	12		17		11		15	
Hepatoblastoma	1		0		0		2	
Hepatocellular Adenoma, Hepatocellular Carcinoma, or Hepatoblastoma[e]	27		29		23		36*	

* Significantly different ($P \leq 0.05$) from the vehicle control group by the logistic regression test
[a] Number of animals with lesion
[b] Average severity grade of lesions in affected animals: 1 = minimal, 2 = mild, 3 = moderate, 4 = marked
[c] Historical incidence for 2-year NTP gavage studies with water vehicle control groups (mean ± standard deviation): 28/366 (7.7% ± 9.8%); range, 2%-29%
[d] Historical incidence: 16/366 (4.4% ± 5.4%); range, 0%-16%
[e] Historical incidence: 43/366 (11.8% ± 14.2%); range, 2%-43%

Other Organs: The incidence of adrenal cortex focal cytoplasmic alteration in males receiving 120 mg/kg was significantly greater than that in the vehicle control group (5/50, 11/49, 8/49, 18/49; Table A4), and the incidences of this lesion occurred with a positive trend. The incidence of bone marrow hyperplasia in females receiving 120 mg/kg was significantly greater than that in the vehicle control group (1/50, 3/49, 3/50, 7/50; Table B4), and the incidences of hyperplasia occurred with a positive trend.

2-YEAR α-INTERFERON A/D STUDY

Survival

Estimates of 2-year survival probabilities for male and female mice are shown in Table 14 and in the Kaplan-Meier survival curves (Figure 3). Survival of dosed mice was similar to that of the vehicle control groups.

Body Weights and Clinical Findings

Mean body weights of dosed males and females were generally similar to those of the vehicle control groups throughout the study (Figure 4; Tables 15 and 16). There were no chemical-related clinical findings.

Hematology and Bone Marrow Analyses

There were no treatment-related alterations in hematology or bone marrow parameters (Table K3).

TABLE 14
Survival of Mice in the 2-Year Subcutaneous Study of α-Interferon A/D

	Vehicle Control	5,000 U α-IFN A	500 U α-IFN A/D	5,000 U α-IFN A/D
Male				
Animals initially in study	50	50	50	50
Accidental death[a]	0	0	0	1
Moribund	13	10	7	10
Natural deaths	10	13	15	11
Animals surviving to study termination	27	27	28	28
Percent probability of survival at end of study[b]	54	54	56	57
Mean survival (days)[c]	679	683	666	664
Survival analysis[d]	P = 0.929N	P = 1.000N	P = 0.973	P = 1.000N
Female				
Animals initially in study	50	50	50	50
Accidental death[a]	0	0	0	1
Moribund	13	11	13	9
Natural deaths	12	8	5	15
Animals surviving to study termination	25	31	32	25
Percent probability of survival at end of study	50	62	64	51
Mean survival (days)	684	674	703	653
Survival analysis	P = 0.471	P = 0.417N	P = 0.174N	P = 1.000

[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 trend test (Tarone, 1975) is in the vehicle control column, and the results of the life table pairwise comparisons (Cox, 1972) with the vehicle controls are in the dosed group columns. The α-interferon A group was excluded from the trend test. A negative trend or lower mortality in a dosed group is indicated by **N**.

FIGURE 3
Kaplan-Meier Survival Curves for Male and Female Mice Administered α-Interferon A/D or A Subcutaneously for 2 Years

FIGURE 4
Growth Curves for Male and Female Mice
Administered α-Interferon A/D or A Subcutaneously for 2 Years

TABLE 15
Mean Body Weights and Survival of Male Mice in the 2-Year Subcutaneous Study of α-Interferon A/D

Weeks on Study	Vehicle Control		5,000 U α-IFN A			500 U α-IFN A/D			5,000 U α-IFN A/D		
	Av. Wt. (g)	No. of Survivors	Av. Wt. (g)	Wt. (% of controls)	No. of Survivors	Av. Wt. (g)	Wt. (% of controls)	No. of Survivors	Av. Wt. (g)	Wt. (% of controls)	No. of Survivors
1	25.5	50	25.3	99	50	25.8	101	50	25.8	101	50
2	27.6	50	27.3	99	50	27.5	100	50	27.6	100	50
3	28.3	50	27.8	98	50	28.1	99	50	28.5	101	50
4	28.9	50	28.5	99	50	29.0	100	50	29.2	101	50
5	30.4	50	30.2	99	50	30.7	101	50	30.5	100	50
6	31.6	50	31.3	99	50	31.6	100	50	31.9	101	50
7	32.3	50	32.2	100	50	32.5	101	50	32.8	102	50
8	33.5	50	33.2	99	50	33.3	99	50	33.6	100	50
9	34.3	50	33.9	99	50	34.1	99	50	34.5	101	50
10	34.1	50	34.0	100	50	33.6	99	50	34.7	102	50
11	34.7	50	34.1	98	50	34.4	99	50	35.1	101	50
12	36.8	50	36.4	99	50	36.4	99	50	36.8	100	50
17	39.6	50	39.4	100	50	39.1	99	50	39.9	101	50
20	42.4	50	42.3	100	50	42.6	101	50	42.9	101	49
24	44.3	50	43.8	99	50	44.3	100	50	44.5	101	49
28	45.8	50	45.8	100	50	46.3	101	50	46.3	101	49
32	46.3	50	46.3	100	50	46.5	100	50	47.1	102	49
36	48.4	50	47.9	99	50	48.4	100	50	48.7	101	49
40	49.3	50	48.6	99	50	49.0	99	50	49.9	101	49
44	49.2	50	48.9	99	50	48.6	99	50	50.1	102	49
48	49.8	50	49.4	99	50	49.4	99	50	50.4	101	49
52	49.2	50	48.8	99	50	49.4	100	50	49.8	101	49
56	49.3	50	48.0	97	50	48.6	99	50	49.6	101	49
60	50.0	49	50.0	100	50	49.3	99	49	50.6	101	49
64	50.1	49	50.1	100	50	49.9	100	49	51.2	102	48
68	51.1	48	50.4	99	50	49.6	97	49	51.9	102	48
72	50.9	47	50.0	98	50	49.6	97	48	52.0	102	47
76	49.8	47	49.4	99	48	49.4	99	47	51.7	104	46
80	48.8	47	48.8	100	45	49.1	101	42	51.0	105	45
84	47.2	44	48.6	103	42	49.5	105	38	50.6	107	39
88	46.4	41	47.2	102	40	47.1	102	36	49.8	107	37
92	46.5	38	46.6	100	39	47.2	102	34	48.9	105	35
96	44.6	35	45.7	103	36	46.9	105	29	47.8	107	33
100	44.9	30	45.4	101	32	45.6	102	29	47.8	107	29
Mean for weeks											
1-13	31.5		31.2	99		31.4	100		31.8	101	
14-52	46.4		46.1	99		46.4	100		47.0	101	
53-100	48.3		48.4	100		48.5	100		50.2	104	

TABLE 16
Mean Body Weights and Survival of Female Mice in the 2-Year Subcutaneous Study of α-Interferon A/D

Weeks on Study	Vehicle Control		5,000 U α-IFN A			500 U α-IFN A/D			5,000 U α-IFN A/D		
	Av. Wt. (g)	No. of Survivors	Av. Wt. (g)	Wt. (% of controls)	No. of Survivors	Av. Wt. (g)	Wt. (% of controls)	No. of Survivors	Av. Wt. (g)	Wt. (% of controls)	No. of Survivors
1	19.6	50	19.5	100	50	19.3	99	50	19.0	97	50
2	21.4	50	21.2	99	50	21.4	100	50	21.3	100	49
3	23.2	50	22.3	96	50	22.6	97	50	22.7	98	49
4	23.7	50	23.3	98	50	23.9	101	50	23.8	100	48
5	25.0	50	24.7	99	50	24.8	99	50	24.6	98	48
6	26.4	50	25.9	98	50	26.1	99	50	25.9	98	48
7	27.6	50	27.3	99	50	27.4	99	50	27.3	99	48
8	27.2	50	27.5	101	50	27.5	101	50	27.4	101	48
9	27.3	50	27.7	102	50	27.4	100	50	27.1	99	48
10	28.4	50	28.1	99	50	28.0	99	50	27.8	98	48
11	29.1	50	29.2	100	50	29.1	100	50	29.1	100	48
13	30.8	50	30.9	100	50	31.1	101	50	30.8	100	48
17	33.9	50	34.5	102	50	33.6	99	50	33.9	100	48
21	37.9	50	38.6	102	50	38.1	101	50	38.5	102	48
25	41.2	50	41.2	100	49	40.7	99	50	41.2	100	48
29	43.6	50	43.6	100	49	43.1	99	50	43.5	100	48
33	46.0	50	46.3	101	49	45.9	100	50	45.9	100	48
37	48.5	50	48.1	99	49	47.4	98	50	47.5	98	48
41	50.4	50	49.7	99	49	49.9	99	50	49.5	98	48
45	52.4	50	52.1	99	49	52.0	99	50	51.5	98	47
49	53.6	50	53.4	100	49	52.9	99	50	52.9	99	47
53	55.7	49	55.1	99	49	54.5	98	50	54.5	98	47
57	56.0	49	54.2	97	49	54.8	98	50	55.1	98	47
61	58.4	48	57.1	98	49	56.9	97	50	56.5	97	47
65	58.6	48	57.3	98	48	57.3	98	50	56.3	96	47
69	61.0	48	60.6	99	47	60.0	98	50	60.0	98	47
73	62.1	48	61.4	99	46	61.7	99	49	60.8	98	47
77	63.1	47	61.2	97	46	62.4	99	49	61.8	98	46
81	62.4	47	61.0	98	46	61.2	98	48	60.8	97	46
85	61.4	46	59.6	97	42	60.4	98	47	61.1	100	42
89	59.7	44	59.7	100	39	59.6	100	46	60.1	101	41
93	58.8	43	61.8	105	37	60.5	103	44	59.4	101	39
97	57.0	35	60.2	106	37	58.6	103	42	57.5	101	31
101	55.1	29	57.9	105	36	57.6	105	36	55.0	100	27
Mean for weeks											
1-13	25.8		25.6	99		25.7	100		25.6	99	
14-52	45.3		45.3	100		44.8	99		44.9	99	
53-101	59.2		59.0	100		58.9	99		58.4	99	

Pathology and Statistical Analysis

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

Lung: The incidences of alveolar/bronchiolar adenoma or carcinoma (combined) in females receiving 5,000 U α-interferon A or 500 U α-interferon A/D were greater than that in the vehicle control group (Tables 17 and D2). These marginal increases were not considered associated with α-interferon exposure since the incidences in these groups were within the range of historical controls (Tables 17 and D3), there was no dose response in groups receiving α-interferon A/D, there was no corresponding increase in the incidences of alveolar/bronchiolar hyperplasia, and there was no increase in the incidence of lung neoplasms in male mice.

TABLE 17
Incidences of Neoplasms of the Lung in Female Mice in the 2-Year Subcutaneous Study of α-Interferon A/D

	Vehicle Control	5,000 U α-IFN A	500 U α-IFN A/D	5,000 U α-IFN A/D
Alveolar/bronchiolar Adenoma[a]				
Overall rate[b]	0/50 (0%)	3/50 (6%)	5/50 (10%)	4/50 (8%)
Adjusted rate[c]	0.0%	7.8%	14.4%	14.0%
Terminal rate[d]	0/25 (0%))	1/31 (3%)	3/32 (9%)	3/25 (12%)
First incidence (days)	—[f]	601	698	581
Logistic regression test[e]	P = 0.234	P = 0.127	P = 0.047	P = 0.057
Alveolar/bronchiolar Carcinoma[g]				
Overall rate	2/50 (4%)	7/50 (14%)	4/50 (8%)	0/50 (0%)
Adjusted rate	7.3%	19.2%	10.3%	0.0%
Terminal rate	1/25 (4%)	3/31 (10%)	2/32 (6%)	0/25 (0%)
First incidence (days)	708	612	483	—
Logistic regression test	P = 0.100N	P = 0.078	P = 0.302	P = 0.253N
Alveolar/bronchiolar Adenoma or Carcinoma[h]				
Overall rate	2/50 (4%)	9/50 (18%)	9/50 (18%)	4/50 (8%)
Adjusted rate	7.3%	23.9%	23.8%	14.0%
Terminal rate	1/25 (4%)	4/31 (13%)	5/32 (16%)	3/25 (12%)
First incidence (days)	708	601	483	581
Logistic regression test	P = 0.505N	P = 0.026	P = 0.028	P = 0.311

[a] Historical incidence for 2-year NTP feed studies with untreated control groups (mean ± standard deviation): 85/1,472 (5.8% ± 4.8%); range, 0%-24%
[b] Number of neoplasm-bearing animals/number of animals microscopically examined
[c] Kaplan-Meier estimated neoplasm incidence at the end of the study after adjustment for intercurrent mortality
[d] Observed incidence at terminal kill
[e] Beneath the vehicle control incidence are the P values associated with the trend test (the α-interferon A group was excluded from the trend test). Beneath the dosed group incidence are the P values corresponding to pairwise comparisons between the vehicle controls and that dosed group. The logistic regression test regards neoplasms in animals dying prior to terminal kill as nonfatal. A negative trend or a lower incidence in a dosed group is indicated by **N**.
[f] Not applicable; no neoplasms in animal group
[g] Historical incidence: 31/1,472 (2.1% ± 2.3%); range, 0%-8%
[h] Historical incidence: 114/1,472 (7.7% ± 5.1%); range, 2%-26%

Liver: Relatively high incidences of chronic inflammation (vehicle control, 15/50; 5,000 U α-IFN A, 20/50; 500 U α-IFN A/D, 17/50; 5,000 U α-IFN A/D, 18/50; Table C3) and hepatocyte karyomegaly (12/50, 12/50, 14/50, 8/50) occurred in all groups of male mice; these lesions were usually observed together in the same liver. Similar lesions were observed in very few females, and the severity was also less than that observed in many males (Table D4). Liver sections from four of five male mice with liver lesions were positive for bacterial organisms consistent with *Helicobacter* when examined using Steiner's modification of the Warthin-Starry silver stain (Appendix R).

2-YEAR AZT/ 500 U α-INTERFERON A/D STUDY

Survival

Estimates of 2-year survival probabilities for male and female mice are shown in Table 18 and in the Kaplan-Meier survival curves (Figure 5). Survival of all dosed groups of mice was similar to that of the vehicle control groups.

Body Weights and Clinical Findings

The mean body weights of dosed mice were generally similar to those of the vehicle control groups throughout the study (Tables 19 and 20; Figure 6). There were no chemical-related clinical findings.

Hematology and Bone Marrow Analyses

The hematology and bone marrow data for mice in the 2-year study of AZT/500 U α-interferon A/D are listed in Table K4. In general, a dose- and time-dependent, minimal to mild, macrocytic, non-responsive anemia, similar to that observed in the 2-year AZT study, occurred in all dosed groups of male and female mice. The data suggest that the addition of 500 U of α-interferon A/D did not affect the hematotoxicity related to treatment with AZT.

TABLE 18
Survival of Mice in the 2-Year Gavage Study of AZT/500 U α-Interferon A/D

	Vehicle Control	30 mg AZT/kg + 500 U α-IFN A/D	60 mg AZT/kg + 500 U α-IFN A/D	120 mg AZT/kg + 500 U α-IFN A/D
Male				
Animals initially in study	50	50	50	50
Accidental deaths[a]	0	2	3	0
Moribund	13	14	5	9
Natural deaths	1	7	4	6
Animals surviving to study termination	36	27	38	35
Percent probability of survival at end of study[b]	72	56	81	70
Mean survival (days)[c]	694	637	680	702
Survival analysis[d]	P = 0.816	P = 0.136	P = 0.393N	P = 0.998
Female				
Animals initially in study	50	50	50	50
Accidental deaths[a]	3	4	2	4
Missing[a]	0	0	0	1
Moribund	7	8	11	12
Natural deaths	7	6	5	9
Animals surviving to study termination	33	32	32	24
Percent probability of survival at end of study	70	70	67	54
Mean survival (days)	662	639	663	627
Survival analysis	P = 0.402	P = 0.906	P = 0.752	P = 0.138

[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 trend test (Tarone, 1975) is in the vehicle control column, and the results of the life table pairwise comparisons (Cox, 1972) with the vehicle controls are in the dosed group columns. Lower mortality in a dosed group is indicated by **N**.

FIGURE 5
Kaplan-Meier Survival Curves for Male and Female Mice Administered AZT in Methylcellulose by Gavage and 500 U α-Interferon A/D by Subcutaneous Injection for 2 Years

TABLE 19
Mean Body Weights and Survival of Male Mice in the 2-Year Gavage Study of AZT/500 U α-Interferon A/D

Weeks on Study	Vehicle Control		30 mg AZT/kg + 500 U α-IFN A/D			60 mg AZT/kg + 500 U α-IFN A/D			120 mg AZT/kg + 500 U α-IFN A/D		
	Av. Wt. (g)	No. of Survivors	Av. Wt. (g)	Wt. (% of controls)	No. of Survivors	Av. Wt. (g)	Wt. (% of controls)	No. of Survivors	Av. Wt. (g)	Wt. (% of controls)	No. of Survivors
1	24.8	50	24.9	100	50	25.0	101	50	25.1	101	50
2	26.0	50	26.1	100	49	26.3	101	50	26.3	101	50
3	27.3	50	27.4	100	48	27.7	102	48	27.3	100	50
4	27.7	50	27.9	101	48	28.0	101	48	27.6	100	50
5	28.4	50	28.9	102	48	29.1	103	48	28.5	100	50
6	29.5	50	29.7	101	48	29.9	101	48	29.6	100	50
7	30.2	50	30.2	100	48	30.6	101	48	30.0	99	50
8	31.2	50	31.3	100	48	31.5	101	48	30.6	98	50
9	32.1	50	32.5	101	48	32.7	102	48	31.8	99	50
10	32.8	50	33.3	102	48	33.3	102	48	32.4	99	50
11	32.9	50	33.4	102	48	33.6	102	48	32.5	99	50
12	34.2	50	34.6	101	48	34.9	102	48	33.9	99	50
13	34.9	50	35.6	102	48	35.8	103	48	34.8	100	50
17	36.5	50	37.5	103	48	37.8	104	48	35.7	98	50
21	39.2	50	39.8	102	47	40.1	102	48	38.2	97	50
25	40.7	50	41.7	103	47	42.0	103	48	39.9	98	50
29	43.7	50	44.6	102	47	44.9	103	48	43.1	99	50
33	45.4	50	46.0	101	47	47.0	104	48	45.4	100	50
37	45.6	50	46.4	102	47	47.0	103	48	46.0	101	50
41	46.8	50	47.1	101	47	47.8	102	48	47.1	101	50
45	46.2	50	46.9	102	46	47.3	102	47	46.9	102	50
49	46.5	50	47.0	101	46	47.5	102	47	46.9	101	50
53	46.8	49	47.3	101	46	47.9	102	47	47.3	101	50
57	46.9	48	47.1	100	45	47.8	102	47	47.2	101	50
61	47.2	48	47.5	101	45	48.7	103	47	47.8	101	50
65	47.7	48	47.2	99	45	48.7	102	47	48.2	101	50
69	47.7	47	46.5	98	45	48.9	103	47	48.2	101	50
73	47.0	47	45.9	98	44	48.5	103	47	47.3	101	50
77	46.7	46	45.2	97	43	47.9	103	47	47.0	101	48
81	46.0	45	44.7	97	40	47.2	103	47	46.2	100	46
85	44.8	45	43.7	98	38	46.1	103	46	44.9	100	45
89	44.1	43	43.5	99	37	46.2	105	45	44.2	100	45
93	44.1	43	42.9	97	36	46.8	106	42	44.0	100	43
97	42.8	42	41.8	98	32	44.8	105	42	42.2	99	41
101	41.9	40	41.0	98	32	44.0	105	40	41.7	100	37
Mean for weeks											
1-13	30.2		30.4	101		30.6	101		30.0	99	
14-52	43.4		44.1	102		44.6	103		43.2	100	
53-101	45.7		44.9	98		47.2	103		45.9	100	

TABLE 20
Mean Body Weights and Survival of Female Mice in the 2-Year Gavage Study of AZT/500 U α-Interferon A/D

Weeks on Study	Vehicle Control		30 mg AZT/kg + 500 U α-IFN A/D			60 mg AZT/kg + 500 U α-IFN A/D			120 mg AZT/kg + 500 U α-IFN A/D		
	Av. Wt. (g)	No. of Survivors	Av. Wt. (g)	Wt. (% of controls)	No. of Survivors	Av. Wt. (g)	Wt. (% of controls)	No. of Survivors	Av. Wt. (g)	Wt. (% of controls)	No. of Survivors
1	19.7	49	19.9	101	49	19.9	101	50	20.0	102	50
2	21.3	49	21.6	101	49	21.4	101	50	21.4	101	50
3	22.3	48	22.7	102	49	22.6	101	49	22.7	102	49
4	22.9	48	23.4	102	48	23.0	100	48	23.3	102	47
5	23.6	47	24.0	102	48	23.7	100	48	23.7	100	46
6	25.0	47	25.4	102	48	25.2	101	48	25.1	100	46
7	25.3	47	25.5	101	48	25.5	101	48	25.6	101	46
8	25.5	47	25.8	101	48	25.7	101	48	25.8	101	46
9	26.4	47	27.0	102	47	27.1	103	48	26.7	101	46
10	26.5	47	27.2	103	47	27.0	102	48	26.9	102	46
11	27.4	47	27.8	102	47	27.7	101	48	27.5	100	46
12	28.6	47	29.4	103	47	28.9	101	48	29.1	102	46
13	29.0	47	29.8	103	47	29.4	101	48	29.5	102	46
17	31.2	47	32.4	104	47	31.4	101	48	31.9	102	46
21	32.9	47	33.2	101	47	33.4	102	48	33.5	102	46
25	34.6	47	36.0	104	47	35.7	103	48	35.4	102	46
29	37.2	47	38.7	104	47	37.9	102	48	38.2	103	46
33	39.1	47	40.3	103	47	40.1	103	48	40.3	103	46
37	41.0	47	42.1	103	47	41.4	101	48	42.2	103	46
41	42.8	47	44.2	103	47	43.5	102	48	43.7	102	46
45	43.1	47	44.6	104	47	43.8	102	48	43.6	101	46
49	44.5	47	46.1	104	47	45.1	101	48	44.9	101	46
53	45.4	47	47.0	104	47	46.1	102	48	45.8	101	46
57	46.4	47	47.9	103	47	47.0	101	48	47.4	102	45
61	47.9	47	49.4	103	47	48.5	101	48	48.6	102	45
65	50.5	47	51.4	102	46	51.1	101	46	50.9	101	44
69	50.9	46	51.9	102	45	51.3	101	46	51.4	101	44
73	50.5	46	52.2	103	44	51.5	102	46	51.3	102	43
77	50.2	45	52.1	104	41	50.7	101	45	50.0	100	43
81	50.1	45	52.4	105	39	50.2	100	45	49.5	99	43
85	49.4	44	51.8	105	39	49.4	100	45	49.2	100	41
89	49.8	42	51.3	103	37	50.0	100	40	49.7	100	36
93	51.1	42	53.6	105	34	51.0	100	38	50.3	98	34
97	49.0	40	51.8	106	33	49.0	100	36	47.8	98	31
101	49.0	38	51.0	104	32	48.7	99	34	46.6	95	29
Mean for weeks											
1-13	24.9		25.3	102		25.2	101		25.2	101	
14-52	38.5		39.7	103		39.1	102		39.3	102	
53-101	49.2		51.1	104		49.6	101		49.1	100	

FIGURE 6
Growth Curves for Male and Female Mice Administered AZT in Methylcellulose by Gavage and 500 U α-Interferon A/D by Subcutaneous Injection for 2 Years

Pathology and Statistical Analyses

This section describes the statistically significant or biologically noteworthy changes in the incidences of neoplasms and nonneoplastic lesions of the vagina, liver, and kidney. Summaries of the incidences of neoplasms and nonneoplastic lesions 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 E for male mice and Appendix F for female mice.

Vagina: The incidences of squamous cell carcinoma of the vagina in females receiving 60 or 120 mg AZT/kg and 500 U α-interferon A/D were significantly greater than in the vehicle controls, and the incidences of this neoplasm occurred with a positive trend (Tables 21 and F2). The incidences of epithelial hyperplasia of the vagina in females receiving 60 or 120 mg AZT/kg with 500 U α-interferon A/D were significantly greater than in the vehicle controls (Tables 21 and F3). These lesions were described for the 2-year AZT study.

TABLE 21
Incidences of Neoplasms and Nonneoplastic Lesions of the Vagina in Female Mice in the 2-Year Gavage Study of AZT/500 U α-Interferon A/D

	Vehicle Control	30 mg AZT/kg + 500 U α-IFN A/D	60 mg AZT/kg + 500 U α-IFN A/D	120 mg AZT/kg + 500 U α-IFN A/D
Number Examined Microscopically	49	44	48	48
Epithelium, Hyperplasia[a]	0	4 (1.5)[b]	6* (2.0)	11** (1.2)
Epithelium, Hyperplasia, Atypical	0	0	2 (3.0)	1 (4.0)
Squamous Cell Carcinoma				
Overall rate[c]	0/49 (0%)	0/44 (0%)	5/48 (10%)	6/48 (12%)
Adjusted rate[d]	0.0%	0.0%	15.6%	21.1%
Terminal rate[e]	0/33 (0%)	0/32 (0%)	5/32 (16%)	3/24 (13%)
First incidence (days)	—[g]	—	729 (T)	631
Logistic regression test[f]	P < 0.001	—	P = 0.030	P = 0.011

(T)Terminal sacrifice
* Significantly different (P≤0.05) from the vehicle control group by the logistic regression test
** P≤0.01
[a] Number of animals with lesion
[b] Average severity of lesions in affected animals: 1 = minimal, 2 = mild, 3 = moderate, 4 = marked
[c] Number of animals with neoplasm per number of animals necropsied
[d] Kaplan-Meier estimated neoplasm incidence at the end of the study after adjustment for intercurrent mortality
[e] Observed incidence at terminal kill
[f] In the vehicle control column are the P values associated with the trend test. In the dosed group columns are the P values corresponding to the pairwise comparisons between the vehicle controls and that dosed group. The logistic regression test regards lesions in animals dying prior to terminal kill as nonfatal.
[g] Not applicable; no neoplasms in animal group

Liver: The incidences of hepatocellular adenoma or carcinoma (combined) and of hepatocellular adenoma, hepatocellular carcinoma, or hepatoblastoma (combined) were marginally increased in males receiving 30 or 60 mg AZT/kg and 500 U α-interferon A/D (Tables 22 and E2). However, the incidences of liver neoplasms in males that received 120 mg/kg AZT and 500 U α-interferon A/D were not significantly increased. While the concurrent vehicle control group provides the most appropriate group for comparison, the incidences of combined liver neoplasms in the male vehicle control groups from the three companion studies (AZT, 36/50; α-interferon A/D, 30/50; AZT/5,000 U α-interferon A/D, 36/50) suggest that the incidence in the concurrent vehicle control group is somewhat low, rather than the incidences in the 30 and 60 mg/kg AZT and 500 U α-interferon A/D groups being high. Also, incidences of potentially preneoplastic foci of alteration in males administered 30 or 60 mg/kg AZT and 500 U α-interferon A/D were not different from the vehicle controls (Table E3). Accordingly, the marginal increases in

hepatocellular neoplasms in these two groups were not considered related to administration of AZT and 500 U α-interferon A/D.

Relatively high incidences of chronic inflammation and hepatocyte karyomegaly occurred in all groups of male mice; these lesions were usually observed together in the same liver (Tables 22 and E3). These changes were generally mild to moderate in severity and observed throughout the liver (usually not within the proliferative lesions), but appeared most pronounced in the portal regions. Similar lesions were observed in very few females, and the severity was also less than that observed in many males (Tables 22 and F3). Liver sections from three of five male mice with liver lesions were positive for bacterial organisms consistent with *Helicobacter* when examined using Steiner's modification of the Warthin-Starry silver stain (Appendix R).

TABLE 22
Incidences of Neoplasms and Nonneoplastic Lesions of the Liver in Mice in the 2-Year Gavage Study of AZT/500 U α-Interferon A/D

	Vehicle Control		30 mg AZT/kg + 500 U α-IFN A/D		60 mg AZT/kg + 500 U α-IFN A/D		120 mg AZT/kg + 500 U α-IFN A/D	
Male								
Number Examined Microscopically	50		50		50		50	
Chronic Inflammation[a]	39	(2.7)[b]	38	(2.8)	38	(2.7)	44	(2.7)
Hepatocyte, Karyomegaly	33	(3.0)	31	(2.7)	35	(3.0)	40	(2.9)
Necrosis, Focal	1	(1.0)	7*	(2.6)	0		4	(3.0)
Hemangiosarcoma	3		5		4		4	
Hepatocellular Adenoma	16		16		19		18	
Hepatocellular Carcinoma	13		20		17		14	
Hepatocellular Adenoma or Carcinoma	24		31*		33*		29	
Hepatoblastoma	1		1		1		0	
Hepatocellular Carcinoma or Hepatoblastoma	13		21		17		14	
Hepatocellular Adenoma, Hepatocellular Carcinoma, or Hepatoblastoma	24		32*		33*		29	
Female								
Number Examined Microscopically	50		50		50		49	
Chronic Inflammation	6	(1.5)	6	(1.3)	5	(1.4)	7	(1.7)
Hepatocyte, Karyomegaly	0		1	(3.0)	1	(2.0)	0	
Necrosis, Focal	4	(2.0)	0		6	(1.5)	8	(2.3)
Hepatocellular Adenoma	11		17		14		14	
Hepatocellular Carcinoma	13		4		5		10	
Hepatocellular Adenoma or Carcinoma	20		20		18		22	

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

Kidney: A renal tubule adenoma was observed in one male mouse administered 60 mg AZT/kg and 500 U α-interferon A/D (0/50,0/501/50,0/50; Table E1).

2-YEAR AZT/ 5,000 U α-INTERFERON A/D STUDY

Survival

Estimates of 2-year survival probabilities for male and female mice are shown in Table 23 and in the Kaplan-Meier survival curves (Figure 7). Survival of all dosed groups of mice was similar to that of the vehicle control groups.

Body Weights and Clinical Findings

The mean body weights of dosed and vehicle control mice were similar throughout the study (Figure 8; Tables 24 and 25). With the exception of head masses observed in all dosed groups of males, there were no chemical-related clinical findings.

Hematology and Bone Marrow Analyses

The hematology and bone marrow data for mice in the 2-year study of AZT/5,000 U α-interferon A/D are listed in Table K5. In general, a dose- and time-dependent, minimal to mild, macrocytic, non-responsive anemia, similar to that observed in the 2-year AZT study, occurred in all dosed groups of male and female mice. The data suggest that the addition of 5,000 U of α-interferon A/D did not affect the hematotoxicity related to treatment with AZT.

TABLE 23
Survival of Mice in the 2-Year Gavage Study of AZT/5,000 U α-Interferon A/D

	Vehicle Control	30 mg AZT/kg + 5,000 U α-IFN A/D	60 mg AZT/kg + 5,000 U α-IFN A/D	120 mg AZT/kg + 5,000 U α-IFN A/D
Male				
Animals initially in study	50	50	50	50
Accidental deaths[a]	0	1	1	0
Moribund	9	11	9	6
Natural deaths	10	3	5	10
Animals surviving to study termination	31	35	35	34
Percent probability of survival at end of study[b]	62	71	72	68
Mean survival (days)[c]	694	683	668	684
Survival analysis[d]	P = 0.836N	P = 0.505N	P = 0.547N	P = 0.782N
Female				
Animals initially in study	50	50	50	50
Accidental deaths[a]	0	0	2	1
Moribund	8	7	6	8
Natural deaths	5	5	6	9
Animals surviving to study termination	37	38[e]	36	32
Percent probability of survival at end of study	74	76	75	65
Mean survival (days)	703	707	669	685
Survival analysis	P = 0.339	P = 0.959N	P = 1.000N	P = 0.496

[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 trend test (Tarone, 1975) is in the vehicle control column, and the results of the life table pairwise comparisons (Cox, 1972) with the vehicle controls are in the dosed group columns. A negative trend or lower mortality in a dosed group is indicated by **N**.
[e] Includes one animal that died during the last week of the study

FIGURE 7
Kaplan-Meier Survival Curves for Male and Female Mice Administered AZT in Methylcellulose by Gavage and 5,000 U α-Interferon A/D by Subcutaneous Injection for 2 Years

FIGURE 8
Growth Curves for Male and Female Mice Administered AZT in Methylcellulose by Gavage and 5,000 U α-Interferon A/D by Subcutaneous Injection for 2 Years

TABLE 24
Mean Body Weights and Survival of Male Mice in the 2-Year Gavage Study of AZT/5,000 U α-Interferon A/D

Weeks on Study	Vehicle Control		30 mg AZT/kg + 5,000 U α-IFN A/D			60 mg AZT/kg + 5,000 U α-IFN A/D			120 mg AZT/kg + 5,000 U α-IFN A/D		
	Av. Wt. (g)	No. of Survivors	Av. Wt. (g)	Wt. (% of controls)	No. of Survivors	Av. Wt. (g)	Wt. (% of controls)	No. of Survivors	Av. Wt. (g)	Wt. (% of controls)	No. of Survivors
1	24.9	50	25.0	100	50	25.4	102	50	25.1	101	50
2	26.5	50	26.6	100	50	26.9	102	50	26.5	100	50
3	27.2	50	27.3	100	50	27.7	102	50	27.2	100	50
4	27.9	50	28.1	101	50	28.5	102	50	28.1	101	50
5	28.6	50	28.6	100	50	29.2	102	50	28.7	100	50
6	29.9	50	30.0	100	50	30.5	102	50	30.0	100	50
7	30.4	50	30.6	101	50	31.0	102	50	30.4	100	50
8	31.1	50	31.6	102	50	32.0	103	50	31.3	101	50
9	32.0	50	32.4	101	50	33.0	103	50	32.1	100	50
10	33.3	50	33.8	102	50	34.1	102	50	33.3	100	50
11	33.8	50	34.6	102	50	34.8	103	50	34.0	101	50
12	34.3	50	35.2	103	50	35.6	104	50	34.7	101	50
13	35.2	50	36.0	102	50	36.6	104	50	35.5	101	50
17	37.9	50	39.4	104	50	39.6	105	50	38.1	101	50
21	41.0	50	42.8	104	50	42.9	105	50	41.3	101	50
25	42.8	50	44.4	104	50	44.6	104	49	43.2	101	50
29	43.3	50	45.6	105	50	45.4	105	49	44.2	102	50
33	45.2	50	47.1	104	50	47.1	104	48	45.8	101	50
37	45.7	50	47.4	104	50	47.4	104	48	46.2	101	50
41	46.0	50	47.5	103	50	47.5	103	48	46.6	101	50
45	46.9	50	47.6	102	50	47.8	102	48	46.9	100	50
49	47.8	50	48.2	101	50	48.1	101	48	47.7	100	50
53	47.4	50	48.4	102	48	47.7	101	47	47.6	100	50
57	47.7	49	48.4	102	48	47.6	100	46	47.7	100	50
61	48.1	49	48.5	101	48	47.8	99	46	48.0	100	49
65	47.7	49	47.8	100	47	47.4	99	46	47.6	100	49
69	47.3	47	47.2	100	46	46.6	99	46	47.0	99	48
73	46.9	47	47.1	100	46	46.5	99	44	46.5	99	47
77	46.4	47	46.8	101	45	46.0	99	44	46.1	99	45
81	45.9	46	47.3	103	42	46.5	101	43	46.3	101	43
85	45.1	45	46.3	103	42	45.5	101	42	45.0	100	41
89	44.0	44	45.8	104	42	44.6	101	41	43.9	100	40
93	43.2	43	44.7	104	42	44.1	102	39	42.9	99	38
97	41.9	42	43.6	104	41	43.3	103	37	42.4	101	38
101	41.0	36	42.9	105	37	42.8	104	37	41.6	102	37
Mean for weeks											
1-13	30.4		30.8	101		31.2	103		30.5	100	
14-52	44.1		45.6	103		45.6	103		44.4	101	
53-101	45.6		46.5	102		45.9	101		45.6	100	

TABLE 25
Mean Body Weights and Survival of Female Mice in the 2-Year Gavage Study of AZT/5,000 U α-Interferon A/D

Weeks on Study	Vehicle Control		30 mg AZT/kg + 5,000 U α-IFN A/D			60 mg AZT/kg + 5,000 U α-IFN A/D			120 mg AZT/kg + 5,000 U α-IFN A/D		
	Av. Wt. (g)	No. of Survivors	Av. Wt. (g)	Wt. (% of controls)	No. of Survivors	Av. Wt. (g)	Wt. (% of controls)	No. of Survivors	Av. Wt. (g)	Wt. (% of controls)	No. of Survivors
1	20.0	50	19.8	99	50	19.8	99	49	20.0	100	50
2	21.4	50	21.4	100	50	21.4	100	49	21.6	101	50
3	22.1	50	22.2	101	50	22.5	102	49	22.4	101	50
4	22.7	50	23.0	101	50	23.3	103	49	23.3	103	50
5	24.0	50	23.9	100	50	24.0	100	49	24.3	101	49
6	24.9	50	24.5	98	50	24.7	99	49	24.8	100	49
7	25.8	50	25.4	98	50	25.7	100	49	25.7	100	49
8	26.3	50	26.2	100	50	26.2	100	49	26.4	100	49
9	27.2	50	26.8	99	50	27.0	99	49	27.0	99	49
10	28.1	50	27.4	98	50	27.7	99	49	28.0	100	49
11	28.9	50	28.2	98	50	28.8	100	49	28.8	100	49
12	29.5	50	29.1	99	50	29.4	100	49	29.7	101	49
13	29.8	50	29.3	98	50	29.7	100	49	29.9	100	49
17	33.4	50	32.8	98	50	33.3	100	49	33.7	101	49
21	36.0	50	35.6	99	50	35.3	98	49	36.1	100	49
25	37.9	50	37.3	98	50	37.0	98	49	38.0	100	49
29	39.2	50	38.6	99	50	38.1	97	48	38.8	99	49
33	41.1	50	40.9	100	50	40.0	97	48	40.9	100	49
37	42.8	50	42.1	98	50	41.4	97	48	42.4	99	49
41	43.5	50	43.2	99	50	42.4	98	48	43.6	100	49
45	44.6	50	44.5	100	50	43.1	97	48	44.5	100	49
49	46.8	50	46.6	100	50	45.1	96	47	46.9	100	49
53	48.0	50	48.1	100	50	47.0	98	46	48.4	101	49
57	49.3	50	49.2	100	50	48.0	97	46	49.3	100	49
61	50.0	50	50.4	101	50	49.0	98	46	50.2	100	49
65	51.1	50	51.1	100	50	49.6	97	46	50.8	99	49
69	51.6	50	52.0	101	50	49.9	97	46	51.5	100	49
73	52.8	49	52.3	99	50	50.7	96	44	52.4	99	48
77	53.7	49	52.7	98	50	51.4	96	44	53.1	99	48
81	53.1	49	52.9	100	48	51.5	97	44	53.3	100	47
85	52.4	46	52.8	101	46	51.2	98	43	53.1	101	46
89	51.1	44	52.0	102	45	50.8	99	41	52.3	102	44
93	50.1	43	50.9	102	43	50.0	100	40	52.0	104	41
97	50.1	40	50.7	101	41	49.6	99	40	52.3	104	37
101	48.8	38	49.1	101	40	48.0	98	39	50.8	104	34
Mean for weeks											
1-13	25.4		25.2	99		25.4	100		25.5	100	
14-52	40.6		40.2	99		39.5	97		40.5	100	
53-101	50.9		51.1	100		49.7	98		51.5	101	

Pathology and Statistical Analyses

This section describes the statistically significant or biologically noteworthy changes in the incidences of neoplasms and/or nonneoplastic lesions of the vagina, adrenal cortex, and liver. Summaries of the incidences of neoplasms and nonneoplastic lesions 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 G for male mice and Appendix H for female mice.

Vagina: The incidences of squamous cell carcinoma of the vagina in females receiving 60 or 120 mg AZT/kg and 5,000 U α-interferon A/D were significantly greater than that in the vehicle controls, and the incidences occurred with a positive trend (Tables 26 and H2). The incidences of epithelial hyperplasia of the vagina in females receiving 60 or 120 mg AZT/kg and 5,000 U α-interferon A/D were significantly greater than that in the vehicle controls (Tables 26 and H3). These lesions were described for the 2-year AZT study.

TABLE 26
Incidences of Neoplasms and Nonneoplastic Lesions of the Vagina in Female Mice in the 2-Year Gavage Study of AZT/5,000 U α-Interferon A/D

	Vehicle Control	30 mg AZT/kg + 5,000 U α-IFN A/D	60 mg AZT/kg + 5,000 U α-IFN A/D	120 mg AZT/kg + 5,000 U α-IFN A/D
Number Examined Microscopically	50	48	48	50
Epithelium, Hyperplasia[a]	1 (2.0)[b]	3 (2.0)	7* (2.0)	12* (1.8)
Epithelium, Hyperplasia, Atypical	0	1 (3.0)	1 (3.0)	3 (2.3)
Squamous Cell Papilloma				
Overall rate[c]	1/50 (2%)	1/48 (2%)	0/48 (0%)	0/50 (0%)
Squamous Cell Carcinoma				
Overall rate	0/50 (0%)	0/48 (0%)	5/48 (10%)	4/50 (8%)
Adjusted rate[d]	0.0%	0.0%	13.9%	12.5%
Terminal rate[e]	0/37 (0%)	0/38 (0%)	5/36 (14%)	4/32 (13%)
First incidence (days)	—[g]	—	730 (T)	730 (T)
Logistic regression test[f]	P = 0.009	—	P = 0.031	P = 0.046
Squamous Cell Papilloma or Squamous Cell Carcinoma				
Overall rate	1/50 (2%)	1/48 (2%)	5/48 (10%)	4/50 (8%)
Adjusted rate	2.7%	2.6%	13.9%	12.5%
Terminal rate	1/37 (3%)	1/38 (3%)	5/36 (14%)	4/32 (13%)
First incidence (days)	733 (T)	733 (T)	730 (T)	730 (T)
Logistic regression test	P = 0.047	P = 0.747N	P = 0.093	P = 0.136

(T)Terminal sacrifice
* Significantly different (P≤0.05) from the vehicle control group by the logistic regression test
[a] Number of animals with lesion
[b] Average severity of lesions in affected animals: 1 = minimal, 2 = mild, 3 = moderate, 4 = marked
[c] Number of animals with neoplasm per number of animals necropsied
[d] Kaplan-Meier estimated neoplasm incidence at the end of the study after adjustment for intercurrent mortality
[e] Observed incidence in animals at terminal kill
[f] In the vehicle control column are the P values associated with the trend test. In the dosed group columns are the P values corresponding to the pairwise comparisons between the vehicle controls and that dosed group. The logistic regression test regards lesions in animals dying prior to terminal kill as nonfatal. A lower incidence in a dose group is indicated by **N**.
[g] Not applicable; no neoplasms in animal group

Adrenal Cortex: The incidences of focal cytoplasmic alteration (vehicle control, 3/49; 30 mg/kg, 10/50; 60 mg/kg, 6/50; 120 mg/kg, 18/50; Table G3) in males administered 120 mg AZT/kg and 5,000 U α-interferon A/D and of focal hyperplasia (0/49, 2/50, 7/50, 3/50) in males administered 60 mg AZT/kg and 5,000 U α-interferon A/D were significantly greater than those in the vehicle controls.

Liver: Relatively high incidences of chronic inflammation (45/50; 43/50; 38/50; 41/50; Table G3) and hepatocyte karyomegaly (37/50, 32/50, 31/50, 32/50) occurred in all groups of male mice; these lesions were usually observed together in the same liver. These changes were generally mild to moderate in severity and observed throughout the liver (usually not within proliferative lesions), but they appeared most pronounced in the portal regions. Similar lesions were observed in very few females, and the severity was also less than that observed in many males (Table H3). Liver sections from four of five males with liver lesions were positive for bacterial organisms consistent with *Helicobacter* when examined using Steiner's modification of the Warthin-Starry silver stain (Appendix R).

GENETIC TOXICOLOGY

AZT is mutagenic. Positive results were obtained with AZT (0.003 to 3 µg/plate) in *S. typhimurium* strain TA102 without S9 activation enzymes and with 30% hamster liver S9; no mutagenic response was detected in strain TA97, TA98, TA100, TA104, or TA1535 (0.001 to 6 µg/plate), with or without hamster or rat liver S9 (Table I1). In cytogenetic tests with cultured Chinese hamster ovary cells, AZT induced sister chromatid exchanges (Table I2), but not chromosomal aberrations (Table I3), with and without S9. The sister chromatid exchange response in the absence of S9 was much stronger and occurred at much lower doses than the response observed in the presence of S9. AZT, administered by gavage three times at 24-hour intervals at doses ranging from 200 to 2,000 mg/kg, induced increased frequencies of micronucleated polychromatic erythrocytes in bone marrow (Table I4) and peripheral blood (Table I5) samples of male mice (Phillips *et al.*, 1991). The increased frequencies of micronuclei were very impressive, with the three treatment groups in the bone marrow analysis showing increases that were from three to nine times the level induced by the positive control, dimethylbenzanthracene (Table I4). The increases noted in peripheral blood (Table I5) were of similar or greater magnitude. Results of a 14-week peripheral blood micronucleus test with male mice showed significant increases in the frequencies of micronucleated polychromatic and normochromatic erythrocytes at doses of 100 and 1,000 mg AZT/kg body weight per day (Table I6). No increased frequency of micronucleated cells was noted at the lowest dose of 25 mg/kg per day.

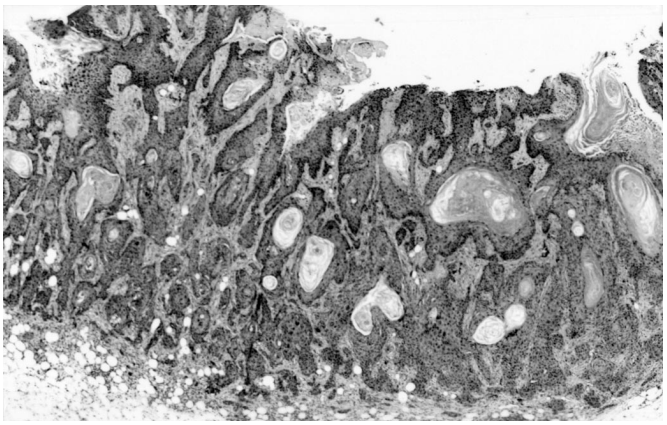


PLATE 1
Squamous cell carcinoma of the vagina in a female B6C3F$_1$ mouse administered 120 mg/kg AZT by gavage for 2 years. Note the marked invasion of the submucosa and muscle wall and numerous keratin-filled pockets in the disorganized proliferation of neoplastic epithelium. H&E; 30×

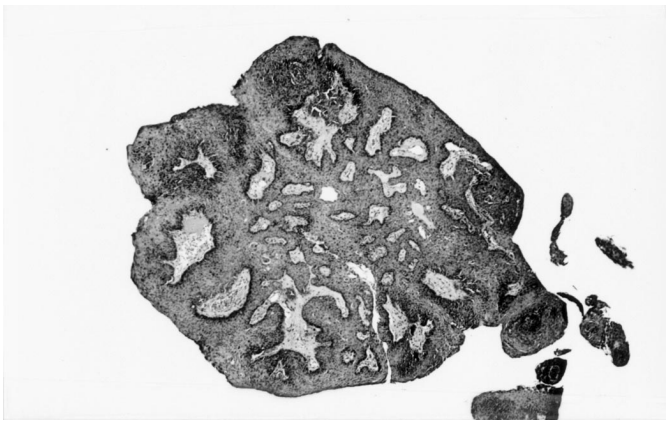


PLATE 2
Squamous cell papilloma of the vagina in a female B6C3F$_1$ mouse administered 120 mg/kg AZT by gavage for 2 years. This protuberant mass has more regular architecture and is more circumscribed than squamous cell carcinima. Note that the continuity of this mass with the vaginal wall was lost in sectioning. H&E; 30×

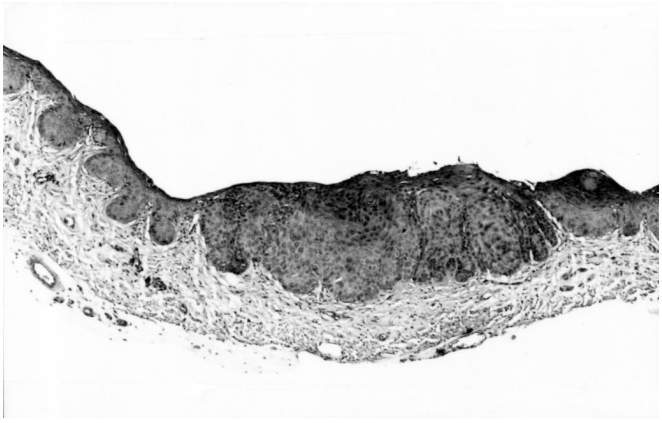


PLATE 3
Hyperplasia of the vaginal epithelium in a female B6C3F$_1$ mouse administered 120 mg/kg AZT by gavage for 2 years. Note the focal thickening of the vaginal mucosal epithelium. Epithelium in the thickened layers remains relatively uniform and ordered. H&E; 75×

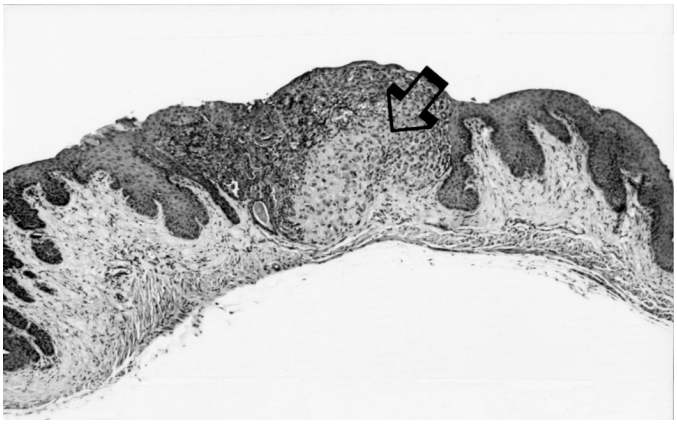


PLATE 4
Atypical hyperplasia of the vaginal epithelium in a female B6C3F$_1$ mouse administered 120 mg/kg AZT by gavage for 2 years. The arrow indicates an area where cells have lost their cohesiveness and become dysplastic. H&E; 60×

DISCUSSION AND CONCLUSIONS

3′-Azido-3′-deoxythymidine (AZT) was the first dideoxynucleoside approved for the treatment of human immunodeficiency virus (HIV) infection and is the best characterized and most widely used drug in this class. However, prolonged AZT monotherapy invariably leads to the emergence of HIV variants with reduced sensitivity and ultimately to the development of resistance. Therefore, a number of combination therapies involving AZT and other drugs have been evaluated. Interferon is an attractive choice for combination therapy with AZT because it inhibits viral replication at steps in the viral life cycle different from reverse transcription. Ideally, the development of resistance to such a combination would be more difficult and require a longer period of treatment, or perhaps might not occur at all. Reports that recombinant human α-interferon A suppressed the replication of HIV *in vitro* (Ho *et al.*, 1985; Yamamoto *et al.*, 1986; Hartshorn *et al.*, 1987a) and the demonstration that coadministration of AZT and recombinant human α-interferon A resulted in synergistic suppression of HIV replication in human cell lines (Hartshorn *et al.*, 1987b; Krown, 1990) prompted the initiation of clinical trials to evaluate this combination in humans (Lane, 1989; Lane *et al.*, 1990). Results reported to date (reviewed in Poli *et al.*, 1994) indicate potential benefits associated with α-interferon therapy in HIV-positive patients who have relatively healthy immune systems (CD4+ counts above 150/mm^3). In general, however, coadministration of α-interferon has failed to produce significant improvement over AZT monotherapy.

The current studies in $B6C3F_1$ mice evaluate the carcinogenic potential of AZT administered as a single agent or in combination with α-interferon A/D. α-Interferon A/D is a recombinant human hybrid interferon with antiviral activity that has been well characterized in mice both *in vivo* and *in vitro* (Ortaldo *et al.*, 1983; Brunda and Rosenbaum, 1984). The toxic response in mice has also been well characterized (Rosenthal *et al.*, 1990), and it is very similar to the responses observed in humans receiving α-interferon therapy. α-Interferon A/D was selected for use in these studies because of its well-characterized activity in mice and the unavailability of adequate quantities of pure mouse interferons at the time this series of studies was initiated. Human α-interferon A exhibits no activity in mice, but a group of mice receiving this interferon was included in the 2-year study to allow any nonspecific effects associated with administration to be distinguished from effects resulting from the actual biological activity of α-interferon A/D.

Twice-daily administration of AZT, 5 days per week, for 14 weeks to male and female $B6C3F_1$ mice resulted in the development of a poorly regenerative macrocytic anemia that increased in severity with dose and duration of chemical treatment (Thompson *et al.*, 1991). Signs of anemia were observed in animals that received the highest doses of AZT at the day 5 sampling point, and by day 23, anemia was apparent in mice at all dose concentrations. Analysis of bone marrow cellularity at the end of this 14-week study revealed significant decreases in erythroid precursors and somewhat less severe reductions in myeloid and lymphoid precursors, but no indications of a regenerative response in the bone marrow. Macrocytic anemia also develops in humans administered AZT but generally requires several weeks of treatment to become evident. The significantly shorter erythrocyte half-life in mice (20 to 40 days) compared to humans (127 days) is probably responsible for the more rapid appearance of anemia in mice. Also, in humans, changes in the peripheral blood associated with AZT treatment are accompanied by erythroid hyperplasia in the bone marrow, which is the expected response to impaired hematopoiesis.

The selection of AZT dose concentrations for the 2-year mouse study was based primarily on the toxic response in the bone marrow. Because animals would be dosed twice daily, a major consideration for the 2-year study was the potential for cumulative toxicity that would eventually exceed the regenerative capacity of the hematopoietic system. Moreover, the absence of bone marrow regenerative hyperplasia and the observed decrease in erythroid precursors in the bone marrow suggested that most regeneration was

associated with extramedullary hematopoiesis in the spleen.

At doses of 200 mg/kg and greater in the 14-week study, reduced hematocrit values, reduced erythrocyte and reticulocyte counts, and increased mean cell volume were apparent early in the study and became more pronounced by study termination. Therefore, these doses were considered too high for a 2-year study. On the other hand, the response to 100 mg/kg was quite mild, particularly in males, where hematocrit values and reticulocyte counts were never significantly different from those of the controls. Therefore, 100 mg/kg was considered too low for the high dose. Single-dose pharmacokinetic studies (Trang *et al.*, 1993), conducted in association with the 14-week study reported here, indicated that AZT exhibited linear kinetics in $B6C3F_1$ mice after oral administration of doses ranging from 15 to 60 mg/kg. In addition, the overall oral bioavailability over this dose range was 86%. These results, in combination with the results from the 14-week study, suggested that total daily doses of 30, 60, or 120 mg/kg, administered as twice-daily doses of 15, 30, or 60 mg/kg, would be within the desired dose range based on both the toxic response and the capacity of the animals to absorb and eliminate AZT.

No formal 14-week studies were conducted with α-interferon A or α-interferon A/D. Studies conducted at NIEHS by Rosenthal *et al*. (1990) examined the toxic responses associated with daily intraperitoneal administration of 1,000, 10,000, or 100,000 U α-interferon A/D to female C57Bl/6 mice for 10 days. Anemia, leukopenia, and thrombocytopenia occurred primarily in animals administered 10,000 or 100,000 U α-interferon A/D, but thrombocytopenia, increased spleen weights, and lower thymus weights were also observed in the group receiving 1,000 U. Separate studies in $B6C3F_1$ mice conducted at NIEHS indicated that daily intraperitoneal administration of 50,000 or 500,000 U α-interferon A/D for 28 days caused anemia, thrombocytopenia, and thymic atrophy. Doses of 500 or 5,000 U had no detectable adverse effect. Daily administration of 500,000 U α-interferon A also produced no response.

Ruprecht *et al*. (1990) examined the antiviral activity of α-interferon A/D *in vivo* in female BALB/c mice and found that daily doses of 2,000 to 10,000 U α-interferon A/D administered intraperitoneally for 20 days blocked the replication of Rauscher murine leukemia virus and prevented the development of associated splenomegaly. These investigators also demonstrated that the combination of AZT and α-interferon A/D was synergistic in preventing viral replication in BALB/c mice. Therefore, based on the work of Rosenthal *et al*. (1990) and Ruprecht *et al*. (1990) and additional studies conducted at NIEHS, doses of 500 or 5,000 U α-interferon A/D and 5,000 U α-interferon A were selected for the 2-year combination study with AZT.

In the studies reported here, administration of AZT and α-interferon A/D or A, individually or in combination, for 105 weeks had no effect on the survival or mean body weights of male or female $B6C3F_1$ mice. Mild anemia characterized by reduced erythrocyte counts and increased mean cell volume was apparent throughout the study in all groups receiving AZT or AZT with α-interferon A/D, and in general, the severity of anemia increased with increasing doses of AZT. Changes in the peripheral blood were not accompanied by a corresponding response in the bone marrow, suggesting that regenerative hematopoiesis in these groups occurred primarily in the spleen, as observed in the 14-week study. Moreover, there was no difference in the response of groups administered AZT in combination with α-interferon A/D compared to those receiving only AZT. The peripheral blood and bone marrow of groups receiving only interferons did not exhibit any treatment-related responses.

Higher doses of AZT undoubtedly would have caused more severe and potentially life-threatening anemia, because in the 14-week study, anemia was progressive at doses of 200 mg/kg and greater; therefore, 120 mg/kg was an adequately high dose. Doses administered to humans receiving long-term AZT therapy also usually result in a mild chronic anemia that is considered dose limiting.

The most significant neoplastic response associated with AZT administration occurred in female mice. In groups of female mice given 60 or 120 mg/kg AZT

alone or AZT in combination with α-interferon A/D, the incidences of squamous cell carcinoma and squamous cell carcinoma or papilloma (combined) of the vagina were significantly increased. The incidence of hyperplasia of the vaginal epithelium was also increased in groups of female mice administered 60 or 120 mg/kg AZT.

These results are similar to those observed by Ayers *et al*. (1996) in CD rats and CD-1 mice. In CD rats administered 80, 220, or 300 mg AZT/kg body weight per day, squamous cell carcinomas of the vagina occurred in two females receiving 300 mg/kg; however, no hyperplasia of the vaginal epithelium occurred in any group of female rats. CD-1 mice received AZT by gavage at doses of 30, 60, or 120 mg/kg per day for 91 days, and then 20, 30, or 40 mg/kg per day for the remainder of the 22-month study. The only neoplasms associated with administration of AZT were squamous cell carcinomas of the vagina in five females receiving 40 mg/kg, squamous cell papillomas of the vagina in one female receiving 30 mg/kg and one female receiving 40 mg/kg, and a squamous polyp in one female receiving 40 mg/kg. Although the incidence of hyperplasia of the vaginal epithelium was not increased above that in the controls, the severity of hyperplasia increased with increasing dose concentrations of AZT.

Ayers *et al*. (1996) administered AZT intravaginally to CD-1 mice for 22 months and observed a higher incidence of vaginal neoplasms than occurred in the above referenced gavage study. They also demonstrated that in female mice there is retrograde flow of urine from the discharge point at the base of the vulva into the region of the vagina where the neoplasms occur. Moreover, in mice, at least 90% of AZT is eliminated in urine as the parent compound following oral administration. Because there is a high rate of cell turnover in the vaginal epithelium as a consequence of the short estrous cycle of mice (4 to 5 days), Ayers *et al*. (1996) concluded that prolonged exposure of the vaginal epithelium to the relatively high concentrations of AZT in urine could explain the observed neoplasm response.

In the present studies, the incidence of hyperplasia of the vaginal epithelium exhibited a clear dose response that was similar among groups receiving the same concentration of AZT but was independent of the coadministration of α-interferon A/D (Table 27). The incidences of squamous cell papilloma or carcinoma (combined) in groups that received AZT alone also increased in a dose-proportional manner. However, among groups that received 120 mg/kg AZT, the incidence of vaginal tumors was highest in the group administered AZT alone and decreased with increasing doses of coadministered α-interferon A/D. This decreasing trend in tumor incidence is suggestive ($P = 0.064$) of a protective or antineoplastic effect of interferon on the carcinogenic response to the highest dose of AZT. However, the increase in the incidence of AZT-associated hyperplasia was not affected by coadministration of α-interferon A/D, and the tumor incidence in groups that received 60 mg/kg AZT was also unaffected by coadministration of α-interferon A/D. This suggests that if interferon was antineoplastic, it was only in the groups that received 120 mg/kg AZT, which seems unlikely. It also seems unlikely that the small quantities of interferon that escape reabsorption in the kidney and are eliminated in the urine of dosed animals could have exerted any nonspecific effect on the vaginal epithelium.

Renal tubule adenomas occurred in three male mice and a renal tubule carcinoma occurred in one male mouse receiving 120 mg/kg AZT alone (Table 28). A renal tubule adenoma was also found in one male mouse receiving 60 mg/kg AZT with 500 U α-interferon A/D. Although no corresponding increase in the incidence of renal tubule hyperplasia was observed in routine kidney sections, examination of step sections revealed the presence of additional hyperplasias. Renal tubule neoplasms occur very infrequently in untreated male $B6C3F_1$ mice, and because mice eliminate AZT essentially unmetabolized in urine, the slight increase in incidences of hyperplasia among groups receiving AZT alone and the presence of neoplasms in the 120 mg/kg group is suggestive of an association with AZT treatment. However, the presence of a renal tubule adenoma in a male mouse receiving 60 mg/kg AZT with 500 U α-interferon A/D, the absence of kidney neoplasms in the groups receiving 120 mg/kg AZT with 500 or 5,000 U α-interferon A/D, and the absence of an increase in incidences of renal tubule hyperplasia in groups receiving AZT with 500 U α-interferon A/D are not consistent with a treatment-related response. Moreover, as many as two renal tubule neoplasms

TABLE 27
Overall Incidences of Vaginal Neoplasms and Hyperplasia of the Vaginal Epithelium in Female Mice in the 2-Year Gavage Studies of AZT and AZT/α-Interferon A/D[a]

	Vehicle Control	30 mg /kg AZT	60 mg/kg AZT	120 mg/kg AZT
AZT alone	2/197 (1%)[b] 1/197	0/49 (0%) 3/49	5/45 (11%) 4/45	11/49 (22%) 11/49
500 U α-Interferon A/D	0/49 (0%) 1/49	0/44 (0%) 4/44	5/48 (10%) 8/48	6/48 (13%) 12/48
5,000 U α-Interferon A/D	1/50 (2%) 0/50	1/48 (2%) 4/48	5/48 (10%) 8/48	4/50 (8%) 15/50

[a] Data are presented as number of vaginal neoplasms/number of animals microscopically examined (first line) and number of vaginal hyperplasias/number of animals microscopically examined (second line)
[b] Combined incidences of controls from the AZT alone study and the AZT/α-interferon A/D studies; incidences in the vehicle control group from the AZT alone study are 0/50 (0%) (neoplasms) and 0/50 (hyperplasia)

TABLE 28
Overall Incidence of Renal Tubule Neoplasms in Male Mice in the 2-Year Gavage Studies of AZT and AZT/α-Interferon A/D[a]

	Vehicle Control	30 mg/kg AZT	60 mg/kg AZT	120 mg/kg AZT
AZT alone	0/198 (0%)[b]	0/48 (0%)	0/49 (0%)	4/50 (8%)
500 U α-Interferon A/D	0/50 (0%)	0/50 (0%)	1/50 (2%)	0/50 (0%)
5,000 U α-Interferon A/D	0/49 (0%)	0/50 (0%)	0/50 (0%)	0/50 (0%)

[a] Data are presented as number of renal tubule neoplasms/number of animals examined microscopically
[b] Combined incidences of controls from the AZT alone study and the AZT/α-interferon A/D studies; incidence in the vehicle control group from the AZT alone study is 0/50 (0%)

have occurred in groups of control male mice in other NTP studies. Therefore, the increased incidence in renal tubule neoplasms that occurred in male mice receiving 120 mg/kg AZT alone has been judged an uncertain finding. Ayers *et al*. (1996) did not observe any AZT-associated response in male mouse kidneys; however, the highest dose used in their 22-month studies was 40 mg/kg.

All animals were observed at necropsy for macroscopic abnormalities of the harderian gland. In male mice, such abnormalities, later microscopically determined to be harderian gland neoplasms, were not detected in control animals, but were observed in four 30 mg/kg, one 60 mg/kg, and nine 120 mg/kg animals (Table 29). In addition, the harderian gland was present in routine sections of the nose in about 40% of animals from each dose group. Additional harderian gland neoplasms were observed on microscopic examination of routine nose sections in males as follows: three in the control group and one each in the 30, 60, and 120 mg/kg groups. These results reveal an increase in the incidence of harderian gland neoplasms in male mice receiving 120 mg/kg AZT.

TABLE 29
Overall Incidence of Harderian Gland Neoplasms in Male Mice in the 2-Year Gavage Studies of AZT and AZT/α-Interferon A/D[a]

	Vehicle Control	30 mg/kg AZT	60 mg/kg AZT	120 mg/kg AZT
AZT alone	13/200 (6%)[b]	5/50 (10%)	2/50 (4%)	10/50 (20%)
500 U α-Interferon A/D	6/50 (12%)	3/50 (6%)	1/50 (2%)	4/50 (8%)
5,000 U α-Interferon A/D	5/50 (10%)	9/50 (18%)	4/50 (8%)	4/50 (8%)

[a] Data are presented as number of harderian gland neoplasms/number of animals necropsied
[b] Combined incidences of controls from the AZT alone study and the AZT/α-interferon A/D studies; incidence in the vehicle control group from the AZT alone study is 3/50 (6%)

The incidence in this group exceeded the historical control range for harderian gland neoplasms in untreated male mice. However, the incidences of harderian gland neoplasms were not increased in a dose-related manner in other groups of male mice. In an extended review of the 120 mg/kg group, additional sections of the nose and slides of harderian gland prepared from wet tissues of control and 120 mg/kg males were examined microscopically. As a result of this extended review, tissues from 13 control males were found to have no additional harderian gland neoplasms, while three additional harderian gland adenomas were found in 27 males receiving 120 mg/kg. However, because unequal numbers of harderian glands were available for review in each group, the results of the extended review were not included in statistical evaluations.

The increased incidence of harderian gland neoplasms in the 120 mg/kg group is suggestive of an association with AZT treatment; however, the incidence of harderian gland hyperplasia was not increased correspondingly in this or other groups administered AZT, and the incidences of harderian gland neoplasms were not increased in a dose-related manner in groups of male mice receiving AZT and α-interferon A/D. Therefore, the increased incidence of harderian gland neoplasms in male mice receiving 120 mg/kg was considered an uncertain finding.

Coadministration of α-interferon A/D had no apparent effect on the observed response to AZT treatment in $B6C3F_1$ mice, nor did administration of α-interferon A/D or A alone elicit any observable toxic or carcinogenic response. In contrast to the well-characterized antiviral activity of α-interferon A/D in mice, its antiproliferative and antineoplastic activities are relatively unknown. Although it displays antiprolif-erative activity against human neoplasms transplanted into nude mice (Gazit *et al.*, 1992), the antiproliferative activity of α-interferon A/D against spontaneous or chemically induced neoplasms in mice has not been demonstrated.

The absence of any evidence of immune complex glomerulonephritis in the kidneys of mice receiving α-interferon A/D or A for 2 years suggests that the animals might not have raised a substantial neutralizing antibody response against the human proteins. However, serum antibody titers against α-interferon A/D were not evaluated. Because a number of factors influence the formation of immune complexes and their deposition in the kidney, the absence of glomerulonephritis cannot be taken as proof that neutralizing antibodies were not formed. In addition, there is the possibility that the biological activity of interferon dose preparations may have varied considerably more than 10%. Although the quantity of interferon protein administered to a particular group was the same throughout the 2-year study and all preparations exhibited antiviral activity, the titer of different dose preparations determined with the cytopathic effect assay varied considerably. Part of this variability is due to the nature of the assay itself; however, the range of titers observed makes it difficult to draw any conclusions about potential effects of interferon coadministration. Therefore, the

apparent lack of effect of coadministration of α-interferon A/D must be interpreted with a degree of uncertainty.

The studies reported here and those of Ayers *et al.* (1996) reveal a very consistent response to AZT treatment in rodents. Humans metabolize AZT to a much greater extent than do rats or mice and no comparable situation regarding urine flow into the vagina exists in humans. Therefore, if the mechanism proposed by Ayers *et al.* (1996) to explain the development of vaginal neoplasms is correct, it is uncertain to what extent the results of these studies will be predictive of potential human risk. AZT is genotoxic both *in vitro* and *in vivo* and is a particularly potent inducer of micronucleated polychromatic erythrocytes in mice (Phillips *et al.*, 1991). AZT is also an alternate substrate for normal cellular DNA polymerases and AZT cytotoxicity is strongly correlated to its incorporation into cellular DNA. It is somewhat surprising, therefore, that a more significant carcinogenic response was not observed.

Based on retrospective analyses, *Helicobacter hepaticus* was determined to have infected mice in 12 recent NTP 2-year studies (Appendix R). Of the 12 studies, mice (primarily males) from nine studies (including these four studies of AZT and AZT/α-interferon A/D) had a *H. hepaticus*-associated hepatitis. Qualitatively, the hepatitis and silver-staining organisms within the liver were similar among the nine studies. Using a polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP)-based assay, *H. hepaticus* was identified in studies from which adequately preserved (frozen) liver tissue was available, including 11 of 20 animals from the study of AZT. In general, efforts to identify *H. hepaticus* from tissue fixed in formalin for over a week were not successful (Malarkey *et al.*, 1997), which was the case for the studies of α-interferon A/D, AZT/500 U α-interferon A/D, and AZT/5,000 U α-interferon A/D, for which frozen liver tissue was not available. However, because of the presence of the typical liver lesions, silver-staining helical organisms, and confirmation with PCR-RFLP-based assays in the AZT study, the mice from all these studies were presumed to be infected with *H. hepaticus*.

Increases in the incidences of hepatocellular neoplasms in male mice have been shown to be associated with *H. hepaticus* infection when hepatitis is also present (Ward *et al.*, 1994; Fox *et al.*, 1996; Appendix R). Additionally, in NTP studies with *H. hepaticus*-associated hepatitis, increased incidences of hemangiosarcoma were seen in the livers of male mice (Appendix R). However, there was no consistent response in the liver of male mice in any of these four studies. Therefore, detection of dose-related differences in incidences of neoplasms in these four studies was not considered to have been significantly impacted by the infection with *H. hepaticus* or its associated hepatitis (Appendix R).

CONCLUSIONS

Under the conditions of these 2-year gavage studies there was *equivocal evidence of carcinogenic activity** of AZT in male mice based on increased incidences of renal tubule and harderian gland neoplasms in groups receiving AZT alone. There was *clear evidence of carcinogenic activity* of AZT in female mice based on increased incidences of squamous cell neoplasms of the vagina in groups that received AZT alone or in combination with α-interferon A/D.

Hematotoxicity occurred in all groups that received AZT.

Treatment with AZT alone and AZT in combination with α-interferon A/D resulted in increased incidences of epithelial hyperplasia of the vagina in all dosed groups of females.

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* Explanation of Levels of Evidence of Carcinogenic Activity is on page 14. A summary of the Technical Reports Review Subcommittee comments and the public discussion on this Technical Report appears on page 16.

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APPENDIX A
SUMMARY OF LESIONS IN MALE MICE IN THE 2-YEAR GAVAGE STUDY OF AZT

TABLE A1
Summary of the Incidence of Neoplasms in Male Mice in the 2-Year Gavage Study of AZT[a]

	Vehicle Control	30 mg/kg	60 mg/kg	120 mg/kg
Disposition Summary				
Animals initially in study	50	50	50	50
Early deaths				
Accidental deaths			3	
Moribund	6	9	9	4
Natural deaths	12	6	9	4
Survivors				
Terminal sacrifice	32	35	29	42
Animals examined microscopically	50	50	50	50
Alimentary System				
Esophagus	(50)	(50)	(49)	(50)
Sarcoma, metastatic, skin	1 (2%)			
Gallbladder	(41)	(42)	(46)	(44)
Intestine large, cecum	(47)	(48)	(45)	(49)
Intestine small, duodenum	(48)	(48)	(47)	(47)
Intestine small, jejunum	(47)	(48)	(45)	(47)
Carcinoma	1 (2%)	2 (4%)	1 (2%)	
Intestine small, ileum	(47)	(48)	(45)	(47)
Liver	(50)	(50)	(50)	(50)
Hemangioma	2 (4%)		1 (2%)	1 (2%)
Hemangiosarcoma	1 (2%)	2 (4%)	3 (6%)	1 (2%)
Hemangiosarcoma, multiple	5 (10%)	2 (4%)	1 (2%)	2 (4%)
Hepatoblastoma	1 (2%)	2 (4%)	5 (10%)	2 (4%)
Hepatoblastoma, multiple			1 (2%)	
Hepatocellular carcinoma	17 (34%)	15 (30%)	15 (30%)	15 (30%)
Hepatocellular carcinoma, multiple	4 (8%)	11 (22%)	7 (14%)	4 (8%)
Hepatocellular adenoma	17 (34%)	19 (38%)	14 (28%)	21 (42%)
Hepatocellular adenoma, multiple	8 (16%)	4 (8%)	9 (18%)	5 (10%)
Hepatocholangiocarcinoma		1 (2%)	1 (2%)	
Histiocytic sarcoma		1 (2%)		
Sarcoma, metastatic, mesentery			1 (2%)	
Sarcoma, metastatic, skin	1 (2%)			
Mesentery	(1)	(4)	(5)	(2)
Hepatocellular carcinoma, metastatic, liver			1 (20%)	
Sarcoma			1 (20%)	
Pancreas	(50)	(49)	(49)	(50)
Histiocytic sarcoma		1 (2%)		
Sarcoma, metastatic, mesentery			1 (2%)	
Salivary glands	(50)	(49)	(49)	(50)
Hemangioma			1 (2%)	
Histiocytic sarcoma		1 (2%)		
Stomach, forestomach	(50)	(48)	(49)	(50)
Stomach, glandular	(50)	(48)	(49)	(50)
Sarcoma, metastatic, mesentery			1 (2%)	
Cardiovascular System				
Heart	(50)	(50)	(50)	(50)
Hepatocholangiocarcinoma, metastatic, liver			1 (2%)	
Sarcoma, metastatic, skin	1 (2%)			

TABLE A1
Summary of the Incidence of Neoplasms in Male Mice in the 2-Year Gavage Study of AZT

	Vehicle Control	30 mg/kg	60 mg/kg	120 mg/kg
Endocrine System				
Adrenal cortex	(50)	(49)	(49)	(49)
Adenoma		1 (2%)		
Hepatocellular carcinoma, metastatic, liver			1 (2%)	
Sarcoma, metastatic, mesentery			1 (2%)	
Capsule, adenoma	5 (10%)	3 (6%)	1 (2%)	2 (4%)
Adrenal medulla	(50)	(49)	(48)	(49)
Sarcoma, metastatic, mesentery			1 (2%)	
Islets, pancreatic	(50)	(49)	(49)	(50)
Adenoma		1 (2%)	1 (2%)	
Thyroid gland	(50)	(49)	(48)	(50)
Bilateral, follicular cell, adenoma		1 (2%)		
Follicular cell, adenoma	2 (4%)	3 (6%)	2 (4%)	1 (2%)
General Body System				
Peritoneum		(1)		
Hepatocholangiocarcinoma, metastatic, liver		1 (100%)		
Tissue NOS	(1)		(1)	
Hepatocellular carcinoma, metastatic, liver			1 (100%)	
Genital System				
Epididymis	(50)	(49)	(50)	(50)
Histiocytic sarcoma		1 (2%)		
Preputial gland	(48)	(50)	(50)	(49)
Hemangiosarcoma		1 (2%)		
Prostate	(50)	(49)	(50)	(50)
Seminal vesicle	(50)	(49)	(50)	(50)
Histiocytic sarcoma		1 (2%)		
Sarcoma, metastatic, mesentery			1 (2%)	
Testes	(50)	(49)	(50)	(50)
Histiocytic sarcoma		1 (2%)		
Hematopoietic System				
Bone marrow	(50)	(50)	(49)	(50)
Hemangiosarcoma	1 (2%)	1 (2%)		1 (2%)
Lymph node	(6)	(7)	(5)	(1)
Mediastinal, sarcoma, metastatic, skin	1 (17%)			
Popliteal, hemangiosarcoma	1 (17%)			
Renal, histiocytic sarcoma		1 (14%)		
Lymph node, mandibular	(49)	(48)	(49)	(50)
Lymph node, mesenteric	(48)	(49)	(49)	(49)
Hemangiosarcoma		1 (2%)		
Spleen	(50)	(49)	(48)	(50)
Hemangioma		1 (2%)		
Hemangiosarcoma	2 (4%)	1 (2%)		
Thymus	(41)	(44)	(41)	(35)
Hepatocholangiocarcinoma, metastatic, liver			1 (2%)	

TABLE A1
Summary of the Incidence of Neoplasms in Male Mice in the 2-Year Gavage Study of AZT

	Vehicle Control	30 mg/kg	60 mg/kg	120 mg/kg
Integumentary System				
Skin	(50)	(50)	(50)	(50)
Subcutaneous tissue, chondrosarcoma		1 (2%)		
Subcutaneous tissue, fibrosarcoma	1 (2%)		2 (4%)	1 (2%)
Subcutaneous tissue, hemangiosarcoma	1 (2%)			
Subcutaneous tissue, histiocytic sarcoma		1 (2%)		
Subcutaneous tissue, sarcoma	1 (2%)	1 (2%)	1 (2%)	
Musculoskeletal System				
Skeletal muscle	(50)	(50)	(50)	(50)
Rhabdomyosarcoma				1 (2%)
Sarcoma, metastatic, mesentery			1 (2%)	
Sarcoma, metastatic, skin	1 (2%)			
Nervous System				
Brain	(50)	(50)	(49)	(50)
Cranial nerve, schwannoma malignant			1 (2%)	
Respiratory System				
Lung	(50)	(50)	(50)	(50)
Alveolar/bronchiolar adenoma	8 (16%)	6 (12%)	9 (18%)	8 (16%)
Alveolar/bronchiolar adenoma, multiple	4 (8%)	1 (2%)	2 (4%)	
Alveolar/bronchiolar carcinoma	4 (8%)	2 (4%)	3 (6%)	2 (4%)
Alveolar/bronchiolar carcinoma, multiple				2 (4%)
Hepatoblastoma, metastatic, liver			2 (4%)	
Hepatocellular carcinoma, metastatic, liver	6 (12%)	2 (4%)	4 (8%)	3 (6%)
Hepatocholangiocarcinoma, metastatic, liver			1 (2%)	
Sarcoma, metastatic, skin	1 (2%)			
Mediastinum, hepatocholangiocarcinoma, metastatic, liver			1 (2%)	
Nose	(50)	(50)	(49)	(50)
Schwannoma malignant, metastatic, brain			1 (2%)	
Special Senses System				
Harderian gland	(3)	(7)	(2)	(10)
Adenoma	3 (100%)	2 (29%)	2 (100%)	10 (100%)
Carcinoma		3 (43%)		
Urinary System				
Kidney	(50)	(48)	(49)	(50)
Hepatocellular carcinoma, metastatic, liver			1 (2%)	
Sarcoma, metastatic, skin	1 (2%)			
Renal tubule, adenoma				3 (6%)
Renal tubule, carcinoma				1 (2%)
Urinary bladder	(50)	(50)	(50)	(50)
Histiocytic sarcoma		1 (2%)		

TABLE A1
Summary of the Incidence of Neoplasms in Male Mice in the 2-Year Gavage Study of AZT

	Vehicle Control	30 mg/kg	60 mg/kg	120 mg/kg
Systemic Lesions				
Multiple organs[b]	(50)	(50)	(50)	(50)
Histiocytic sarcoma		2 (4%)		
Lymphoma malignant	1 (2%)	6 (12%)	7 (14%)	5 (10%)
Neoplasm Summary				
Total animals with primary neoplasms[c]	43	49	45	50
Total primary neoplasms	90	96	91	88
Total animals with benign neoplasms	33	31	29	42
Total benign neoplasms	49	42	42	51
Total animals with malignant neoplasms	28	40	39	29
Total malignant neoplasms	41	54	49	37
Total animals with metastatic neoplasms	6	3	9	3
Total metastatic neoplasms	13	3	22	3

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

TABLE A2
Statistical Analysis of Primary Neoplasms in Male Mice in the 2-Year Gavage Study of AZT

	Vehicle Control	30 mg/kg	60 mg/kg	120 mg/kg
Adrenal Cortex: Adenoma				
Overall rate[a]	5/50 (10%)	4/49 (8%)	1/49 (2%)	2/49 (4%)
Adjusted rate[b]	14.9%	11.8%	3.4%	4.9%
Terminal rate[c]	4/32 (13%)	4/34 (12%)	1/29 (3%)	2/41 (5%)
First incidence (days)	698	729 (T)	729 (T)	729 (T)
Life table test[d]	P = 0.073N	P = 0.464N	P = 0.131N	P = 0.136N
Logistic regression test[d]	P = 0.083N	P = 0.479N	P = 0.126N	P = 0.161N
Cochran-Armitage test[d]	P = 0.118N			
Fisher exact test[d]		P = 0.513N	P = 0.107N	P = 0.226N
Harderian Gland: Adenoma				
Overall rate	3/50 (6%)	2/50 (4%)	2/50 (4%)	10/50 (20%)
Adjusted rate	9.4%	5.7%	6.3%	23.1%
Terminal rate	3/32 (9%)	2/35 (6%)	1/29 (3%)	9/42 (21%)
First incidence (days)	729 (T)	729 (T)	667	612
Life table test	P = 0.016	P = 0.459N	P = 0.546N	P = 0.096
Logistic regression test	P = 0.009	P = 0.459N	P = 0.546N	P = 0.059
Cochran-Armitage test	P = 0.004			
Fisher exact test		P = 0.500N	P = 0.500N	P = 0.036
Harderian Gland: Carcinoma				
Overall rate	0/50 (0%)	3/50 (6%)	0/50 (0%)	0/50 (0%)
Adjusted rate	0.0%	7.7%	0.0%	0.0%
Terminal rate	0/32 (0%)	2/35 (6%)	0/29 (0%)	0/42 (0%)
First incidence (days)	—[e]	458	—	—
Life table test	P = 0.278N	P = 0.132	—[f]	—
Logistic regression test	P = 0.321N	P = 0.126	—	—
Cochran-Armitage test	P = 0.311N			
Fisher exact test		P = 0.121	—	—
Harderian Gland: Adenoma or Carcinoma				
Overall rate	3/50 (6%)	5/50 (10%)	2/50 (4%)	10/50 (20%)
Adjusted rate	9.4%	13.3%	6.3%	23.1%
Terminal rate	3/32 (9%)	4/35 (11%)	1/29 (3%)	9/42 (21%)
First incidence (days)	729 (T)	458	667	612
Life table test	P = 0.055	P = 0.399	P = 0.546N	P = 0.096
Logistic regression test	P = 0.027	P = 0.355	P = 0.546N	P = 0.059
Cochran-Armitage test	P = 0.019			
Fisher exact test		P = 0.357	P = 0.500N	P = 0.036
Kidney (Renal Tubule): Adenoma				
Overall rate	0/50 (0%)	0/48 (0%)	0/49 (0%)	3/50 (6%)
Adjusted rate	0.0%	0.0%	0.0%	7.1%
Terminal rate	0/32 (0%)	0/35 (0%)	0/29 (0%)	3/42 (7%)
First incidence (days)	—	—	—	729 (T)
Life table test	P = 0.022	—	—	P = 0.173
Logistic regression test	P = 0.022	—	—	P = 0.173
Cochran-Armitage test	P = 0.013			
Fisher exact test		—	—	P = 0.121

TABLE A2
Statistical Analysis of Primary Neoplasms in Male Mice in the 2-Year Gavage Study of AZT

	Vehicle Control	30 mg/kg	60 mg/kg	120 mg/kg
Kidney (Renal Tubule): Adenoma or Carcinoma				
Overall rate	0/50 (0%)	0/48 (0%)	0/49 (0%)	4/50 (8%)
Adjusted rate	0.0%	0.0%	0.0%	9.5%
Terminal rate	0/32 (0%)	0/35 (0%)	0/29 (0%)	4/42 (10%)
First incidence (days)	—	—	—	729 (T)
Life table test	P = 0.007	—	—	P = 0.103
Logistic regression test	P = 0.007	—	—	P = 0.103
Cochran-Armitage test	P = 0.003			
Fisher exact test		—	—	P = 0.059
Liver: Hemangiosarcoma				
Overall rate	6/50 (12%)	4/50 (8%)	4/50 (8%)	3/50 (6%)
Adjusted rate	13.5%	11.0%	12.8%	6.4%
Terminal rate	0/32 (0%)	3/35 (9%)	3/29 (10%)	1/42 (2%)
First incidence (days)	570	711	639	513
Life table test	P = 0.160N	P = 0.350N	P = 0.440N	P = 0.209N
Logistic regression test	P = 0.301N	P = 0.359N	P = 0.435N	P = 0.536N
Cochran-Armitage test	P = 0.208N			
Fisher exact test		P = 0.370N	P = 0.370N	P = 0.243N
Liver: Hepatocellular Adenoma				
Overall rate	25/50 (50%)	23/50 (46%)	23/50 (46%)	26/50 (52%)
Adjusted rate	65.2%	58.3%	66.8%	57.5%
Terminal rate	19/32 (59%)	19/35 (54%)	18/29 (62%)	23/42 (55%)
First incidence (days)	576	458	473	540
Life table test	P = 0.239N	P = 0.292N	P = 0.550	P = 0.215N
Logistic regression test	P = 0.537N	P = 0.422N	P = 0.574	P = 0.528N
Cochran-Armitage test	P = 0.415			
Fisher exact test		P = 0.421N	P = 0.421N	P = 0.500
Liver: Hepatocellular Carcinoma				
Overall rate	21/50 (42%)	26/50 (52%)	22/50 (44%)	19/50 (38%)
Adjusted rate	46.1%	61.6%	57.0%	40.4%
Terminal rate	8/32 (25%)	19/35 (54%)	13/29 (45%)	14/42 (33%)
First incidence (days)	425	350	505	584
Life table test	P = 0.091N	P = 0.345	P = 0.358	P = 0.192N
Logistic regression test	P = 0.256N	P = 0.211	P = 0.422	P = 0.521N
Cochran-Armitage test	P = 0.250N			
Fisher exact test		P = 0.212	P = 0.500	P = 0.419N
Liver: Hepatocellular Adenoma or Carcinoma				
Overall rate	36/50 (72%)	39/50 (78%)	34/50 (68%)	39/50 (78%)
Adjusted rate	76.5%	88.5%	84.7%	79.6%
Terminal rate	21/32 (66%)	30/35 (86%)	23/29 (79%)	32/42 (76%)
First incidence (days)	425	350	473	540
Life table test	P = 0.160N	P = 0.543	P = 0.469	P = 0.236N
Logistic regression test	P = 0.487	P = 0.301	P = 0.580N	P = 0.341
Cochran-Armitage test	P = 0.372			
Fisher exact test		P = 0.322	P = 0.414N	P = 0.322

TABLE A2
Statistical Analysis of Primary Neoplasms in Male Mice in the 2-Year Gavage Study of AZT

	Vehicle Control	30 mg/kg	60 mg/kg	120 mg/kg
Liver: Hepatoblastoma				
Overall rate	1/50 (2%)	2/50 (4%)	6/50 (12%)	2/50 (4%)
Adjusted rate	3.1%	5.7%	18.1%	4.8%
Terminal rate	1/32 (3%)	2/35 (6%)	3/29 (10%)	2/42 (5%)
First incidence (days)	729 (T)	729 (T)	638	729 (T)
Life table test	P = 0.472	P = 0.531	P = 0.048	P = 0.595
Logistic regression test	P = 0.407	P = 0.531	P = 0.044	P = 0.595
Cochran-Armitage test	P = 0.357			
Fisher exact test		P = 0.500	P = 0.056	P = 0.500
Liver: Hepatocellular Carcinoma or Hepatoblastoma				
Overall rate	21/50 (42%)	27/50 (54%)	26/50 (52%)	19/50 (38%)
Adjusted rate	46.1%	64.0%	64.6%	40.4%
Terminal rate	8/32 (25%)	20/35 (57%)	15/29 (52%)	14/42 (33%)
First incidence (days)	425	350	505	584
Life table test	P = 0.091N	P = 0.289	P = 0.153	P = 0.192N
Logistic regression test	P = 0.260N	P = 0.157	P = 0.140	P = 0.521N
Cochran-Armitage test	P = 0.259N			
Fisher exact test		P = 0.158	P = 0.212	P = 0.419N
Liver: Hepatocellular Adenoma, Hepatocellular Carcinoma, or Hepatoblastoma				
Overall rate	36/50 (72%)	39/50 (78%)	36/50 (72%)	39/50 (78%)
Adjusted rate	76.5%	88.5%	87.6%	79.6%
Terminal rate	21/32 (66%)	30/35 (86%)	24/29 (83%)	32/42 (76%)
First incidence (days)	425	350	473	540
Life table test	P = 0.165N	P = 0.543	P = 0.341	P = 0.236N
Logistic regression test	P = 0.468	P = 0.301	P = 0.404	P = 0.341
Cochran-Armitage test	P = 0.350			
Fisher exact test		P = 0.322	P = 0.588N	P = 0.322
Lung: Alveolar/bronchiolar Adenoma				
Overall rate	12/50 (24%)	7/50 (14%)	11/50 (22%)	8/50 (16%)
Adjusted rate	33.2%	19.1%	32.8%	18.6%
Terminal rate	9/32 (28%)	6/35 (17%)	7/29 (24%)	7/42 (17%)
First incidence (days)	565	624	584	694
Life table test	P = 0.146N	P = 0.118N	P = 0.572	P = 0.093N
Logistic regression test	P = 0.228N	P = 0.150N	P = 0.592N	P = 0.172N
Cochran-Armitage test	P = 0.292N			
Fisher exact test		P = 0.154N	P = 0.500N	P = 0.227N
Lung: Alveolar/bronchiolar Carcinoma				
Overall rate	4/50 (8%)	2/50 (4%)	3/50 (6%)	4/50 (8%)
Adjusted rate	11.2%	5.7%	10.3%	9.3%
Terminal rate	2/32 (6%)	2/35 (6%)	3/29 (10%)	3/42 (7%)
First incidence (days)	596	729 (T)	729 (T)	695
Life table test	P = 0.545N	P = 0.304N	P = 0.550N	P = 0.514N
Logistic regression test	P = 0.536	P = 0.335N	P = 0.550N	P = 0.616N
Cochran-Armitage test	P = 0.481			
Fisher exact test		P = 0.339N	P = 0.500N	P = 0.643N

TABLE A2
Statistical Analysis of Primary Neoplasms in Male Mice in the 2-Year Gavage Study of AZT

	Vehicle Control	30 mg/kg	60 mg/kg	120 mg/kg
Lung: Alveolar/bronchiolar Adenoma or Carcinoma				
Overall rate	14/50 (28%)	9/50 (18%)	14/50 (28%)	11/50 (22%)
Adjusted rate	38.0%	24.7%	41.9%	25.0%
Terminal rate	10/32 (31%)	8/35 (23%)	10/29 (34%)	9/42 (21%)
First incidence (days)	565	624	584	694
Life table test	P = 0.201N	P = 0.127N	P = 0.462	P = 0.134N
Logistic regression test	P = 0.312N	P = 0.163N	P = 0.476	P = 0.238N
Cochran-Armitage test	P = 0.411N			
Fisher exact test		P = 0.171N	P = 0.588N	P = 0.322N
Skin (Subcutaneous Tissue): Fibrosarcoma or Sarcoma				
Overall rate	2/50 (4%)	1/50 (2%)	3/50 (6%)	1/50 (2%)
Adjusted rate	5.0%	2.2%	8.3%	2.4%
Terminal rate	0/32 (0%)	0/35 (0%)	1/29 (3%)	1/42 (2%)
First incidence (days)	325	568	422	729 (T)
Life table test	P = 0.425N	P = 0.492N	P = 0.465	P = 0.441N
Logistic regression test	P = 0.524N	P = 0.421N	P = 0.616	P = 0.695N
Cochran-Armitage test	P = 0.474N			
Fisher exact test		P = 0.500N	P = 0.500	P = 0.500N
Thyroid Gland (Follicular Cell): Adenoma				
Overall rate	2/50 (4%)	4/49 (8%)	2/48 (4%)	1/50 (2%)
Adjusted rate	5.5%	11.4%	6.5%	2.4%
Terminal rate	1/32 (3%)	4/35 (11%)	1/29 (3%)	1/42 (2%)
First incidence (days)	638	729 (T)	691	729 (T)
Life table test	P = 0.196N	P = 0.374	P = 0.657	P = 0.424N
Logistic regression test	P = 0.233N	P = 0.337	P = 0.661	P = 0.496N
Cochran-Armitage test	P = 0.263N			
Fisher exact test		P = 0.329	P = 0.676	P = 0.500N
All Organs: Hemangiosarcoma				
Overall rate	7/50 (14%)	6/50 (12%)	4/50 (8%)	3/50 (6%)
Adjusted rate	16.2%	16.1%	12.8%	6.4%
Terminal rate	1/32 (3%)	4/35 (11%)	3/29 (10%)	1/42 (2%)
First incidence (days)	570	711	639	513
Life table test	P = 0.072N	P = 0.460N	P = 0.332N	P = 0.129N
Logistic regression test	P = 0.146N	P = 0.497N	P = 0.250N	P = 0.357N
Cochran-Armitage test	P = 0.101N			
Fisher exact test		P = 0.500N	P = 0.262N	P = 0.159N
All Organs: Hemangioma or Hemangiosarcoma				
Overall rate	9/50 (18%)	6/50 (12%)	6/50 (12%)	4/50 (8%)
Adjusted rate	21.6%	16.1%	19.5%	8.7%
Terminal rate	3/32 (9%)	4/35 (11%)	5/29 (17%)	2/42 (5%)
First incidence (days)	570	711	639	513
Life table test	P = 0.064N	P = 0.259N	P = 0.372N	P = 0.081N
Logistic regression test	P = 0.101N	P = 0.288N	P = 0.307N	P = 0.239N
Cochran-Armitage test	P = 0.103N			
Fisher exact test		P = 0.288N	P = 0.288N	P = 0.117N

TABLE A2
Statistical Analysis of Primary Neoplasms in Male Mice in the 2-Year Gavage Study of AZT

	Vehicle Control	30 mg/kg	60 mg/kg	120 mg/kg
All Organs: Malignant Lymphoma				
Overall rate	1/50 (2%)	6/50 (12%)	7/50 (14%)	5/50 (10%)
Adjusted rate	2.5%	13.3%	22.0%	11.5%
Terminal rate	0/32 (0%)	1/35 (3%)	5/29 (17%)	4/42 (10%)
First incidence (days)	638	257	596	612
Life table test	P = 0.277	P = 0.070	P = 0.027	P = 0.164
Logistic regression test	P = 0.141	P = 0.073	P = 0.025	P = 0.097
Cochran-Armitage test	P = 0.174			
Fisher exact test		P = 0.056	P = 0.030	P = 0.102
All Organs: Benign Neoplasms				
Overall rate	33/50 (66%)	31/50 (62%)	29/50 (58%)	42/50 (84%)
Adjusted rate	78.2%	77.1%	78.0%	89.3%
Terminal rate	23/32 (72%)	26/35 (74%)	21/29 (72%)	37/42 (88%)
First incidence (days)	565	458	473	540
Life table test	P = 0.392	P = 0.264N	P = 0.507N	P = 0.566
Logistic regression test	P = 0.048	P = 0.431N	P = 0.464N	P = 0.075
Cochran-Armitage test	P = 0.022			
Fisher exact test		P = 0.418N	P = 0.268N	P = 0.032
All Organs: Malignant Neoplasms				
Overall rate	28/50 (56%)	40/50 (80%)	39/50 (78%)	29/50 (58%)
Adjusted rate	58.0%	80.0%	84.8%	60.4%
Terminal rate	12/32 (38%)	25/35 (71%)	22/29 (76%)	23/42 (55%)
First incidence (days)	325	257	422	513
Life table test	P = 0.109N	P = 0.098	P = 0.028	P = 0.270N
Logistic regression test	P = 0.512N	P = 0.004	P = 0.006	P = 0.335
Cochran-Armitage test	P = 0.379N			
Fisher exact test		P = 0.009	P = 0.016	P = 0.500
All Organs: Benign or Malignant Neoplasms				
Overall rate	43/50 (86%)	49/50 (98%)	45/50 (90%)	50/50 (100%)
Adjusted rate	86.0%	98.0%	97.8%	100.0%
Terminal rate	25/32 (78%)	34/35 (97%)	28/29 (97%)	42/42 (100%)
First incidence (days)	325	257	422	513
Life table test	P = 0.244N	P = 0.379	P = 0.206	P = 0.341N
Logistic regression test	P = 0.010	P = 0.022	P = 0.151	P = 0.003
Cochran-Armitage test	P = 0.019			
Fisher exact test		P = 0.030	P = 0.380	P = 0.006

(T)Terminal sacrifice
[a] Number of neoplasm-bearing animals/number of animals examined. Denominator is number of animals examined microscopically for adrenal gland, kidney, liver, lung, 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 incidence are the P values associated with the trend test. Beneath the dosed group incidence are the P values corresponding to pairwise comparisons between the vehicle controls and that 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 Cochran-Armitage and Fisher exact tests compare directly the overall incidence rates. For all tests, a negative trend or a lower incidence in a dose group is indicated by **N**.
[e] Not applicable; no neoplasms in animal group
[f] Value of statistic cannot be computed.

TABLE A3a
Historical Incidence of Renal Tubule Neoplasms in Water Gavage Vehicle Control Male B6C3F$_1$ Mice[a]

	Incidence in Controls		
	Adenoma	Carcinoma	Adenoma or Carcinoma
Overall Historical Incidence			
Total	0/365	2/365 (0.6%)	2/365 (0.6%)
Standard deviation		1.5%	1.5%
Range		0%-4%	0%-4%

[a] Data as of 12 May 1995

TABLE A3b
Historical Incidence of Harderian Gland Neoplasms in Water Gavage Vehicle Control Male B6C3F$_1$ Mice[a]

	Incidence in Controls		
	Adenoma	Carcinoma	Adenoma or Carcinoma
Overall Historical Incidence			
Total	18/365 (4.9%)	1/365 (0.3%)	19/365 (5.2%)
Standard deviation	3.5%	0.8%	3.3%
Range	2%-10%	0%-2%	2%-10%

[a] Data as of 12 May 1995

TABLE A3c
Historical Incidence of Liver Neoplasms in Water Gavage Vehicle Control Male B6C3F$_1$ Mice[a]

	Incidence in Controls			
	Hepatocellular Adenoma	Hepatocellular Carcinoma	Hepatoblastoma	Hepatocellular Adenoma, Hepatocellular Carcinoma, or Hepatoblastoma
Overall Historical Incidence				
Total	66/365 (18.1%)	45/365 (12.3%)	0/365	104/365 (28.5%)
Standard deviation	15.6%	5.6%		15.4%
Range	4%-52%	6%-24%		14%-60%

[a] Data as of 12 May 1995

TABLE A4
Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the 2-Year Gavage Study of AZT[a]

	Vehicle Control	30 mg/kg	60 mg/kg	120 mg/kg
Disposition Summary				
Animals initially in study	50	50	50	50
Early deaths				
Accidental deaths			3	
Moribund	6	9	9	4
Natural deaths	12	6	9	4
Survivors				
Terminal sacrifice	32	35	29	42
Animals examined microscopically	50	50	50	50
Alimentary System				
Esophagus	(50)	(50)	(49)	(50)
Necrosis			1 (2%)	
Muscularis, inflammation, chronic			1 (2%)	
Gallbladder	(41)	(42)	(46)	(44)
Cyst		1 (2%)		
Intestine large, cecum	(47)	(48)	(45)	(49)
Hyperplasia, lymphoid			1 (2%)	
Intestine small, duodenum	(48)	(48)	(47)	(47)
Cyst			1 (2%)	
Inflammation, chronic, focal				1 (2%)
Intestine small, jejunum	(47)	(48)	(45)	(47)
Hyperplasia, adenomatous	1 (2%)			
Intestine small, ileum	(47)	(48)	(45)	(47)
Peyer's patch, hyperplasia, lymphoid		1 (2%)	1 (2%)	
Liver	(50)	(50)	(50)	(50)
Angiectasis	3 (6%)	1 (2%)		
Basophilic focus	5 (10%)	1 (2%)	3 (6%)	3 (6%)
Clear cell focus	4 (8%)	3 (6%)		4 (8%)
Eosinophilic focus	12 (24%)	12 (24%)	7 (14%)	12 (24%)
Inflammation, chronic	17 (34%)	24 (48%)	24 (48%)	16 (32%)
Mixed cell focus	2 (4%)	4 (8%)	7 (14%)	4 (8%)
Necrosis, focal	8 (16%)	8 (16%)	9 (18%)	3 (6%)
Vacuolization cytoplasmic	3 (6%)	1 (2%)	4 (8%)	3 (6%)
Bile duct, cyst	1 (2%)			1 (2%)
Bile duct, hyperplasia	1 (2%)	9 (18%)	4 (8%)	3 (6%)
Hepatocyte, karyomegaly	7 (14%)	10 (20%)	15 (30%)	5 (10%)
Mesentery	(1)	(4)	(5)	(2)
Hemorrhage			1 (20%)	
Inflammation, chronic			1 (20%)	
Inflammation, granulomatous	1 (100%)			
Thrombosis		1 (25%)		
Artery, inflammation, chronic		1 (25%)		
Fat, necrosis		2 (50%)	2 (40%)	2 (100%)
Pancreas	(50)	(49)	(49)	(50)
Atrophy	1 (2%)	3 (6%)	3 (6%)	
Inflammation, granulomatous	1 (2%)			
Necrosis		1 (2%)		
Thrombosis			1 (2%)	
Artery, inflammation, chronic		1 (2%)		
Duct, cyst		1 (2%)	1 (2%)	

[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 Male Mice in the 2-Year Gavage Study of AZT

	Vehicle Control	30 mg/kg	60 mg/kg	120 mg/kg
Alimentary System (continued)				
Stomach, forestomach	(50)	(48)	(49)	(50)
Erosion	1 (2%)		1 (2%)	1 (2%)
Inflammation, chronic	2 (4%)	1 (2%)		
Ulcer	2 (4%)			1 (2%)
Epithelium, hyperplasia	7 (14%)	4 (8%)	3 (6%)	1 (2%)
Stomach, glandular	(50)	(48)	(49)	(50)
Erosion		1 (2%)	4 (8%)	
Mineralization	1 (2%)	1 (2%)	2 (4%)	2 (4%)
Pigmentation, focal			1 (2%)	
Glands, degeneration, cystic, focal		2 (4%)	1 (2%)	2 (4%)
Tooth	(2)	(2)	(7)	(1)
Developmental malformation	2 (100%)	2 (100%)	7 (100%)	1 (100%)
Cardiovascular System				
Blood vessel	(50)	(48)	(50)	(50)
Inflammation, chronic	1 (2%)			2 (4%)
Heart	(50)	(50)	(50)	(50)
Fibrosis	1 (2%)			
Inflammation, chronic, focal	2 (4%)	4 (8%)		1 (2%)
Mineralization			1 (2%)	
Thrombosis		1 (2%)	2 (4%)	1 (2%)
Artery, inflammation, chronic	1 (2%)			
Endocrine System				
Adrenal cortex	(50)	(49)	(49)	(49)
Accessory adrenal cortical nodule	1 (2%)	1 (2%)		
Cyst			1 (2%)	1 (2%)
Cytoplasmic alteration, focal	5 (10%)	11 (22%)	8 (16%)	18 (37%)
Hyperplasia, focal	3 (6%)	1 (2%)	3 (6%)	5 (10%)
Hypertrophy, focal	10 (20%)	17 (35%)	8 (16%)	7 (14%)
Inflammation, chronic, focal			1 (2%)	
Capsule, hyperplasia, focal	3 (6%)		2 (4%)	1 (2%)
Adrenal medulla	(50)	(49)	(48)	(49)
Hyperplasia		1 (2%)	1 (2%)	
Parathyroid gland	(46)	(45)	(45)	(49)
Cyst	1 (2%)		1 (2%)	1 (2%)
Pituitary gland	(40)	(46)	(42)	(47)
Pars distalis, cyst	1 (3%)	2 (4%)	1 (2%)	3 (6%)
Pars distalis, cytoplasmic alteration, focal				1 (2%)
Pars distalis, hyperplasia, focal				1 (2%)
Thyroid gland	(50)	(49)	(48)	(50)
Degeneration, cystic, focal	15 (30%)	18 (37%)	11 (23%)	16 (32%)
Follicle, cyst	8 (16%)	4 (8%)	2 (4%)	5 (10%)
Follicular cell, hyperplasia	8 (16%)	10 (20%)	11 (23%)	9 (18%)
General Body System				
None				

TABLE A4
Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the 2-Year Gavage Study of AZT

	Vehicle Control	30 mg/kg	60 mg/kg	120 mg/kg
Genital System				
Epididymis	(50)	(49)	(50)	(50)
Granuloma sperm	1 (2%)			
Spermatocele	1 (2%)	1 (2%)		
Preputial gland	(48)	(50)	(50)	(49)
Degeneration, cystic	39 (81%)	46 (92%)	44 (88%)	45 (92%)
Inflammation, chronic	4 (8%)	5 (10%)	2 (4%)	
Prostate	(50)	(49)	(50)	(50)
Inflammation, chronic		3 (6%)		
Inflammation, chronic, focal	3 (6%)			2 (4%)
Epithelium, hyperplasia, focal	2 (4%)			1 (2%)
Seminal vesicle	(50)	(49)	(50)	(50)
Angiectasis	1 (2%)	1 (2%)		4 (8%)
Congestion	1 (2%)			
Inflammation, chronic	1 (2%)			1 (2%)
Testes	(50)	(49)	(50)	(50)
Germinal epithelium, degeneration	1 (2%)	1 (2%)		1 (2%)
Hematopoietic System				
Bone marrow	(50)	(50)	(49)	(50)
Angiectasis		1 (2%)	1 (2%)	1 (2%)
Hyperplasia	2 (4%)	6 (12%)	6 (12%)	1 (2%)
Lymph node	(6)	(7)	(5)	(1)
Inguinal, hyperplasia, lymphoid			1 (20%)	
Inguinal, pigmentation	1 (17%)	2 (29%)	1 (20%)	
Mediastinal, hyperplasia, lymphoid	1 (17%)		1 (20%)	
Mediastinal, inflammation, granulomatous	1 (17%)			
Pancreatic, hyperplasia, lymphoid	1 (17%)			
Lymph node, mandibular	(49)	(48)	(49)	(50)
Hemorrhage		1 (2%)		
Hyperplasia, histiocytic				1 (2%)
Hyperplasia, lymphoid		1 (2%)	1 (2%)	1 (2%)
Infiltration cellular, mast cell			1 (2%)	
Lymph node, mesenteric	(48)	(49)	(49)	(49)
Ectasia	5 (10%)	4 (8%)	1 (2%)	3 (6%)
Fibrosis	1 (2%)			
Hemorrhage	20 (42%)	31 (63%)	21 (43%)	25 (51%)
Hyperplasia, lymphoid	3 (6%)	3 (6%)	3 (6%)	4 (8%)
Inflammation, granulomatous	1 (2%)			
Spleen	(50)	(49)	(48)	(50)
Angiectasis	1 (2%)			
Depletion cellular	1 (2%)		1 (2%)	6 (12%)
Hematopoietic cell proliferation	18 (36%)	16 (33%)	14 (29%)	11 (22%)
Hyperplasia, lymphoid	2 (4%)	1 (2%)	2 (4%)	2 (4%)
Necrosis, focal		1 (2%)		
Thymus	(41)	(44)	(41)	(35)
Cyst	6 (15%)	11 (25%)	5 (12%)	4 (11%)
Mineralization		1 (2%)		
Necrosis			1 (2%)	
Integumentary System				
Mammary gland	(15)	(10)	(15)	(5)
Inflammation, chronic		1 (10%)		
Skin	(50)	(50)	(50)	(50)
Subcutaneous tissue, edema		1 (2%)		

TABLE A4
Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the 2-Year Gavage Study of AZT

	Vehicle Control	30 mg/kg	60 mg/kg	120 mg/kg
Musculoskeletal System				
Bone	(50)	(50)	(50)	(50)
Hyperostosis	30 (60%)	36 (72%)	28 (56%)	41 (82%)
Skeletal muscle	(50)	(50)	(50)	(50)
Necrosis			1 (2%)	
Nervous System				
Brain	(50)	(50)	(49)	(50)
Hemorrhage		1 (2%)		
Spinal cord	(1)	(1)		
Degeneration	1 (100%)			
Hemorrhage, focal	1 (100%)			
Respiratory System				
Lung	(50)	(50)	(50)	(50)
Hemorrhage	2 (4%)	1 (2%)	2 (4%)	3 (6%)
Hyperplasia, histiocytic	2 (4%)	2 (4%)	1 (2%)	
Hyperplasia, lymphoid			1 (2%)	
Infiltration cellular, mixed cell		1 (2%)	1 (2%)	1 (2%)
Inflammation, chronic		1 (2%)	1 (2%)	1 (2%)
Alveolar epithelium, hyperplasia	6 (12%)	3 (6%)	1 (2%)	8 (16%)
Nose	(50)	(50)	(49)	(50)
Nasolacrimal duct, inflammation, suppurative			1 (2%)	
Special Senses System				
Eye				(1)
Cornea, inflammation, chronic				1 (100%)
Harderian gland	(3)	(7)	(2)	(10)
Hyperplasia, focal		1 (14%)		
Urinary System				
Kidney	(50)	(48)	(49)	(50)
Cyst	2 (4%)		1 (2%)	
Infarct	1 (2%)	2 (4%)	1 (2%)	2 (4%)
Metaplasia, focal, osseous	1 (2%)	3 (6%)		1 (2%)
Nephropathy	45 (90%)	44 (92%)	44 (90%)	49 (98%)
Thrombosis				1 (2%)
Papilla, necrosis				1 (2%)
Pelvis, dilatation		1 (2%)		
Renal tubule, accumulation, hyaline droplet		1 (2%)		
Renal tubule, dilatation		1 (2%)		1 (2%)
Renal tubule, hyperplasia, focal		1 (2%)		
Renal tubule, pigmentation	2 (4%)		1 (2%)	1 (2%)
Urethra	(1)	(1)		(1)
Inflammation, chronic	1 (100%)	1 (100%)		1 (100%)
Urinary bladder	(50)	(50)	(50)	(50)
Hemorrhage	1 (2%)			

APPENDIX B
SUMMARY OF LESIONS IN FEMALE MICE IN THE 2-YEAR GAVAGE STUDY OF AZT

TABLE B1
Summary of the Incidence of Neoplasms in Female Mice in the 2-Year Gavage Study of AZT[a]

	Vehicle Control	30 mg/kg	60 mg/kg	120 mg/kg
Disposition Summary				
Animals initially in study	50	50	50	50
Early deaths				
Accidental deaths			3	1
Moribund	5	5	9	7
Natural deaths	11	6	7	11
Survivors				
Died last week of study		1		
Terminal sacrifice	34	38	31	31
Animals examined microscopically	50	50	50	50
Alimentary System				
Gallbladder	(48)	(44)	(49)	(45)
Intestine large, rectum	(46)	(48)	(46)	(45)
Squamous cell carcinoma, metastatic, vagina				1 (2%)
Intestine small, jejunum	(46)	(46)	(44)	(42)
Intestine small, ileum	(46)	(44)	(45)	(42)
Liver	(50)	(50)	(50)	(50)
Hemangioma				1 (2%)
Hemangiosarcoma		2 (4%)		
Hepatoblastoma	1 (2%)			2 (4%)
Hepatocellular carcinoma	10 (20%)	14 (28%)	10 (20%)	11 (22%)
Hepatocellular carcinoma, multiple	2 (4%)	3 (6%)	1 (2%)	4 (8%)
Hepatocellular adenoma	14 (28%)	11 (22%)	9 (18%)	19 (38%)
Hepatocellular adenoma, multiple	6 (12%)	7 (14%)	8 (16%)	9 (18%)
Histiocytic sarcoma	2 (4%)	1 (2%)	1 (2%)	1 (2%)
Mesentery	(13)	(17)	(8)	(11)
Carcinoma, metastatic, pancreas	1 (8%)			
Carcinoma, metastatic, uterus		1 (6%)		
Fibrosarcoma, metastatic, skeletal muscle	1 (8%)			
Histiocytic sarcoma		1 (6%)	1 (13%)	
Sarcoma	2 (15%)			
Sarcoma, metastatic, pancreas				1 (9%)
Pancreas	(50)	(49)	(49)	(48)
Carcinoma	1 (2%)			
Carcinoma, metastatic, uterus		1 (2%)		
Histiocytic sarcoma			1 (2%)	
Sarcoma				1 (2%)
Salivary glands	(50)	(50)	(50)	(50)
Stomach, forestomach	(49)	(49)	(49)	(49)
Histiocytic sarcoma			1 (2%)	
Squamous cell carcinoma				1 (2%)
Squamous cell papilloma	3 (6%)	3 (6%)	1 (2%)	1 (2%)
Stomach, glandular	(49)	(49)	(48)	(49)
Histiocytic sarcoma			1 (2%)	
Sarcoma, metastatic, pancreas				1 (2%)
Tongue			(1)	
Squamous cell papilloma			1 (100%)	
Cardiovascular System				
Heart	(49)	(50)	(50)	(50)
Carcinoma, metastatic, uterus		1 (2%)		
Histiocytic sarcoma	1 (2%)			

TABLE B1
Summary of the Incidence of Neoplasms in Female Mice in the 2-Year Gavage Study of AZT

	Vehicle Control	30 mg/kg	60 mg/kg	120 mg/kg
Endocrine System				
Adrenal cortex	(50)	(49)	(50)	(50)
Histiocytic sarcoma			1 (2%)	
Capsule, carcinoma, metastatic, uterus		1 (2%)		
Capsule, fibrosarcoma, metastatic, skeletal muscle	1 (2%)			
Islets, pancreatic	(49)	(49)	(50)	(47)
Adenoma		2 (4%)	1 (2%)	1 (2%)
Pituitary gland	(46)	(49)	(46)	(46)
Pars distalis, adenoma	2 (4%)	5 (10%)	1 (2%)	
Thyroid gland	(49)	(50)	(50)	(50)
Follicular cell, adenoma	3 (6%)	2 (4%)	4 (8%)	
Follicular cell, carcinoma	1 (2%)	1 (2%)		
General Body System				
Peritoneum			(1)	
Tissue NOS				(1)
Genital System				
Clitoral gland	(49)	(49)	(49)	(48)
Carcinoma				1 (2%)
Ovary	(50)	(50)	(47)	(48)
Cystadenoma	2 (4%)	2 (4%)	3 (6%)	
Granulosa cell tumor benign		2 (4%)		
Hemangioma				1 (2%)
Histiocytic sarcoma	1 (2%)	1 (2%)		
Teratoma benign	1 (2%)			
Uterus	(50)	(50)	(49)	(50)
Histiocytic sarcoma	1 (2%)	1 (2%)	1 (2%)	1 (2%)
Leiomyosarcoma				1 (2%)
Endometrium, carcinoma		1 (2%)	1 (2%)	
Endometrium, polyp stromal	1 (2%)	2 (4%)		
Endometrium, sarcoma stromal				1 (2%)
Vagina	(50)	(49)	(45)	(49)
Histiocytic sarcoma			1 (2%)	
Squamous cell carcinoma			5 (11%)	9 (18%)
Squamous cell papilloma				2 (4%)
Hematopoietic System				
Bone marrow	(50)	(49)	(50)	(50)
Hemangiosarcoma			1 (2%)	
Histiocytic sarcoma			1 (2%)	
Lymph node	(7)	(5)	(7)	(10)
Fibrosarcoma, metastatic, skin				1 (10%)
Iliac, histiocytic sarcoma		1 (20%)		
Inguinal, carcinoma, metastatic, clitoral gland				1 (10%)
Inguinal, histiocytic sarcoma		1 (20%)		
Mediastinal, histiocytic sarcoma			1 (14%)	
Renal, carcinoma, metastatic, clitoral gland				1 (10%)
Renal, histiocytic sarcoma			1 (14%)	
Lymph node, mandibular	(50)	(46)	(48)	(48)
Histiocytic sarcoma	1 (2%)		1 (2%)	

TABLE B1
Summary of the Incidence of Neoplasms in Female Mice in the 2-Year Gavage Study of AZT

	Vehicle Control	30 mg/kg	60 mg/kg	120 mg/kg
Hematopoietic System (continued)				
Lymph node, mesenteric	(50)	(47)	(48)	(47)
Histiocytic sarcoma	1 (2%)	1 (2%)		1 (2%)
Spleen	(49)	(48)	(49)	(50)
Hemangiosarcoma	1 (2%)		1 (2%)	
Sarcoma, metastatic, pancreas				1 (2%)
Thymus	(48)	(46)	(49)	(46)
Carcinoma, metastatic, uterus		1 (2%)		
Histiocytic sarcoma	1 (2%)			
Integumentary System				
Skin	(50)	(49)	(50)	(50)
Trichoepithelioma	1 (2%)			
Pinna, squamous cell carcinoma			1 (2%)	
Subcutaneous tissue, fibrosarcoma		1 (2%)	2 (4%)	2 (4%)
Subcutaneous tissue, histiocytic sarcoma			1 (2%)	
Musculoskeletal System				
Bone	(50)	(50)	(50)	(50)
Carcinoma, metastatic, uterus		1 (2%)		
Skeletal muscle	(50)	(50)	(50)	(50)
Carcinoma, metastatic, uterus		1 (2%)		
Fibrosarcoma	1 (2%)			
Hemangiosarcoma				1 (2%)
Sarcoma			1 (2%)	
Sarcoma, metastatic, pancreas				1 (2%)
Nervous System				
Brain	(50)	(50)	(50)	(50)
Respiratory System				
Lung	(49)	(50)	(50)	(50)
Alveolar/bronchiolar adenoma	3 (6%)	3 (6%)	2 (4%)	7 (14%)
Alveolar/bronchiolar carcinoma	3 (6%)	5 (10%)		4 (8%)
Carcinoma, metastatic, clitoral gland				1 (2%)
Carcinoma, metastatic, harderian gland	1 (2%)			1 (2%)
Carcinoma, metastatic, pancreas	1 (2%)			
Carcinoma, metastatic, uterus		1 (2%)		
Fibrosarcoma, metastatic, skin				2 (4%)
Hepatocellular carcinoma, metastatic, liver	3 (6%)	4 (8%)	1 (2%)	2 (4%)
Histiocytic sarcoma	1 (2%)	1 (2%)		
Leiomyosarcoma, metastatic, uterus				1 (2%)
Squamous cell carcinoma, metastatic, vagina			1 (2%)	
Nose	(50)	(50)	(50)	(50)
Special Senses System				
Harderian gland	(5)	(2)	(2)	(2)
Adenoma	4 (80%)	2 (100%)		1 (50%)
Carcinoma	1 (20%)		1 (50%)	1 (50%)

TABLE B1
Summary of the Incidence of Neoplasms in Female Mice in the 2-Year Gavage Study of AZT

	Vehicle Control	30 mg/kg	60 mg/kg	120 mg/kg
Urinary System				
Kidney	(50)	(50)	(50)	(50)
Histiocytic sarcoma		1 (2%)		1 (2%)
Urethra			(1)	
Squamous cell carcinoma, metastatic, vagina			1 (100%)	
Urinary bladder	(50)	(50)	(49)	(49)
Hemangioma			1 (2%)	
Hemangiosarcoma				1 (2%)
Systemic Lesions				
Multiple organs[b]	(50)	(50)	(50)	(50)
Histiocytic sarcoma	2 (4%)	1 (2%)	3 (6%)	1 (2%)
Lymphoma malignant	5 (10%)	10 (20%)	7 (14%)	9 (18%)
Mesothelioma malignant			1 (2%)	
Neoplasm Summary				
Total animals with primary neoplasms[c]	41	42	41	43
Total primary neoplasms	70	79	66	92
Total animals with benign neoplasms	30	33	26	31
Total benign neoplasms	40	41	31	42
Total animals with malignant neoplasms	26	30	28	35
Total malignant neoplasms	30	38	35	50
Total animals with metastatic neoplasms	5	4	3	9
Total metastatic neoplasms	8	12	3	15

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

TABLE B2
Statistical Analysis of Primary Neoplasms in Female Mice in the 2-Year Gavage Study of AZT

	Vehicle Control	30 mg/kg	60 mg/kg	120 mg/kg
Harderian Gland: Adenoma				
Overall rate[a]	4/50 (8%)	2/50 (4%)	0/50 (0%)	1/50 (2%)
Adjusted rate[b]	11.8%	5.1%	0.0%	3.2%
Terminal rate[c]	4/34 (12%)	2/39 (5%)	0/31 (0%)	1/31 (3%)
First incidence (days)	731 (T)	731 (T)	—[e]	731 (T)
Life table test[d]	P = 0.107N	P = 0.275N	P = 0.074N	P = 0.207N
Logistic regression test[d]	P = 0.107N	P = 0.275N	P = 0.074N	P = 0.207N
Cochran-Armitage test[d]	P = 0.086N			
Fisher exact test[d]		P = 0.339N	P = 0.059N	P = 0.181N
Harderian Gland: Adenoma or Carcinoma				
Overall rate	5/50 (10%)	2/50 (4%)	1/50 (2%)	2/50 (4%)
Adjusted rate	14.7%	5.1%	2.8%	6.5%
Terminal rate	5/34 (15%)	2/39 (5%)	0/31 (0%)	2/31 (6%)
First incidence (days)	731 (T)	731 (T)	689	731 (T)
Life table test	P = 0.200N	P = 0.163N	P = 0.125N	P = 0.253N
Logistic regression test	P = 0.173N	P = 0.163N	P = 0.121N	P = 0.253N
Cochran-Armitage test	P = 0.162N			
Fisher exact test		P = 0.218N	P = 0.102N	P = 0.218N
Liver: Hepatocellular Adenoma				
Overall rate	20/50 (40%)	18/50 (36%)	17/50 (34%)	28/50 (56%)
Adjusted rate	53.6%	44.9%	53.1%	67.5%
Terminal rate	17/34 (50%)	17/39 (44%)	16/31 (52%)	18/31 (58%)
First incidence (days)	607	648	722	467
Life table test	P = 0.010	P = 0.234N	P = 0.475N	P = 0.058
Logistic regression test	P = 0.032	P = 0.317N	P = 0.457N	P = 0.082
Cochran-Armitage test	P = 0.043			
Fisher exact test		P = 0.418N	P = 0.339N	P = 0.080
Liver: Hepatocellular Carcinoma				
Overall rate	12/50 (24%)	17/50 (34%)	11/50 (22%)	15/50 (30%)
Adjusted rate	30.3%	37.6%	30.7%	40.4%
Terminal rate	8/34 (24%)	11/39 (28%)	7/31 (23%)	10/31 (32%)
First incidence (days)	470	527	556	556
Life table test	P = 0.309	P = 0.314	P = 0.588N	P = 0.273
Logistic regression test	P = 0.411	P = 0.159	P = 0.544N	P = 0.325
Cochran-Armitage test	P = 0.426			
Fisher exact test		P = 0.189	P = 0.500N	P = 0.326
Liver: Hepatocellular Adenoma or Carcinoma				
Overall rate	27/50 (54%)	29/50 (58%)	23/50 (46%)	36/50 (72%)
Adjusted rate	65.2%	63.0%	63.6%	85.3%
Terminal rate	20/34 (59%)	22/39 (56%)	18/31 (58%)	25/31 (81%)
First incidence (days)	470	527	556	467
Life table test	P = 0.018	P = 0.478N	P = 0.443N	P = 0.038
Logistic regression test	P = 0.040	P = 0.463	P = 0.394N	P = 0.046
Cochran-Armitage test	P = 0.053			
Fisher exact test		P = 0.420	P = 0.274N	P = 0.048

TABLE B2
Statistical Analysis of Primary Neoplasms in Female Mice in the 2-Year Gavage Study of AZT

	Vehicle Control	30 mg/kg	60 mg/kg	120 mg/kg
Liver: Hepatocellular Carcinoma or Hepatoblastoma				
Overall rate	13/50 (26%)	17/50 (34%)	11/50 (22%)	16/50 (32%)
Adjusted rate	33.0%	37.6%	30.7%	43.2%
Terminal rate	9/34 (26%)	11/39 (28%)	7/31 (23%)	11/31 (35%)
First incidence (days)	470	527	556	556
Life table test	P = 0.288	P = 0.396	P = 0.503N	P = 0.271
Logistic regression test	P = 0.390	P = 0.225	P = 0.455N	P = 0.329
Cochran-Armitage test	P = 0.406			
Fisher exact test		P = 0.257	P = 0.408N	P = 0.330
Liver: Hepatocellular Adenoma, Hepatocellular Carcinoma, or Hepatoblastoma				
Overall rate	27/50 (54%)	29/50 (58%)	23/50 (46%)	36/50 (72%)
Adjusted rate	65.2%	63.0%	63.6%	85.3%
Terminal rate	20/34 (59%)	22/39 (56%)	18/31 (58%)	25/31 (81%)
First incidence (days)	470	527	556	467
Life table test	P = 0.018	P = 0.478N	P = 0.443N	P = 0.038
Logistic regression test	P = 0.040	P = 0.463	P = 0.394N	P = 0.046
Cochran-Armitage test	P = 0.053			
Fisher exact test		P = 0.420	P = 0.274N	P = 0.048
Lung: Alveolar/bronchiolar Adenoma				
Overall rate	3/49 (6%)	3/50 (6%)	2/50 (4%)	7/50 (14%)
Adjusted rate	7.6%	7.7%	5.3%	21.5%
Terminal rate	1/34 (3%)	3/39 (8%)	1/31 (3%)	6/31 (19%)
First incidence (days)	647	731 (T)	288	709
Life table test	P = 0.057	P = 0.611N	P = 0.538N	P = 0.140
Logistic regression test	P = 0.082	P = 0.649N	P = 0.415N	P = 0.164
Cochran-Armitage test	P = 0.083			
Fisher exact test		P = 0.651N	P = 0.490N	P = 0.167
Lung: Alveolar/bronchiolar Carcinoma				
Overall rate	3/49 (6%)	5/50 (10%)	0/50 (0%)	4/50 (8%)
Adjusted rate	8.8%	11.6%	0.0%	10.4%
Terminal rate	3/34 (9%)	3/39 (8%)	0/31 (0%)	1/31 (3%)
First incidence (days)	731 (T)	589	—	625
Life table test	P = 0.532	P = 0.426	P = 0.137N	P = 0.480
Logistic regression test	P = 0.578N	P = 0.365	P = 0.137N	P = 0.509
Cochran-Armitage test	P = 0.572N			
Fisher exact test		P = 0.369	P = 0.117N	P = 0.511
Lung: Alveolar/bronchiolar Adenoma or Carcinoma				
Overall rate	6/49 (12%)	8/50 (16%)	2/50 (4%)	11/50 (22%)
Adjusted rate	16.0%	18.9%	5.3%	30.3%
Terminal rate	4/34 (12%)	6/39 (15%)	1/31 (3%)	7/31 (23%)
First incidence (days)	647	589	288	625
Life table test	P = 0.101	P = 0.479	P = 0.169N	P = 0.128
Logistic regression test	P = 0.142	P = 0.405	P = 0.112N	P = 0.151
Cochran-Armitage test	P = 0.146			
Fisher exact test		P = 0.403	P = 0.128N	P = 0.154

TABLE B2
Statistical Analysis of Primary Neoplasms in Female Mice in the 2-Year Gavage Study of AZT

	Vehicle Control	30 mg/kg	60 mg/kg	120 mg/kg
Ovary: Cystadenoma				
Overall rate	2/50 (4%)	2/50 (4%)	3/47 (6%)	0/48 (0%)
Adjusted rate	5.9%	4.7%	10.0%	0.0%
Terminal rate	2/34 (6%)	1/39 (3%)	2/28 (7%)	0/29 (0%)
First incidence (days)	731 (T)	617	713	—
Life table test	P = 0.251N	P = 0.648N	P = 0.422	P = 0.274N
Logistic regression test	P = 0.221N	P = 0.691N	P = 0.417	P = 0.274N
Cochran-Armitage test	P = 0.213N			
Fisher exact test		P = 0.691N	P = 0.470	P = 0.258N
Pituitary Gland (Pars Distalis): Adenoma				
Overall rate	2/46 (4%)	5/49 (10%)	1/46 (2%)	0/46 (0%)
Adjusted rate	6.3%	12.1%	3.4%	0.0%
Terminal rate	2/32 (6%)	4/39 (10%)	1/29 (3%)	0/29 (0%)
First incidence (days)	731 (T)	589	731 (T)	—
Life table test	P = 0.093N	P = 0.295	P = 0.535N	P = 0.260N
Logistic regression test	P = 0.077N	P = 0.257	P = 0.535N	P = 0.260N
Cochran-Armitage test	P = 0.073N			
Fisher exact test		P = 0.245	P = 0.500N	P = 0.247N
Stomach (Forestomach): Squamous Cell Papilloma				
Overall rate	3/50 (6%)	3/50 (6%)	1/50 (2%)	1/50 (2%)
Adjusted rate	8.8%	7.7%	3.2%	3.2%
Terminal rate	3/34 (9%)	3/39 (8%)	1/31 (3%)	1/31 (3%)
First incidence (days)	731 (T)	731 (T)	731 (T)	731 (T)
Life table test	P = 0.202N	P = 0.599N	P = 0.338N	P = 0.338N
Logistic regression test	P = 0.202N	P = 0.599N	P = 0.338N	P = 0.338N
Cochran-Armitage test	P = 0.165N			
Fisher exact test		P = 0.661N	P = 0.309N	P = 0.309N
Stomach (Forestomach): Squamous Cell Papilloma or Squamous Cell Carcinoma				
Overall rate	3/50 (6%)	3/50 (6%)	1/50 (2%)	2/50 (4%)
Adjusted rate	8.8%	7.7%	3.2%	5.4%
Terminal rate	3/34 (9%)	3/39 (8%)	1/31 (3%)	1/31 (3%)
First incidence (days)	731 (T)	731 (T)	731 (T)	612
Life table test	P = 0.399N	P = 0.599N	P = 0.338N	P = 0.529N
Logistic regression test	P = 0.351N	P = 0.599N	P = 0.338N	P = 0.498N
Cochran-Armitage test	P = 0.343N			
Fisher exact test		P = 0.661N	P = 0.309N	P = 0.500N
Thyroid Gland (Follicular Cell): Adenoma				
Overall rate	3/49 (6%)	2/50 (4%)	4/50 (8%)	0/50 (0%)
Adjusted rate	8.1%	5.1%	12.9%	0.0%
Terminal rate	2/34 (6%)	2/39 (5%)	4/31 (13%)	0/31 (0%)
First incidence (days)	647	731 (T)	731 (T)	—
Life table test	P = 0.170N	P = 0.446N	P = 0.449	P = 0.134N
Logistic regression test	P = 0.142N	P = 0.475N	P = 0.460	P = 0.118N
Cochran-Armitage test	P = 0.132N			
Fisher exact test		P = 0.490N	P = 0.511	P = 0.117N

TABLE B2
Statistical Analysis of Primary Neoplasms in Female Mice in the 2-Year Gavage Study of AZT

	Vehicle Control	30 mg/kg	60 mg/kg	120 mg/kg
Thyroid Gland (Follicular Cell): Adenoma or Carcinoma				
Overall rate	4/49 (8%)	3/50 (6%)	4/50 (8%)	0/50 (0%)
Adjusted rate	10.7%	7.7%	12.9%	0.0%
Terminal rate	2/34 (6%)	3/39 (8%)	4/31 (13%)	0/31 (0%)
First incidence (days)	647	731 (T)	731 (T)	—
Life table test	P = 0.088N	P = 0.438N	P = 0.586	P = 0.077N
Logistic regression test	P = 0.068N	P = 0.467N	P = 0.603	P = 0.061N
Cochran-Armitage test	P = 0.061N			
Fisher exact test		P = 0.489N	P = 0.631N	P = 0.056N
Vagina: Squamous Cell Carcinoma				
Overall rate	0/50 (0%)	0/49 (0%)	5/45 (11%)	9/49 (18%)
Adjusted rate	0.0%	0.0%	12.8%	26.8%
Terminal rate	0/34 (0%)	0/39 (0%)	1/30 (3%)	7/31 (23%)
First incidence (days)	—	—	493	695
Life table test	P < 0.001	—[f]	P = 0.031	P = 0.002
Logistic regression test	P < 0.001	—	P = 0.028	P = 0.002
Cochran-Armitage test	P < 0.001			
Fisher exact test		—	P = 0.021	P = 0.001
Vagina: Squamous Cell Papilloma or Squamous Cell Carcinoma				
Overall rate	0/50 (0%)	0/49 (0%)	5/45 (11%)	11/49 (22%)
Adjusted rate	0.0%	0.0%	12.8%	32.9%
Terminal rate	0/34 (0%)	0/39 (0%)	1/30 (3%)	9/31 (29%)
First incidence (days)	—	—	493	695
Life table test	P < 0.001	—	P = 0.031	P < 0.001
Logistic regression test	P < 0.001	—	P = 0.028	P < 0.001
Cochran-Armitage test	P < 0.001			
Fisher exact test		—	P = 0.021	P < 0.001
All Organs: Hemangioma or Hemangiosarcoma				
Overall rate	1/50 (2%)	2/50 (4%)	2/50 (4%)	4/50 (8%)
Adjusted rate	2.2%	5.1%	4.7%	9.8%
Terminal rate	0/34 (0%)	2/39 (5%)	0/31 (0%)	0/31 (0%)
First incidence (days)	523	731 (T)	556	601
Life table test	P = 0.109	P = 0.541	P = 0.487	P = 0.189
Logistic regression test	P = 0.119	P = 0.445	P = 0.603	P = 0.189
Cochran-Armitage test	P = 0.113			
Fisher exact test		P = 0.500	P = 0.500	P = 0.181
All Organs: Histiocytic Sarcoma				
Overall rate	2/50 (4%)	1/50 (2%)	3/50 (6%)	1/50 (2%)
Adjusted rate	4.0%	2.0%	8.3%	2.7%
Terminal rate	0/34 (0%)	0/39 (0%)	1/31 (3%)	0/31 (0%)
First incidence (days)	379	527	582	709
Life table test	P = 0.486N	P = 0.488N	P = 0.461	P = 0.499N
Logistic regression test	P = 0.404N	P = 0.319	P = 0.637	P = 0.396N
Cochran-Armitage test	P = 0.474N			
Fisher exact test		P = 0.500N	P = 0.500	P = 0.500N

TABLE B2
Statistical Analysis of Primary Neoplasms in Female Mice in the 2-Year Gavage Study of AZT

	Vehicle Control	30 mg/kg	60 mg/kg	120 mg/kg
All Organs: Malignant Lymphoma				
Overall rate	5/50 (10%)	10/50 (20%)	7/50 (14%)	9/50 (18%)
Adjusted rate	12.6%	24.0%	18.4%	25.3%
Terminal rate	2/34 (6%)	8/39 (21%)	3/31 (10%)	6/31 (19%)
First incidence (days)	603	636	219	625
Life table test	P = 0.203	P = 0.195	P = 0.328	P = 0.180
Logistic regression test	P = 0.268	P = 0.139	P = 0.450	P = 0.194
Cochran-Armitage test	P = 0.265			
Fisher exact test		P = 0.131	P = 0.380	P = 0.194
All Organs: Benign Neoplasms				
Overall rate	30/50 (60%)	33/50 (66%)	26/50 (52%)	31/50 (62%)
Adjusted rate	76.7%	76.6%	69.8%	73.3%
Terminal rate	25/34 (74%)	29/39 (74%)	20/31 (65%)	20/31 (65%)
First incidence (days)	607	589	288	467
Life table test	P = 0.288	P = 0.504N	P = 0.462N	P = 0.362
Logistic regression test	P = 0.535N	P = 0.490	P = 0.414N	P = 0.534
Cochran-Armitage test	P = 0.500N			
Fisher exact test		P = 0.339	P = 0.273N	P = 0.500
All Organs: Malignant Neoplasms				
Overall rate	26/50 (52%)	30/50 (60%)	28/50 (56%)	35/50 (70%)
Adjusted rate	55.8%	62.5%	60.8%	77.4%
Terminal rate	14/34 (41%)	21/39 (54%)	13/31 (42%)	21/31 (68%)
First incidence (days)	379	527	219	556
Life table test	P = 0.044	P = 0.500	P = 0.309	P = 0.071
Logistic regression test	P = 0.031	P = 0.190	P = 0.335	P = 0.051
Cochran-Armitage test	P = 0.051			
Fisher exact test		P = 0.273	P = 0.421	P = 0.050
All Organs: Benign or Malignant Neoplasms				
Overall rate	41/50 (82%)	42/50 (84%)	41/50 (82%)	43/50 (86%)
Adjusted rate	85.3%	87.5%	87.2%	91.4%
Terminal rate	27/34 (79%)	33/39 (85%)	25/31 (81%)	27/31 (87%)
First incidence (days)	379	527	219	467
Life table test	P = 0.161	P = 0.318N	P = 0.345	P = 0.293
Logistic regression test	P = 0.317	P = 0.480	P = 0.535	P = 0.382
Cochran-Armitage test	P = 0.362			
Fisher exact test		P = 0.500	P = 0.602N	P = 0.393

(T)Terminal sacrifice
[a] Number of neoplasm-bearing animals/number of animals examined. Denominator is number of animals examined microscopically for liver, lung, ovary, pituitary gland, thyroid gland, and vagina; 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 incidence are the P values associated with the trend test. Beneath the dosed group incidence are the P values corresponding to pairwise comparisons between the vehicle controls and that 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 Cochran-Armitage and Fisher exact tests compare directly the overall incidence rates. For all tests, a negative trend or a lower incidence in a dose group is indicated by **N**.
[e] Not applicable; no neoplasms in animal group
[f] Value of statistic cannot be computed.

TABLE B3
Historical Incidence of Liver Neoplasms in Water Gavage Vehicle Control Female B6C3F$_1$ Mice[a]

	Incidence in Controls			
	Hepatocellular Adenoma	**Hepatocellular Carcinoma**	**Hepatoblastoma**	**Hepatocellular Adenoma, Hepatocellular Carcinoma, or Hepatoblastoma**
Overall Historical Incidence				
Total	28/366 (7.7%)	16/366 (4.4%)	0/366	43/366 (11.8%)
Standard deviation	9.8%	5.4%		14.2%
Range	2%-29%	0%-16%		2%-43%

[a] Data as of 12 May 1995

TABLE B4
Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 2-Year Gavage Study of AZT[a]

	Vehicle Control	30 mg/kg	60 mg/kg	120 mg/kg
Disposition Summary				
Animals initially in study	50	50	50	50
Early deaths				
Accidental deaths			3	1
Moribund	5	5	9	7
Natural deaths	11	6	7	11
Survivors				
Died last week of study		1		
Terminal sacrifice	34	38	31	31
Animals examined microscopically	50	50	50	50
Alimentary System				
Esophagus	(50)	(49)	(50)	(50)
Necrosis				1 (2%)
Muscularis, inflammation, chronic			1 (2%)	1 (2%)
Intestine large, colon	(46)	(48)	(46)	(45)
Inflammation, chronic			1 (2%)	
Intestine large, cecum	(46)	(47)	(46)	(45)
Hemorrhage				1 (2%)
Inflammation, chronic				1 (2%)
Intestine small, duodenum	(46)	(45)	(46)	(44)
Erosion			1 (2%)	
Intestine small, jejunum	(46)	(46)	(44)	(42)
Peyer's patch, hyperplasia, lymphoid		1 (2%)		
Intestine small, ileum	(46)	(44)	(45)	(42)
Peyer's patch, hyperplasia, lymphoid	1 (2%)			
Liver	(50)	(50)	(50)	(50)
Angiectasis		1 (2%)		
Basophilic focus		1 (2%)		3 (6%)
Clear cell focus	1 (2%)	3 (6%)	1 (2%)	
Eosinophilic focus	6 (12%)	16 (32%)	7 (14%)	7 (14%)
Fibrosis, focal				1 (2%)
Hematopoietic cell proliferation		1 (2%)	1 (2%)	1 (2%)
Hepatodiaphragmatic nodule	1 (2%)			
Inflammation, chronic	1 (2%)	2 (4%)	2 (4%)	1 (2%)
Mixed cell focus	1 (2%)	1 (2%)	5 (10%)	
Necrosis, focal	3 (6%)	3 (6%)	2 (4%)	10 (20%)
Vacuolization cytoplasmic	3 (6%)	4 (8%)	3 (6%)	3 (6%)
Hepatocyte, karyomegaly	1 (2%)	1 (2%)		
Mesentery	(13)	(17)	(8)	(11)
Inflammation, chronic	1 (8%)			1 (9%)
Fat, necrosis	8 (62%)	16 (94%)	5 (63%)	10 (91%)
Pancreas	(50)	(49)	(49)	(48)
Atrophy	1 (2%)	1 (2%)	2 (4%)	1 (2%)
Atrophy, diffuse	1 (2%)			
Inflammation, chronic		2 (4%)		
Necrosis	1 (2%)			
Duct, cyst	2 (4%)	1 (2%)	1 (2%)	1 (2%)

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

TABLE B4
Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 2-Year Gavage Study of AZT

	Vehicle Control	30 mg/kg	60 mg/kg	120 mg/kg
Alimentary System (continued)				
Stomach, forestomach	(49)	(49)	(49)	(49)
Cyst		1 (2%)		
Erosion			1 (2%)	
Hemorrhage			1 (2%)	
Inflammation, chronic		1 (2%)	2 (4%)	
Ulcer		1 (2%)	1 (2%)	
Epithelium, hyperplasia	4 (8%)	9 (18%)	7 (14%)	3 (6%)
Stomach, glandular	(49)	(49)	(48)	(49)
Erosion	1 (2%)	2 (4%)	1 (2%)	1 (2%)
Mineralization	1 (2%)			1 (2%)
Necrosis		1 (2%)		
Glands, degeneration, cystic, focal	1 (2%)	1 (2%)	4 (8%)	4 (8%)
Cardiovascular System				
Heart	(49)	(50)	(50)	(50)
Inflammation, chronic, focal	1 (2%)	4 (8%)	3 (6%)	3 (6%)
Mineralization		1 (2%)	1 (2%)	
Thrombosis				1 (2%)
Endocrine System				
Adrenal cortex	(50)	(49)	(50)	(50)
Accessory adrenal cortical nodule			1 (2%)	
Cyst			1 (2%)	
Cytoplasmic alteration, focal		4 (8%)	4 (8%)	2 (4%)
Hematopoietic cell proliferation				1 (2%)
Hyperplasia, focal	1 (2%)			1 (2%)
Hypertrophy, focal		2 (4%)	1 (2%)	4 (8%)
Islets, pancreatic	(49)	(49)	(50)	(47)
Hyperplasia				2 (4%)
Parathyroid gland	(47)	(45)	(48)	(50)
Cyst			1 (2%)	1 (2%)
Pituitary gland	(46)	(49)	(46)	(46)
Angiectasis	1 (2%)	2 (4%)		1 (2%)
Pars distalis, cyst		1 (2%)		
Pars distalis, cytoplasmic alteration, focal	7 (15%)		1 (2%)	3 (7%)
Pars distalis, hyperplasia, focal	4 (9%)	7 (14%)	6 (13%)	5 (11%)
Pars intermedia, hyperplasia, focal				2 (4%)
Thyroid gland	(49)	(50)	(50)	(50)
Degeneration, cystic, focal	25 (51%)	19 (38%)	23 (46%)	20 (40%)
Follicle, cyst	2 (4%)	6 (12%)	2 (4%)	7 (14%)
Follicular cell, hyperplasia	6 (12%)	11 (22%)	5 (10%)	11 (22%)
General Body System				
None				
Genital System				
Clitoral gland	(49)	(49)	(49)	(48)
Degeneration, cystic	35 (71%)	46 (94%)	33 (67%)	43 (90%)
Inflammation, chronic		1 (2%)	1 (2%)	

TABLE B4
Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 2-Year Gavage Study of AZT

	Vehicle Control	30 mg/kg	60 mg/kg	120 mg/kg
Genital System (continued)				
Ovary	(50)	(50)	(47)	(48)
Angiectasis	1 (2%)			
Cyst	10 (20%)	10 (20%)	5 (11%)	10 (21%)
Hemorrhage	3 (6%)	1 (2%)		1 (2%)
Hyperplasia, tubular			1 (2%)	
Thrombosis			1 (2%)	1 (2%)
Bilateral, cyst				1 (2%)
Uterus	(50)	(50)	(49)	(50)
Cyst	3 (6%)			
Hemorrhage	1 (2%)	2 (4%)	2 (4%)	1 (2%)
Hydrometra	11 (22%)	20 (40%)	22 (45%)	13 (26%)
Inflammation, suppurative	1 (2%)	1 (2%)	1 (2%)	1 (2%)
Thrombosis		1 (2%)	2 (4%)	
Endometrium, hyperplasia, cystic	45 (90%)	45 (90%)	36 (73%)	42 (84%)
Vagina	(50)	(49)	(45)	(49)
Cyst			1 (2%)	
Fibrosis				1 (2%)
Inflammation, suppurative				1 (2%)
Epithelium, hyperplasia		3 (6%)	2 (4%)	7 (14%)
Epithelium, hyperplasia, atypical			2 (4%)	4 (8%)
Hematopoietic System				
Bone marrow	(50)	(49)	(50)	(50)
Angiectasis			1 (2%)	1 (2%)
Hyperplasia	1 (2%)	3 (6%)	3 (6%)	7 (14%)
Necrosis	1 (2%)			
Lymph node	(7)	(5)	(7)	(10)
Bronchial, hyperplasia	1 (14%)			
Iliac, ectasia				1 (10%)
Iliac, hematopoietic cell proliferation			1 (14%)	
Iliac, hemorrhage		1 (20%)		
Iliac, hyperplasia, histiocytic	1 (14%)			
Inguinal, hyperplasia, histiocytic				1 (10%)
Inguinal, hyperplasia, lymphoid		1 (20%)	1 (14%)	2 (20%)
Mediastinal, hemorrhage	1 (14%)	1 (20%)		
Mediastinal, hyperplasia, histiocytic				1 (10%)
Mediastinal, hyperplasia, lymphoid				1 (10%)
Renal, hyperplasia, lymphoid				1 (10%)
Lymph node, mandibular	(50)	(46)	(48)	(48)
Hemorrhage		1 (2%)	1 (2%)	
Hyperplasia, lymphoid		2 (4%)	3 (6%)	6 (13%)
Infiltration cellular, mast cell	1 (2%)		1 (2%)	
Lymph node, mesenteric	(50)	(47)	(48)	(47)
Ectasia		1 (2%)	2 (4%)	
Hematopoietic cell proliferation			1 (2%)	
Hemorrhage	3 (6%)	5 (11%)	2 (4%)	5 (11%)
Hyperplasia, lymphoid		5 (11%)	3 (6%)	5 (11%)
Spleen	(49)	(48)	(49)	(50)
Congestion	1 (2%)		2 (4%)	
Depletion cellular		1 (2%)	3 (6%)	1 (2%)
Hematopoietic cell proliferation	13 (27%)	12 (25%)	10 (20%)	14 (28%)
Hyperplasia, lymphoid	8 (16%)	6 (13%)	2 (4%)	6 (12%)

TABLE B4
Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 2-Year Gavage Study of AZT

	Vehicle Control	30 mg/kg	60 mg/kg	120 mg/kg
Hematopoietic System (continued)				
Thymus	(48)	(46)	(49)	(46)
Angiectasis		1 (2%)		
Cyst			3 (6%)	1 (2%)
Hyperplasia, lymphoid	4 (8%)	1 (2%)	1 (2%)	4 (9%)
Necrosis			2 (4%)	2 (4%)
Integumentary System				
Mammary gland	(47)	(47)	(48)	(47)
Hyperplasia		3 (6%)		1 (2%)
Skin	(50)	(49)	(50)	(50)
Inflammation, chronic, focal	1 (2%)		1 (2%)	
Subcutaneous tissue, cyst epithelial inclusion			1 (2%)	
Subcutaneous tissue, edema	1 (2%)			
Musculoskeletal System				
Bone	(50)	(50)	(50)	(50)
Fibrous osteodystrophy		4 (8%)		
Hyperostosis	37 (74%)	35 (70%)	33 (66%)	37 (74%)
Cranium, fibrous osteodystrophy				1 (2%)
Skeletal muscle	(50)	(50)	(50)	(50)
Hyperplasia, focal, lymphoid			1 (2%)	
Inflammation, suppurative	1 (2%)			
Nervous System				
Brain	(50)	(50)	(50)	(50)
Atrophy, focal	1 (2%)	3 (6%)		
Hemorrhage	1 (2%)			
Vacuolization cytoplasmic	1 (2%)		1 (2%)	
Respiratory System				
Lung	(49)	(50)	(50)	(50)
Congestion		2 (4%)		1 (2%)
Foreign body			1 (2%)	1 (2%)
Hemorrhage	3 (6%)		3 (6%)	1 (2%)
Hyperplasia, histiocytic		2 (4%)	1 (2%)	2 (4%)
Infiltration cellular, mixed cell	1 (2%)			
Pigmentation			1 (2%)	1 (2%)
Alveolar epithelium, hyperplasia	2 (4%)		4 (8%)	1 (2%)
Mediastinum, hemorrhage			1 (2%)	1 (2%)
Mediastinum, inflammation, chronic			2 (4%)	1 (2%)
Mediastinum, necrosis			1 (2%)	
Nose	(50)	(50)	(50)	(50)
Hemorrhage	1 (2%)			
Mucosa, glands, dilatation, focal	1 (2%)	2 (4%)		2 (4%)
Nasolacrimal duct, cyst		1 (2%)		

TABLE B4
Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 2-Year Gavage Study of AZT

	Vehicle Control	30 mg/kg	60 mg/kg	120 mg/kg
Special Senses System				
Eye	(3)			(1)
Cataract	1 (33%)			
Fibrosis	2 (67%)			
Cornea, inflammation, chronic				1 (100%)
Urinary System				
Kidney	(50)	(50)	(50)	(50)
Cyst				1 (2%)
Fibrosis, focal				1 (2%)
Infarct		1 (2%)	2 (4%)	
Metaplasia, focal, osseous	1 (2%)		2 (4%)	
Nephropathy	29 (58%)	30 (60%)	31 (62%)	35 (70%)
Pelvis, dilatation			3 (6%)	3 (6%)
Renal tubule, accumulation, hyaline droplet		1 (2%)		1 (2%)
Renal tubule, dilatation	1 (2%)	1 (2%)	3 (6%)	
Renal tubule, necrosis	1 (2%)			
Renal tubule, pigmentation	2 (4%)	1 (2%)		2 (4%)
Transitional epithelium, hyperplasia	1 (2%)			
Urinary bladder	(50)	(50)	(49)	(49)
Hyperplasia, lymphoid	1 (2%)	1 (2%)		

APPENDIX C
SUMMARY OF LESIONS IN MALE MICE IN THE 2-YEAR SUBCUTANEOUS STUDY OF α-INTERFERON A/D

TABLE C1
Summary of the Incidence of Neoplasms in Male Mice in the 2-Year Subcutaneous Study of α-Interferon A/D[a]

	Vehicle Control	5,000 U α-IFN A	500 U α-IFN A/D	5,000 U α-IFN A/D
Disposition Summary				
Animals initially in study	50	50	50	50
Early deaths				
Accidental death				1
Moribund	13	10	7	10
Natural deaths	10	13	15	11
Survivors				
Terminal sacrifice	27	27	28	28
Animals examined microscopically	50	50	50	50
Alimentary System				
Gallbladder	(45)	(43)	(45)	(48)
Hepatocholangiocarcinoma, metastatic, liver		1 (2%)		
Intestine small, duodenum	(49)		(47)	(49)
Fibrosarcoma, metastatic, mesentery				1 (2%)
Polyp adenomatous			1 (2%)	
Intestine small, jejunum	(49)	(50)	(47)	(49)
Carcinoma	1 (2%)		1 (2%)	1 (2%)
Hepatoblastoma, metastatic, liver	1 (2%)			
Hepatocholangiocarcinoma, metastatic, liver	1 (2%)			
Intestine small, ileum	(49)	(50)	(47)	(49)
Fibrous histiocytoma			1 (2%)	
Hepatoblastoma, metastatic, liver	1 (2%)			
Liver	(50)	(50)	(50)	(50)
Fibrosarcoma, metastatic, mesentery				1 (2%)
Fibrous histiocytoma			1 (2%)	
Hemangioma, multiple				1 (2%)
Hemangiosarcoma	1 (2%)	2 (4%)	1 (2%)	2 (4%)
Hemangiosarcoma, multiple	3 (6%)	2 (4%)	3 (6%)	2 (4%)
Hepatoblastoma	2 (4%)	3 (6%)	1 (2%)	1 (2%)
Hepatocellular carcinoma	10 (20%)	13 (26%)	17 (34%)	10 (20%)
Hepatocellular carcinoma, multiple	8 (16%)	6 (12%)	6 (12%)	4 (8%)
Hepatocellular adenoma	11 (22%)	14 (28%)	10 (20%)	11 (22%)
Hepatocellular adenoma, multiple	3 (6%)	5 (10%)	4 (8%)	5 (10%)
Hepatocholangiocarcinoma	1 (2%)	2 (4%)		1 (2%)
Histiocytic sarcoma		1 (2%)		1 (2%)
Mesentery	(7)	(9)	(5)	(6)
Fibrosarcoma				1 (17%)
Fibrous histiocytoma			1 (20%)	1 (17%)
Hepatocholangiocarcinoma, metastatic, liver	1 (14%)	1 (11%)		1 (17%)
Histiocytic sarcoma		1 (11%)		
Pancreas	(49)	(49)	(49)	(49)
Fibrosarcoma, metastatic, mesentery				1 (2%)
Fibrous histiocytoma, metastatic, mesentery				1 (2%)
Hepatocholangiocarcinoma, metastatic, liver	1 (2%)	1 (2%)		1 (2%)
Salivary glands	(50)	(50)	(50)	(49)
Hepatocholangiocarcinoma, metastatic, liver	1 (2%)			
Stomach, forestomach	(50)		(48)	(49)
Squamous cell papilloma			1 (2%)	
Stomach, glandular	(50)	(50)	(48)	(49)
Adenoma	1 (2%)			
Fibrosarcoma, metastatic, mesentery				1 (2%)
Tooth	(24)		(14)	(24)
Odontoma				1 (4%)

TABLE C1
Summary of the Incidence of Neoplasms in Male Mice in the 2-Year Subcutaneous Study of α-Interferon A/D

	Vehicle Control	5,000 U α-IFN A	500 U α-IFN A/D	5,000 U α-IFN A/D
Cardiovascular System				
Heart	(50)	(50)	(50)	(50)
Hepatoblastoma, metastatic, liver	1 (2%)			
Hepatocholangiocarcinoma, metastatic, liver	1 (2%)	1 (2%)		
Endocrine System				
Adrenal cortex	(50)	(49)	(49)	(50)
Fibrosarcoma, metastatic, mesentery				1 (2%)
Hepatoblastoma, metastatic, liver	1 (2%)			
Bilateral, capsule, adenoma				1 (2%)
Capsule, adenoma	1 (2%)	3 (6%)	1 (2%)	3 (6%)
Adrenal medulla	(49)	(49)	(49)	(50)
Fibrosarcoma, metastatic, mesentery				1 (2%)
Pheochromocytoma benign		1 (2%)	1 (2%)	
Bilateral, pheochromocytoma benign	1 (2%)		1 (2%)	
Islets, pancreatic	(50)		(48)	(50)
Adenoma				1 (2%)
Carcinoma			1 (2%)	
Thyroid gland	(50)	(50)	(49)	(50)
Follicular cell, adenoma	1 (2%)			1 (2%)
General Body System				
Peritoneum			(1)	
Tissue NOS	(1)	(1)	(2)	(1)
Hepatoblastoma, metastatic, liver	1 (100%)			
Genital System				
Epididymis	(50)	(50)	(50)	(50)
Preputial gland	(50)	(50)	(50)	(50)
Adenoma				1 (2%)
Prostate	(49)	(49)	(49)	(50)
Fibrosarcoma, metastatic, mesentery				1 (2%)
Seminal vesicle	(50)	(50)	(50)	(50)
Fibrosarcoma, metastatic, mesentery				1 (2%)
Hepatocholangiocarcinoma, metastatic, liver		1 (2%)		
Testes	(50)		(50)	(50)
Sertoli cell, adenoma			1 (2%)	
Hematopoietic System				
Bone marrow	(50)	(50)	(50)	(50)
Hemangiosarcoma			2 (4%)	
Histiocytic sarcoma		1 (2%)		
Lymph node	(3)	(3)	(3)	(6)
Iliac, fibrous histiocytoma			1 (33%)	
Mediastinal, fibrosarcoma, metastatic, mesentery				1 (17%)
Mediastinal, fibrous histiocytoma			1 (33%)	
Mediastinal, fibrous histiocytoma, metastatic, mesentery				1 (17%)
Mediastinal, hepatocholangiocarcinoma, metastatic, liver	1 (33%)	1 (33%)		1 (17%)
Mediastinal, histiocytic sarcoma		1 (33%)		

TABLE C1
Summary of the Incidence of Neoplasms in Male Mice in the 2-Year Subcutaneous Study of α-Interferon A/D

	Vehicle Control	5,000 U α-IFN A	500 U α-IFN A/D	5,000 U α-IFN A/D
Hematopoietic System (continued)				
Lymph node (continued)	(3)	(3)	(3)	(6)
Pancreatic, hepatocholangiocarcinoma, metastatic, liver		1 (33%)		
Renal, fibrous histiocytoma			1 (33%)	
Lymph node, mandibular	(47)	(45)		
Histiocytic sarcoma		1 (2%)		
Lymph node, mesenteric	(50)	(50)	(48)	(46)
Fibrous histiocytoma, metastatic, mesentery				1 (2%)
Hepatocholangiocarcinoma, metastatic, liver	1 (2%)			
Histiocytic sarcoma		1 (2%)		1 (2%)
Spleen	(49)	(50)	(49)	(49)
Fibrosarcoma, metastatic, mesentery				1 (2%)
Fibrous histiocytoma			1 (2%)	
Hemangiosarcoma			5 (10%)	2 (4%)
Histiocytic sarcoma		1 (2%)		1 (2%)
Thymus	(38)		(38)	(35)
Fibrous histiocytoma			1 (3%)	
Integumentary System				
Skin	(50)	(50)	(49)	(50)
Squamous cell papilloma				1 (2%)
Subcutaneous tissue, hemangioma		1 (2%)		
Subcutaneous tissue, hemangiosarcoma			1 (2%)	
Subcutaneous tissue, hepatoblastoma, metastatic, liver	1 (2%)			
Subcutaneous tissue, histiocytic sarcoma		1 (2%)		
Subcutaneous tissue, sarcoma				1 (2%)
Musculoskeletal System				
Skeletal muscle	(50)	(50)	(50)	(50)
Fibrosarcoma, metastatic, mesentery				1 (2%)
Hepatocholangiocarcinoma, metastatic, liver	1 (2%)	1 (2%)		1 (2%)
Nervous System				
None				
Respiratory System				
Lung	(50)	(50)	(50)	(50)
Alveolar/bronchiolar adenoma	8 (16%)	5 (10%)	10 (20%)	8 (16%)
Alveolar/bronchiolar adenoma, multiple	1 (2%)	1 (2%)	1 (2%)	1 (2%)
Alveolar/bronchiolar carcinoma	4 (8%)	3 (6%)	4 (8%)	3 (6%)
Alveolar/bronchiolar carcinoma, multiple	1 (2%)			
Carcinoma, metastatic, harderian gland		1 (2%)		
Fibrosarcoma, metastatic, mesentery				1 (2%)
Fibrous histiocytoma			1 (2%)	
Hepatoblastoma, metastatic, liver	1 (2%)	2 (4%)		
Hepatocellular carcinoma, metastatic, liver	6 (12%)	7 (14%)	10 (20%)	2 (4%)
Hepatocholangiocarcinoma, metastatic, liver	1 (2%)	2 (4%)		1 (2%)
Histiocytic sarcoma		1 (2%)		1 (2%)

TABLE C1
Summary of the Incidence of Neoplasms in Male Mice in the 2-Year Subcutaneous Study of α-Interferon A/D

	Vehicle Control	5,000 U α-IFN A	500 U α-IFN A/D	5,000 U α-IFN A/D
Respiratory System (continued)				
Lung (continued)	(50)	(50)	(50)	(50)
Mediastinum, fibrosarcoma, metastatic, mesentery				1 (2%)
Mediastinum, fibrous histiocytoma, metastatic, mesentery				1 (2%)
Mediastinum, hepatocholangiocarcinoma, metastatic, liver		1 (2%)		
Nose	(50)	(50)	(50)	(50)
Carcinoma, metastatic, harderian gland	2 (4%)			
Special Senses System				
Harderian gland	(4)	(4)	(6)	(8)
Adenoma	2 (50%)	3 (75%)	5 (83%)	4 (50%)
Carcinoma	2 (50%)	1 (25%)	1 (17%)	1 (13%)
Urinary System				
Kidney	(49)	(50)	(49)	(49)
Fibrous histiocytoma			1 (2%)	
Hemangioma			1 (2%)	
Hepatoblastoma, metastatic, liver	1 (2%)			
Hepatocholangiocarcinoma, metastatic, liver	1 (2%)	1 (2%)		
Histiocytic sarcoma				1 (2%)
Urinary bladder	(49)	(50)	(49)	(50)
Hemangioma		1 (2%)		
Transitional epithelium, papilloma			1 (2%)	
Systemic Lesions				
Multiple organs[b]	(50)	(50)	(50)	(50)
Histiocytic sarcoma		2 (4%)		1 (2%)
Lymphoma malignant	4 (8%)	2 (4%)	2 (4%)	5 (10%)
Mesothelioma malignant			1 (2%)	
Neoplasm Summary				
Total animals with primary neoplasms[c]	42	47	40	41
Total primary neoplasms	66	70	94	75
Total animals with benign neoplasms	22	29	26	28
Total benign neoplasms	29	34	38	39
Total animals with malignant neoplasms	32	30	30	25
Total malignant neoplasms	37	36	56	36
Total animals with metastatic neoplasms	10	11	10	5
Total metastatic neoplasms	26	22	10	24

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

TABLE C2
Statistical Analysis of Primary Neoplasms in Male Mice in the 2-Year Subcutaneous Study of α-Interferon A/D

	Vehicle Control	5,000 U α-IFN A	500 U α-IFN A/D	5,000 U α-IFN A/D
Adrenal Cortex: Adenoma				
Overall rate[a]	1/50 (2%)	3/49 (6%)	1/49 (2%)	4/50 (8%)
Adjusted rate[b]	3.7%	10.9%	3.6%	12.8%
Terminal rate[c]	1/27 (4%)	2/26 (8%)	1/28 (4%)	3/28 (11%)
First incidence (days)	728 (T)	723	728 (T)	572
Life table test[d]	P = 0.093	P = 0.302	P = 0.754N	P = 0.185
Logistic regression test[d]	P = 0.088	P = 0.312	P = 0.754N	P = 0.170
Cochran-Armitage test[d]	P = 0.092			
Fisher exact test[d]		P = 0.301	P = 0.747	P = 0.181
Harderian Gland: Adenoma				
Overall rate	2/50 (4%)	3/50 (6%)	5/50 (10%)	4/50 (8%)
Adjusted rate	7.4%	9.5%	17.0%	12.8%
Terminal rate	2/27 (7%)	2/27 (7%)	4/28 (14%)	3/28 (11%)
First incidence (days)	728 (T)	567	661	583
Life table test	P = 0.503	P = 0.496	P = 0.220	P = 0.345
Logistic regression test	P = 0.491	P = 0.505	P = 0.190	P = 0.321
Cochran-Armitage test	P = 0.495			
Fisher exact test		P = 0.500	P = 0.218	P = 0.339
Harderian Gland: Adenoma or Carcinoma				
Overall rate	4/50 (8%)	4/50 (8%)	6/50 (12%)	5/50 (10%)
Adjusted rate	12.6%	11.8%	20.4%	16.3%
Terminal rate	2/27 (7%)	2/27 (7%)	5/28 (18%)	4/28 (14%)
First incidence (days)	671	567	661	583
Life table test	P = 0.592	P = 0.638N	P = 0.353	P = 0.500
Logistic regression test	P = 0.578	P = 0.643N	P = 0.328	P = 0.480
Cochran-Armitage test	P = 0.584			
Fisher exact test		P = 0.643N	P = 0.370	P = 0.500
Liver: Hemangiosarcoma				
Overall rate	4/50 (8%)	4/50 (8%)	4/50 (8%)	4/50 (8%)
Adjusted rate	11.5%	11.7%	11.6%	11.5%
Terminal rate	1/27 (4%)	2/27 (7%)	1/28 (4%)	2/28 (7%)
First incidence (days)	503	532	615	571
Life table test	P = 0.606	P = 0.629N	P = 0.609	P = 0.630
Logistic regression test	P = 0.604N	P = 0.630	P = 0.624N	P = 0.625N
Cochran-Armitage test	P = 0.618			
Fisher exact test		P = 0.643N	P = 0.643N	P = 0.643N
Liver: Hepatocellular Adenoma				
Overall rate	14/50 (28%)	19/50 (38%)	14/50 (28%)	16/50 (32%)
Adjusted rate	43.3%	55.6%	45.5%	48.3%
Terminal rate	10/27 (37%)	13/27 (48%)	12/28 (43%)	12/28 (43%)
First incidence (days)	503	547	540	556
Life table test	P = 0.390	P = 0.208	P = 0.579N	P = 0.430
Logistic regression test	P = 0.351	P = 0.205	P = 0.521	P = 0.374
Cochran-Armitage test	P = 0.372			
Fisher exact test		P = 0.198	P = 0.588N	P = 0.414

TABLE C2
Statistical Analysis of Primary Neoplasms in Male Mice in the 2-Year Subcutaneous Study of α-Interferon A/D

	Vehicle Control	5,000 U α-IFN A	500 U α-IFN A/D	5,000 U α-IFN A/D
Liver: Hepatocellular Carcinoma				
Overall rate	18/50 (36%)	19/50 (38%)	23/50 (46%)	14/50 (28%)
Adjusted rate	45.4%	47.2%	57.3%	40.8%
Terminal rate	7/27 (26%)	8/27 (30%)	12/28 (43%)	9/28 (32%)
First incidence (days)	586	524	405	585
Life table test	P = 0.133N	P = 0.519	P = 0.200	P = 0.308N
Logistic regression test	P = 0.102N	P = 0.469	P = 0.218	P = 0.453N
Cochran-Armitage test	P = 0.099N			
Fisher exact test		P = 0.500	P = 0.208	P = 0.260N
Liver: Hepatocellular Adenoma or Carcinoma				
Overall rate	28/50 (56%)	33/50 (66%)	30/50 (60%)	26/50 (52%)
Adjusted rate	67.1%	79.4%	73.9%	70.9%
Terminal rate	14/27 (52%)	19/27 (70%)	18/28 (64%)	18/28 (64%)
First incidence (days)	503	524	405	556
Life table test	P = 0.335N	P = 0.282	P = 0.386	P = 0.447N
Logistic regression test	P = 0.334N	P = 0.209	P = 0.404	P = 0.469N
Cochran-Armitage test	P = 0.311N			
Fisher exact test		P = 0.206	P = 0.420	P = 0.421N
Liver: Hepatoblastoma				
Overall rate	2/50 (4%)	3/50 (6%)	1/50 (2%)	1/50 (2%)
Adjusted rate	5.8%	10.6%	3.4%	3.6%
Terminal rate	1/27 (4%)	2/27 (7%)	0/28 (0%)	1/28 (4%)
First incidence (days)	566	723	720	728 (T)
Life table test	P = 0.530N	P = 0.503	P = 0.503N	P = 0.499N
Logistic regression test	P = 0.542N	P = 0.505	P = 0.499N	P = 0.501N
Cochran-Armitage test	P = 0.537N			
Fisher exact test		P = 0.500	P = 0.500N	P = 0.500N
Liver: Hepatocellular Carcinoma or Hepatoblastoma				
Overall rate	20/50 (40%)	21/50 (42%)	24/50 (48%)	15/50 (30%)
Adjusted rate	49.2%	51.7%	58.7%	43.9%
Terminal rate	8/27 (30%)	9/27 (33%)	12/28 (43%)	10/28 (36%)
First incidence (days)	566	524	405	585
Life table test	P = 0.114N	P = 0.519	P = 0.257	P = 0.251N
Logistic regression test	P = 0.083N	P = 0.486	P = 0.284	P = 0.329N
Cochran-Armitage test	P = 0.080N			
Fisher exact test		P = 0.500	P = 0.273	P = 0.201N
Liver: Hepatocellular Adenoma, Hepatocellular Carcinoma, or Hepatoblastoma				
Overall rate	30/50 (60%)	34/50 (68%)	31/50 (62%)	26/50 (52%)
Adjusted rate	70.3%	80.1%	74.8%	70.9%
Terminal rate	15/27 (56%)	19/27 (70%)	18/28 (64%)	18/28 (64%)
First incidence (days)	503	524	405	556
Life table test	P = 0.236N	P = 0.341	P = 0.448	P = 0.322N
Logistic regression test	P = 0.211N	P = 0.269	P = 0.484	P = 0.311N
Cochran-Armitage test	P = 0.194N			
Fisher exact test		P = 0.266	P = 0.500	P = 0.273N

TABLE C2
Statistical Analysis of Primary Neoplasms in Male Mice in the 2-Year Subcutaneous Study of α-Interferon A/D

	Vehicle Control	5,000 U α-IFN A	500 U α-IFN A/D	5,000 U α-IFN A/D
Lung: Alveolar/bronchiolar Adenoma				
Overall rate	9/50 (18%)	6/50 (12%)	11/50 (22%)	9/50 (18%)
Adjusted rate	30.1%	20.5%	31.6%	29.6%
Terminal rate	7/27 (26%)	5/27 (19%)	6/28 (21%)	7/28 (25%)
First incidence (days)	603	591	540	656
Life table test	P = 0.481N	P = 0.287N	P = 0.391	P = 0.590N
Logistic regression test	P = 0.498N	P = 0.270N	P = 0.364	P = 0.577
Cochran-Armitage test	P = 0.485N			
Fisher exact test		P = 0.288N	P = 0.402	P = 0.602N
Lung: Alveolar/bronchiolar Carcinoma				
Overall rate	5/50 (10%)	3/50 (6%)	4/50 (8%)	3/50 (6%)
Adjusted rate	15.4%	9.5%	12.5%	10.0%
Terminal rate	3/27 (11%)	2/27 (7%)	2/28 (7%)	2/28 (7%)
First incidence (days)	469	567	622	689
Life table test	P = 0.353N	P = 0.358N	P = 0.517N	P = 0.348N
Logistic regression test	P = 0.363N	P = 0.363N	P = 0.501N	P = 0.366N
Cochran-Armitage test	P = 0.356N			
Fisher exact test		P = 0.357N	P = 0.500N	P = 0.357N
Lung: Alveolar/bronchiolar Adenoma or Carcinoma				
Overall rate	13/50 (26%)	9/50 (18%)	12/50 (24%)	11/50 (22%)
Adjusted rate	40.1%	29.3%	34.7%	35.0%
Terminal rate	9/27 (33%)	7/27 (26%)	7/28 (25%)	8/28 (29%)
First incidence (days)	469	567	540	656
Life table test	P = 0.401N	P = 0.237N	P = 0.516N	P = 0.393N
Logistic regression test	P = 0.423N	P = 0.226N	P = 0.532N	P = 0.445N
Cochran-Armitage test	P = 0.408N			
Fisher exact test		P = 0.235N	P = 0.500N	P = 0.408N
Spleen: Hemangiosarcoma				
Overall rate	0/49 (0%)	0/50 (0%)	5/49 (10%)	2/49 (4%)
Adjusted rate	0.0%	0.0%	15.5%	6.0%
Terminal rate	0/27 (0%)	0/27 (0%)	3/28 (11%)	1/28 (4%)
First incidence (days)	—[e]	—	615	587
Life table test	P = 0.632N	—[f]	P = 0.033	P = 0.233
Logistic regression test	P = 0.631N	—	P = 0.031	P = 0.242
Cochran-Armitage test	P = 0.629N			
Fisher exact test		—	P = 0.028	P = 0.247
All Organs: Hemangiosarcoma				
Overall rate	4/50 (8%)	4/50 (8%)	6/50 (12%)	4/50 (8%)
Adjusted rate	11.5%	11.7%	18.2%	11.5%
Terminal rate	1/27 (4%)	2/27 (7%)	3/28 (11%)	2/28 (7%)
First incidence (days)	503	532	615	571
Life table test	P = 0.486N	P = 0.629N	P = 0.352	P = 0.630
Logistic regression test	P = 0.475N	P = 0.630	P = 0.373	P = 0.625N
Cochran-Armitage test	P = 0.479N			
Fisher exact test		P = 0.643N	P = 0.370	P = 0.643N

TABLE C2
Statistical Analysis of Primary Neoplasms in Male Mice in the 2-Year Subcutaneous Study of α-Interferon A/D

	Vehicle Control	5,000 U α-IFN A	500 U α-IFN A/D	5,000 U α-IFN A/D
All Organs: Hemangioma or Hemangiosarcoma				
Overall rate	4/50 (8%)	5/50 (10%)	7/50 (14%)	5/50 (10%)
Adjusted rate	11.5%	13.6%	21.5%	14.9%
Terminal rate	1/27 (4%)	2/27 (7%)	4/28 (14%)	3/28 (11%)
First incidence (days)	503	532	615	571
Life table test	P = 0.568N	P = 0.507	P = 0.253	P = 0.494
Logistic regression test	P = 0.569N	P = 0.475	P = 0.258	P = 0.512
Cochran-Armitage test	P = 0.566N			
Fisher exact test		P = 0.500	P = 0.262	P = 0.500
All Organs: Malignant Lymphoma				
Overall rate	4/50 (8%)	2/50 (4%)	2/50 (4%)	5/50 (10%)
Adjusted rate	11.8%	7.1%	7.1%	16.3%
Terminal rate	2/27 (7%)	1/27 (4%)	2/28 (7%)	3/28 (11%)
First incidence (days)	603	725	728 (T)	656
Life table test	P = 0.314	P = 0.343N	P = 0.351N	P = 0.494
Logistic regression test	P = 0.302	P = 0.334N	P = 0.353N	P = 0.482
Cochran-Armitage test	P = 0.309			
Fisher exact test		P = 0.339N	P = 0.339N	P = 0.500
All Organs: Benign Neoplasms				
Overall rate	22/50 (44%)	29/50 (58%)	26/50 (52%)	28/50 (56%)
Adjusted rate	63.7%	79.5%	73.8%	76.8%
Terminal rate	15/27 (56%)	20/27 (74%)	19/28 (68%)	20/28 (71%)
First incidence (days)	503	547	540	556
Life table test	P = 0.230	P = 0.136	P = 0.273	P = 0.184
Logistic regression test	P = 0.166	P = 0.119	P = 0.166	P = 0.110
Cochran-Armitage test	P = 0.203			
Fisher exact test		P = 0.115	P = 0.274	P = 0.159
All Organs: Malignant Neoplasms				
Overall rate	32/50 (64%)	30/50 (60%)	30/50 (60%)	25/50 (50%)
Adjusted rate	69.1%	65.8%	69.2%	62.7%
Terminal rate	13/27 (48%)	12/27 (44%)	15/28 (54%)	14/28 (50%)
First incidence (days)	469	524	405	435
Life table test	P = 0.173N	P = 0.420N	P = 0.514N	P = 0.199N
Logistic regression test	P = 0.101N	P = 0.390N	P = 0.391N	P = 0.114N
Cochran-Armitage test	P = 0.102N			
Fisher exact test		P = 0.418N	P = 0.418N	P = 0.113N

TABLE C2
Statistical Analysis of Primary Neoplasms in Male Mice in the 2-Year Subcutaneous Study of α-Interferon A/D

	Vehicle Control	5,000 U α-IFN A	500 U α-IFN A/D	5,000 U α-IFN A/D
All Organs: Benign or Malignant Neoplasms				
Overall rate	42/50 (84%)	47/50 (94%)	40/50 (80%)	41/50 (82%)
Adjusted rate	89.3%	95.9%	90.7%	93.0%
Terminal rate	22/27 (81%)	25/27 (93%)	24/28 (86%)	25/28 (89%)
First incidence (days)	469	524	405	435
Life table test	P = 0.525N	P = 0.304	P = 0.497N	P = 0.509N
Logistic regression test	P = 0.539	P = 0.103	P = 0.456N	P = 0.588N
Cochran-Armitage test	P = 0.566N			
Fisher exact test		P = 0.100	P = 0.398N	P = 0.500N

(T)Terminal sacrifice
[a] Number of neoplasm-bearing animals/number of animals examined. Denominator is number of animals examined microscopically for adrenal gland, liver, lung, and spleen; 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 incidence are the P values associated with the trend test (the α-IFN A group was excluded from the trend test). Beneath the dosed group incidence are the P values corresponding to pairwise comparisons between the vehicle controls and that 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 Cochran-Armitage and Fisher exact tests compare directly the overall incidence rates. For all tests, a negative trend or a lower incidence in a dosed group is indicated by **N**.
[e] Not applicable; no neoplasms in animal group
[f] Value of statistic cannot be computed.

TABLE C3
Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the 2-Year Subcutaneous Study of α-Interferon A/D[a]

	Vehicle Control	5,000 U α-IFN A	500 U α-IFN A/D	5,000 U α-IFN A/D
Disposition Summary				
Animals initially in study	50	50	50	50
Early deaths				
Accidental death				1
Moribund	13	10	7	10
Natural deaths	10	13	15	11
Survivors				
Terminal sacrifice	27	27	28	28
Animals examined microscopically	50	50	50	50
Alimentary System				
Gallbladder	(45)		(45)	(48)
Inflammation, chronic				1 (2%)
Intestine large, cecum	(49)	(50)	(49)	(49)
Congestion	1 (2%)		1 (2%)	
Liver	(50)	(50)	(50)	(50)
Angiectasis	1 (2%)	1 (2%)	1 (2%)	1 (2%)
Basophilic focus		1 (2%)	1 (2%)	2 (4%)
Clear cell focus	1 (2%)	2 (4%)	1 (2%)	6 (12%)
Congestion				1 (2%)
Eosinophilic focus	9 (18%)	5 (10%)	3 (6%)	4 (8%)
Hematopoietic cell proliferation	1 (2%)			
Infarct	1 (2%)			
Inflammation, chronic	15 (30%)	20 (40%)	17 (34%)	18 (36%)
Mixed cell focus	1 (2%)	2 (4%)		4 (8%)
Necrosis, focal	4 (8%)	7 (14%)	1 (2%)	5 (10%)
Pigmentation, focal	2 (4%)	3 (6%)		1 (2%)
Vacuolization cytoplasmic	1 (2%)	1 (2%)	2 (4%)	
Bile duct, cyst			1 (2%)	
Bile duct, hyperplasia	8 (16%)	7 (14%)	9 (18%)	8 (16%)
Centrilobular, necrosis		1 (2%)		
Hepatocyte, karyomegaly	12 (24%)	12 (24%)	14 (28%)	8 (16%)
Mesentery	(7)	(9)	(5)	(6)
Angiectasis	1 (14%)		1 (20%)	
Inflammation, chronic	1 (14%)	3 (33%)	1 (20%)	2 (33%)
Artery, inflammation, chronic	2 (29%)	4 (44%)		1 (17%)
Fat, necrosis	1 (14%)			
Pancreas	(49)	(49)	(49)	(49)
Duct, cyst		1 (2%)		
Inflammation, chronic			1 (2%)	1 (2%)
Acinus, atrophy, diffuse				2 (4%)
Stomach, forestomach	(50)	(50)	(48)	(49)
Diverticulum	1 (2%)		1 (2%)	1 (2%)
Erosion	2 (4%)	2 (4%)		2 (4%)
Inflammation, chronic	3 (6%)	1 (2%)	2 (4%)	4 (8%)
Epithelium, cyst				1 (2%)
Epithelium, hyperplasia	5 (10%)	2 (4%)	3 (6%)	5 (10%)
Muscularis, serosa, inflammation, suppurative				1 (2%)

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

TABLE C3
Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the 2-Year Subcutaneous Study of α-Interferon A/D

	Vehicle Control	5,000 U α-IFN A	500 U α-IFN A/D	5,000 U α-IFN A/D
Alimentary System (continued)				
Stomach, glandular	(50)	(50)	(48)	(49)
Erosion		1 (2%)		2 (4%)
Inflammation, chronic				2 (4%)
Metaplasia, hepatocyte	1 (2%)			1 (2%)
Mineralization				1 (2%)
Pigmentation, focal		3 (6%)	1 (2%)	2 (4%)
Epithelium, hyperplasia				2 (4%)
Glands, degeneration, cystic, focal	2 (4%)		2 (4%)	1 (2%)
Muscularis, serosa, inflammation, suppurative				1 (2%)
Tooth	(24)	(20)	(14)	(24)
Developmental malformation	24 (100%)	20 (100%)	14 (100%)	24 (100%)
Inflammation, chronic, suppurative	1 (4%)			
Cardiovascular System				
Blood vessel	(50)	(50)	(50)	(48)
Mineralization	1 (2%)			
Heart	(50)	(50)	(50)	(50)
Mineralization	1 (2%)			
Thrombosis	1 (2%)	1 (2%)	1 (2%)	
Artery, inflammation, chronic	1 (2%)			1 (2%)
Endocrine System				
Adrenal cortex	(50)	(49)	(49)	(50)
Accessory adrenal cortical nodule	1 (2%)		1 (2%)	1 (2%)
Angiectasis	1 (2%)			
Cyst	1 (2%)			1 (2%)
Cytoplasmic alteration, focal	3 (6%)	1 (2%)	2 (4%)	5 (10%)
Hyperplasia, focal	1 (2%)			1 (2%)
Inflammation, chronic, focal	1 (2%)			
Capsule, hyperplasia, focal	3 (6%)	6 (12%)	10 (20%)	3 (6%)
Adrenal medulla	(49)	(49)	(49)	(50)
Hyperplasia	6 (12%)	3 (6%)	1 (2%)	1 (2%)
Islets, pancreatic	(50)	(50)	(48)	(50)
Hyperplasia	1 (2%)			
Parathyroid gland	(49)	(43)	(41)	(45)
Cyst	1 (2%)	1 (2%)		2 (4%)
Pituitary gland	(45)	(41)	(47)	(47)
Pars distalis, cyst	2 (4%)	1 (2%)	1 (2%)	2 (4%)
Pars distalis, cytoplasmic alteration, focal		1 (2%)	1 (2%)	1 (2%)
Pars distalis, hyperplasia, focal			1 (2%)	
Thyroid gland	(50)	(50)	(49)	(50)
Degeneration, cystic, focal	3 (6%)	4 (8%)	3 (6%)	7 (14%)
Inflammation, chronic, focal				1 (2%)
C-cell, hyperplasia	1 (2%)			
Follicle, cyst			1 (2%)	1 (2%)
Follicular cell, hyperplasia	7 (14%)	8 (16%)	6 (12%)	11 (22%)
General Body System				
None				

TABLE C3
Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the 2-Year Subcutaneous Study of α-Interferon A/D

	Vehicle Control	5,000 U α-IFN A	500 U α-IFN A/D	5,000 U α-IFN A/D
Genital System				
Coagulating gland				(2)
Inflammation, chronic				1 (50%)
Epididymis	(50)	(50)	(50)	(50)
Granuloma sperm		1 (2%)	1 (2%)	
Inflammation, chronic				1 (2%)
Mineralization, focal	1 (2%)			
Spermatocele			1 (2%)	1 (2%)
Preputial gland	(50)	(50)	(50)	(50)
Degeneration, cystic	17 (34%)	11 (22%)	16 (32%)	14 (28%)
Inflammation, chronic	2 (4%)	5 (10%)	3 (6%)	6 (12%)
Prostate	(49)	(49)	(49)	(50)
Inflammation, chronic, focal	2 (4%)		2 (4%)	4 (8%)
Epithelium, hyperplasia, focal			1 (2%)	
Seminal vesicle	(50)		(50)	(50)
Inflammation, chronic			1 (2%)	1 (2%)
Testes	(50)	(50)	(50)	(50)
Cyst				1 (2%)
Germinal epithelium, degeneration		1 (2%)		
Mineralization, focal				2 (4%)
Hematopoietic System				
Bone marrow	(50)	(50)	(50)	(50)
Angiectasis			1 (2%)	
Hyperplasia		1 (2%)		2 (4%)
Hyperplasia, focal, histiocytic			1 (2%)	
Lymph node	(3)	(3)	(3)	(6)
Iliac, hyperplasia		1 (33%)		
Inguinal, hyperplasia		1 (33%)		1 (17%)
Inguinal, hyperplasia, lymphoid				1 (17%)
Inguinal, pigmentation		1 (33%)		
Lymph node, mandibular	(47)	(45)	(46)	(45)
Hyperplasia	1 (2%)			1 (2%)
Lymph node, mesenteric	(50)	(50)	(48)	(46)
Angiectasis	3 (6%)	1 (2%)	2 (4%)	1 (2%)
Hematopoietic cell proliferation	2 (4%)	5 (10%)	3 (6%)	3 (7%)
Hemorrhage	13 (26%)	12 (24%)	9 (19%)	15 (33%)
Hyperplasia, histiocytic			1 (2%)	
Hyperplasia, lymphoid	1 (2%)	4 (8%)	2 (4%)	4 (9%)
Spleen	(49)	(50)	(49)	(49)
Angiectasis			1 (2%)	
Hematopoietic cell proliferation	21 (43%)	15 (30%)	19 (39%)	16 (33%)
Hemorrhage		1 (2%)		
Hyperplasia, lymphoid		1 (2%)	1 (2%)	
Thymus	(38)	(39)	(38)	(35)
Cyst	2 (5%)	2 (5%)	5 (13%)	4 (11%)

TABLE C3
Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the 2-Year Subcutaneous Study of α-Interferon A/D

	Vehicle Control	5,000 U α-IFN A	500 U α-IFN A/D	5,000 U α-IFN A/D
Integumentary System				
Skin	(50)	(50)	(49)	(50)
Cyst epithelial inclusion		1 (2%)		
Inflammation, chronic, focal				1 (2%)
Artery, subcutaneous tissue, inflammation, chronic	1 (2%)			
Hair follicle, atrophy				2 (4%)
Subcutaneous tissue, angiectasis, focal		1 (2%)		
Subcutaneous tissue, edema	2 (4%)	1 (2%)	3 (6%)	
Subcutaneous tissue, inflammation, chronic, focal				1 (2%)
Musculoskeletal System				
Bone	(50)	(50)	(50)	(50)
Fracture	1 (2%)			
Hyperostosis	1 (2%)			
Skeletal muscle	(50)		(50)	(50)
Hemorrhage, focal				1 (2%)
Inflammation, suppurative				1 (2%)
Nervous System				
Spinal cord	(1)	(2)	(2)	(4)
Hemorrhage, focal		1 (50%)		1 (25%)
Respiratory System				
Lung	(50)	(50)	(50)	(50)
Hemorrhage	1 (2%)	2 (4%)	2 (4%)	
Hyperplasia, histiocytic	4 (8%)	2 (4%)	2 (4%)	1 (2%)
Hyperplasia, lymphoid	1 (2%)			
Infiltration cellular, mixed cell			1 (2%)	
Inflammation, chronic	1 (2%)			
Thrombosis	1 (2%)			
Alveolar epithelium, hyperplasia	1 (2%)	2 (4%)	1 (2%)	
Bronchus, glands, cyst		1 (2%)		3 (6%)
Mediastinum, hemorrhage		1 (2%)		
Nose	(50)	(50)	(50)	(50)
Inflammation, suppurative	1 (2%)	1 (2%)	1 (2%)	2 (4%)
Mucosa, polyp, inflammatory	2 (4%)	2 (4%)		
Mucosa, glands, dilatation, focal	25 (50%)	26 (52%)	24 (48%)	26 (52%)
Nasolacrimal duct, cyst	1 (2%)			
Nasolacrimal duct, dilatation				1 (2%)
Nasopharyngeal duct, hyperplasia, focal			1 (2%)	
Special Senses System				
Harderian gland	(4)	(4)	(6)	(8)
Degeneration, cystic, focal				1 (13%)
Hyperplasia, focal				1 (13%)
Inflammation, chronic, focal	1 (25%)			1 (13%)

TABLE C3
Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the 2-Year Subcutaneous Study of α-Interferon A/D

	Vehicle Control	5,000 U α-IFN A	500 U α-IFN A/D	5,000 U α-IFN A/D
Urinary System				
Kidney	(49)	(50)	(49)	(49)
Congestion	1 (2%)	1 (2%)		
Cyst	1 (2%)			
Infarct			2 (4%)	2 (4%)
Metaplasia, focal, osseous	2 (4%)		4 (8%)	
Nephropathy	46 (94%)	49 (98%)	44 (90%)	46 (94%)
Artery, inflammation, chronic	1 (2%)			
Pelvis, dilatation		1 (2%)	2 (4%)	3 (6%)
Renal tubule, dilatation	1 (2%)	3 (6%)	2 (4%)	
Renal tubule, pigmentation	1 (2%)	2 (4%)		
Urethra	(9)	(15)	(14)	(16)
Inflammation, chronic	2 (22%)	2 (13%)	6 (43%)	4 (25%)

APPENDIX D
SUMMARY OF LESIONS IN FEMALE MICE IN THE 2-YEAR SUBCUTANEOUS STUDY OF α-INTERFERON A/D

TABLE D1
Summary of the Incidence of Neoplasms in Female Mice in the 2-Year Subcutaneous Study of α-Interferon A/D[a]

	Vehicle Control	5,000 U α-IFN A	500 U α-IFN A/D	5,000 U α-IFN A/D
Disposition Summary				
Animals initially in study	50	50	50	50
Early deaths				
Accidental death				1
Moribund	13	11	13	9
Natural deaths	12	8	5	15
Survivors				
Terminal sacrifice	25	31	32	25
Animals examined microscopically	50	50	50	50
Alimentary System				
Gallbladder	(45)	(49)	(50)	(48)
Intestine large, colon	(47)		(50)	(50)
Intestine large, cecum	(48)	(49)	(50)	(50)
Liposarcoma, metastatic, mesentery	1 (2%)			
Intestine small, duodenum	(47)		(50)	(49)
Intestine small, jejunum	(47)	(48)	(50)	(49)
Histiocytic sarcoma	1 (2%)			
Intestine small, ileum	(47)	(48)	(50)	(49)
Histiocytic sarcoma	1 (2%)			
Liver	(49)	(50)	(50)	(50)
Carcinoma, metastatic, harderian gland	1 (2%)			
Fibrosarcoma, metastatic, mesentery		1 (2%)		
Hemangioma	1 (2%)			
Hemangiosarcoma				1 (2%)
Hemangiosarcoma, multiple		1 (2%)	1 (2%)	
Hepatocellular carcinoma	9 (18%)	12 (24%)	10 (20%)	10 (20%)
Hepatocellular carcinoma, multiple	7 (14%)	6 (12%)	2 (4%)	3 (6%)
Hepatocellular adenoma	12 (24%)	13 (26%)	16 (32%)	12 (24%)
Hepatocellular adenoma, multiple	12 (24%)	9 (18%)	9 (18%)	10 (20%)
Hepatocholangiocarcinoma	1 (2%)			
Histiocytic sarcoma	1 (2%)	1 (2%)	1 (2%)	1 (2%)
Liposarcoma, metastatic, mesentery	1 (2%)			
Mast cell tumor malignant, metastatic, uncertain primary site				1 (2%)
Plasma cell tumor malignant, metastatic, spleen			1 (2%)	
Mesentery	(21)	(16)	(21)	(18)
Carcinoma, metastatic, harderian gland	1 (5%)			
Fibrosarcoma		1 (6%)		
Fibrosarcoma, metastatic, skin	1 (5%)	1 (6%)		
Fibrosarcoma, metastatic, tissue NOS			1 (5%)	
Hemangiosarcoma		1 (6%)		
Hepatocellular carcinoma, metastatic, liver	1 (5%)			
Histiocytic sarcoma	1 (5%)		1 (5%)	
Liposarcoma	1 (5%)			
Mast cell tumor malignant, metastatic, uncertain primary site				1 (6%)

TABLE D1
Summary of the Incidence of Neoplasms in Female Mice in the 2-Year Subcutaneous Study of α-Interferon A/D

	Vehicle Control	5,000 U α-IFN A	500 U α-IFN A/D	5,000 U α-IFN A/D
Alimentary System (continued)				
Pancreas	(48)	(50)	(50)	(50)
Fibrosarcoma, metastatic, skin	1 (2%)			
Fibrosarcoma, metastatic, tissue NOS			1 (2%)	
Liposarcoma, metastatic, mesentery	1 (2%)			
Mast cell tumor malignant, metastatic, uncertain primary site				1 (2%)
Acinus, adenoma	1 (2%)			
Salivary glands	(50)	(49)	(50)	(48)
Mast cell tumor malignant, metastatic, uncertain primary site				1 (2%)
Stomach, forestomach	(48)	(46)	(50)	(50)
Liposarcoma, metastatic, mesentery	1 (2%)			
Mast cell tumor malignant, metastatic, uncertain primary site				1 (2%)
Squamous cell papilloma			2 (4%)	
Stomach, glandular	(48)	(46)	(50)	(50)
Hepatocellular carcinoma, metastatic, liver	1 (2%)			
Liposarcoma, metastatic, mesentery	1 (2%)			
Mast cell tumor malignant, metastatic, uncertain primary site				1 (2%)
Cardiovascular System				
Heart	(50)	(50)	(50)	(50)
Carcinoma, metastatic, harderian gland	1 (2%)			
Endocrine System				
Adrenal cortex	(50)	(49)	(49)	(50)
Adenoma			1 (2%)	
Hepatocellular carcinoma, metastatic, liver			1 (2%)	
Capsule, adenoma	1 (2%)			
Adrenal medulla	(50)	(49)	(49)	(50)
Pheochromocytoma malignant	1 (2%)			1 (2%)
Pheochromocytoma benign				1 (2%)
Islets, pancreatic	(48)	(50)		
Adenoma		1 (2%)		
Pituitary gland	(46)	(43)	(47)	(44)
Pars distalis, adenoma	11 (24%)	5 (12%)	8 (17%)	7 (16%)
Pars intermedia, adenoma			1 (2%)	
Thyroid gland	(50)	(50)	(50)	(49)
Carcinoma, metastatic, harderian gland	1 (2%)			
Follicular cell, adenoma	5 (10%)	4 (8%)	3 (6%)	2 (4%)
General Body System				
Peritoneum	(2)			(1)
Fibrosarcoma, metastatic, skin	1 (50%)			
Tissue NOS	(1)		(1)	(2)
Abdominal, fibrosarcoma			1 (100%)	

TABLE D1
Summary of the Incidence of Neoplasms in Female Mice in the 2-Year Subcutaneous Study of α-Interferon A/D

	Vehicle Control	5,000 U α-IFN A	500 U α-IFN A/D	5,000 U α-IFN A/D
Genital System				
Clitoral gland	(48)	(49)	(49)	(47)
Hemangioma				1 (2%)
Ovary	(46)	(48)	(48)	(49)
Carcinoma, metastatic, harderian gland	1 (2%)			
Cystadenoma	4 (9%)	1 (2%)	2 (4%)	
Granulosa cell tumor benign	1 (2%)			
Hemangiosarcoma		1 (2%)		
Histiocytic sarcoma			1 (2%)	
Liposarcoma, metastatic, mesentery	1 (2%)			
Teratoma benign	1 (2%)			1 (2%)
Uterus	(50)	(50)	(50)	(50)
Hemangioma		1 (2%)		
Histiocytic sarcoma	1 (2%)		1 (2%)	
Liposarcoma, metastatic, mesentery	1 (2%)			
Endometrium, polyp stromal	1 (2%)	2 (4%)		1 (2%)
Endometrium, sarcoma stromal	1 (2%)			
Vagina	(48)	(46)	(50)	(47)
Sarcoma				1 (2%)
Squamous cell carcinoma	1 (2%)			
Hematopoietic System				
Bone marrow	(50)	(50)	(50)	(50)
Plasma cell tumor malignant, metastatic, spleen			1 (2%)	
Lymph node	(12)	(11)	(13)	(9)
Bronchial, alveolar/bronchiolar carcinoma, metastatic, lung			1 (8%)	
Iliac, histiocytic sarcoma	1 (8%)		1 (8%)	
Inguinal, mast cell tumor malignant, metastatic, uncertain primary site				1 (11%)
Mediastinal, carcinoma, metastatic, harderian gland	1 (8%)			
Mediastinal, fibrosarcoma, metastatic, mesentery		1 (9%)		
Mediastinal, fibrosarcoma, metastatic, skin	1 (8%)			
Mediastinal, fibrosarcoma, metastatic, tissue NOS			1 (8%)	
Mediastinal, hepatocellular carcinoma, metastatic, liver	1 (8%)			
Mediastinal, liposarcoma, metastatic, mesentery	1 (8%)			
Pancreatic, histiocytic sarcoma			1 (8%)	
Renal, histiocytic sarcoma	1 (8%)			1 (11%)
Renal, liposarcoma, metastatic, mesentery	1 (8%)			
Lymph node, mandibular	(49)	(48)	(49)	(47)
Histiocytic sarcoma			1 (2%)	1 (2%)
Mast cell tumor malignant, metastatic, uncertain primary site				1 (2%)
Lymph node, mesenteric	(45)	(47)	(50)	(50)
Histiocytic sarcoma	2 (4%)			1 (2%)
Liposarcoma, metastatic, mesentery	1 (2%)			
Mast cell tumor malignant, metastatic, uncertain primary site				1 (2%)

TABLE D1
Summary of the Incidence of Neoplasms in Female Mice in the 2-Year Subcutaneous Study of α-Interferon A/D

	Vehicle Control	5,000 U α-IFN A	500 U α-IFN A/D	5,000 U α-IFN A/D
Hematopoietic System (continued)				
Spleen	(47)	(49)	(50)	(50)
Alveolar/bronchiolar carcinoma, metastatic, lung		1 (2%)		
Fibrosarcoma, metastatic, mesentery		1 (2%)		
Hemangiosarcoma	1 (2%)	2 (4%)	1 (2%)	
Histiocytic sarcoma	1 (2%)			1 (2%)
Mast cell tumor malignant, metastatic, uncertain primary site				1 (2%)
Plasma cell tumor malignant			1 (2%)	
Thymus	(41)	(39)	(48)	(48)
Alveolar/bronchiolar carcinoma, metastatic, lung		1 (3%)		
Carcinoma, metastatic, harderian gland	1 (2%)			
Histiocytic sarcoma	1 (2%)			
Liposarcoma, metastatic, mesentery	1 (2%)			
Integumentary System				
Mammary gland	(50)		(48)	(50)
Carcinoma			1 (2%)	
Skin	(50)	(50)	(50)	(50)
Basal cell carcinoma	1 (2%)			
Squamous cell papilloma	1 (2%)			
Subcutaneous tissue, carcinoma, metastatic, harderian gland	1 (2%)			
Subcutaneous tissue, fibroma		1 (2%)		
Subcutaneous tissue, fibrosarcoma	2 (4%)	1 (2%)		
Subcutaneous tissue, hemangiosarcoma	2 (4%)	2 (4%)	2 (4%)	
Subcutaneous tissue, mast cell tumor malignant, metastatic, uncertain primary site				1 (2%)
Musculoskeletal System				
Bone	(50)		(50)	(50)
Osteosarcoma			1 (2%)	1 (2%)
Skeletal muscle	(50)	(50)	(50)	(50)
Carcinoma, metastatic, harderian gland	1 (2%)			
Fibrosarcoma, metastatic, mesentery		1 (2%)		
Fibrosarcoma, metastatic, skin	1 (2%)			
Fibrosarcoma, metastatic, tissue NOS			1 (2%)	
Liposarcoma, metastatic, mesentery	1 (2%)			
Nervous System				
Brain	(50)	(50)	(49)	(50)
Spinal cord	(2)	(1)	(2)	(4)

TABLE D1
Summary of the Incidence of Neoplasms in Female Mice in the 2-Year Subcutaneous Study of α-Interferon A/D

	Vehicle Control	5,000 U α-IFN A	500 U α-IFN A/D	5,000 U α-IFN A/D
Respiratory System				
Lung	(50)	(50)	(50)	(50)
Alveolar/bronchiolar adenoma		3 (6%)	5 (10%)	4 (8%)
Alveolar/bronchiolar carcinoma	2 (4%)	7 (14%)	4 (8%)	
Basal cell carcinoma, metastatic, skin	1 (2%)			
Carcinoma, metastatic, harderian gland	1 (2%)			
Hepatocellular carcinoma, metastatic, liver	2 (4%)	4 (8%)	2 (4%)	3 (6%)
Histiocytic sarcoma			1 (2%)	1 (2%)
Liposarcoma, metastatic, mesentery	1 (2%)			
Mast cell tumor malignant, metastatic, uncertain primary site				1 (2%)
Osteosarcoma, metastatic, bone			1 (2%)	
Mediastinum, alveolar/bronchiolar carcinoma, metastatic, lung			1 (2%)	
Mediastinum, mast cell tumor malignant, metastatic, uncertain primary site				1 (2%)
Nose	(50)	(50)	(50)	(50)
Carcinoma, metastatic, harderian gland	1 (2%)			
Special Senses System				
Harderian gland	(3)	(3)	(8)	(4)
Adenoma	2 (67%)	3 (100%)	5 (63%)	3 (75%)
Carcinoma	1 (33%)		2 (25%)	
Urinary System				
Kidney	(48)	(50)	(50)	(49)
Carcinoma, metastatic, harderian gland	1 (2%)			
Mast cell tumor malignant, metastatic, uncertain primary site				1 (2%)
Ureter		(1)		
Fibrosarcoma, metastatic, skin		1 (100%)		
Urinary bladder	(50)	(50)	(50)	(50)
Systemic Lesions				
Multiple organs[b]	(50)	(50)	(50)	(50)
Histiocytic sarcoma	2 (4%)	1 (2%)	1 (2%)	2 (4%)
Lymphoma malignant	11 (22%)	6 (12%)	13 (26%)	11 (22%)
Neoplasm Summary				
Total animals with primary neoplasms[c]	48	44	48	44
Total primary neoplasms	96	84	92	72
Total animals with benign neoplasms	34	31	32	33
Total benign neoplasms	53	43	52	42
Total animals with malignant neoplasms	35	30	33	27
Total malignant neoplasms	43	41	40	30
Total animals with metastatic neoplasms	7	7	6	4
Total metastatic neoplasms	36	12	12	17
Total animals with malignant neoplasms of uncertain primary site				1

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

TABLE D2
Statistical Analysis of Primary Neoplasms in Female Mice in the 2-Year Subcutaneous Study of α-Interferon A/D

	Vehicle Control	5,000 U α-IFN A	500 U α-IFN A/D	5,000 U α-IFN A/D
Harderian Gland: Adenoma				
Overall rate[a]	2/50 (4%)	3/50 (6%)	5/50 (10%)	3/50 (6%)
Adjusted rate[b]	8.0%	8.9%	15.6%	10.9%
Terminal rate[c]	2/25 (8%)	2/31 (6%)	5/32 (16%)	2/25 (8%)
First incidence (days)	729 (T)	642	729 (T)	672
Life table test[d]	P = 0.611	P = 0.567	P = 0.323	P = 0.487
Logistic regression test[d]	P = 0.597	P = 0.503	P = 0.323	P = 0.467
Cochran-Armitage test[d]	P = 0.582N			
Fisher exact test[d]		P = 0.500	P = 0.218	P = 0.500
Harderian Gland: Adenoma or Carcinoma				
Overall rate	3/50 (6%)	3/50 (6%)	7/50 (14%)	3/50 (6%)
Adjusted rate	10.8%	8.9%	20.5%	10.9%
Terminal rate	2/25 (8%)	2/31 (6%)	6/32 (19%)	2/25 (8%)
First incidence (days)	681	642	610	672
Life table test	P = 0.424N	P = 0.595N	P = 0.266	P = 0.643
Logistic regression test	P = 0.414N	P = 0.661	P = 0.195	P = 0.632
Cochran-Armitage test	P = 0.345N			
Fisher exact test		P = 0.661N	P = 0.159	P = 0.661N
Liver: Hepatocellular Adenoma				
Overall rate	24/49 (49%)	22/50 (44%)	25/50 (50%)	22/50 (44%)
Adjusted rate	73.8%	59.2%	65.1%	63.0%
Terminal rate	17/25 (68%)	16/31 (52%)	19/32 (59%)	13/25 (52%)
First incidence (days)	597	575	553	506
Life table test	P = 0.533	P = 0.168N	P = 0.249N	P = 0.476N
Logistic regression test	P = 0.510N	P = 0.394N	P = 0.456N	P = 0.492N
Cochran-Armitage test	P = 0.323N			
Fisher exact test		P = 0.384N	P = 0.540	P = 0.384N
Liver: Hepatocellular Carcinoma				
Overall rate	16/49 (33%)	18/50 (36%)	12/50 (24%)	13/50 (26%)
Adjusted rate	42.9%	47.5%	34.8%	43.8%
Terminal rate	7/25 (28%)	12/31 (39%)	10/32 (31%)	9/25 (36%)
First incidence (days)	533	563	645	581
Life table test	P = 0.546	P = 0.564	P = 0.121N	P = 0.384N
Logistic regression test	P = 0.524N	P = 0.431	P = 0.212N	P = 0.360N
Cochran-Armitage test	P = 0.422N			
Fisher exact test		P = 0.445	P = 0.232N	P = 0.306N
Liver: Hepatocellular Adenoma or Carcinoma				
Overall rate	33/49 (67%)	34/50 (68%)	31/50 (62%)	29/50 (58%)
Adjusted rate	86.1%	82.8%	77.1%	75.7%
Terminal rate	20/25 (80%)	24/31 (77%)	23/32 (72%)	16/25 (64%)
First incidence (days)	533	563	553	506
Life table test	P = 0.517	P = 0.293N	P = 0.082N	P = 0.376N
Logistic regression test	P = 0.452N	P = 0.478	P = 0.221N	P = 0.328N
Cochran-Armitage test	P = 0.252N			
Fisher exact test		P = 0.558	P = 0.365N	P = 0.226N

TABLE D2
Statistical Analysis of Primary Neoplasms in Female Mice in the 2-Year Subcutaneous Study of α-Interferon A/D

	Vehicle Control	5,000 U α-IFN A	500 U α-IFN A/D	5,000 U α-IFN A/D
Lung: Alveolar/bronchiolar Adenoma				
Overall rate	0/50 (0%)	3/50 (6%)	5/50 (10%)	4/50 (8%)
Adjusted rate	0.0%	7.8%	14.4%	14.0%
Terminal rate	0/25 (0%)	1/31 (3%)	3/32 (9%)	3/25 (12%)
First incidence (days)	—[e]	601	698	581
Life table test	P = 0.227	P = 0.128	P = 0.061	P = 0.062
Logistic regression test	P = 0.234	P = 0.127	P = 0.047	P = 0.057
Cochran-Armitage test	P = 0.283			
Fisher exact test		P = 0.121	P = 0.028	P = 0.059
Lung: Alveolar/bronchiolar Carcinoma				
Overall rate	2/50 (4%)	7/50 (14%)	4/50 (8%)	0/50 (0%)
Adjusted rate	7.3%	19.2%	10.3%	0.0%
Terminal rate	1/25 (4%)	3/31 (10%)	2/32 (6%)	0/25 (0%)
First incidence (days)	708	612	483	—
Life table test	P = 0.130N	P = 0.133	P = 0.437	P = 0.248N
Logistic regression test	P = 0.100N	P = 0.078	P = 0.302	P = 0.253N
Cochran-Armitage test	P = 0.105N			
Fisher exact test		P = 0.080	P = 0.339	P = 0.247N
Lung: Alveolar/bronchiolar Adenoma or Carcinoma				
Overall rate	2/50 (4%)	9/50 (18%)	9/50 (18%)	4/50 (8%)
Adjusted rate	7.3%	23.9%	23.8%	14.0%
Terminal rate	1/25 (4%)	4/31 (13%)	5/32 (16%)	3/25 (12%)
First incidence (days)	708	601	483	581
Life table test	P = 0.552N	P = 0.054	P = 0.069	P = 0.330
Logistic regression test	P = 0.505N	P = 0.026	P = 0.028	P = 0.311
Cochran-Armitage test	P = 0.464N			
Fisher exact test		P = 0.026	P = 0.026	P = 0.339
Ovary: Cystadenoma				
Overall rate	4/46 (9%)	1/48 (2%)	2/48 (4%)	0/49 (0%)
Adjusted rate	16.1%	3.4%	4.8%	0.0%
Terminal rate	3/22 (14%)	1/29 (3%)	0/32 (0%)	0/25 (0%)
First incidence (days)	675	729 (T)	685	—
Life table test	P = 0.093N	P = 0.117N	P = 0.213N	P = 0.055N
Logistic regression test	P = 0.078N	P = 0.153N	P = 0.290N	P = 0.060N
Cochran-Armitage test	P = 0.069N			
Fisher exact test		P = 0.168N	P = 0.318N	P = 0.051N
Pituitary Gland (Pars Distalis): Adenoma				
Overall rate	11/46 (24%)	5/43 (12%)	8/47 (17%)	7/44 (16%)
Adjusted rate	38.9%	16.7%	23.9%	31.8%
Terminal rate	9/25 (36%)	4/27 (15%)	5/29 (17%)	7/22 (32%)
First incidence (days)	638	563	687	729 (T)
Life table test	P = 0.436N	P = 0.069N	P = 0.193N	P = 0.300N
Logistic regression test	P = 0.464N	P = 0.131N	P = 0.226N	P = 0.338N
Cochran-Armitage test	P = 0.314N			
Fisher exact test		P = 0.108N	P = 0.286N	P = 0.247N

TABLE D2
Statistical Analysis of Primary Neoplasms in Female Mice in the 2-Year Subcutaneous Study of α-Interferon A/D

	Vehicle Control	5,000 U α-IFN A	500 U α-IFN A/D	5,000 U α-IFN A/D
Thyroid Gland (Follicular Cell): Adenoma				
Overall rate	5/50 (10%)	4/50 (8%)	3/50 (6%)	2/49 (4%)
Adjusted rate	18.0%	12.9%	9.4%	8.0%
Terminal rate	4/25 (16%)	4/31 (13%)	3/32 (9%)	2/25 (8%)
First incidence (days)	654	729 (T)	729 (T)	729 (T)
Life table test	P = 0.302N	P = 0.387N	P = 0.239N	P = 0.220N
Logistic regression test	P = 0.320N	P = 0.463N	P = 0.278N	P = 0.247N
Cochran-Armitage test	P = 0.262N			
Fisher exact test		P = 0.500N	P = 0.357N	P = 0.226N
All Organs: Hemangiosarcoma				
Overall rate	2/50 (4%)	5/50 (10%)	3/50 (6%)	1/50 (2%)
Adjusted rate	6.5%	15.0%	8.8%	3.0%
Terminal rate	1/25 (4%)	4/31 (13%)	2/32 (6%)	0/25 (0%)
First incidence (days)	671	612	701	667
Life table test	P = 0.403N	P = 0.276	P = 0.595	P = 0.542N
Logistic regression test	P = 0.371N	P = 0.212	P = 0.540	P = 0.514N
Cochran-Armitage test	P = 0.338N			
Fisher exact test		P = 0.218	P = 0.500	P = 0.500N
All Organs: Hemangioma or Hemangiosarcoma				
Overall rate	3/50 (6%)	6/50 (12%)	3/50 (6%)	2/50 (4%)
Adjusted rate	10.4%	18.2%	8.8%	6.9%
Terminal rate	2/25 (8%)	5/31 (16%)	2/32 (6%)	1/25 (4%)
First incidence (days)	671	612	701	667
Life table test	P = 0.518N	P = 0.323	P = 0.558N	P = 0.533N
Logistic regression test	P = 0.496N	P = 0.240	P = 0.615N	P = 0.528N
Cochran-Armitage test	P = 0.441N			
Fisher exact test		P = 0.243	P = 0.661N	P = 0.500N
All Organs: Malignant Lymphoma				
Overall rate	11/50 (22%)	6/50 (12%)	13/50 (26%)	11/50 (22%)
Adjusted rate	32.8%	15.5%	33.3%	33.9%
Terminal rate	5/25 (20%)	3/31 (10%)	8/32 (25%)	6/25 (24%)
First incidence (days)	597	449	623	567
Life table test	P = 0.511	P = 0.108N	P = 0.552N	P = 0.547
Logistic regression test	P = 0.548N	P = 0.138N	P = 0.428	P = 0.555
Cochran-Armitage test	P = 0.486N			
Fisher exact test		P = 0.143N	P = 0.408	P = 0.595N
All Organs: Benign Neoplasms				
Overall rate	34/50 (68%)	31/50 (62%)	32/50 (64%)	33/50 (66%)
Adjusted rate	94.1%	73.7%	77.7%	88.5%
Terminal rate	23/25 (92%)	20/31 (65%)	23/32 (72%)	21/25 (84%)
First incidence (days)	597	563	553	293
Life table test	P = 0.262	P = 0.111N	P = 0.064N	P = 0.572N
Logistic regression test	P = 0.350	P = 0.394N	P = 0.211N	P = 0.530
Cochran-Armitage test	P = 0.553N			
Fisher exact test		P = 0.338N	P = 0.417N	P = 0.500N

TABLE D2
Statistical Analysis of Primary Neoplasms in Female Mice in the 2-Year Subcutaneous Study of α-Interferon A/D

	Vehicle Control	5,000 U α-IFN A	500 U α-IFN A/D	5,000 U α-IFN A/D
All Organs: Malignant Neoplasms				
Overall rate	35/50 (70%)	30/50 (60%)	33/50 (66%)	28/50 (56%)
Adjusted rate	73.6%	66.0%	71.2%	72.1%
Terminal rate	13/25 (52%)	16/31 (52%)	19/32 (59%)	15/25 (60%)
First incidence (days)	409	426	483	506
Life table test	P = 0.389N	P = 0.155N	P = 0.153N	P = 0.260N
Logistic regression test	P = 0.107N	P = 0.299N	P = 0.546N	P = 0.133N
Cochran-Armitage test	P = 0.096N			
Fisher exact test		P = 0.201N	P = 0.415N	P = 0.107N
All Organs: Benign or Malignant Neoplasms				
Overall rate	48/50 (96%)	44/50 (88%)	48/50 (96%)	44/50 (88%)
Adjusted rate	98.0%	93.6%	96.0%	97.7%
Terminal rate	24/25 (96%)	28/31 (90%)	30/32 (94%)	24/25 (96%)
First incidence (days)	409	426	483	293
Life table test	P = 0.445	P = 0.086N	P = 0.101N	P = 0.433N
Logistic regression test	P = 0.238N	P = 0.185N	P = 0.610N	P = 0.296N
Cochran-Armitage test	P = 0.065N			
Fisher exact test		P = 0.134N	P = 0.691N	P = 0.134N

(T)Terminal sacrifice
[a] Number of neoplasm-bearing animals/number of animals examined. Denominator is number of animals examined microscopically for liver, lung, ovary, pituitary gland, and thyroid gland; for other tissues, denominator is number of animals necropsied.
[b] 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 incidence are the P values associated with the trend test (the α-IFN A group was excluded from the trend test). Beneath the dosed group incidence are the P values corresponding to pairwise comparisons between the vehicle controls and that 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 Cochran-Armitage and Fisher exact tests compare directly the overall incidence rates. For all tests, a negative trend or a lower incidence in a dosed group is indicated by **N**.
[e] Not applicable; no neoplasms in animal group

TABLE D3
Historical Incidence of Alveolar/bronchiolar Neoplasms in Untreated Feed Control Female B6C3F$_1$ Mice[a]

	Incidence in Controls		
	Adenoma	**Carcinoma**	**Adenoma or Carcinoma**
Overall Historical Incidence			
Total	85/1,472 (5.8%)	31/1,472 (2.1%)	114/1,472 (7.7%)
Standard deviation	4.8%	2.3%	5.1%
Range	0%-24%	0%-8%	2%-26%

[a] Data as of 12 May 1995

TABLE D4
Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 2-Year Subcutaneous Study of α-Interferon A/D[a]

	Vehicle Control	5,000 U α-IFN A	500 U α-IFN A/D	5,000 U α-IFN A/D
Disposition Summary				
Animals initially in study	50	50	50	50
Early deaths				
Accidental death				1
Moribund	13	11	13	9
Natural deaths	12	8	5	15
Survivors				
Terminal sacrifice	25	31	32	25
Animals examined microscopically	50	50	50	50
Alimentary System				
Intestine large, rectum	(47)	(49)	(50)	(50)
Artery, inflammation, chronic	1 (2%)			
Intestine small, jejunum	(47)	(48)	(50)	(49)
Peyer's patch, hyperplasia, lymphoid	1 (2%)			
Liver	(49)	(50)	(50)	(50)
Angiectasis	1 (2%)	3 (6%)	2 (4%)	
Basophilic focus		1 (2%)		3 (6%)
Clear cell focus	1 (2%)		1 (2%)	1 (2%)
Congestion	1 (2%)			
Eosinophilic focus	1 (2%)	8 (16%)	8 (16%)	8 (16%)
Fibrosis, focal				1 (2%)
Hematopoietic cell proliferation	1 (2%)	1 (2%)	3 (6%)	
Hyperplasia, focal, lymphoid				1 (2%)
Inflammation, chronic	4 (8%)	9 (18%)	6 (12%)	10 (20%)
Mixed cell focus	4 (8%)	1 (2%)	4 (8%)	
Necrosis, focal	3 (6%)	3 (6%)	5 (10%)	5 (10%)
Pigmentation, focal	2 (4%)	1 (2%)	2 (4%)	1 (2%)
Vacuolization cytoplasmic	5 (10%)	3 (6%)	2 (4%)	3 (6%)
Artery, inflammation, chronic	1 (2%)			
Bile duct, cyst		1 (2%)	1 (2%)	
Bile duct, hyperplasia	1 (2%)	1 (2%)		
Hepatocyte, karyomegaly	2 (4%)		1 (2%)	1 (2%)
Mesentery	(21)	(16)	(21)	(18)
Accessory spleen			1 (5%)	
Angiectasis			1 (5%)	
Artery, inflammation, chronic	1 (5%)	2 (13%)		
Fibrosis, focal				1 (6%)
Infiltration cellular, mixed cell				1 (6%)
Inflammation, chronic			1 (5%)	3 (17%)
Fat, necrosis	13 (62%)	10 (63%)	12 (57%)	12 (67%)
Pancreas	(48)		(50)	(50)
Inflammation, chronic				1 (2%)
Necrosis, focal				1 (2%)
Acinus, atrophy, diffuse				2 (4%)
Acinus, atrophy, focal			1 (2%)	1 (2%)
Duct, cyst				3 (6%)
Salivary glands	(50)	(49)		
Inflammation, chronic		1 (2%)		

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

TABLE D4
Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 2-Year Subcutaneous Study of α-Interferon A/D

	Vehicle Control	5,000 U α-IFN A	500 U α-IFN A/D	5,000 U α-IFN A/D
Alimentary System (continued)				
Stomach, forestomach	(48)	(46)	(50)	(50)
Diverticulum	2 (4%)			
Edema		1 (2%)		
Erosion	5 (10%)	1 (2%)		3 (6%)
Inflammation, chronic	3 (6%)	3 (7%)		3 (6%)
Epithelium, cyst		1 (2%)		
Epithelium, hyperplasia	7 (15%)	4 (9%)		4 (8%)
Stomach, glandular	(48)	(46)	(50)	(50)
Erosion	1 (2%)	1 (2%)	1 (2%)	1 (2%)
Mineralization	1 (2%)			
Pigmentation, focal	1 (2%)		2 (4%)	2 (4%)
Artery, inflammation, chronic	1 (2%)			
Glands, degeneration, cystic, focal	1 (2%)	1 (2%)		
Cardiovascular System				
Blood vessel	(50)	(49)	(50)	(50)
Inflammation, chronic		1 (2%)		
Pulmonary vein, intima, mineralization, focal			1 (2%)	
Heart	(50)	(50)	(50)	(50)
Inflammation, chronic, focal		1 (2%)	1 (2%)	
Thrombosis				1 (2%)
Artery, inflammation, chronic	1 (2%)	1 (2%)		
Endocrine System				
Adrenal cortex	(50)	(49)	(49)	(50)
Accessory adrenal cortical nodule	3 (6%)			1 (2%)
Cyst	1 (2%)			
Cytoplasmic alteration, focal		1 (2%)		
Hyperplasia		1 (2%)		
Hypertrophy, focal		1 (2%)		
Capsule, hyperplasia, focal	1 (2%)	2 (4%)	2 (4%)	1 (2%)
Islets, pancreatic	(48)		(50)	(50)
Hyperplasia			1 (2%)	
Adrenal medulla	(50)	(49)		
Hyperplasia		2 (4%)		
Parathyroid gland	(44)	(47)	(46)	(46)
Cyst		1 (2%)	1 (2%)	
Pituitary gland	(46)	(43)	(47)	(44)
Angiectasis	1 (2%)	3 (7%)	3 (6%)	1 (2%)
Pars distalis, cytoplasmic alteration, focal	1 (2%)	2 (5%)	3 (6%)	4 (9%)
Pars distalis, hyperplasia, focal	1 (2%)	1 (2%)	2 (4%)	1 (2%)
Thyroid gland	(50)	(50)	(50)	(49)
Angiectasis				1 (2%)
Degeneration, cystic, focal	8 (16%)	8 (16%)	9 (18%)	10 (20%)
Inflammation, chronic, focal		1 (2%)	2 (4%)	1 (2%)
C-cell, hyperplasia		1 (2%)		1 (2%)
Follicle, cyst	2 (4%)		1 (2%)	1 (2%)
Follicular cell, hyperplasia	17 (34%)	14 (28%)	21 (42%)	18 (37%)

TABLE D4
Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 2-Year Subcutaneous Study of α-Interferon A/D

	Vehicle Control	5,000 U α-IFN A	500 U α-IFN A/D	5,000 U α-IFN A/D
General Body System				
Peritoneum	(2)			(1)
Infiltration cellular, histiocyte	1 (50%)			
Infiltration cellular, mixed cell				1 (100%)
Tissue NOS	(1)		(1)	(2)
Hemorrhage				1 (50%)
Genital System				
Clitoral gland	(48)	(49)	(49)	(47)
Degeneration, cystic	3 (6%)	6 (12%)	3 (6%)	2 (4%)
Ovary	(46)	(48)	(48)	(49)
Angiectasis		3 (6%)	2 (4%)	
Atrophy		1 (2%)		
Cyst	10 (22%)	8 (17%)	11 (23%)	7 (14%)
Inflammation, suppurative				1 (2%)
Thrombosis				1 (2%)
Bilateral, cyst		1 (2%)	1 (2%)	2 (4%)
Oviduct				(1)
Inflammation, suppurative				1 (100%)
Uterus	(50)	(50)	(50)	(50)
Angiectasis				1 (2%)
Hydrometra	10 (20%)	20 (40%)	11 (22%)	11 (22%)
Inflammation, suppurative	1 (2%)	1 (2%)	2 (4%)	1 (2%)
Thrombosis		1 (2%)		
Endometrium, hyperplasia, cystic	48 (96%)	48 (96%)	49 (98%)	46 (92%)
Vagina	(48)	(46)	(50)	(47)
Inflammation, chronic	1 (2%)			
Inflammation, focal, granulomatous	1 (2%)			
Epithelium, hyperplasia			1 (2%)	
Hematopoietic System				
Bone marrow	(50)	(50)	(50)	(50)
Depletion cellular			1 (2%)	
Hyperplasia	2 (4%)		2 (4%)	
Lymph node	(12)	(11)	(13)	(9)
Iliac, hemorrhage	1 (8%)			
Iliac, hyperplasia		1 (9%)		
Iliac, hyperplasia, lymphoid			1 (8%)	
Inguinal, hyperplasia	2 (17%)			
Inguinal, hyperplasia, lymphoid		1 (9%)		1 (11%)
Mediastinal, hyperplasia		1 (9%)	1 (8%)	2 (22%)
Mediastinal, hyperplasia, lymphoid	1 (8%)		2 (15%)	1 (11%)
Mediastinal, inflammation, focal, suppurative		1 (9%)		1 (11%)
Pancreatic, hyperplasia, lymphoid			1 (8%)	
Renal, hemorrhage	1 (8%)			
Renal, hyperplasia, lymphoid		1 (9%)	1 (8%)	
Lymph node, mandibular	(49)	(48)	(49)	(47)
Hemorrhage			1 (2%)	
Hyperplasia			1 (2%)	1 (2%)
Hyperplasia, lymphoid	1 (2%)	2 (4%)	2 (4%)	1 (2%)

TABLE D4
Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 2-Year Subcutaneous Study of α-Interferon A/D

	Vehicle Control	5,000 U α-IFN A	500 U α-IFN A/D	5,000 U α-IFN A/D
Hematopoietic System (continued)				
Lymph node, mesenteric	(45)	(47)	(50)	(50)
Angiectasis	1 (2%)			1 (2%)
Ectasia		1 (2%)	2 (4%)	
Hematopoietic cell proliferation			1 (2%)	
Hemorrhage	2 (4%)		2 (4%)	1 (2%)
Hyperplasia				2 (4%)
Hyperplasia, histiocytic				1 (2%)
Hyperplasia, lymphoid	3 (7%)	2 (4%)	4 (8%)	3 (6%)
Inflammation, focal, suppurative				1 (2%)
Pigmentation			1 (2%)	
Spleen	(47)	(49)	(50)	(50)
Hematopoietic cell proliferation	21 (45%)	20 (41%)	24 (48%)	26 (52%)
Hyperplasia, histiocytic				1 (2%)
Hyperplasia, lymphoid	3 (6%)	5 (10%)	4 (8%)	2 (4%)
Necrosis, focal	1 (2%)			
Thymus	(41)	(39)	(48)	(48)
Cyst	1 (2%)		2 (4%)	2 (4%)
Hyperplasia, histiocytic		1 (3%)		
Hyperplasia, lymphoid	1 (2%)			1 (2%)
Epithelial cell, hyperplasia			1 (2%)	
Integumentary System				
Mammary gland	(50)	(50)	(48)	(50)
Ectasia	1 (2%)	2 (4%)	1 (2%)	
Hyperplasia		1 (2%)	1 (2%)	1 (2%)
Skin	(50)	(50)	(50)	(50)
Cyst epithelial inclusion				1 (2%)
Inflammation, chronic, focal	1 (2%)			
Ulcer	1 (2%)			
Artery, subcutaneous tissue, inflammation, chronic	1 (2%)			
Subcutaneous tissue, edema	1 (2%)		2 (4%)	
Subcutaneous tissue, hemorrhage, focal		1 (2%)		
Subcutaneous tissue, inflammation, chronic, focal		1 (2%)		1 (2%)
Musculoskeletal System				
Bone	(50)	(50)	(50)	(50)
Fibrous osteodystrophy				1 (2%)
Osteoporosis	1 (2%)			
Nervous System				
Brain	(50)	(50)	(49)	(50)
Atrophy, focal	2 (4%)	1 (2%)	2 (4%)	1 (2%)
Hemorrhage, focal	1 (2%)			
Spinal cord	(2)		(2)	(4)
Hemorrhage, focal				1 (25%)
Meninges, inflammation, focal				1 (25%)

TABLE D4
Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 2-Year Subcutaneous Study of α-Interferon A/D

	Vehicle Control	5,000 U α-IFN A	500 U α-IFN A/D	5,000 U α-IFN A/D
Respiratory System				
Lung	(50)	(50)	(50)	(50)
Hemorrhage	2 (4%)	1 (2%)	2 (4%)	2 (4%)
Hyperplasia, histiocytic	4 (8%)	3 (6%)	2 (4%)	1 (2%)
Hyperplasia, lymphoid	1 (2%)			1 (2%)
Infiltration cellular, mixed cell		1 (2%)		
Pigmentation, focal	1 (2%)			
Alveolar epithelium, hyperplasia	2 (4%)	1 (2%)	1 (2%)	2 (4%)
Bronchus, glands, cyst				1 (2%)
Mediastinum, infiltration cellular, mixed cell				1 (2%)
Mediastinum, inflammation, chronic		1 (2%)		1 (2%)
Mediastinum, necrosis, focal				1 (2%)
Nose	(50)	(50)	(50)	(50)
Inflammation, suppurative		1 (2%)		
Mucosa, glands, dilatation, focal	41 (82%)	40 (80%)	42 (84%)	41 (82%)
Nasolacrimal duct, cyst		1 (2%)		
Special Senses System				
Eye		(1)	(3)	
Atrophy			1 (33%)	
Inflammation, chronic			1 (33%)	
Anterior chamber, infiltration cellular, polymorphonuclear			1 (33%)	
Cornea, inflammation, chronic		1 (100%)	2 (67%)	
Cornea, necrosis, focal			1 (33%)	
Harderian gland	(3)		(8)	(4)
Hyperplasia, focal			1 (13%)	1 (25%)
Urinary System				
Kidney	(48)	(50)	(50)	(49)
Cyst	1 (2%)	1 (2%)		
Metaplasia, focal, osseous	3 (6%)		1 (2%)	2 (4%)
Nephropathy	29 (60%)	31 (62%)	38 (76%)	31 (63%)
Artery, inflammation, chronic	1 (2%)			
Pelvis, dilatation	2 (4%)	1 (2%)		
Renal tubule, accumulation, hyaline droplet		2 (4%)	3 (6%)	1 (2%)
Renal tubule, dilatation	2 (4%)		3 (6%)	
Renal tubule, hyperplasia, focal				1 (2%)
Renal tubule, necrosis	1 (2%)			1 (2%)
Renal tubule, pigmentation		2 (4%)		2 (4%)
Urethra	(1)			(1)
Inflammation, chronic				1 (100%)
Artery, inflammation, chronic	1 (100%)			
Urinary bladder	(50)	(50)	(50)	(50)
Artery, inflammation, chronic	1 (2%)			

APPENDIX E
SUMMARY OF LESIONS IN MALE MICE IN THE 2-YEAR GAVAGE STUDY OF AZT/500 U α-INTERFERON A/D

TABLE E1
Summary of the Incidence of Neoplasms in Male Mice in the 2-Year Gavage Study of AZT/500 U α-Interferon A/D[a]

	Vehicle Control	30 mg AZT/kg + 500 U α-IFN A/D	60 mg AZT/kg + 500 U α-IFN A/D	120 mg AZT/kg + 500 U α-IFN A/D
Disposition Summary				
Animals initially in study	50	50	50	50
Early deaths				
Accidental deaths		2	3	
Moribund	13	14	5	9
Natural deaths	1	7	4	6
Survivors				
Terminal sacrifice	36	27	38	35
Animals examined microscopically	50	50	50	50
Alimentary System				
Esophagus	(50)	(50)	(50)	(50)
Squamous cell papilloma				1 (2%)
Intestine small, jejunum	(50)	(50)	(48)	(50)
Carcinoma				1 (2%)
Fibrous histiocytoma, metastatic, lymph node, mesenteric				1 (2%)
Intestine small, ileum	(50)	(48)	(49)	(50)
Liver	(50)	(50)	(50)	(50)
Carcinoid tumor malignant, metastatic, uncertain primary site		1 (2%)		
Cholangiocarcinoma		1 (2%)		
Fibrous histiocytoma, metastatic, lymph node, mesenteric				1 (2%)
Hemangiosarcoma	1 (2%)	2 (4%)	1 (2%)	1 (2%)
Hemangiosarcoma, multiple	2 (4%)	3 (6%)	3 (6%)	3 (6%)
Hepatoblastoma	1 (2%)	1 (2%)	1 (2%)	
Hepatocellular carcinoma	12 (24%)	13 (26%)	15 (30%)	9 (18%)
Hepatocellular carcinoma, multiple	1 (2%)	7 (14%)	2 (4%)	5 (10%)
Hepatocellular adenoma	10 (20%)	12 (24%)	14 (28%)	14 (28%)
Hepatocellular adenoma, multiple	6 (12%)	4 (8%)	5 (10%)	4 (8%)
Histiocytic sarcoma	2 (4%)	1 (2%)		
Ito cell tumor benign			1 (2%)	
Sarcoma, metastatic, mesentery		1 (2%)		
Sarcoma, metastatic, skeletal muscle		1 (2%)		
Mesentery	(1)	(2)	(1)	
Cholangiocarcinoma, metastatic, liver		1 (50%)		
Sarcoma		1 (50%)		
Pancreas	(50)	(50)	(50)	(50)
Cholangiocarcinoma, metastatic, liver		1 (2%)		
Histiocytic sarcoma		1 (2%)		
Sarcoma, metastatic, mesentery		1 (2%)		
Sarcoma, metastatic, skeletal muscle		1 (2%)		
Salivary glands	(50)	(50)	(50)	(50)
Stomach, forestomach	(50)	(50)	(50)	(50)
Sarcoma, metastatic, mesentery		1 (2%)		
Sarcoma, metastatic, skeletal muscle		1 (2%)		
Squamous cell papilloma	1 (2%)			2 (4%)
Stomach, glandular	(50)	(50)	(50)	(50)
Carcinoma				1 (2%)
Hepatocellular carcinoma, metastatic, liver				1 (2%)

TABLE E1
Summary of the Incidence of Neoplasms in Male Mice in the 2-Year Gavage Study of AZT/500 U α-Interferon A/D

	Vehicle Control	30 mg AZT/kg + 500 U α-IFN A/D	60 mg AZT/kg + 500 U α-IFN A/D	120 mg AZT/kg + 500 U α-IFN A/D
Cardiovascular System				
Heart	(50)	(50)	(50)	(50)
Carcinoid tumor malignant, metastatic, uncertain primary site		1 (2%)		
Cholangiocarcinoma, metastatic, liver		1 (2%)		
Endocrine System				
Adrenal cortex	(50)	(50)	(50)	(50)
Adenoma			1 (2%)	
Sarcoma, metastatic, skeletal muscle		1 (2%)		
Bilateral, capsule, adenoma				1 (2%)
Capsule, adenoma				2 (4%)
Adrenal medulla	(50)	(50)	(50)	(50)
Pheochromocytoma malignant	1 (2%)			
Islets, pancreatic	(50)	(50)	(50)	(50)
Adenoma			1 (2%)	
Pituitary gland	(48)	(43)	(48)	(47)
Pars distalis, adenoma				1 (2%)
Pars intermedia, adenoma	1 (2%)			
Pars intermedia, carcinoma		1 (2%)		
Thyroid gland	(50)	(50)	(50)	(49)
Bilateral, follicular cell, adenoma	1 (2%)			
Follicular cell, adenoma	3 (6%)	2 (4%)		1 (2%)
General Body System				
None				
Genital System				
Epididymis	(50)	(50)	(50)	(50)
Hemangiosarcoma		1 (2%)		
Hepatocellular carcinoma, metastatic, liver				1 (2%)
Histiocytic sarcoma		1 (2%)		
Preputial gland	(48)	(48)	(50)	(50)
Carcinoma				1 (2%)
Prostate	(50)	(50)	(48)	(50)
Testes	(50)	(50)	(50)	(50)
Histiocytic sarcoma		1 (2%)		
Interstitial cell, adenoma	1 (2%)			
Hematopoietic System				
Bone marrow	(50)	(50)	(50)	(50)
Hemangiosarcoma	1 (2%)			1 (2%)
Lymph node	(5)	(8)	(5)	(5)
Iliac, histiocytic sarcoma	1 (20%)			
Inguinal, histiocytic sarcoma	1 (20%)			
Pancreatic, fibrous histiocytoma, metastatic, lymph node, mesenteric		1 (13%)		
Pancreatic, sarcoma, metastatic, skeletal muscle		1 (13%)		
Renal, fibrous histiocytoma, metastatic, lymph node, mesenteric				1 (20%)
Renal, histiocytic sarcoma	1 (20%)	1 (13%)		

TABLE E1
Summary of the Incidence of Neoplasms in Male Mice in the 2-Year Gavage Study of AZT/500 U α-Interferon A/D

	Vehicle Control	30 mg AZT/kg + 500 U α-IFN A/D	60 mg AZT/kg + 500 U α-IFN A/D	120 mg AZT/kg + 500 U α-IFN A/D
Hematopoietic System (continued)				
Lymph node, mandibular	(46)	(47)	(49)	(46)
Carcinoma, metastatic, harderian gland				1 (2%)
Lymph node, mesenteric	(50)	(48)	(50)	(47)
Fibrous histiocytoma		1 (2%)		1 (2%)
Hemangiosarcoma			1 (2%)	
Histiocytic sarcoma	2 (4%)	1 (2%)		
Sarcoma, metastatic, mesentery		1 (2%)		
Sarcoma, metastatic, skeletal muscle		1 (2%)		
Spleen	(50)	(49)	(49)	(50)
Fibrous histiocytoma, metastatic, lymph node, mesenteric				1 (2%)
Hemangiosarcoma		1 (2%)	1 (2%)	1 (2%)
Histiocytic sarcoma	1 (2%)			
Thymus	(45)	(40)	(42)	(43)
Fibrosarcoma	1 (2%)			
Fibrous histiocytoma, metastatic, lymph node, mesenteric				1 (2%)
Histiocytic sarcoma	1 (2%)	1 (3%)		
Integumentary System				
Skin	(50)	(50)	(50)	(50)
Subcutaneous tissue, fibrosarcoma		1 (2%)		1 (2%)
Subcutaneous tissue, hemangiosarcoma		1 (2%)		
Subcutaneous tissue, sarcoma	1 (2%)			
Musculoskeletal System				
Bone	(50)	(50)	(50)	(50)
Alveolar/bronchiolar carcinoma, metastatic, lung	1 (2%)			
Skeletal muscle	(50)	(50)	(50)	(50)
Cholangiocarcinoma, metastatic, liver		1 (2%)		
Sarcoma		1 (2%)		
Nervous System				
None				
Respiratory System				
Lung	(49)	(50)	(50)	(50)
Alveolar/bronchiolar adenoma	7 (14%)	3 (6%)	7 (14%)	7 (14%)
Alveolar/bronchiolar adenoma, multiple	3 (6%)	1 (2%)	2 (4%)	1 (2%)
Alveolar/bronchiolar carcinoma	4 (8%)	2 (4%)	6 (12%)	6 (12%)
Alveolar/bronchiolar carcinoma, multiple	2 (4%)		1 (2%)	
Carcinoid tumor malignant, metastatic, uncertain primary site		1 (2%)		
Carcinoma, metastatic, harderian gland				1 (2%)
Cholangiocarcinoma, metastatic, liver		1 (2%)		
Fibrous histiocytoma, metastatic, lymph node, mesenteric				1 (2%)
Hepatocellular carcinoma, metastatic, liver	3 (6%)	3 (6%)	2 (4%)	3 (6%)
Histiocytic sarcoma	1 (2%)	1 (2%)		
Sarcoma, metastatic, skeletal muscle		1 (2%)		

TABLE E1
Summary of the Incidence of Neoplasms in Male Mice in the 2-Year Gavage Study of AZT/500 U α-Interferon A/D

	Vehicle Control	30 mg AZT/kg + 500 U α-IFN A/D	60 mg AZT/kg + 500 U α-IFN A/D	120 mg AZT/kg + 500 U α-IFN A/D
Special Senses System				
Harderian gland	(3)	(3)	(1)	(5)
Adenoma	3 (100%)	3 (100%)	1 (100%)	2 (40%)
Carcinoma				2 (40%)
Urinary System				
Kidney	(50)	(50)	(50)	(50)
Histiocytic sarcoma	1 (2%)			
Renal tubule, adenoma			1 (2%)	
Urinary bladder	(50)	(50)	(50)	(50)
Systemic Lesions				
Multiple organs[b]	(50)	(50)	(50)	(50)
Histiocytic sarcoma	2 (4%)	2 (4%)		
Lymphoma malignant	7 (14%)	8 (16%)	5 (10%)	6 (12%)
Neoplasm Summary				
Total animals with primary neoplasms[c]	40	41	42	47
Total primary neoplasms	72	72	69	75
Total animals with benign neoplasms	26	20	26	30
Total benign neoplasms	36	25	33	36
Total animals with malignant neoplasms	30	32	29	33
Total malignant neoplasms	36	47	36	39
Total animals with metastatic neoplasms	4	8	2	5
Total metastatic neoplasms	4	23	2	13
Total animals with malignant neoplasms of uncertain primary site		1		

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

TABLE E2
Statistical Analysis of Primary Neoplasms in Male Mice in the 2-Year Gavage Study of AZT/500 U α-Interferon A/D

	Vehicle Control	30 mg AZT/kg + 500 U α-IFN A/D	60 mg AZT/kg + 500 U α-IFN A/D	120 mg AZT/kg + 500 U α-IFN A/D
Adrenal Cortex: Adenoma				
Overall rate[a]	0/50 (0%)	0/50 (0%)	1/50 (2%)	3/50 (6%)
Adjusted rate[b]	0.0%	0.0%	2.6%	8.3%
Terminal rate[c]	0/36 (0%)	0/27 (0%)	1/38 (3%)	2/35 (6%)
First incidence (days)	—[e]	—	731 (T)	727
Life table test[d]	P = 0.027	—[f]	P = 0.511	P = 0.120
Logistic regression test[d]	P = 0.024	—	P = 0.511	P = 0.113
Cochran-Armitage test[d]	P = 0.021			
Fisher exact test[d]		—	P = 0.500	P = 0.121
Harderian Gland: Adenoma				
Overall rate	3/50 (6%)	3/50 (6%)	1/50 (2%)	2/50 (4%)
Adjusted rate	7.2%	10.4%	2.1%	5.7%
Terminal rate	1/36 (3%)	2/27 (7%)	0/38 (0%)	2/35 (6%)
First incidence (days)	618	708	563	731 (T)
Life table test	P = 0.255N	P = 0.542	P = 0.300N	P = 0.506N
Logistic regression test	P = 0.266N	P = 0.622	P = 0.280N	P = 0.503N
Cochran-Armitage test	P = 0.271N			
Fisher exact test		P = 0.661N	P = 0.309N	P = 0.500N
Harderian Gland: Adenoma or Carcinoma				
Overall rate	3/50 (6%)	3/50 (6%)	1/50 (2%)	4/50 (8%)
Adjusted rate	7.2%	10.4%	2.1%	10.6%
Terminal rate	1/36 (3%)	2/27 (7%)	0/38 (0%)	3/35 (9%)
First incidence (days)	618	708	563	632
Life table test	P = 0.532	P = 0.542	P = 0.300N	P = 0.497
Logistic regression test	P = 0.506	P = 0.622	P = 0.280N	P = 0.493
Cochran-Armitage test	P = 0.500			
Fisher exact test		P = 0.661N	P = 0.309N	P = 0.500
Liver: Hemangiosarcoma				
Overall rate	3/50 (6%)	5/50 (10%)	4/50 (8%)	4/50 (8%)
Adjusted rate	7.5%	16.4%	10.1%	10.1%
Terminal rate	1/36 (3%)	3/27 (11%)	3/38 (8%)	2/35 (6%)
First incidence (days)	675	663	685	638
Life table test	P = 0.491	P = 0.231	P = 0.520	P = 0.487
Logistic regression test	P = 0.547N	P = 0.282	P = 0.498	P = 0.502
Cochran-Armitage test	P = 0.454			
Fisher exact test		P = 0.357	P = 0.500	P = 0.500
Liver: Hepatocellular Adenoma				
Overall rate	16/50 (32%)	16/50 (32%)	19/50 (38%)	18/50 (36%)
Adjusted rate	40.5%	46.5%	47.3%	48.3%
Terminal rate	13/36 (36%)	9/27 (33%)	17/38 (45%)	16/35 (46%)
First incidence (days)	477	518	563	638
Life table test	P = 0.394	P = 0.261	P = 0.406	P = 0.380
Logistic regression test	P = 0.368	P = 0.414	P = 0.331	P = 0.429
Cochran-Armitage test	P = 0.297			
Fisher exact test		P = 0.585N	P = 0.338	P = 0.417

TABLE E2
Statistical Analysis of Primary Neoplasms in Male Mice in the 2-Year Gavage Study of AZT/500 U α-Interferon A/D

	Vehicle Control	30 mg AZT/kg + 500 U α-IFN A/D	60 mg AZT/kg + 500 U α-IFN A/D	120 mg AZT/kg + 500 U α-IFN A/D
Liver: Hepatocellular Carcinoma				
Overall rate	13/50 (26%)	20/50 (40%)	17/50 (34%)	14/50 (28%)
Adjusted rate	31.9%	52.9%	40.1%	32.2%
Terminal rate	9/36 (25%)	11/27 (41%)	13/38 (34%)	7/35 (20%)
First incidence (days)	477	376	598	527
Life table test	P = 0.435N	P = 0.029	P = 0.316	P = 0.483
Logistic regression test	P = 0.511N	P = 0.087	P = 0.245	P = 0.481
Cochran-Armitage test	P = 0.527			
Fisher exact test		P = 0.101	P = 0.257	P = 0.500
Liver: Hepatocellular Adenoma or Carcinoma				
Overall rate	24/50 (48%)	31/50 (62%)	33/50 (66%)	29/50 (58%)
Adjusted rate	56.8%	75.0%	74.9%	65.4%
Terminal rate	18/36 (50%)	17/27 (63%)	27/38 (71%)	20/35 (57%)
First incidence (days)	477	376	563	527
Life table test	P = 0.307	P = 0.016	P = 0.112	P = 0.213
Logistic regression test	P = 0.194	P = 0.050	P = 0.043	P = 0.226
Cochran-Armitage test	P = 0.152			
Fisher exact test		P = 0.114	P = 0.053	P = 0.212
Liver: Hepatocellular Carcinoma or Hepatoblastoma				
Overall rate	13/50 (26%)	21/50 (42%)	17/50 (34%)	14/50 (28%)
Adjusted rate	31.9%	54.5%	40.1%	32.2%
Terminal rate	9/36 (25%)	11/27 (41%)	13/38 (34%)	7/35 (20%)
First incidence (days)	477	376	598	527
Life table test	P = 0.411N	P = 0.019	P = 0.316	P = 0.483
Logistic regression test	P = 0.481N	P = 0.057	P = 0.245	P = 0.481
Cochran-Armitage test	P = 0.500N			
Fisher exact test		P = 0.069	P = 0.257	P = 0.500
Liver: Hepatocellular Adenoma, Hepatocellular Carcinoma, or Hepatoblastoma				
Overall rate	24/50 (48%)	32/50 (64%)	33/50 (66%)	29/50 (58%)
Adjusted rate	56.8%	75.8%	74.9%	65.4%
Terminal rate	18/36 (50%)	17/27 (63%)	27/38 (71%)	20/35 (57%)
First incidence (days)	477	376	563	527
Life table test	P = 0.328	P = 0.011	P = 0.112	P = 0.213
Logistic regression test	P = 0.213	P = 0.030	P = 0.043	P = 0.226
Cochran-Armitage test	P = 0.167			
Fisher exact test		P = 0.079	P = 0.053	P = 0.212
Lung: Alveolar/bronchiolar Adenoma				
Overall rate	10/49 (20%)	4/50 (8%)	9/50 (18%)	8/50 (16%)
Adjusted rate	26.4%	14.8%	23.7%	22.0%
Terminal rate	8/35 (23%)	4/27 (15%)	9/38 (24%)	7/35 (20%)
First incidence (days)	660	731 (T)	731 (T)	682
Life table test	P = 0.416N	P = 0.174N	P = 0.430N	P = 0.399N
Logistic regression test	P = 0.432N	P = 0.128N	P = 0.463N	P = 0.374N
Cochran-Armitage test	P = 0.484N			
Fisher exact test		P = 0.068N	P = 0.480N	P = 0.379N

TABLE E2
Statistical Analysis of Primary Neoplasms in Male Mice in the 2-Year Gavage Study of AZT/500 U α-Interferon A/D

	Vehicle Control	30 mg AZT/kg + 500 U α-IFN A/D	60 mg AZT/kg + 500 U α-IFN A/D	120 mg AZT/kg + 500 U α-IFN A/D
Lung: Alveolar/bronchiolar Carcinoma				
Overall rate	6/49 (12%)	2/50 (4%)	7/50 (14%)	6/50 (12%)
Adjusted rate	15.6%	7.4%	17.8%	15.8%
Terminal rate	4/35 (11%)	2/27 (7%)	6/38 (16%)	4/35 (11%)
First incidence (days)	542	731 (T)	699	672
Life table test	P = 0.399	P = 0.224N	P = 0.552	P = 0.612
Logistic regression test	P = 0.389	P = 0.165N	P = 0.513	P = 0.599N
Cochran-Armitage test	P = 0.352			
Fisher exact test		P = 0.128N	P = 0.516	P = 0.606N
Lung: Alveolar/bronchiolar Adenoma or Carcinoma				
Overall rate	16/49 (33%)	6/50 (12%)	14/50 (28%)	14/50 (28%)
Adjusted rate	40.3%	22.2%	35.8%	36.4%
Terminal rate	12/35 (34%)	6/27 (22%)	13/38 (34%)	11/35 (31%)
First incidence (days)	542	731 (T)	699	672
Life table test	P = 0.479N	P = 0.063N	P = 0.330N	P = 0.421N
Logistic regression test	P = 0.494N	P = 0.031N	P = 0.379N	P = 0.369N
Cochran-Armitage test	P = 0.493			
Fisher exact test		P = 0.012N	P = 0.388N	P = 0.388N
Thyroid Gland (Follicular Cell): Adenoma				
Overall rate	4/50 (8%)	2/50 (4%)	0/50 (0%)	1/49 (2%)
Adjusted rate	11.1%	7.4%	0.0%	2.9%
Terminal rate	4/36 (11%)	2/27 (7%)	0/38 (0%)	1/35 (3%)
First incidence (days)	731 (T)	731 (T)	—	731 (T)
Life table test	P = 0.038N	P = 0.475N	P = 0.056N	P = 0.187N
Logistic regression test	P = 0.038N	P = 0.475N	P = 0.056N	P = 0.187N
Cochran-Armitage test	P = 0.044N			
Fisher exact test		P = 0.339N	P = 0.059N	P = 0.187N
All Organs: Hemangiosarcoma				
Overall rate	3/50 (6%)	6/50 (12%)	5/50 (10%)	4/50 (8%)
Adjusted rate	7.5%	18.7%	12.7%	10.1%
Terminal rate	1/36 (3%)	3/27 (11%)	4/38 (11%)	2/35 (6%)
First incidence (days)	675	624	685	638
Life table test	P = 0.497	P = 0.145	P = 0.381	P = 0.487
Logistic regression test	P = 0.532N	P = 0.191	P = 0.355	P = 0.502
Cochran-Armitage test	P = 0.456			
Fisher exact test		P = 0.243	P = 0.357	P = 0.500
All Organs: Malignant Lymphoma				
Overall rate	7/50 (14%)	8/50 (16%)	5/50 (10%)	6/50 (12%)
Adjusted rate	18.8%	25.2%	12.5%	15.6%
Terminal rate	6/36 (17%)	5/27 (19%)	4/38 (11%)	4/35 (11%)
First incidence (days)	716	579	624	522
Life table test	P = 0.278N	P = 0.290	P = 0.345N	P = 0.517N
Logistic regression test	P = 0.292N	P = 0.383	P = 0.374N	P = 0.492N
Cochran-Armitage test	P = 0.319N			
Fisher exact test		P = 0.500	P = 0.380N	P = 0.500N

TABLE E2
Statistical Analysis of Primary Neoplasms in Male Mice in the 2-Year Gavage Study of AZT/500 U α-Interferon A/D

	Vehicle Control	30 mg AZT/kg + 500 U α-IFN A/D	60 mg AZT/kg + 500 U α-IFN A/D	120 mg AZT/kg + 500 U α-IFN A/D
All Organs: Benign Neoplasms				
Overall rate	26/50 (52%)	20/50 (40%)	26/50 (52%)	30/50 (60%)
Adjusted rate	63.0%	58.4%	64.8%	76.8%
Terminal rate	21/36 (58%)	13/27 (48%)	24/38 (63%)	26/35 (74%)
First incidence (days)	477	518	563	638
Life table test	P = 0.243	P = 0.569	P = 0.478N	P = 0.230
Logistic regression test	P = 0.207	P = 0.341N	P = 0.582N	P = 0.283
Cochran-Armitage test	P = 0.141			
Fisher exact test		P = 0.158N	P = 0.579N	P = 0.273
All Organs: Malignant Neoplasms				
Overall rate	30/50 (60%)	33/50 (66%)	29/50 (58%)	33/50 (66%)
Adjusted rate	63.7%	74.2%	64.3%	67.3%
Terminal rate	19/36 (53%)	16/27 (59%)	22/38 (58%)	19/35 (54%)
First incidence (days)	374	296	598	522
Life table test	P = 0.484N	P = 0.081	P = 0.418N	P = 0.347
Logistic regression test	P = 0.401	P = 0.313	P = 0.529N	P = 0.446
Cochran-Armitage test	P = 0.397			
Fisher exact test		P = 0.339	P = 0.500N	P = 0.339
All Organs: Benign or Malignant Neoplasms				
Overall rate	40/50 (80%)	41/50 (82%)	42/50 (84%)	47/50 (94%)
Adjusted rate	83.3%	89.1%	89.4%	95.9%
Terminal rate	28/36 (78%)	22/27 (81%)	33/38 (87%)	33/35 (94%)
First incidence (days)	374	296	563	522
Life table test	P = 0.272	P = 0.064	P = 0.559	P = 0.121
Logistic regression test	P = 0.044	P = 0.293	P = 0.311	P = 0.043
Cochran-Armitage test	P = 0.031			
Fisher exact test		P = 0.500	P = 0.398	P = 0.036

(T)Terminal sacrifice
[a] Number of neoplasm-bearing animals/number of animals examined. Denominator is number of animals examined microscopically for adrenal gland, liver, lung, and thyroid gland; for other tissues, denominator is number of animals necropsied.
[b] 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 incidence are the P values associated with the trend test. Beneath the dosed group incidence are the P values corresponding to pairwise comparisons between the vehicle controls and that 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 Cochran-Armitage and Fisher exact tests compare directly the overall incidence rates. For all tests, a negative trend or a lower incidence in a dose group is indicated by **N**.
[e] Not applicable; no neoplasms in animal group
[f] Value of statistic cannot be computed.

TABLE E3
Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the 2-Year Gavage Study of AZT/500 U α-Interferon A/D[a]

	Vehicle Control	30 mg AZT/kg + 500 U α-IFN A/D	60 mg AZT/kg + 500 U α-IFN A/D	120 mg AZT/kg + 500 U α-IFN A/D
Disposition Summary				
Animals initially in study	50	50	50	50
Early deaths				
Accidental deaths		2	3	
Moribund	13	14	5	9
Natural deaths	1	7	4	6
Survivors				
Terminal sacrifice	36	27	38	35
Animals examined microscopically	50	50	50	50
Alimentary System				
Esophagus	(50)	(50)	(50)	(50)
Inflammation, chronic				1 (2%)
Perforation		2 (4%)	1 (2%)	
Gallbladder	(50)	(47)	(50)	(46)
Inflammation, chronic	1 (2%)			
Intestine large, colon	(50)	(50)	(50)	(50)
Edema	2 (4%)			
Parasite metazoan		1 (2%)		
Intestine large, cecum	(50)	(50)	(50)	(49)
Edema	1 (2%)	2 (4%)	1 (2%)	
Parasite metazoan	3 (6%)	7 (14%)	3 (6%)	5 (10%)
Intestine small, ileum	(50)	(48)	(49)	(50)
Peyer's patch, hyperplasia, lymphoid	1 (2%)			1 (2%)
Liver	(50)	(50)	(50)	(50)
Angiectasis	2 (4%)	2 (4%)	1 (2%)	
Basophilic focus	4 (8%)	1 (2%)	2 (4%)	1 (2%)
Clear cell focus	1 (2%)	1 (2%)	1 (2%)	1 (2%)
Eosinophilic focus	2 (4%)	1 (2%)	6 (12%)	1 (2%)
Hematopoietic cell proliferation	1 (2%)			1 (2%)
Inflammation, chronic	39 (78%)	38 (76%)	38 (76%)	44 (88%)
Metaplasia, osseous	2 (4%)	1 (2%)	1 (2%)	
Mixed cell focus	1 (2%)		2 (4%)	1 (2%)
Necrosis, focal	1 (2%)	7 (14%)		4 (8%)
Pigmentation, focal	2 (4%)		1 (2%)	1 (2%)
Vacuolization cytoplasmic	3 (6%)	2 (4%)	1 (2%)	
Bile duct, hyperplasia	26 (52%)	26 (52%)	26 (52%)	23 (46%)
Hepatocyte, karyomegaly	33 (66%)	31 (62%)	35 (70%)	40 (80%)
Mesentery	(1)	(2)	(1)	
Fat, necrosis	1 (100%)		1 (100%)	
Pancreas	(50)	(50)	(50)	(50)
Cyst	1 (2%)		2 (4%)	
Acinus, atrophy, diffuse	2 (4%)	1 (2%)	2 (4%)	
Salivary glands	(50)	(50)	(50)	(50)
Inflammation, chronic	1 (2%)	3 (6%)	1 (2%)	1 (2%)

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

TABLE E3
Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the 2-Year Gavage Study of AZT/500 U α-Interferon A/D

	Vehicle Control	30 mg AZT/kg + 500 U α-IFN A/D	60 mg AZT/kg + 500 U α-IFN A/D	120 mg AZT/kg + 500 U α-IFN A/D
Alimentary System (continued)				
Stomach, forestomach	(50)	(50)	(50)	(50)
Ulcer	1 (2%)			1 (2%)
Epithelium, hyperplasia	2 (4%)		2 (4%)	3 (6%)
Stomach, glandular	(50)	(50)	(50)	(50)
Edema				2 (4%)
Erosion		1 (2%)		
Ulcer	1 (2%)			
Cardiovascular System				
Blood vessel	(50)	(50)	(50)	(50)
Hypertrophy		1 (2%)		1 (2%)
Inflammation, chronic		1 (2%)	2 (4%)	2 (4%)
Heart	(50)	(50)	(50)	(50)
Fibrosis		1 (2%)		
Hemorrhage		1 (2%)		
Inflammation, chronic		5 (10%)	1 (2%)	
Mineralization		2 (4%)		1 (2%)
Thrombosis	1 (2%)		1 (2%)	
Endocrine System				
Adrenal cortex	(50)	(50)	(50)	(50)
Accessory adrenal cortical nodule	7 (14%)	6 (12%)	1 (2%)	1 (2%)
Cytoplasmic alteration, focal	9 (18%)	7 (14%)	10 (20%)	12 (24%)
Hyperplasia, focal	7 (14%)	3 (6%)	8 (16%)	16 (32%)
Hypertrophy, diffuse		1 (2%)		
Hypertrophy, focal	11 (22%)	5 (10%)	14 (28%)	13 (26%)
Capsule, hyperplasia, focal	4 (8%)	2 (4%)	3 (6%)	4 (8%)
Adrenal medulla	(50)	(50)	(50)	(50)
Hyperplasia	2 (4%)	1 (2%)	1 (2%)	
Islets, pancreatic	(50)	(50)	(50)	(50)
Hyperplasia	4 (8%)	4 (8%)	5 (10%)	7 (14%)
Parathyroid gland	(48)	(47)	(48)	(47)
Cyst		1 (2%)	1 (2%)	1 (2%)
Pituitary gland	(48)	(43)	(48)	(47)
Pars distalis, cyst	1 (2%)	1 (2%)		
Pars distalis, hemorrhage			1 (2%)	
Pars distalis, hyperplasia, focal			1 (2%)	
Thyroid gland	(50)	(50)	(50)	(49)
Degeneration, cystic, focal	12 (24%)	14 (28%)	11 (22%)	14 (29%)
Follicle, cyst	3 (6%)	4 (8%)	7 (14%)	5 (10%)
Follicular cell, hyperplasia	12 (24%)	15 (30%)	19 (38%)	10 (20%)
General Body System				
None				

TABLE E3
Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the 2-Year Gavage Study of AZT/500 U α-Interferon A/D

	Vehicle Control	30 mg AZT/kg + 500 U α-IFN A/D	60 mg AZT/kg + 500 U α-IFN A/D	120 mg AZT/kg + 500 U α-IFN A/D
Genital System				
Epididymis	(50)	(50)	(50)	(50)
Granuloma sperm			2 (4%)	
Preputial gland	(48)	(48)	(50)	(50)
Cyst	10 (21%)	7 (15%)	4 (8%)	4 (8%)
Inflammation, chronic	7 (15%)	13 (27%)	6 (12%)	4 (8%)
Testes	(50)	(50)	(50)	(50)
Atrophy	1 (2%)	1 (2%)	3 (6%)	2 (4%)
Cyst			1 (2%)	
Hematopoietic System				
Bone marrow	(50)	(50)	(50)	(50)
Hyperplasia	14 (28%)	23 (46%)	16 (32%)	21 (42%)
Lymph node	(5)	(8)	(5)	(5)
Bronchial, hyperplasia, lymphoid			1 (20%)	1 (20%)
Mediastinal, hemorrhage		1 (13%)		
Mediastinal, hyperplasia, lymphoid	1 (20%)		1 (20%)	
Pancreatic, hyperplasia, lymphoid			1 (20%)	
Renal, hemorrhage		1 (13%)		
Lymph node, mandibular	(46)	(47)	(49)	(46)
Hyperplasia, lymphoid	2 (4%)	4 (9%)	2 (4%)	2 (4%)
Pigmentation	4 (9%)	10 (21%)	13 (27%)	8 (17%)
Lymph node, mesenteric	(50)	(48)	(50)	(47)
Hematopoietic cell proliferation	7 (14%)	6 (13%)	1 (2%)	7 (15%)
Hemorrhage	19 (38%)	15 (31%)	17 (34%)	18 (38%)
Hyperplasia, lymphoid	6 (12%)	5 (10%)	12 (24%)	8 (17%)
Spleen	(50)	(49)	(49)	(50)
Atrophy	1 (2%)	1 (2%)	1 (2%)	
Hematopoietic cell proliferation	20 (40%)	29 (59%)	17 (35%)	23 (46%)
Hyperplasia, lymphoid	6 (12%)	4 (8%)	4 (8%)	1 (2%)
Necrosis, focal				1 (2%)
Pigmentation	1 (2%)	1 (2%)		
Thymus	(45)	(40)	(42)	(43)
Atrophy	1 (2%)	3 (8%)		
Integumentary System				
Skin	(50)	(50)	(50)	(50)
Mineralization	1 (2%)			
Ulcer		2 (4%)		2 (4%)
Subcutaneous tissue, edema	4 (8%)	4 (8%)	2 (4%)	1 (2%)
Musculoskeletal System				
Bone	(50)	(50)	(50)	(50)
Hyperostosis	42 (84%)	31 (62%)	39 (78%)	39 (78%)
Femur, osteopetrosis				1 (2%)
Skeletal muscle	(50)	(50)	(50)	(50)
Atrophy		2 (4%)		

TABLE E3
Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the 2-Year Gavage Study of AZT/500 U α-Interferon A/D

	Vehicle Control	30 mg AZT/kg + 500 U α-IFN A/D	60 mg AZT/kg + 500 U α-IFN A/D	120 mg AZT/kg + 500 U α-IFN A/D
Nervous System				
Brain	(50)	(50)	(50)	(50)
Atrophy, focal		1 (2%)		
Necrosis				1 (2%)
Respiratory System				
Lung	(49)	(50)	(50)	(50)
Hemorrhage	1 (2%)	1 (2%)	5 (10%)	1 (2%)
Infiltration cellular, histiocyte	6 (12%)	6 (12%)	8 (16%)	4 (8%)
Inflammation, chronic	1 (2%)	1 (2%)	1 (2%)	1 (2%)
Inflammation, suppurative		1 (2%)		
Thrombosis		1 (2%)	1 (2%)	
Alveolar epithelium, hyperplasia	1 (2%)		2 (4%)	
Nose	(50)	(50)	(50)	(50)
Inflammation, suppurative	1 (2%)	1 (2%)	2 (4%)	5 (10%)
Special Senses System				
Eye	(1)	(1)		(1)
Atrophy	1 (100%)			1 (100%)
Inflammation, chronic		1 (100%)		
Urinary System				
Kidney	(50)	(50)	(50)	(50)
Infarct		1 (2%)	1 (2%)	
Inflammation, chronic	1 (2%)			
Metaplasia, focal, osseous	2 (4%)	1 (2%)		
Nephropathy	47 (94%)	46 (92%)	44 (88%)	49 (98%)
Pelvis, dilatation		1 (2%)	1 (2%)	
Renal tubule, accumulation, hyaline droplet	1 (2%)			
Renal tubule, hyaline droplet		1 (2%)		
Renal tubule, necrosis				1 (2%)
Renal tubule, pigmentation	1 (2%)	1 (2%)	1 (2%)	1 (2%)
Transitional epithelium, hyperplasia			1 (2%)	

APPENDIX F
SUMMARY OF LESIONS IN FEMALE MICE IN THE 2-YEAR GAVAGE STUDY OF AZT/500 U α-INTERFERON A/D

TABLE F1
Summary of the Incidence of Neoplasms in Female Mice in the 2-Year Gavage Study of AZT/500 U α-Interferon A/D[a]

	Vehicle Control	30 mg AZT/kg + 500 U α-IFN A/D	60 mg AZT/kg + 500 U α-IFN A/D	120 mg AZT/kg + 500 U α-IFN A/D
Disposition Summary				
Animals initially in study	50	50	50	50
Early deaths				
Accidental deaths	3	4	2	4
Moribund	7	8	11	12
Natural deaths	7	6	5	9
Survivors				
Terminal sacrifice	33	32	32	24
Missing				1
Animals examined microscopically	50	50	50	49
Alimentary System				
Gallbladder	(48)	(47)	(49)	(48)
Fibrosarcoma, metastatic, uterus			1 (2%)	
Intestine large, colon	(50)	(48)	(50)	(49)
Leiomyoma		1 (2%)		
Intestine small, jejunum	(50)	(49)	(49)	(49)
Histiocytic sarcoma		1 (2%)		
Intestine small, ileum	(49)	(49)	(46)	(47)
Liver	(50)	(50)	(50)	(49)
Carcinoma, metastatic, uterus			1 (2%)	
Fibrosarcoma, metastatic, mesentery			1 (2%)	
Fibrous histiocytoma, metastatic, lymph node, mesenteric			1 (2%)	
Hemangiosarcoma				1 (2%)
Hemangiosarcoma, multiple				1 (2%)
Hepatocellular carcinoma	12 (24%)	2 (4%)	3 (6%)	6 (12%)
Hepatocellular carcinoma, multiple	1 (2%)	2 (4%)	2 (4%)	4 (8%)
Hepatocellular adenoma	8 (16%)	14 (28%)	11 (22%)	11 (22%)
Hepatocellular adenoma, multiple	3 (6%)	3 (6%)	3 (6%)	3 (6%)
Histiocytic sarcoma	2 (4%)	3 (6%)	1 (2%)	
Mesentery	(10)	(11)	(9)	(6)
Carcinoma, metastatic, uterus			1 (11%)	
Fibrosarcoma			1 (11%)	
Hemangioma	1 (10%)			
Squamous cell carcinoma, metastatic, vagina				1 (17%)
Pancreas	(50)	(50)	(50)	(49)
Carcinoma, metastatic, uterus			1 (2%)	
Fibrosarcoma, metastatic, mesentery			1 (2%)	
Histiocytic sarcoma		1 (2%)		
Salivary glands	(50)	(49)	(49)	(48)
Stomach, forestomach	(50)	(50)	(50)	(49)
Carcinoma, metastatic, uterus			1 (2%)	
Squamous cell carcinoma		1 (2%)		
Squamous cell papilloma	1 (2%)	1 (2%)	1 (2%)	1 (2%)
Stomach, glandular	(50)	(50)	(50)	(49)
Carcinoma, metastatic, uterus			1 (2%)	
Fibrosarcoma, metastatic, mesentery			1 (2%)	
Histiocytic sarcoma		1 (2%)		

TABLE F1
Summary of the Incidence of Neoplasms in Female Mice in the 2-Year Gavage Study of AZT/500 U α-Interferon A/D

	Vehicle Control	30 mg AZT/kg + 500 U α-IFN A/D	60 mg AZT/kg + 500 U α-IFN A/D	120 mg AZT/kg + 500 U α-IFN A/D
Cardiovascular System				
Blood vessel	(50)	(50)	(50)	(49)
Heart	(50)	(50)	(50)	(49)
Endocrine System				
Adrenal cortex	(49)	(50)	(50)	(49)
Histiocytic sarcoma		1 (2%)		
Capsule, adenoma	1 (2%)			
Adrenal medulla	(49)	(49)	(49)	(48)
Pheochromocytoma malignant			2 (4%)	
Pheochromocytoma benign		1 (2%)		
Islets, pancreatic	(50)	(50)	(50)	(49)
Adenoma	1 (2%)			
Pituitary gland	(50)	(47)	(48)	(47)
Pars distalis, adenoma	7 (14%)	3 (6%)	4 (8%)	5 (11%)
Pars distalis, carcinoma	1 (2%)			
Pars intermedia, adenoma			2 (4%)	1 (2%)
Thyroid gland	(50)	(50)	(50)	(49)
Bilateral, follicular cell, carcinoma				1 (2%)
Follicular cell, adenoma	1 (2%)			1 (2%)
General Body System				
None				
Genital System				
Ovary	(49)	(49)	(49)	(49)
Cystadenoma		4 (8%)		2 (4%)
Fibrosarcoma, metastatic, uterus			1 (2%)	
Histiocytic sarcoma	1 (2%)	2 (4%)	1 (2%)	
Luteoma		1 (2%)		
Uterus	(50)	(50)	(50)	(49)
Fibrosarcoma			1 (2%)	
Hemangiosarcoma			1 (2%)	
Histiocytic sarcoma	2 (4%)	3 (6%)	1 (2%)	
Leiomyosarcoma			1 (2%)	
Endometrium, carcinoma			1 (2%)	1 (2%)
Endometrium, polyp stromal	4 (8%)		3 (6%)	2 (4%)
Endometrium, sarcoma stromal				1 (2%)
Vagina	(49)	(44)	(48)	(48)
Leiomyosarcoma, metastatic, uterus			1 (2%)	
Squamous cell carcinoma			5 (10%)	6 (13%)

TABLE F1
Summary of the Incidence of Neoplasms in Female Mice in the 2-Year Gavage Study of AZT/500 U α-Interferon A/D

	Vehicle Control	30 mg AZT/kg + 500 U α-IFN A/D	60 mg AZT/kg + 500 U α-IFN A/D	120 mg AZT/kg + 500 U α-IFN A/D
Hematopoietic System				
Bone marrow	(50)	(50)	(50)	(49)
Histiocytic sarcoma		1 (2%)		
Lymph node	(4)	(8)	(10)	(10)
Histiocytic sarcoma		1 (13%)		
Iliac, histiocytic sarcoma		1 (13%)	1 (10%)	
Inguinal, histiocytic sarcoma		1 (13%)		
Inguinal, squamous cell carcinoma, metastatic, vagina				1 (10%)
Mediastinal, fibrosarcoma, metastatic, mesentery			1 (10%)	
Mediastinal, fibrous histiocytoma, metastatic, lymph node, mesenteric			1 (10%)	
Mediastinal, histiocytic sarcoma		1 (13%)		
Renal, histiocytic sarcoma		1 (13%)	1 (10%)	
Lymph node, mandibular	(49)	(45)	(46)	(48)
Histiocytic sarcoma		1 (2%)		
Lymph node, mesenteric	(50)	(47)	(49)	(49)
Fibrous histiocytoma		1 (2%)	1 (2%)	
Histiocytic sarcoma		2 (4%)	1 (2%)	
Spleen	(50)	(50)	(50)	(49)
Hemangiosarcoma			1 (2%)	
Histiocytic sarcoma	1 (2%)	2 (4%)		
Thymus	(47)	(46)	(46)	(45)
Fibrosarcoma, metastatic, mesentery			1 (2%)	
Histiocytic sarcoma		2 (4%)		
Integumentary System				
Mammary gland	(50)	(49)	(50)	(49)
Carcinoma		1 (2%)		
Skin	(49)	(50)	(50)	(49)
Squamous cell carcinoma, metastatic, vagina				1 (2%)
Subcutaneous tissue, fibrosarcoma	1 (2%)	4 (8%)	2 (4%)	1 (2%)
Musculoskeletal System				
Bone	(49)	(50)	(50)	(49)
Osteosarcoma		1 (2%)		1 (2%)
Skeletal muscle	(50)	(50)	(50)	(49)
Carcinoma, metastatic, uterus			1 (2%)	
Fibrosarcoma, metastatic, mesentery			1 (2%)	
Fibrosarcoma, metastatic, uterus			1 (2%)	
Sarcoma	1 (2%)			
Nervous System				
Brain	(50)	(50)	(50)	(49)
Carcinoma, metastatic, pituitary gland	1 (2%)			
Spinal cord	(2)	(2)	(7)	(3)

TABLE F1
Summary of the Incidence of Neoplasms in Female Mice in the 2-Year Gavage Study of AZT/500 U α-Interferon A/D

	Vehicle Control	30 mg AZT/kg + 500 U α-IFN A/D	60 mg AZT/kg + 500 U α-IFN A/D	120 mg AZT/kg + 500 U α-IFN A/D
Respiratory System				
Lung	(50)	(50)	(50)	(49)
Alveolar/bronchiolar adenoma	1 (2%)	3 (6%)	1 (2%)	1 (2%)
Alveolar/bronchiolar carcinoma		2 (4%)	1 (2%)	1 (2%)
Carcinoma, metastatic, uterus			1 (2%)	
Hepatocellular carcinoma, metastatic, liver	1 (2%)			
Histiocytic sarcoma	1 (2%)	1 (2%)	1 (2%)	
Special Senses System				
Harderian gland		(2)	(1)	
Adenoma		2 (100%)	1 (100%)	
Urinary System				
Kidney	(50)	(50)	(50)	(49)
Histiocytic sarcoma		2 (4%)		
Osteosarcoma, metastatic, bone		1 (2%)		
Squamous cell carcinoma, metastatic, vagina				1 (2%)
Urinary bladder	(50)	(50)	(50)	(49)
Systemic Lesions				
Multiple organs[b]	(50)	(50)	(50)	(49)
Histiocytic sarcoma	3 (6%)	3 (6%)	1 (2%)	
Lymphoma malignant	13 (26%)	8 (16%)	12 (24%)	11 (22%)
Neoplasm Summary				
Total animals with primary neoplasms[c]	35	39	38	36
Total primary neoplasms	60	58	61	62
Total animals with benign neoplasms	23	25	23	20
Total benign neoplasms	28	33	26	27
Total animals with malignant neoplasms	23	23	28	28
Total malignant neoplasms	32	25	35	35
Total animals with metastatic neoplasms	2	1	5	1
Total metastatic neoplasms	2	1	19	4

[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 F2
Statistical Analysis of Primary Neoplasms in Female Mice in the 2-Year Gavage Study of AZT/500 U α-Interferon A/D

	Vehicle Control	30 mg AZT/kg + 500 U α-IFN A/D	60 mg AZT/kg + 500 U α-IFN A/D	120 mg AZT/kg + 500 U α-IFN A/D
Liver: Hepatocellular Adenoma				
Overall rate[a]	11/50 (22%)	17/50 (34%)	14/50 (28%)	14/49 (29%)
Adjusted rate[b]	31.1%	51.5%	42.4%	49.0%
Terminal rate[c]	9/33 (27%)	16/32 (50%)	13/32 (41%)	10/24 (42%)
First incidence (days)	649	667	713	617
Life table test[d]	P = 0.103	P = 0.097	P = 0.282	P = 0.096
Logistic regression test[d]	P = 0.173	P = 0.052	P = 0.239	P = 0.161
Cochran-Armitage test[d]	P = 0.340			
Fisher exact test[d]		P = 0.133	P = 0.322	P = 0.301
Liver: Hepatocellular Carcinoma				
Overall rate	13/50 (26%)	4/50 (8%)	5/50 (10%)	10/49 (20%)
Adjusted rate	35.4%	11.8%	14.7%	32.5%
Terminal rate	10/33 (30%)	3/32 (9%)	3/32 (9%)	5/24 (21%)
First incidence (days)	649	628	707	589
Life table test	P = 0.473N	P = 0.025N	P = 0.047N	P = 0.573
Logistic regression test	P = 0.357N	P = 0.026N	P = 0.041N	P = 0.448N
Cochran-Armitage test	P = 0.287N			
Fisher exact test		P = 0.016N	P = 0.033N	P = 0.337N
Liver: Hepatocellular Adenoma or Carcinoma				
Overall rate	20/50 (40%)	20/50 (40%)	18/50 (36%)	22/49 (45%)
Adjusted rate	53.6%	58.7%	52.9%	65.9%
Terminal rate	16/33 (48%)	18/32 (56%)	16/32 (50%)	13/24 (54%)
First incidence (days)	649	628	707	589
Life table test	P = 0.099	P = 0.499	P = 0.478N	P = 0.092
Logistic regression test	P = 0.198	P = 0.360	P = 0.533N	P = 0.191
Cochran-Armitage test	P = 0.393			
Fisher exact test		P = 0.581N	P = 0.418N	P = 0.386
Lung: Alveolar/bronchiolar Adenoma				
Overall rate	1/50 (2%)	3/50 (6%)	1/50 (2%)	1/49 (2%)
Adjusted rate	3.0%	9.4%	3.1%	4.2%
Terminal rate	1/33 (3%)	3/32 (9%)	1/32 (3%)	1/24 (4%)
First incidence (days)	729 (T)	729 (T)	729 (T)	729 (T)
Life table test	P = 0.526N	P = 0.293	P = 0.755	P = 0.689
Logistic regression test	P = 0.526N	P = 0.293	P = 0.755	P = 0.689
Cochran-Armitage test	P = 0.433N			
Fisher exact test		P = 0.309	P = 0.753N	P = 0.747
Lung: Alveolar/bronchiolar Adenoma or Carcinoma				
Overall rate	1/50 (2%)	4/50 (8%)	2/50 (4%)	2/49 (4%)
Adjusted rate	3.0%	12.5%	5.6%	7.2%
Terminal rate	1/33 (3%)	4/32 (13%)	1/32 (3%)	1/24 (4%)
First incidence (days)	729 (T)	729 (T)	647	673
Life table test	P = 0.385	P = 0.169	P = 0.484	P = 0.398
Logistic regression test	P = 0.445	P = 0.169	P = 0.495	P = 0.451
Cochran-Armitage test	P = 0.492			
Fisher exact test		P = 0.181	P = 0.500	P = 0.492

TABLE F2
Statistical Analysis of Primary Neoplasms in Female Mice in the 2-Year Gavage Study of AZT/500 U α-Interferon A/D

	Vehicle Control	30 mg AZT/kg + 500 U α-IFN A/D	60 mg AZT/kg + 500 U α-IFN A/D	120 mg AZT/kg + 500 U α-IFN A/D
Ovary: Cystadenoma				
Overall rate	0/49 (0%)	4/49 (8%)	0/49 (0%)	2/49 (4%)
Adjusted rate	0.0%	12.5%	0.0%	6.7%
Terminal rate	0/33 (0%)	4/32 (13%)	0/31 (0%)	1/24 (4%)
First incidence (days)	—[e]	729 (T)	—	604
Life table test	P = 0.336	P = 0.058	—[f]	P = 0.193
Logistic regression test	P = 0.395	P = 0.058	—	P = 0.231
Cochran-Armitage test	P = 0.426			
Fisher exact test		P = 0.059	—	P = 0.247
Pituitary Gland (Pars Distalis): Adenoma				
Overall rate	7/50 (14%)	3/47 (6%)	4/48 (8%)	5/47 (11%)
Adjusted rate	18.3%	9.4%	10.9%	17.9%
Terminal rate	4/33 (12%)	3/32 (9%)	2/31 (6%)	3/24 (13%)
First incidence (days)	593	729 (T)	436	589
Life table test	P = 0.480N	P = 0.190N	P = 0.299N	P = 0.562N
Logistic regression test	P = 0.385N	P = 0.196N	P = 0.285N	P = 0.456N
Cochran-Armitage test	P = 0.365N			
Fisher exact test		P = 0.185N	P = 0.286N	P = 0.424N
Pituitary Gland (Pars Distalis): Adenoma or Carcinoma				
Overall rate	8/50 (16%)	3/47 (6%)	4/48 (8%)	5/47 (11%)
Adjusted rate	20.7%	9.4%	10.9%	17.9%
Terminal rate	4/33 (12%)	3/32 (9%)	2/31 (6%)	3/24 (13%)
First incidence (days)	593	729 (T)	436	589
Life table test	P = 0.364N	P = 0.129N	P = 0.214N	P = 0.457N
Logistic regression test	P = 0.276N	P = 0.130N	P = 0.198N	P = 0.350N
Cochran-Armitage test	P = 0.258N			
Fisher exact test		P = 0.120N	P = 0.199N	P = 0.318N
Skin (Subcutaneous Tissue): Fibrosarcoma				
Overall rate	1/50 (2%)	4/50 (8%)	2/50 (4%)	1/49 (2%)
Adjusted rate	2.5%	10.9%	5.7%	2.6%
Terminal rate	0/33 (0%)	2/32 (6%)	1/32 (3%)	0/24 (0%)
First incidence (days)	688	467	656	603
Life table test	P = 0.517N	P = 0.158	P = 0.472	P = 0.721
Logistic regression test	P = 0.446N	P = 0.179	P = 0.498	P = 0.759
Cochran-Armitage test	P = 0.443N			
Fisher exact test		P = 0.181	P = 0.500	P = 0.747
Uterus: Stromal Polyp				
Overall rate	4/50 (8%)	0/50 (0%)	3/50 (6%)	2/49 (4%)
Adjusted rate	10.7%	0.0%	8.7%	7.4%
Terminal rate	2/33 (6%)	0/32 (0%)	2/32 (6%)	1/24 (4%)
First incidence (days)	593	—	656	699
Life table test	P = 0.477N	P = 0.076N	P = 0.518N	P = 0.461N
Logistic regression test	P = 0.415N	P = 0.067N	P = 0.504N	P = 0.382N
Cochran-Armitage test	P = 0.388N			
Fisher exact test		P = 0.059N	P = 0.500N	P = 0.349N

TABLE F2
Statistical Analysis of Primary Neoplasms in Female Mice in the 2-Year Gavage Study of AZT/500 U α-Interferon A/D

	Vehicle Control	30 mg AZT/kg + 500 U α-IFN A/D	60 mg AZT/kg + 500 U α-IFN A/D	120 mg AZT/kg + 500 U α-IFN A/D
Uterus: Stromal Polyp or Stromal Sarcoma				
Overall rate	4/50 (8%)	0/50 (0%)	3/50 (6%)	3/49 (6%)
Adjusted rate	10.7%	0.0%	8.7%	10.9%
Terminal rate	2/33 (6%)	0/32 (0%)	2/32 (6%)	1/24 (4%)
First incidence (days)	593	—	656	699
Life table test	P = 0.454	P = 0.076N	P = 0.518N	P = 0.633N
Logistic regression test	P = 0.516	P = 0.067N	P = 0.504N	P = 0.559N
Cochran-Armitage test	P = 0.549			
Fisher exact test		P = 0.059N	P = 0.500N	P = 0.511N
Vagina: Squamous Cell Carcinoma				
Overall rate	0/50 (0%)	0/50 (0%)	5/50 (10%)	6/49 (12%)
Adjusted rate	0.0%	0.0%	15.6%	21.1%
Terminal rate	0/33 (0%)	0/32 (0%)	5/32 (16%)	3/24 (13%)
First incidence (days)	—	—	729 (T)	631
Life table test	P < 0.001	—	P = 0.030	P = 0.008
Logistic regression test	P < 0.001	—	P = 0.030	P = 0.011
Cochran-Armitage test	P = 0.001			
Fisher exact test		—	P = 0.028	P = 0.012
All Organs: Histiocytic Sarcoma				
Overall rate	3/50 (6%)	3/50 (6%)	1/50 (2%)	0/49 (0%)
Adjusted rate	7.8%	8.0%	2.5%	0.0%
Terminal rate	1/33 (3%)	1/32 (3%)	0/32 (0%)	0/24 (0%)
First incidence (days)	675	561	634	—
Life table test	P = 0.064N	P = 0.606	P = 0.339N	P = 0.179N
Logistic regression test	P = 0.045N	P = 0.658	P = 0.216N	P = 0.137N
Cochran-Armitage test	P = 0.044N			
Fisher exact test		P = 0.661N	P = 0.309N	P = 0.125N
All Organs: Malignant Lymphoma				
Overall rate	13/50 (26%)	8/50 (16%)	12/50 (24%)	11/49 (22%)
Adjusted rate	34.6%	19.6%	32.5%	34.9%
Terminal rate	9/33 (27%)	2/32 (6%)	8/32 (25%)	5/24 (21%)
First incidence (days)	675	441	514	604
Life table test	P = 0.365	P = 0.232N	P = 0.547N	P = 0.477
Logistic regression test	P = 0.528	P = 0.177N	P = 0.525N	P = 0.551N
Cochran-Armitage test	P = 0.490N			
Fisher exact test		P = 0.163N	P = 0.500N	P = 0.430N
All Organs: Benign Neoplasms				
Overall rate	23/50 (46%)	25/50 (50%)	23/50 (46%)	20/49 (41%)
Adjusted rate	57.2%	75.7%	59.8%	61.1%
Terminal rate	16/33 (48%)	24/32 (75%)	17/32 (53%)	12/24 (50%)
First incidence (days)	593	667	436	589
Life table test	P = 0.352	P = 0.329	P = 0.516	P = 0.366
Logistic regression test	P = 0.437N	P = 0.180	P = 0.559	P = 0.539N
Cochran-Armitage test	P = 0.291N			
Fisher exact test		P = 0.421	P = 0.579N	P = 0.376N

TABLE F2
Statistical Analysis of Primary Neoplasms in Female Mice in the 2-Year Gavage Study of AZT/500 U α-Interferon A/D

	Vehicle Control	30 mg AZT/kg + 500 U α-IFN A/D	60 mg AZT/kg + 500 U α-IFN A/D	120 mg AZT/kg + 500 U α-IFN A/D
All Organs: Malignant Neoplasms				
Overall rate	23/50 (46%)	23/50 (46%)	28/50 (56%)	28/49 (57%)
Adjusted rate	57.2%	52.9%	64.9%	71.3%
Terminal rate	16/33 (48%)	12/32 (38%)	17/32 (53%)	13/24 (54%)
First incidence (days)	649	441	436	589
Life table test	P = 0.025	P = 0.461	P = 0.190	P = 0.036
Logistic regression test	P = 0.081	P = 0.521	P = 0.190	P = 0.135
Cochran-Armitage test	P = 0.096			
Fisher exact test		P = 0.579N	P = 0.212	P = 0.182
All Organs: Benign or Malignant Neoplasms				
Overall rate	35/50 (70%)	39/50 (78%)	38/50 (76%)	36/49 (73%)
Adjusted rate	81.3%	90.6%	84.4%	89.9%
Terminal rate	25/33 (76%)	28/32 (88%)	25/32 (78%)	20/24 (83%)
First incidence (days)	593	441	436	589
Life table test	P = 0.059	P = 0.178	P = 0.280	P = 0.052
Logistic regression test	P = 0.232	P = 0.110	P = 0.295	P = 0.160
Cochran-Armitage test	P = 0.407			
Fisher exact test		P = 0.247	P = 0.326	P = 0.437

(T)Terminal sacrifice
[a] Number of neoplasm-bearing animals/number of animals examined. Denominator is number of animals examined microscopically for liver, lung, ovary, pituitary gland, and uterus; 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 incidence are the P values associated with the trend test. Beneath the dosed group incidence are the P values corresponding to pairwise comparisons between the vehicle controls and that 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 Cochran-Armitage and Fisher exact tests compare directly the overall incidence rates. For all tests, a negative trend or a lower incidence in a dose group is indicated by **N**.
[e] Not applicable; no neoplasms in animal group
[f] Value of statistic cannot be computed.

TABLE F3
Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 2-Year Gavage Study of AZT/500 U α-Interferon A/D[a]

	Vehicle Control	30 mg AZT/kg + 500 U α-IFN A/D	60 mg AZT/kg + 500 U α-IFN A/D	120 mg AZT/kg + 500 U α-IFN A/D
Disposition Summary				
Animals initially in study	50	50	50	50
Early deaths				
Accidental deaths	3	4	2	4
Moribund	7	8	11	12
Natural deaths	7	6	5	9
Survivors				
Terminal sacrifice	33	32	32	24
Missing				1
Animals examined microscopically	50	50	50	49
Alimentary System				
Esophagus	(50)	(50)	(50)	(48)
Inflammation, chronic				1 (2%)
Perforation	2 (4%)	2 (4%)	1 (2%)	2 (4%)
Intestine large, colon	(50)	(48)	(50)	(49)
Parasite metazoan				1 (2%)
Intestine large, rectum	(50)	(50)	(50)	(49)
Parasite metazoan	1 (2%)			
Intestine large, cecum	(50)	(49)	(50)	(48)
Edema	1 (2%)	2 (4%)		1 (2%)
Parasite metazoan			1 (2%)	2 (4%)
Intestine small, duodenum	(48)	(49)	(48)	(48)
Erosion	1 (2%)			
Ulcer			1 (2%)	
Intestine small, jejunum	(50)	(49)	(49)	(49)
Peyer's patch, hyperplasia, lymphoid				1 (2%)
Intestine small, ileum	(49)	(49)	(46)	(47)
Peyer's patch, hyperplasia, lymphoid			1 (2%)	1 (2%)
Liver	(50)	(50)	(50)	(49)
Angiectasis		1 (2%)		
Basophilic focus			1 (2%)	3 (6%)
Clear cell focus				2 (4%)
Eosinophilic focus	5 (10%)	1 (2%)	5 (10%)	3 (6%)
Hematopoietic cell proliferation	3 (6%)	3 (6%)	4 (8%)	4 (8%)
Inflammation, chronic	6 (12%)	6 (12%)	5 (10%)	7 (14%)
Mixed cell focus	2 (4%)		1 (2%)	1 (2%)
Necrosis, focal	4 (8%)		6 (12%)	8 (16%)
Pigmentation, focal		1 (2%)		1 (2%)
Vacuolization cytoplasmic			1 (2%)	2 (4%)
Bile duct, hyperplasia		1 (2%)		
Centrilobular, necrosis				1 (2%)
Centrilobular, necrosis, focal		1 (2%)		
Hepatocyte, karyomegaly		1 (2%)	1 (2%)	
Hepatocyte, mixed cell focus			1 (2%)	
Mesentery	(10)	(11)	(9)	(6)
Fat, necrosis	8 (80%)	9 (82%)	7 (78%)	3 (50%)
Pancreas	(50)	(50)	(50)	(49)
Cyst	3 (6%)			1 (2%)
Acinus, atrophy, diffuse				3 (6%)

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

TABLE F3
Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 2-Year Gavage Study of AZT/500 U α-Interferon A/D

	Vehicle Control	30 mg AZT/kg + 500 U α-IFN A/D	60 mg AZT/kg + 500 U α-IFN A/D	120 mg AZT/kg + 500 U α-IFN A/D
Alimentary System (continued)				
Salivary glands	(50)	(49)	(49)	(48)
Inflammation, chronic	2 (4%)	5 (10%)	2 (4%)	3 (6%)
Stomach, forestomach	(50)	(50)	(50)	(49)
Edema		1 (2%)		
Epithelium, hyperplasia	2 (4%)	2 (4%)	2 (4%)	1 (2%)
Stomach, glandular	(50)	(50)	(50)	(49)
Edema		2 (4%)		1 (2%)
Erosion				3 (6%)
Cardiovascular System				
Blood vessel	(50)	(50)	(50)	(49)
Hypertrophy				1 (2%)
Inflammation, chronic				1 (2%)
Heart	(50)	(50)	(50)	(49)
Inflammation, chronic	1 (2%)	2 (4%)	1 (2%)	1 (2%)
Mineralization		3 (6%)		
Thrombosis	2 (4%)			
Endocrine System				
Adrenal cortex	(49)	(50)	(50)	(49)
Accessory adrenal cortical nodule	7 (14%)	5 (10%)	6 (12%)	5 (10%)
Hyperplasia, focal	1 (2%)	2 (4%)	1 (2%)	3 (6%)
Hypertrophy, focal				2 (4%)
Capsule, hyperplasia, focal	2 (4%)	1 (2%)		2 (4%)
Adrenal medulla	(49)	(49)	(49)	(48)
Hyperplasia	2 (4%)	1 (2%)	1 (2%)	
Islets, pancreatic	(50)	(50)	(50)	(49)
Hyperplasia	1 (2%)	2 (4%)	3 (6%)	2 (4%)
Parathyroid gland	(45)	(43)	(46)	(44)
Cyst			3 (7%)	1 (2%)
Pituitary gland	(50)	(47)	(48)	(47)
Pars distalis, angiectasis		3 (6%)	1 (2%)	
Pars distalis, hyperplasia, focal	3 (6%)	9 (19%)	5 (10%)	4 (9%)
Thyroid gland	(50)	(50)	(50)	(49)
Degeneration, cystic, focal	12 (24%)	15 (30%)	13 (26%)	9 (18%)
Follicle, cyst	8 (16%)	4 (8%)	7 (14%)	9 (18%)
Follicular cell, hyperplasia	27 (54%)	16 (32%)	22 (44%)	13 (27%)
General Body System				
None				
Genital System				
Ovary	(49)	(49)	(49)	(49)
Angiectasis	5 (10%)	10 (20%)	7 (14%)	6 (12%)
Cyst	9 (18%)	6 (12%)	13 (27%)	7 (14%)
Hyperplasia, tubular				1 (2%)

TABLE F3
Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 2-Year Gavage Study of AZT/500 U α-Interferon A/D

	Vehicle Control	30 mg AZT/kg + 500 U α-IFN A/D	60 mg AZT/kg + 500 U α-IFN A/D	120 mg AZT/kg + 500 U α-IFN A/D
Genital System (continued)				
Uterus	(50)	(50)	(50)	(49)
Angiectasis	1 (2%)		1 (2%)	2 (4%)
Hydrometra	14 (28%)	17 (34%)	19 (38%)	25 (51%)
Inflammation, suppurative	2 (4%)	2 (4%)	2 (4%)	3 (6%)
Endometrium, hyperplasia, cystic	35 (70%)	41 (82%)	36 (72%)	31 (63%)
Vagina	(49)	(44)	(48)	(48)
Epithelium, hyperplasia		4 (9%)	6 (13%)	11 (23%)
Epithelium, hyperplasia, atypical			2 (4%)	1 (2%)
Hematopoietic System				
Bone marrow	(50)	(50)	(50)	(49)
Hyperplasia	10 (20%)	14 (28%)	16 (32%)	14 (29%)
Myelofibrosis	2 (4%)	1 (2%)	2 (4%)	3 (6%)
Lymph node	(4)	(8)	(10)	(10)
Iliac, hemorrhage			1 (10%)	
Iliac, hyperplasia, lymphoid			2 (20%)	
Inguinal, hyperplasia, lymphoid			1 (10%)	1 (10%)
Mediastinal, hematopoietic cell proliferation			1 (10%)	
Mediastinal, hyperplasia, lymphoid	1 (25%)		1 (10%)	1 (10%)
Renal, hemorrhage			1 (10%)	
Renal, hyperplasia, lymphoid			1 (10%)	
Lymph node, mandibular	(49)	(45)	(46)	(48)
Hematopoietic cell proliferation		1 (2%)	1 (2%)	
Hemorrhage		2 (4%)		
Hyperplasia, lymphoid	2 (4%)	5 (11%)	4 (9%)	2 (4%)
Pigmentation	7 (14%)	8 (18%)	12 (26%)	14 (29%)
Lymph node, mesenteric	(50)	(47)	(49)	(49)
Hematopoietic cell proliferation		3 (6%)	1 (2%)	3 (6%)
Hemorrhage	5 (10%)	5 (11%)	2 (4%)	2 (4%)
Hyperplasia, lymphoid	1 (2%)	6 (13%)	8 (16%)	2 (4%)
Spleen	(50)	(50)	(50)	(49)
Hematopoietic cell proliferation	25 (50%)	28 (56%)	26 (52%)	30 (61%)
Hyperplasia, lymphoid	6 (12%)	17 (34%)	10 (20%)	3 (6%)
Pigmentation	1 (2%)	2 (4%)	3 (6%)	2 (4%)
Thymus	(47)	(46)	(46)	(45)
Atrophy	1 (2%)		3 (7%)	2 (4%)
Hyperplasia, lymphoid				1 (2%)
Integumentary System				
Mammary gland	(50)	(49)	(50)	(49)
Hyperplasia	5 (10%)		7 (14%)	2 (4%)
Skin	(49)	(50)	(50)	(49)
Ulcer			1 (2%)	
Epidermis, hyperplasia, focal		1 (2%)		1 (2%)
Subcutaneous tissue, edema	1 (2%)	3 (6%)	1 (2%)	
Subcutaneous tissue, hemorrhage, focal				1 (2%)
Subcutaneous tissue, inflammation, chronic, focal	1 (2%)	1 (2%)		1 (2%)

TABLE F3
Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 2-Year Gavage Study of AZT/500 U α-Interferon A/D

	Vehicle Control	30 mg AZT/kg + 500 U α-IFN A/D	60 mg AZT/kg + 500 U α-IFN A/D	120 mg AZT/kg + 500 U α-IFN A/D
Musculoskeletal System				
Bone	(49)	(50)	(50)	(49)
Hyperostosis	40 (82%)	39 (78%)	41 (82%)	34 (69%)
Femur, osteopetrosis		1 (2%)	3 (6%)	
Skeletal muscle	(50)	(50)	(50)	(49)
Hemorrhage			1 (2%)	
Nervous System				
Brain	(50)	(50)	(50)	(49)
Atrophy, focal	4 (8%)	1 (2%)	3 (6%)	1 (2%)
Developmental malformation				1 (2%)
Hydrocephalus			1 (2%)	1 (2%)
Necrosis	1 (2%)	1 (2%)		1 (2%)
Peripheral nerve	(2)	(1)	(6)	(3)
Atrophy		1 (100%)	1 (17%)	1 (33%)
Respiratory System				
Lung	(50)	(50)	(50)	(49)
Hemorrhage	5 (10%)	2 (4%)	2 (4%)	1 (2%)
Infiltration cellular, histiocyte	2 (4%)	2 (4%)		1 (2%)
Inflammation, chronic	3 (6%)			1 (2%)
Inflammation, suppurative	2 (4%)	1 (2%)	1 (2%)	3 (6%)
Thrombosis	1 (2%)			
Alveolar epithelium, hyperplasia	3 (6%)	2 (4%)	1 (2%)	1 (2%)
Nose	(50)	(50)	(50)	(49)
Inflammation, suppurative	1 (2%)		1 (2%)	2 (4%)
Special Senses System				
None				
Urinary System				
Kidney	(50)	(50)	(50)	(49)
Congestion				1 (2%)
Metaplasia, focal, osseous		2 (4%)	2 (4%)	1 (2%)
Nephropathy	36 (72%)	34 (68%)	30 (60%)	30 (61%)
Renal tubule, accumulation, hyaline droplet	1 (2%)		1 (2%)	1 (2%)
Renal tubule, dilatation	1 (2%)		1 (2%)	1 (2%)
Renal tubule, hyaline droplet		1 (2%)		
Renal tubule, necrosis	1 (2%)	1 (2%)		1 (2%)
Renal tubule, pigmentation		2 (4%)	1 (2%)	

APPENDIX G
SUMMARY OF LESIONS IN MALE MICE IN THE 2-YEAR GAVAGE STUDY OF AZT/5,000 U α-INTERFERON A/D

TABLE G1
Summary of the Incidence of Neoplasms in Male Mice in the 2-Year Gavage Study of AZT/5,000 U α-Interferon A/D[a]

	Vehicle Control	30 mg AZT/kg + 5,000 U α-IFN A/D	60 mg AZT/kg + 5,000 U α-IFN A/D	120 mg AZT/kg + 5,000 U α-IFN A/D
Disposition Summary				
Animals initially in study	50	50	50	50
Early deaths				
Accidental deaths		1	1	
Moribund	9	11	9	6
Natural deaths	10	3	5	10
Survivors				
Terminal sacrifice	31	35	35	34
Animals examined microscopically	50	50	50	50
Alimentary System				
Intestine small, jejunum	(45)	(50)	(46)	(47)
Carcinoma				1 (2%)
Intestine small, ileum	(45)	(49)	(46)	(46)
Hemangiosarcoma		1 (2%)		
Liver	(50)	(50)	(50)	(50)
Carcinoma, metastatic, islets, pancreatic		1 (2%)		
Hemangioma				1 (2%)
Hemangiosarcoma	1 (2%)	1 (2%)	1 (2%)	1 (2%)
Hemangiosarcoma, multiple	1 (2%)	3 (6%)	3 (6%)	4 (8%)
Hepatoblastoma	1 (2%)			
Hepatocellular carcinoma	15 (30%)	17 (34%)	17 (34%)	14 (28%)
Hepatocellular carcinoma, multiple	4 (8%)	7 (14%)	1 (2%)	2 (4%)
Hepatocellular adenoma	9 (18%)	13 (26%)	13 (26%)	13 (26%)
Hepatocellular adenoma, multiple	10 (20%)	4 (8%)	2 (4%)	4 (8%)
Hepatocholangiocarcinoma			1 (2%)	1 (2%)
Histiocytic sarcoma	1 (2%)			
Mesentery	(3)	(5)	(1)	(1)
Carcinoma, metastatic, islets, pancreatic		1 (20%)		
Hepatocholangiocarcinoma, metastatic, liver				1 (100%)
Pancreas	(48)	(50)	(50)	(50)
Carcinoma, metastatic, islets, pancreatic		1 (2%)		
Stomach, forestomach	(49)	(50)	(50)	(47)
Squamous cell papilloma		1 (2%)	1 (2%)	
Stomach, glandular	(49)	(50)	(50)	(47)
Carcinoma			1 (2%)	
Carcinoma, metastatic, islets, pancreatic		1 (2%)		
Cardiovascular System				
Heart	(50)	(50)	(50)	(50)
Hemangiosarcoma	1 (2%)		1 (2%)	
Endocrine System				
Adrenal cortex	(49)	(50)	(50)	(50)
Adenoma	2 (4%)			2 (4%)
Carcinoma, metastatic, islets, pancreatic		1 (2%)		
Bilateral, capsule, adenoma		1 (2%)		
Capsule, adenoma		5 (10%)	3 (6%)	2 (4%)

TABLE G1
Summary of the Incidence of Neoplasms in Male Mice in the 2-Year Gavage Study of AZT/5,000 U α-Interferon A/D

	Vehicle Control	30 mg AZT/kg + 5,000 U α-IFN A/D	60 mg AZT/kg + 5,000 U α-IFN A/D	120 mg AZT/kg + 5,000 U α-IFN A/D
Endocrine System (continued)				
Adrenal medulla	(48)	(50)	(50)	(50)
Pheochromocytoma malignant			1 (2%)	1 (2%)
Pheochromocytoma benign	1 (2%)	1 (2%)		
Bilateral, pheochromocytoma benign		1 (2%)		
Islets, pancreatic	(48)	(50)	(50)	(50)
Carcinoma		1 (2%)		
Pituitary gland	(47)	(43)	(48)	(43)
Pars intermedia, adenoma				1 (2%)
Thyroid gland	(50)	(50)	(50)	(49)
Bilateral, follicular cell, adenoma	1 (2%)			
Follicular cell, adenoma	5 (10%)	2 (4%)	1 (2%)	5 (10%)
Follicular cell, carcinoma		1 (2%)		
General Body System				
None				
Genital System				
Epididymis	(50)	(50)	(50)	(50)
Seminal vesicle	(50)	(50)	(50)	(49)
Testes	(50)	(50)	(50)	(50)
Interstitial cell, adenoma			1 (2%)	1 (2%)
Hematopoietic System				
Bone marrow	(50)	(50)	(50)	(50)
Hemangiosarcoma		2 (4%)	1 (2%)	1 (2%)
Histiocytic sarcoma	1 (2%)			
Lymph node	(2)	(4)	(5)	(2)
Mediastinal, alveolar/bronchiolar carcinoma, metastatic, lung	1 (50%)			
Mediastinal, histiocytic sarcoma	1 (50%)			
Pancreatic, hepatocellular carcinoma, metastatic, liver				1 (50%)
Lymph node, mesenteric	(46)	(50)	(50)	(50)
Alveolar/bronchiolar carcinoma, metastatic, lung		1 (2%)		
Carcinoma, metastatic, islets, pancreatic		1 (2%)		
Histiocytic sarcoma	1 (2%)			
Spleen	(48)	(50)	(50)	(49)
Hemangiosarcoma	1 (2%)	2 (4%)	4 (8%)	4 (8%)
Thymus	(42)	(45)	(46)	(42)
Alveolar/bronchiolar carcinoma, metastatic, lung		1 (2%)		
Carcinoma, metastatic, islets, pancreatic		1 (2%)		

TABLE G1
Summary of the Incidence of Neoplasms in Male Mice in the 2-Year Gavage Study of AZT/5,000 U α-Interferon A/D

	Vehicle Control	30 mg AZT/kg + 5,000 U α-IFN A/D	60 mg AZT/kg + 5,000 U α-IFN A/D	120 mg AZT/kg + 5,000 U α-IFN A/D
Integumentary System				
Skin	(50)	(49)	(50)	(50)
Subcutaneous tissue, fibrosarcoma		2 (4%)		
Subcutaneous tissue, hemangiosarcoma	1 (2%)			
Subcutaneous tissue, hepatocellular carcinoma, metastatic, liver				1 (2%)
Musculoskeletal System				
Skeletal muscle	(50)	(50)	(50)	(50)
Fibrosarcoma, metastatic, skin		1 (2%)		
Nervous System				
None				
Respiratory System				
Lung	(50)	(50)	(50)	(50)
Alveolar/bronchiolar adenoma	6 (12%)	7 (14%)	5 (10%)	6 (12%)
Alveolar/bronchiolar adenoma, multiple		1 (2%)	2 (4%)	
Alveolar/bronchiolar carcinoma	2 (4%)	4 (8%)	3 (6%)	
Carcinoma, metastatic, harderian gland			1 (2%)	
Carcinoma, metastatic, islets, pancreatic		1 (2%)		
Fibrosarcoma		1 (2%)		
Fibrosarcoma, metastatic, skin		1 (2%)		
Hepatocellular carcinoma, metastatic, liver	6 (12%)	3 (6%)	1 (2%)	3 (6%)
Hepatocholangiocarcinoma, metastatic, liver				1 (2%)
Special Senses System				
Ear	(1)	(1)	(1)	
External ear, histiocytic sarcoma			1 (100%)	
Eye	(1)	(6)		(2)
Retrobulbar, fibrosarcoma		1 (17%)		
Harderian gland	(4)	(9)	(4)	(4)
Adenoma	3 (75%)	9 (100%)	3 (75%)	4 (100%)
Carcinoma			1 (25%)	
Urinary System				
Kidney	(49)	(50)	(50)	(50)
Carcinoma, metastatic, islets, pancreatic		1 (2%)		
Carcinoma, metastatic, liver				1 (2%)
Hepatocellular carcinoma, metastatic, liver				1 (2%)
Histiocytic sarcoma	1 (2%)			
Systemic Lesions				
Multiple organs[b]	(50)	(50)	(50)	(50)
Histiocytic sarcoma	1 (2%)		1 (2%)	
Lymphoma malignant	2 (4%)	3 (6%)	6 (12%)	3 (6%)

TABLE G1
Summary of the Incidence of Neoplasms in Male Mice in the 2-Year Gavage Study of AZT/5,000 U α-Interferon A/D

	Vehicle Control	30 mg AZT/kg + 5,000 U α-IFN A/D	60 mg AZT/kg + 5,000 U α-IFN A/D	120 mg AZT/kg + 5,000 U α-IFN A/D
Neoplasm Summary				
Total animals with primary neoplasms[c]	41	44	40	43
Total primary neoplasms	67	91	73	71
Total animals with benign neoplasms	28	30	26	31
Total benign neoplasms	37	45	31	39
Total animals with malignant neoplasms	28	34	29	26
Total malignant neoplasms	30	46	42	32
Total animals with metastatic neoplasms	7	5	2	5
Total metastatic neoplasms	7	16	2	9

[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 G2
Statistical Analysis of Primary Neoplasms in Male Mice in the 2-Year Gavage Study of AZT/5,000 U α-Interferon A/D

	Vehicle Control	30 mg AZT/kg + 5,000 U α-IFN A/D	60 mg AZT/kg + 5,000 U α-IFN A/D	120 mg AZT/kg + 5,000 U α-IFN A/D
Adrenal Cortex: Adenoma				
Overall rate[a]	2/49 (4%)	6/50 (12%)	3/50 (6%)	4/50 (8%)
Adjusted rate[b]	6.2%	16.2%	8.6%	10.7%
Terminal rate[c]	1/31 (3%)	5/35 (14%)	3/35 (9%)	2/34 (6%)
First incidence (days)	724	554	729 (T)	632
Life table test[d]	P = 0.472	P = 0.169	P = 0.552	P = 0.361
Logistic regression test[d]	P = 0.438	P = 0.134	P = 0.527	P = 0.333
Cochran-Armitage test[d]	P = 0.455			
Fisher exact test[d]		P = 0.141	P = 0.510	P = 0.349
Harderian Gland: Adenoma				
Overall rate	3/50 (6%)	9/50 (18%)	3/50 (6%)	4/50 (8%)
Adjusted rate	7.9%	22.9%	8.6%	11.8%
Terminal rate	1/31 (3%)	6/35 (17%)	3/35 (9%)	4/34 (12%)
First incidence (days)	613	528	729 (T)	729 (T)
Life table test	P = 0.396N	P = 0.082	P = 0.633N	P = 0.527
Logistic regression test	P = 0.432N	P = 0.064	P = 0.644	P = 0.484
Cochran-Armitage test	P = 0.419N			
Fisher exact test		P = 0.061	P = 0.661N	P = 0.500
Harderian Gland: Adenoma or Carcinoma				
Overall rate	3/50 (6%)	9/50 (18%)	4/50 (8%)	4/50 (8%)
Adjusted rate	7.9%	22.9%	11.0%	11.8%
Terminal rate	1/31 (3%)	6/35 (17%)	3/35 (9%)	4/34 (12%)
First incidence (days)	613	528	665	729 (T)
Life table test	P = 0.418N	P = 0.082	P = 0.519	P = 0.527
Logistic regression test	P = 0.448N	P = 0.064	P = 0.481	P = 0.484
Cochran-Armitage test	P = 0.437N			
Fisher exact test		P = 0.061	P = 0.500	P = 0.500
Liver: Hemangiosarcoma				
Overall rate	2/50 (4%)	4/50 (8%)	4/50 (8%)	5/50 (10%)
Adjusted rate	6.3%	10.3%	10.4%	12.5%
Terminal rate	1/31 (3%)	2/35 (6%)	2/35 (6%)	1/34 (3%)
First incidence (days)	727	661	581	565
Life table test	P = 0.202	P = 0.373	P = 0.380	P = 0.227
Logistic regression test	P = 0.154	P = 0.327	P = 0.319	P = 0.224
Cochran-Armitage test	P = 0.194			
Fisher exact test		P = 0.339	P = 0.339	P = 0.218
Liver: Hepatocellular Adenoma				
Overall rate	19/50 (38%)	17/50 (34%)	15/50 (30%)	17/50 (34%)
Adjusted rate	57.0%	47.0%	40.1%	43.9%
Terminal rate	17/31 (55%)	16/35 (46%)	13/35 (37%)	13/34 (38%)
First incidence (days)	613	661	488	498
Life table test	P = 0.304N	P = 0.254N	P = 0.151N	P = 0.311N
Logistic regression test	P = 0.433N	P = 0.428N	P = 0.322N	P = 0.467N
Cochran-Armitage test	P = 0.381N			
Fisher exact test		P = 0.418N	P = 0.263N	P = 0.418N

TABLE G2
Statistical Analysis of Primary Neoplasms in Male Mice in the 2-Year Gavage Study of AZT/5,000 U α-Interferon A/D

	Vehicle Control	30 mg AZT/kg + 5,000 U α-IFN A/D	60 mg AZT/kg + 5,000 U α-IFN A/D	120 mg AZT/kg + 5,000 U α-IFN A/D
Liver: Hepatocellular Carcinoma				
Overall rate	19/50 (38%)	24/50 (48%)	18/50 (36%)	16/50 (32%)
Adjusted rate	41.7%	58.0%	45.3%	38.0%
Terminal rate	6/31 (19%)	18/35 (51%)	14/35 (40%)	9/34 (26%)
First incidence (days)	462	528	386	526
Life table test	P = 0.171N	P = 0.321	P = 0.434N	P = 0.331N
Logistic regression test	P = 0.139N	P = 0.134	P = 0.561	P = 0.274N
Cochran-Armitage test	P = 0.169N			
Fisher exact test		P = 0.210	P = 0.500N	P = 0.338N
Liver: Hepatocellular Adenoma or Carcinoma				
Overall rate	35/50 (70%)	33/50 (66%)	28/50 (56%)	29/50 (58%)
Adjusted rate	77.3%	78.3%	67.8%	65.5%
Terminal rate	21/31 (68%)	26/35 (74%)	22/35 (63%)	19/34 (56%)
First incidence (days)	462	528	386	498
Life table test	P = 0.104N	P = 0.268N	P = 0.082N	P = 0.145N
Logistic regression test	P = 0.097N	P = 0.460N	P = 0.138N	P = 0.150N
Cochran-Armitage test	P = 0.104N			
Fisher exact test		P = 0.415N	P = 0.107N	P = 0.149N
Liver: Hepatocellular Carcinoma or Hepatoblastoma				
Overall rate	20/50 (40%)	24/50 (48%)	18/50 (36%)	16/50 (32%)
Adjusted rate	43.2%	58.0%	45.3%	38.0%
Terminal rate	6/31 (19%)	18/35 (51%)	14/35 (40%)	9/34 (26%)
First incidence (days)	462	528	386	526
Life table test	P = 0.137N	P = 0.384	P = 0.369N	P = 0.273N
Logistic regression test	P = 0.104N	P = 0.180	P = 0.533N	P = 0.209N
Cochran-Armitage test	P = 0.130N			
Fisher exact test		P = 0.273	P = 0.418N	P = 0.266N
Liver: Hepatocellular Adenoma, Hepatocellular Carcinoma, or Hepatoblastoma				
Overall rate	36/50 (72%)	33/50 (66%)	28/50 (56%)	29/50 (58%)
Adjusted rate	77.9%	78.3%	67.8%	65.5%
Terminal rate	21/31 (68%)	26/35 (74%)	22/35 (63%)	19/34 (56%)
First incidence (days)	462	528	386	498
Life table test	P = 0.082N	P = 0.220N	P = 0.063N	P = 0.115N
Logistic regression test	P = 0.068N	P = 0.375N	P = 0.096N	P = 0.105N
Cochran-Armitage test	P = 0.076N			
Fisher exact test		P = 0.333N	P = 0.072N	P = 0.104N
Lung: Alveolar/bronchiolar Adenoma				
Overall rate	6/50 (12%)	8/50 (16%)	7/50 (14%)	6/50 (12%)
Adjusted rate	16.2%	22.9%	20.0%	16.1%
Terminal rate	3/31 (10%)	8/35 (23%)	7/35 (20%)	4/34 (12%)
First incidence (days)	474	729 (T)	729 (T)	600
Life table test	P = 0.448N	P = 0.458	P = 0.567	P = 0.592N
Logistic regression test	P = 0.511N	P = 0.371	P = 0.467	P = 0.615N
Cochran-Armitage test	P = 0.486N			
Fisher exact test		P = 0.387	P = 0.500	P = 0.620N

TABLE G2
Statistical Analysis of Primary Neoplasms in Male Mice in the 2-Year Gavage Study of AZT/5,000 U α-Interferon A/D

	Vehicle Control	30 mg AZT/kg + 5,000 U α-IFN A/D	60 mg AZT/kg + 5,000 U α-IFN A/D	120 mg AZT/kg + 5,000 U α-IFN A/D
Lung: Alveolar/bronchiolar Carcinoma				
Overall rate	2/50 (4%)	4/50 (8%)	3/50 (6%)	0/50 (0%)
Adjusted rate	6.5%	10.6%	7.9%	0.0%
Terminal rate	2/31 (6%)	2/35 (6%)	2/35 (6%)	0/34 (0%)
First incidence (days)	729 (T)	683	562	—[e]
Life table test	P = 0.127N	P = 0.386	P = 0.540	P = 0.218N
Logistic regression test	P = 0.143N	P = 0.328	P = 0.487	P = 0.218N
Cochran-Armitage test	P = 0.137N			
Fisher exact test		P = 0.339	P = 0.500	P = 0.247N
Lung: Alveolar/bronchiolar Adenoma or Carcinoma				
Overall rate	8/50 (16%)	12/50 (24%)	10/50 (20%)	6/50 (12%)
Adjusted rate	22.2%	32.2%	27.4%	16.1%
Terminal rate	5/31 (16%)	10/35 (29%)	9/35 (26%)	4/34 (12%)
First incidence (days)	474	683	562	600
Life table test	P = 0.198N	P = 0.307	P = 0.479	P = 0.357N
Logistic regression test	P = 0.248N	P = 0.208	P = 0.361	P = 0.388N
Cochran-Armitage test	P = 0.228N			
Fisher exact test		P = 0.227	P = 0.398	P = 0.387N
Spleen: Hemangiosarcoma				
Overall rate	1/48 (2%)	2/50 (4%)	4/50 (8%)	4/49 (8%)
Adjusted rate	3.2%	5.2%	10.4%	9.9%
Terminal rate	1/31 (3%)	1/35 (3%)	2/35 (6%)	1/34 (3%)
First incidence (days)	729 (T)	661	581	565
Life table test	P = 0.117	P = 0.525	P = 0.210	P = 0.179
Logistic regression test	P = 0.114	P = 0.507	P = 0.181	P = 0.188
Cochran-Armitage test	P = 0.115			
Fisher exact test		P = 0.515	P = 0.194	P = 0.187
Thyroid Gland (Follicular Cell): Adenoma				
Overall rate	6/50 (12%)	2/50 (4%)	1/50 (2%)	5/49 (10%)
Adjusted rate	17.2%	5.7%	2.9%	14.7%
Terminal rate	4/31 (13%)	2/35 (6%)	1/35 (3%)	5/34 (15%)
First incidence (days)	677	729 (T)	729 (T)	729 (T)
Life table test	P = 0.510N	P = 0.112N	P = 0.051N	P = 0.454N
Logistic regression test	P = 0.563N	P = 0.139N	P = 0.065N	P = 0.533N
Cochran-Armitage test	P = 0.549N			
Fisher exact test		P = 0.134N	P = 0.056N	P = 0.514N
Thyroid Gland (Follicular Cell): Adenoma or Carcinoma				
Overall rate	6/50 (12%)	3/50 (6%)	1/50 (2%)	5/49 (10%)
Adjusted rate	17.2%	8.6%	2.9%	14.7%
Terminal rate	4/31 (13%)	3/35 (9%)	1/35 (3%)	5/34 (15%)
First incidence (days)	677	729 (T)	729 (T)	729 (T)
Life table test	P = 0.453N	P = 0.203N	P = 0.051N	P = 0.454N
Logistic regression test	P = 0.508N	P = 0.249N	P = 0.065N	P = 0.533N
Cochran-Armitage test	P = 0.494N			
Fisher exact test		P = 0.243N	P = 0.056N	P = 0.514N

TABLE G2
Statistical Analysis of Primary Neoplasms in Male Mice in the 2-Year Gavage Study of AZT/5,000 U α-Interferon A/D

	Vehicle Control	30 mg AZT/kg + 5,000 U α-IFN A/D	60 mg AZT/kg + 5,000 U α-IFN A/D	120 mg AZT/kg + 5,000 U α-IFN A/D
All Organs: Hemangiosarcoma				
Overall rate	5/50 (10%)	5/50 (10%)	4/50 (8%)	6/50 (12%)
Adjusted rate	15.6%	13.0%	10.4%	15.2%
Terminal rate	4/31 (13%)	3/35 (9%)	2/35 (6%)	2/34 (6%)
First incidence (days)	727	661	581	565
Life table test	P = 0.452	P = 0.571N	P = 0.440N	P = 0.526
Logistic regression test	P = 0.426	P = 0.619	P = 0.530N	P = 0.493
Cochran-Armitage test	P = 0.437			
Fisher exact test		P = 0.630N	P = 0.500N	P = 0.500
All Organs: Malignant Lymphoma				
Overall rate	2/50 (4%)	3/50 (6%)	6/50 (12%)	3/50 (6%)
Adjusted rate	4.7%	7.7%	14.9%	7.8%
Terminal rate	0/31 (0%)	2/35 (6%)	2/35 (6%)	1/34 (3%)
First incidence (days)	670	473	605	586
Life table test	P = 0.384	P = 0.516	P = 0.140	P = 0.487
Logistic regression test	P = 0.395	P = 0.526	P = 0.054	P = 0.309
Cochran-Armitage test	P = 0.389			
Fisher exact test		P = 0.500	P = 0.134	P = 0.500
All Organs: Benign Neoplasms				
Overall rate	28/50 (56%)	30/50 (60%)	26/50 (52%)	31/50 (62%)
Adjusted rate	71.1%	74.6%	68.1%	73.5%
Terminal rate	20/31 (65%)	25/35 (71%)	23/35 (66%)	23/34 (68%)
First incidence (days)	474	528	488	498
Life table test	P = 0.464	P = 0.534N	P = 0.254N	P = 0.484
Logistic regression test	P = 0.292	P = 0.358	P = 0.536N	P = 0.282
Cochran-Armitage test	P = 0.358			
Fisher exact test		P = 0.420	P = 0.421N	P = 0.342
All Organs: Malignant Neoplasms				
Overall rate	28/50 (56%)	34/50 (68%)	29/50 (58%)	26/50 (52%)
Adjusted rate	58.1%	72.3%	64.4%	55.3%
Terminal rate	11/31 (35%)	22/35 (63%)	19/35 (54%)	13/34 (38%)
First incidence (days)	462	439	386	517
Life table test	P = 0.251N	P = 0.323	P = 0.538N	P = 0.399N
Logistic regression test	P = 0.182N	P = 0.064	P = 0.273	P = 0.451N
Cochran-Armitage test	P = 0.226N			
Fisher exact test		P = 0.151	P = 0.500	P = 0.421N

TABLE G2
Statistical Analysis of Primary Neoplasms in Male Mice in the 2-Year Gavage Study of AZT/5,000 U α-Interferon A/D

	Vehicle Control	30 mg AZT/kg + 5,000 U α-IFN A/D	60 mg AZT/kg + 5,000 U α-IFN A/D	120 mg AZT/kg + 5,000 U α-IFN A/D
All Organs: Benign or Malignant Neoplasms				
Overall rate	41/50 (82%)	44/50 (88%)	40/50 (80%)	43/50 (86%)
Adjusted rate	83.7%	91.7%	87.0%	89.6%
Terminal rate	23/31 (74%)	31/35 (89%)	29/35 (83%)	29/34 (85%)
First incidence (days)	462	439	386	498
Life table test	P = 0.497N	P = 0.554N	P = 0.337N	P = 0.560N
Logistic regression test	P = 0.483	P = 0.247	P = 0.390	P = 0.370
Cochran-Armitage test	P = 0.448			
Fisher exact test		P = 0.288	P = 0.500N	P = 0.393

(T)Terminal sacrifice
[a] Number of neoplasm-bearing animals/number of animals examined. Denominator is number of animals examined microscopically for adrenal gland, liver, lung, spleen, 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 incidence are the P values associated with the trend test. Beneath the dosed group incidence are the P values corresponding to pairwise comparisons between the vehicle controls and that 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 Cochran-Armitage and Fisher exact tests compare directly the overall incidence rates. For all tests, a negative trend or a lower incidence in a dose group is indicated by **N**.
[e] Not applicable; no neoplasms in animal group

TABLE G3
Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the 2-Year Gavage Study of AZT/5,000 U α-Interferon A/D[a]

	Vehicle Control	30 mg AZT/kg + 5,000 U α-IFN A/D	60 mg AZT/kg + 5,000 U α-IFN A/D	120 mg AZT/kg + 5,000 U α-IFN A/D
Disposition Summary				
Animals initially in study	50	50	50	50
Early deaths				
Accidental deaths		1	1	
Moribund	9	11	9	6
Natural deaths	10	3	5	10
Survivors				
Terminal sacrifice	31	35	35	34
Animals examined microscopically	50	50	50	50
Alimentary System				
Esophagus	(50)	(50)	(50)	(50)
Necrosis			1 (2%)	
Perforation		1 (2%)		
Muscularis, inflammation, chronic		1 (2%)	1 (2%)	
Gallbladder	(44)	(46)	(45)	(42)
Inflammation, chronic				1 (2%)
Intestine small, duodenum	(46)	(48)	(48)	(46)
Hyperplasia, adenomatous				1 (2%)
Liver	(50)	(50)	(50)	(50)
Basophilic focus	1 (2%)	1 (2%)		
Clear cell focus	1 (2%)	6 (12%)	2 (4%)	2 (4%)
Congestion		1 (2%)		
Degeneration, cystic				1 (2%)
Eosinophilic focus	6 (12%)	7 (14%)	3 (6%)	3 (6%)
Hemorrhage	2 (4%)			1 (2%)
Inflammation, chronic	45 (90%)	43 (86%)	38 (76%)	41 (82%)
Inflammation, focal		1 (2%)		
Mixed cell focus	3 (6%)	3 (6%)	6 (12%)	4 (8%)
Necrosis, focal	2 (4%)	2 (4%)	3 (6%)	8 (16%)
Pigmentation, focal	1 (2%)			
Vacuolization cytoplasmic	6 (12%)	7 (14%)	2 (4%)	6 (12%)
Bile duct, cyst	1 (2%)	1 (2%)	2 (4%)	
Bile duct, hyperplasia	29 (58%)	31 (62%)	33 (66%)	29 (58%)
Centrilobular, necrosis		1 (2%)		
Hepatocyte, karyomegaly	37 (74%)	32 (64%)	31 (62%)	32 (64%)
Mesentery	(3)	(5)	(1)	(1)
Inflammation, chronic		1 (20%)		
Thrombosis		1 (20%)		
Artery, inflammation, chronic	1 (33%)	1 (20%)		
Fat, necrosis	1 (33%)		1 (100%)	
Pancreas	(48)	(50)	(50)	(50)
Inflammation, chronic		1 (2%)		
Acinus, atrophy, diffuse				1 (2%)
Acinus, atrophy, focal			2 (4%)	
Duct, cyst	1 (2%)	1 (2%)		
Stomach, forestomach	(49)	(50)	(50)	(47)
Cyst		1 (2%)		1 (2%)
Diverticulum			1 (2%)	
Edema			1 (2%)	
Inflammation, chronic	1 (2%)			
Ulcer		3 (6%)		
Epithelium, hyperplasia	3 (6%)	2 (4%)	5 (10%)	3 (6%)

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

TABLE G3
Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the 2-Year Gavage Study of AZT/5,000 U α-Interferon A/D

	Vehicle Control	30 mg AZT/kg + 5,000 U α-IFN A/D	60 mg AZT/kg + 5,000 U α-IFN A/D	120 mg AZT/kg + 5,000 U α-IFN A/D
Alimentary System (continued)				
Stomach, glandular	(49)	(50)	(50)	(47)
Edema			1 (2%)	
Erosion				1 (2%)
Hyperplasia, adenomatous			1 (2%)	
Inflammation, chronic			1 (2%)	
Mineralization	1 (2%)	1 (2%)	3 (6%)	2 (4%)
Necrosis				1 (2%)
Glands, degeneration, cystic, focal		4 (8%)	4 (8%)	1 (2%)
Tooth	(2)	(2)	(2)	(1)
Developmental malformation	2 (100%)	2 (100%)	1 (50%)	1 (100%)
Cardiovascular System				
Blood vessel	(50)	(49)	(50)	(49)
Inflammation, chronic	1 (2%)			
Heart	(50)	(50)	(50)	(50)
Inflammation, chronic, focal				1 (2%)
Mineralization				2 (4%)
Thrombosis	1 (2%)			
Artery, inflammation, chronic	1 (2%)	1 (2%)		
Endocrine System				
Adrenal cortex	(49)	(50)	(50)	(50)
Cytoplasmic alteration, focal	3 (6%)	10 (20%)	6 (12%)	18 (36%)
Hyperplasia, focal		2 (4%)	7 (14%)	3 (6%)
Hypertrophy, focal	7 (14%)	11 (22%)	9 (18%)	11 (22%)
Capsule, hyperplasia, focal	2 (4%)	2 (4%)	3 (6%)	2 (4%)
Adrenal medulla	(48)	(50)	(50)	(50)
Hyperplasia	1 (2%)			
Islets, pancreatic	(48)	(50)	(50)	(50)
Hyperplasia	2 (4%)	1 (2%)		1 (2%)
Parathyroid gland	(50)	(45)	(48)	(46)
Cyst	3 (6%)		1 (2%)	1 (2%)
Pituitary gland	(47)	(43)	(48)	(43)
Pars distalis, cyst		1 (2%)	3 (6%)	2 (5%)
Pars distalis, hyperplasia, focal	1 (2%)		1 (2%)	1 (2%)
Thyroid gland	(50)	(50)	(50)	(49)
Degeneration, cystic, focal	7 (14%)	11 (22%)	14 (28%)	10 (20%)
Inflammation, chronic, focal			1 (2%)	
C-cell, hyperplasia				1 (2%)
Follicle, cyst	5 (10%)	5 (10%)	6 (12%)	6 (12%)
Follicular cell, hyperplasia	13 (26%)	14 (28%)	7 (14%)	10 (20%)
General Body System				
None				
Genital System				
Epididymis	(50)	(50)	(50)	(50)
Granuloma sperm			2 (4%)	
Inflammation, suppurative	1 (2%)			
Spermatocele			1 (2%)	

TABLE G3
Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the 2-Year Gavage Study of AZT/5,000 U α-Interferon A/D

	Vehicle Control	30 mg AZT/kg + 5,000 U α-IFN A/D	60 mg AZT/kg + 5,000 U α-IFN A/D	120 mg AZT/kg + 5,000 U α-IFN A/D
Genital System (continued)				
Preputial gland	(50)	(49)	(47)	(50)
Degeneration, cystic	44 (88%)	41 (84%)	42 (89%)	48 (96%)
Inflammation, chronic	2 (4%)	2 (4%)		
Prostate	(49)	(49)	(50)	(49)
Inflammation, chronic	1 (2%)			
Seminal vesicle	(50)	(50)	(50)	(49)
Angiectasis				1 (2%)
Inflammation, chronic	1 (2%)			1 (2%)
Testes	(50)	(50)	(50)	(50)
Germinal epithelium, degeneration	1 (2%)			
Hematopoietic System				
Bone marrow	(50)	(50)	(50)	(50)
Hyperplasia	1 (2%)	7 (14%)	1 (2%)	1 (2%)
Lymph node	(2)	(4)	(5)	(2)
Mediastinal, hyperplasia, lymphoid			1 (20%)	
Mediastinal, necrosis			1 (20%)	
Pancreatic, hyperplasia, lymphoid		1 (25%)		
Lymph node, mandibular	(45)	(46)	(44)	(47)
Hyperplasia, lymphoid	1 (2%)			2 (4%)
Lymph node, mesenteric	(46)	(50)	(50)	(50)
Ectasia		3 (6%)	1 (2%)	2 (4%)
Hemorrhage	17 (37%)	21 (42%)	12 (24%)	13 (26%)
Hyperplasia, histiocytic	1 (2%)			
Hyperplasia, lymphoid	3 (7%)	1 (2%)	1 (2%)	3 (6%)
Inflammation, chronic	2 (4%)			
Spleen	(48)	(50)	(50)	(49)
Angiectasis			1 (2%)	
Congestion	3 (6%)	1 (2%)		2 (4%)
Depletion cellular			2 (4%)	
Fibrosis, focal			1 (2%)	
Hematopoietic cell proliferation	18 (38%)	16 (32%)	12 (24%)	14 (29%)
Hyperplasia, lymphoid	3 (6%)		3 (6%)	
Necrosis, focal		1 (2%)		
Capsule, fibrosis		1 (2%)		
Thymus	(42)	(45)	(46)	(42)
Atrophy	3 (7%)		2 (4%)	3 (7%)
Cyst	2 (5%)	6 (13%)	8 (17%)	7 (17%)
Necrosis		1 (2%)	1 (2%)	
Integumentary System				
Skin	(50)	(49)	(50)	(50)
Cyst epithelial inclusion	2 (4%)			
Edema	1 (2%)	1 (2%)	7 (14%)	3 (6%)
Infiltration cellular, mast cell			1 (2%)	
Inflammation, chronic, focal	1 (2%)	3 (6%)	1 (2%)	2 (4%)
Ulcer		2 (4%)		
Subcutaneous tissue, edema				1 (2%)
Subcutaneous tissue, foreign body			1 (2%)	
Subcutaneous tissue, hemorrhage	1 (2%)			
Subcutaneous tissue, inflammation, focal, suppurative			1 (2%)	

TABLE G3
Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the 2-Year Gavage Study of AZT/5,000 U α-Interferon A/D

	Vehicle Control	30 mg AZT/kg + 5,000 U α-IFN A/D	60 mg AZT/kg + 5,000 U α-IFN A/D	120 mg AZT/kg + 5,000 U α-IFN A/D
Musculoskeletal System				
Bone	(50)	(50)	(50)	(50)
Hyperostosis	40 (80%)	26 (52%)	36 (72%)	31 (62%)
Nervous System				
Brain	(50)	(50)	(50)	(49)
Necrosis	1 (2%)			
Respiratory System				
Lung	(50)	(50)	(50)	(50)
Congestion	2 (4%)	1 (2%)		
Foreign body		2 (4%)		
Hemorrhage	1 (2%)		1 (2%)	1 (2%)
Hyperplasia, histiocytic	4 (8%)	1 (2%)	1 (2%)	2 (4%)
Pigmentation		1 (2%)		
Thrombosis				1 (2%)
Alveolar epithelium, hyperplasia	2 (4%)	2 (4%)	1 (2%)	3 (6%)
Mediastinum, inflammation, chronic		1 (2%)		
Nose	(50)	(50)	(50)	(50)
Hemorrhage				1 (2%)
Inflammation, suppurative	2 (4%)	1 (2%)		
Special Senses System				
Ear	(1)	(1)	(1)	
External ear, inflammation, chronic		1 (100%)		
Eye	(1)	(6)		(2)
Cataract		2 (33%)		1 (50%)
Fibrosis		1 (17%)		
Cornea, inflammation, chronic	1 (100%)	5 (83%)		2 (100%)
Harderian gland	(4)	(9)	(4)	(4)
Hyperplasia, focal	1 (25%)			
Urinary System				
Kidney	(49)	(50)	(50)	(50)
Cyst	3 (6%)	3 (6%)		2 (4%)
Infarct	1 (2%)	5 (10%)	4 (8%)	
Metaplasia, focal, osseous		1 (2%)		
Nephropathy	49 (100%)	50 (100%)	47 (94%)	44 (88%)
Renal tubule, accumulation, hyaline droplet	1 (2%)			
Renal tubule, dilatation			1 (2%)	
Renal tubule, hyperplasia, focal				2 (4%)
Renal tubule, necrosis			1 (2%)	
Renal tubule, pigmentation	1 (2%)			
Urethra	(3)	(2)	(2)	(6)
Inflammation, chronic				1 (17%)

APPENDIX H
SUMMARY OF LESIONS IN FEMALE MICE IN THE 2-YEAR GAVAGE STUDY OF AZT/5,000 U α-INTERFERON A/D

TABLE H1
Summary of the Incidence of Neoplasms in Female Mice in the 2-Year Gavage Study of AZT/5,000 U α-Interferon A/D[a]

	Vehicle Control	30 mg AZT/kg + 5,000 U α-IFN A/D	60 mg AZT/kg + 5,000 U α-IFN A/D	120 mg AZT/kg + 5,000 U α-IFN A/D
Disposition Summary				
Animals initially in study	50	50	50	50
Early deaths				
Accidental deaths			2	1
Moribund	8	7	6	8
Natural deaths	5	5	6	9
Survivors				
Died last week of study		1		
Terminal sacrifice	37	37	36	32
Animals examined microscopically	50	50	50	50
Alimentary System				
Gallbladder	(47)	(47)	(48)	(45)
Hepatocholangiocarcinoma, metastatic, liver				1 (2%)
Intestine large, colon	(49)	(49)	(48)	(47)
Intestine small, jejunum	(47)	(46)	(46)	(45)
Intestine small, ileum	(47)	(46)	(46)	(45)
Liver	(50)	(50)	(50)	(50)
Carcinoma, metastatic, harderian gland	1 (2%)			
Hemangiosarcoma		1 (2%)		
Hemangiosarcoma, multiple	1 (2%)			
Hepatocellular carcinoma	9 (18%)	12 (24%)	11 (22%)	10 (20%)
Hepatocellular carcinoma, multiple	5 (10%)	3 (6%)	3 (6%)	2 (4%)
Hepatocellular adenoma	16 (32%)	6 (12%)	11 (22%)	9 (18%)
Hepatocellular adenoma, multiple	3 (6%)	4 (8%)	3 (6%)	6 (12%)
Hepatocholangiocarcinoma				1 (2%)
Histiocytic sarcoma	2 (4%)	1 (2%)	1 (2%)	1 (2%)
Osteosarcoma, metastatic, bone			1 (2%)	
Sarcoma			1 (2%)	
Mesentery	(10)	(12)	(9)	(10)
Fibrous histiocytoma		1 (8%)		
Hepatocholangiocarcinoma, metastatic, liver				1 (10%)
Histiocytic sarcoma				1 (10%)
Sarcoma			1 (11%)	
Pancreas	(48)	(50)	(50)	(49)
Fibrous histiocytoma		1 (2%)		
Hepatocholangiocarcinoma, metastatic, liver				1 (2%)
Histiocytic sarcoma	1 (2%)			
Sarcoma			1 (2%)	
Salivary glands	(50)	(49)	(50)	(48)
Fat, hemangioma	1 (2%)			
Stomach, forestomach	(50)	(50)	(49)	(48)
Fibrous histiocytoma		1 (2%)		
Histiocytic sarcoma	1 (2%)			
Squamous cell papilloma			1 (2%)	
Stomach, glandular	(49)	(50)	(48)	(49)
Fibrous histiocytoma		1 (2%)		
Hepatocholangiocarcinoma, metastatic, liver				1 (2%)
Histiocytic sarcoma				1 (2%)
Tongue	(1)			
Squamous cell carcinoma	1 (100%)			

TABLE H1
Summary of the Incidence of Neoplasms in Female Mice in the 2-Year Gavage Study of AZT/5,000 U α-Interferon A/D

	Vehicle Control	30 mg AZT/kg + 5,000 U α-IFN A/D	60 mg AZT/kg + 5,000 U α-IFN A/D	120 mg AZT/kg + 5,000 U α-IFN A/D
Cardiovascular System				
Heart	(50)	(50)	(50)	(50)
Endocrine System				
Adrenal cortex	(50)	(49)	(50)	(49)
Adenoma			1 (2%)	1 (2%)
Fibrous histiocytoma		1 (2%)		
Hepatocholangiocarcinoma, metastatic, liver				1 (2%)
Adrenal medulla	(50)	(49)	(50)	(49)
Pheochromocytoma malignant	1 (2%)			
Pheochromocytoma benign	2 (4%)	1 (2%)		1 (2%)
Islets, pancreatic	(48)	(49)	(50)	(48)
Adenoma	1 (2%)		1 (2%)	
Pituitary gland	(49)	(44)	(48)	(44)
Pars distalis, adenoma	8 (16%)	7 (16%)	6 (13%)	2 (5%)
Pars intermedia, adenoma	2 (4%)		1 (2%)	
Thyroid gland	(49)	(50)	(50)	(50)
Follicular cell, adenoma	2 (4%)	4 (8%)	6 (12%)	2 (4%)
General Body System				
None				
Genital System				
Clitoral gland	(50)	(50)	(50)	(49)
Carcinoma		1 (2%)	1 (2%)	1 (2%)
Fibrosarcoma, metastatic, skin	1 (2%)			
Ovary	(50)	(49)	(49)	(50)
Cystadenoma	3 (6%)		2 (4%)	1 (2%)
Fibrous histiocytoma		1 (2%)		
Granulosa cell tumor benign				1 (2%)
Hemangioma	1 (2%)			
Hemangiosarcoma	1 (2%)			
Histiocytic sarcoma			1 (2%)	1 (2%)
Luteoma		1 (2%)		
Uterus	(50)	(50)	(50)	(50)
Fibrous histiocytoma		1 (2%)		
Hemangiosarcoma	1 (2%)			
Hepatocholangiocarcinoma, metastatic, liver				1 (2%)
Histiocytic sarcoma		1 (2%)	1 (2%)	
Leiomyosarcoma	1 (2%)			
Endometrium, carcinoma	1 (2%)			
Endometrium, polyp stromal		3 (6%)		1 (2%)
Vagina	(50)	(48)	(48)	(50)
Histiocytic sarcoma		1 (2%)		
Squamous cell carcinoma			5 (10%)	4 (8%)
Squamous cell papilloma	1 (2%)	1 (2%)		

TABLE H1
Summary of the Incidence of Neoplasms in Female Mice in the 2-Year Gavage Study of AZT/5,000 U α-Interferon A/D

	Vehicle Control	30 mg AZT/kg + 5,000 U α-IFN A/D	60 mg AZT/kg + 5,000 U α-IFN A/D	120 mg AZT/kg + 5,000 U α-IFN A/D
Hematopoietic System				
Bone marrow	(50)	(50)	(50)	(48)
Hemangiosarcoma	1 (2%)		1 (2%)	
Lymph node	(8)	(7)	(4)	(6)
Fibrosarcoma, metastatic, skin			1 (25%)	
Inguinal, fibrosarcoma, metastatic, skin	1 (13%)		1 (25%)	
Mediastinal, carcinoma, metastatic, uncertain primary site				1 (17%)
Renal, hemangiosarcoma		1 (14%)		
Lymph node, mandibular	(46)	(46)	(48)	(44)
Fibrosarcoma, metastatic, skin			1 (2%)	
Lymph node, mesenteric	(48)	(49)	(48)	(49)
Fibrous histiocytoma		1 (2%)		
Hepatocholangiocarcinoma, metastatic, liver				1 (2%)
Histiocytic sarcoma	2 (4%)	1 (2%)		
Spleen	(49)	(49)	(49)	(49)
Fibrous histiocytoma		1 (2%)		
Hemangiosarcoma	3 (6%)		1 (2%)	1 (2%)
Hepatocholangiocarcinoma, metastatic, liver				1 (2%)
Histiocytic sarcoma				1 (2%)
Thymus	(47)	(46)	(48)	(48)
Hepatocholangiocarcinoma, metastatic, liver				1 (2%)
Histiocytic sarcoma		1 (2%)		
Osteosarcoma, metastatic, bone			1 (2%)	
Thymoma malignant		1 (2%)		
Integumentary System				
Skin	(50)	(50)	(50)	(50)
Subcutaneous tissue, fibrosarcoma	1 (2%)	1 (2%)	2 (4%)	1 (2%)
Subcutaneous tissue, hemangiosarcoma	3 (6%)			
Subcutaneous tissue, sarcoma	1 (2%)			
Vulva, squamous cell papilloma			1 (2%)	
Musculoskeletal System				
Bone	(50)	(50)	(50)	(50)
Osteosarcoma				1 (2%)
Skeletal muscle	(47)	(50)	(49)	(50)
Alveolar/bronchiolar carcinoma, metastatic, lung	1 (2%)			
Hepatocholangiocarcinoma, metastatic, liver				1 (2%)
Nervous System				
None				

TABLE H1
Summary of the Incidence of Neoplasms in Female Mice in the 2-Year Gavage Study of AZT/5,000 U α-Interferon A/D

	Vehicle Control	30 mg AZT/kg + 5,000 U α-IFN A/D	60 mg AZT/kg + 5,000 U α-IFN A/D	120 mg AZT/kg + 5,000 U α-IFN A/D
Respiratory System				
Lung	(50)	(50)	(50)	(50)
Alveolar/bronchiolar adenoma	4 (8%)	4 (8%)		2 (4%)
Alveolar/bronchiolar carcinoma	2 (4%)	1 (2%)	3 (6%)	1 (2%)
Carcinoma, metastatic, clitoral gland			1 (2%)	
Carcinoma, metastatic, harderian gland	1 (2%)			
Carcinoma, metastatic, uncertain primary site				1 (2%)
Fibrosarcoma, metastatic, skin	1 (2%)			
Hepatocellular carcinoma, metastatic, liver		1 (2%)	3 (6%)	1 (2%)
Hepatocholangiocarcinoma, metastatic, liver				1 (2%)
Histiocytic sarcoma	1 (2%)	1 (2%)		1 (2%)
Osteosarcoma, metastatic, bone			1 (2%)	
Mediastinum, alveolar/bronchiolar carcinoma	1 (2%)			
Mediastinum, carcinoma, metastatic, uncertain primary site				1 (2%)
Mediastinum, fibrous histiocytoma		1 (2%)		
Mediastinum, osteosarcoma, metastatic, bone			1 (2%)	
Nose	(50)	(50)	(50)	(50)
Carcinoma, metastatic, harderian gland	1 (2%)			
Special Senses System				
Eye	(2)		(1)	
Carcinoma, metastatic, harderian gland	1 (50%)			
Harderian gland	(5)	(2)	(2)	(1)
Adenoma	3 (60%)	2 (100%)	1 (50%)	1 (100%)
Carcinoma	1 (20%)		1 (50%)	
Urinary System				
Kidney	(50)	(50)	(50)	(49)
Carcinoma, metastatic, uncertain primary site				1 (2%)
Hepatocholangiocarcinoma, metastatic, liver				1 (2%)
Histiocytic sarcoma	1 (2%)	1 (2%)		
Osteosarcoma, metastatic, bone			1 (2%)	
Urinary bladder	(50)	(50)	(50)	(50)
Systemic Lesions				
Multiple organs[b]	(50)	(50)	(50)	(50)
Histiocytic sarcoma	2 (4%)	1 (2%)	1 (2%)	1 (2%)
Lymphoma malignant	8 (16%)	12 (24%)	8 (16%)	6 (12%)

TABLE H1
Summary of the Incidence of Neoplasms in Female Mice in the 2-Year Gavage Study of AZT/5,000 U α-Interferon A/D

	Vehicle Control	30 mg AZT/kg + 5,000 U α-IFN A/D	60 mg AZT/kg + 5,000 U α-IFN A/D	120 mg AZT/kg + 5,000 U α-IFN A/D
Neoplasm Summary				
Total animals with primary neoplasms[c]	44	40	41	39
Total primary neoplasms	91	77	74	56
Total animals with benign neoplasms	36	24	24	22
Total benign neoplasms	47	33	34	27
Total animals with malignant neoplasms	32	28	33	28
Total malignant neoplasms	44	44	40	29
Total animals with metastatic neoplasms	3	1	6	3
Total metastatic neoplasms	8	1	12	17
Total animals with malignant neoplasms of uncertain primary site				1

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

TABLE H2
Statistical Analysis of Primary Neoplasms in Female Mice in the 2-Year Gavage Study of AZT/5,000 U α-Interferon A/D

	Vehicle Control	30 mg AZT/kg + 5,000 U α-IFN A/D	60 mg AZT/kg + 5,000 U α-IFN A/D	120 mg AZT/kg + 5,000 U α-IFN A/D
Adrenal Medulla: Benign or Malignant Pheochromocytoma				
Overall rate[a]	3/50 (6%)	1/49 (2%)	0/50 (0%)	1/49 (2%)
Adjusted rate[b]	7.3%	2.2%	0.0%	3.1%
Terminal rate[c]	1/37 (3%)	0/38 (0%)	0/36 (0%)	1/32 (3%)
First incidence (days)	618	638	—[e]	730 (T)
Life table test[d]	P = 0.226N	P = 0.300N	P = 0.130N	P = 0.348N
Logistic regression test[d]	P = 0.197N	P = 0.332N	P = 0.116N	P = 0.312N
Cochran-Armitage test[d]	P = 0.203N			
Fisher exact test[d]		P = 0.316N	P = 0.121N	P = 0.316N
Harderian Gland: Adenoma				
Overall rate	3/50 (6%)	2/50 (4%)	1/50 (2%)	1/50 (2%)
Adjusted rate	8.1%	5.3%	2.8%	3.1%
Terminal rate	3/37 (8%)	2/38 (5%)	1/36 (3%)	1/32 (3%)
First incidence (days)	730 (T)	730 (T)	730 (T)	730 (T)
Life table test	P = 0.239N	P = 0.488N	P = 0.315N	P = 0.358N
Logistic regression test	P = 0.239N	P = 0.488N	P = 0.315N	P = 0.358N
Cochran-Armitage test	P = 0.199N			
Fisher exact test		P = 0.500N	P = 0.309N	P = 0.309N
Harderian Gland: Adenoma or Carcinoma				
Overall rate	4/50 (8%)	2/50 (4%)	2/50 (4%)	1/50 (2%)
Adjusted rate	10.8%	5.3%	5.6%	3.1%
Terminal rate	4/37 (11%)	2/38 (5%)	2/36 (6%)	1/32 (3%)
First incidence (days)	730 (T)	730 (T)	730 (T)	730 (T)
Life table test	P = 0.172N	P = 0.324N	P = 0.349N	P = 0.225N
Logistic regression test	P = 0.172N	P = 0.324N	P = 0.349N	P = 0.225N
Cochran-Armitage test	P = 0.137N			
Fisher exact test		P = 0.339N	P = 0.339N	P = 0.181N
Liver: Hepatocellular Adenoma				
Overall rate	19/50 (38%)	10/50 (20%)	14/50 (28%)	15/50 (30%)
Adjusted rate	46.0%	24.6%	36.8%	45.1%
Terminal rate	15/37 (41%)	8/38 (21%)	12/36 (33%)	14/32 (44%)
First incidence (days)	589	638	722	630
Life table test	P = 0.495	P = 0.038N	P = 0.229N	P = 0.437N
Logistic regression test	P = 0.487N	P = 0.035N	P = 0.234N	P = 0.329N
Cochran-Armitage test	P = 0.396N			
Fisher exact test		P = 0.038N	P = 0.198N	P = 0.263N
Liver: Hepatocellular Carcinoma				
Overall rate	14/50 (28%)	15/50 (30%)	14/50 (28%)	12/50 (24%)
Adjusted rate	35.7%	36.5%	34.6%	32.4%
Terminal rate	12/37 (32%)	12/38 (32%)	10/36 (28%)	8/32 (25%)
First incidence (days)	651	656	488	630
Life table test	P = 0.496N	P = 0.535	P = 0.553	P = 0.555N
Logistic regression test	P = 0.386N	P = 0.532	P = 0.524	P = 0.465N
Cochran-Armitage test	P = 0.325N			
Fisher exact test		P = 0.500	P = 0.588N	P = 0.410N

TABLE H2
Statistical Analysis of Primary Neoplasms in Female Mice in the 2-Year Gavage Study of AZT/5,000 U α-Interferon A/D

	Vehicle Control	30 mg AZT/kg + 5,000 U α-IFN A/D	60 mg AZT/kg + 5,000 U α-IFN A/D	120 mg AZT/kg + 5,000 U α-IFN A/D
Liver: Hepatocellular Adenoma or Carcinoma				
Overall rate	24/50 (48%)	23/50 (46%)	23/50 (46%)	23/50 (46%)
Adjusted rate	58.3%	54.6%	55.9%	63.4%
Terminal rate	20/37 (54%)	19/38 (50%)	18/36 (50%)	19/32 (59%)
First incidence (days)	589	638	488	630
Life table test	P = 0.334	P = 0.450N	P = 0.547N	P = 0.415
Logistic regression test	P = 0.489	P = 0.460N	P = 0.555	P = 0.561
Cochran-Armitage test	P = 0.471N			
Fisher exact test		P = 0.500N	P = 0.500N	P = 0.500N
Lung: Alveolar/bronchiolar Adenoma				
Overall rate	4/50 (8%)	4/50 (8%)	0/50 (0%)	2/50 (4%)
Adjusted rate	9.4%	9.9%	0.0%	5.1%
Terminal rate	2/37 (5%)	3/38 (8%)	0/36 (0%)	1/32 (3%)
First incidence (days)	575	592	—	557
Life table test	P = 0.197N	P = 0.631N	P = 0.074N	P = 0.382N
Logistic regression test	P = 0.144N	P = 0.617	P = 0.048N	P = 0.284N
Cochran-Armitage test	P = 0.162N			
Fisher exact test		P = 0.643N	P = 0.059N	P = 0.339N
Lung: Alveolar/bronchiolar Carcinoma				
Overall rate	2/50 (4%)	1/50 (2%)	3/50 (6%)	1/50 (2%)
Adjusted rate	5.4%	2.2%	7.6%	3.1%
Terminal rate	2/37 (5%)	0/38 (0%)	2/36 (6%)	1/32 (3%)
First incidence (days)	730 (T)	598	344	730 (T)
Life table test	P = 0.521N	P = 0.491N	P = 0.484	P = 0.551N
Logistic regression test	P = 0.439N	P = 0.512N	P = 0.546	P = 0.551N
Cochran-Armitage test	P = 0.474N			
Fisher exact test		P = 0.500N	P = 0.500	P = 0.500N
Lung: Alveolar/bronchiolar Adenoma or Carcinoma				
Overall rate	6/50 (12%)	5/50 (10%)	3/50 (6%)	3/50 (6%)
Adjusted rate	14.5%	11.8%	7.6%	8.2%
Terminal rate	4/37 (11%)	3/38 (8%)	2/36 (6%)	2/32 (6%)
First incidence (days)	575	592	344	557
Life table test	P = 0.212N	P = 0.487N	P = 0.269N	P = 0.302N
Logistic regression test	P = 0.134N	P = 0.532N	P = 0.193N	P = 0.221N
Cochran-Armitage test	P = 0.162N			
Fisher exact test		P = 0.500N	P = 0.243N	P = 0.243N
Ovary: Cystadenoma				
Overall rate	3/50 (6%)	0/49 (0%)	2/49 (4%)	1/50 (2%)
Adjusted rate	8.1%	0.0%	5.6%	2.6%
Terminal rate	3/37 (8%)	0/37 (0%)	2/36 (6%)	0/32 (0%)
First incidence (days)	730 (T)	—	730 (T)	676
Life table test	P = 0.381N	P = 0.121N	P = 0.513N	P = 0.351N
Logistic regression test	P = 0.360N	P = 0.121N	P = 0.513N	P = 0.324N
Cochran-Armitage test	P = 0.336N			
Fisher exact test		P = 0.125N	P = 0.510N	P = 0.309N

TABLE H2
Statistical Analysis of Primary Neoplasms in Female Mice in the 2-Year Gavage Study of AZT/5,000 U α-Interferon A/D

	Vehicle Control	30 mg AZT/kg + 5,000 U α-IFN A/D	60 mg AZT/kg + 5,000 U α-IFN A/D	120 mg AZT/kg + 5,000 U α-IFN A/D
Pituitary Gland (Pars Distalis): Adenoma				
Overall rate	8/49 (16%)	7/44 (16%)	6/48 (13%)	2/44 (5%)
Adjusted rate	19.9%	20.6%	16.6%	5.6%
Terminal rate	5/36 (14%)	7/34 (21%)	5/35 (14%)	1/31 (3%)
First incidence (days)	618	730 (T)	729	658
Life table test	P = 0.053N	P = 0.536N	P = 0.411N	P = 0.075N
Logistic regression test	P = 0.050N	P = 0.572N	P = 0.436N	P = 0.070N
Cochran-Armitage test	P = 0.044N			
Fisher exact test		P = 0.591N	P = 0.403N	P = 0.065N
Skin (Subcutaneous Tissue): Hemangiosarcoma				
Overall rate	3/50 (6%)	0/50 (0%)	0/50 (0%)	0/50 (0%)
Adjusted rate	8.1%	0.0%	0.0%	0.0%
Terminal rate	3/37 (8%)	0/38 (0%)	0/36 (0%)	0/32 (0%)
First incidence (days)	730 (T)	—	—	—
Life table test	P = 0.054N	P = 0.116N	P = 0.126N	P = 0.147N
Logistic regression test	P = 0.054N	P = 0.116N	P = 0.126N	P = 0.147N
Cochran-Armitage test	P = 0.047N			
Fisher exact test		P = 0.121N	P = 0.121N	P = 0.121N
Spleen: Hemangiosarcoma				
Overall rate	3/49 (6%)	0/49 (0%)	1/49 (2%)	1/49 (2%)
Adjusted rate	8.1%	0.0%	2.4%	3.2%
Terminal rate	3/37 (8%)	0/38 (0%)	0/36 (0%)	1/31 (3%)
First incidence (days)	730 (T)	—	648	730 (T)
Life table test	P = 0.341N	P = 0.116N	P = 0.318N	P = 0.370N
Logistic regression test	P = 0.312N	P = 0.116N	P = 0.321N	P = 0.370N
Cochran-Armitage test	P = 0.296N			
Fisher exact test		P = 0.121N	P = 0.309N	P = 0.309N
Thyroid Gland (Follicular Cell): Adenoma				
Overall rate	2/49 (4%)	4/50 (8%)	6/50 (12%)	2/50 (4%)
Adjusted rate	5.6%	10.5%	16.7%	6.3%
Terminal rate	2/36 (6%)	4/38 (11%)	6/36 (17%)	2/32 (6%)
First incidence (days)	730 (T)	730 (T)	730 (T)	730 (T)
Life table test	P = 0.536	P = 0.361	P = 0.132	P = 0.652
Logistic regression test	P = 0.536	P = 0.361	P = 0.132	P = 0.652
Cochran-Armitage test	P = 0.528N			
Fisher exact test		P = 0.349	P = 0.141	P = 0.684N
Uterus: Stromal Polyp				
Overall rate	0/50 (0%)	3/50 (6%)	0/50 (0%)	1/50 (2%)
Adjusted rate	0.0%	7.3%	0.0%	3.1%
Terminal rate	0/37 (0%)	2/38 (5%)	0/36 (0%)	1/32 (3%)
First incidence (days)	—	598	—	730 (T)
Life table test	P = 0.600	P = 0.128	—[f]	P = 0.471
Logistic regression test	P = 0.630	P = 0.114	—	P = 0.471
Cochran-Armitage test	P = 0.634			
Fisher exact test		P = 0.121	—	P = 0.500

TABLE H2
Statistical Analysis of Primary Neoplasms in Female Mice in the 2-Year Gavage Study of AZT/5,000 U α-Interferon A/D

	Vehicle Control	30 mg AZT/kg + 5,000 U α-IFN A/D	60 mg AZT/kg + 5,000 U α-IFN A/D	120 mg AZT/kg + 5,000 U α-IFN A/D
Vagina: Squamous Cell Carcinoma				
Overall rate	0/50 (0%)	0/50 (0%)	5/50 (10%)	4/50 (8%)
Adjusted rate	0.0%	0.0%	13.9%	12.5%
Terminal rate	0/37 (0%)	0/38 (0%)	5/36 (14%)	4/32 (13%)
First incidence (days)	—	—	730 (T)	730 (T)
Life table test	P = 0.009	—	P = 0.031	P = 0.046
Logistic regression test	P = 0.009	—	P = 0.031	P = 0.046
Cochran-Armitage test	P = 0.016			
Fisher exact test		—	P = 0.028	P = 0.059
Vagina: Squamous Cell Papilloma or Squamous Cell Carcinoma				
Overall rate	1/50 (2%)	1/50 (2%)	5/50 (10%)	4/50 (8%)
Adjusted rate	2.7%	2.6%	13.9%	12.5%
Terminal rate	1/37 (3%)	1/38 (3%)	5/36 (14%)	4/32 (13%)
First incidence (days)	733 (T)	733 (T)	730 (T)	730 (T)
Life table test	P = 0.047	P = 0.747N	P = 0.093	P = 0.136
Logistic regression test	P = 0.047	P = 0.747N	P = 0.093	P = 0.136
Cochran-Armitage test	P = 0.078			
Fisher exact test		P = 0.753	P = 0.102	P = 0.181
All Organs: Hemangiosarcoma				
Overall rate	5/50 (10%)	2/50 (4%)	1/50 (2%)	1/50 (2%)
Adjusted rate	13.5%	5.3%	2.4%	3.1%
Terminal rate	5/37 (14%)	2/38 (5%)	0/36 (0%)	1/32 (3%)
First incidence (days)	730 (T)	730 (T)	648	730 (T)
Life table test	P = 0.078N	P = 0.205N	P = 0.112N	P = 0.138N
Logistic regression test	P = 0.068N	P = 0.205N	P = 0.114N	P = 0.138N
Cochran-Armitage test	P = 0.060N			
Fisher exact test		P = 0.218N	P = 0.102N	P = 0.102N
All Organs: Hemangioma or Hemangiosarcoma				
Overall rate	7/50 (14%)	2/50 (4%)	1/50 (2%)	1/50 (2%)
Adjusted rate	18.3%	5.3%	2.4%	3.1%
Terminal rate	6/37 (16%)	2/38 (5%)	0/36 (0%)	1/32 (3%)
First incidence (days)	682	730 (T)	648	730 (T)
Life table test	P = 0.023N	P = 0.076N	P = 0.038N	P = 0.051N
Logistic regression test	P = 0.019N	P = 0.073N	P = 0.038N	P = 0.041N
Cochran-Armitage test	P = 0.016N			
Fisher exact test		P = 0.080N	P = 0.030N	P = 0.030N
All Organs: Malignant Lymphoma				
Overall rate	8/50 (16%)	12/50 (24%)	8/50 (16%)	6/50 (12%)
Adjusted rate	18.7%	28.3%	21.3%	15.6%
Terminal rate	4/37 (11%)	8/38 (21%)	7/36 (19%)	2/32 (6%)
First incidence (days)	589	592	604	557
Life table test	P = 0.301N	P = 0.260	P = 0.574	P = 0.462N
Logistic regression test	P = 0.215N	P = 0.217	P = 0.585	P = 0.358N
Cochran-Armitage test	P = 0.204N			
Fisher exact test		P = 0.227	P = 0.607N	P = 0.387N

TABLE H2
Statistical Analysis of Primary Neoplasms in Female Mice in the 2-Year Gavage Study of AZT/5,000 U α-Interferon A/D

	Vehicle Control	30 mg AZT/kg + 5,000 U α-IFN A/D	60 mg AZT/kg + 5,000 U α-IFN A/D	120 mg AZT/kg + 5,000 U α-IFN A/D
All Organs: Benign Neoplasms				
Overall rate	36/50 (72%)	24/50 (48%)	24/50 (48%)	22/50 (44%)
Adjusted rate	78.1%	56.7%	61.5%	60.3%
Terminal rate	27/37 (73%)	20/38 (53%)	21/36 (58%)	18/32 (56%)
First incidence (days)	575	592	620	557
Life table test	P = 0.063N	P = 0.017N	P = 0.029N	P = 0.040N
Logistic regression test	P = 0.016N	P = 0.011N	P = 0.024N	P = 0.006N
Cochran-Armitage test	P = 0.009N			
Fisher exact test		P = 0.012N	P = 0.012N	P = 0.004N
All Organs: Malignant Neoplasms				
Overall rate	32/50 (64%)	28/50 (56%)	33/50 (66%)	28/50 (56%)
Adjusted rate	69.4%	60.8%	74.7%	61.6%
Terminal rate	23/37 (62%)	20/38 (53%)	25/36 (69%)	15/32 (47%)
First incidence (days)	589	592	318	501
Life table test	P = 0.448	P = 0.262N	P = 0.431	P = 0.517N
Logistic regression test	P = 0.357N	P = 0.299N	P = 0.419	P = 0.283N
Cochran-Armitage test	P = 0.321N			
Fisher exact test		P = 0.270N	P = 0.500	P = 0.270N
All Organs: Benign or Malignant Neoplasms				
Overall rate	44/50 (88%)	40/50 (80%)	41/50 (82%)	39/50 (78%)
Adjusted rate	91.7%	85.1%	91.0%	86.5%
Terminal rate	33/37 (89%)	31/38 (82%)	32/36 (89%)	26/32 (81%)
First incidence (days)	575	592	318	501
Life table test	P = 0.432	P = 0.225N	P = 0.445N	P = 0.562N
Logistic regression test	P = 0.247N	P = 0.169N	P = 0.515N	P = 0.200N
Cochran-Armitage test	P = 0.160N			
Fisher exact test		P = 0.207N	P = 0.288N	P = 0.143N

(T)Terminal sacrifice
[a] Number of neoplasm-bearing animals/number of animals examined. Denominator is number of animals examined microscopically for adrenal gland, liver, lung, ovary, pituitary gland, spleen, thyroid gland, and uterus; 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 incidence are the P values associated with the trend test. Beneath the dosed group incidence are the P values corresponding to pairwise comparisons between the vehicle controls and that 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 Cochran-Armitage and Fisher exact tests compare directly the overall incidence rates. For all tests, a negative trend or a lower incidence in a dose group is indicated by **N**.
[e] Not applicable; no neoplasms in animal group
[f] Value of statistic cannot be computed.

TABLE H3
Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 2-Year Gavage Study of AZT/5,000 U α-Interferon A/D[a]

	Vehicle Control	30 mg AZT/kg + 5,000 U α-IFN A/D	60 mg AZT/kg + 5,000 U α-IFN A/D	120 mg AZT/kg + 5,000 U α-IFN A/D
Disposition Summary				
Animals initially in study	50	50	50	50
Early deaths				
Accidental deaths			2	1
Moribund	8	7	6	8
Natural deaths	5	5	6	9
Survivors				
Died last week of study		1		
Terminal sacrifice	37	37	36	32
Animals examined microscopically	50	50	50	50
Alimentary System				
Esophagus	(50)	(50)	(49)	(49)
Necrosis			2 (4%)	
Perforation			2 (4%)	
Muscularis, inflammation, chronic			2 (4%)	
Periesophageal tissue, inflammation, chronic			1 (2%)	
Intestine small, duodenum	(48)	(48)	(47)	(47)
Hyperplasia, adenomatous				1 (2%)
Intestine small, jejunum	(47)	(46)	(46)	(45)
Hyperplasia, adenomatous	1 (2%)			
Peyer's patch, hyperplasia, lymphoid		1 (2%)	2 (4%)	
Intestine small, ileum	(47)	(46)	(46)	(45)
Amyloid deposition	1 (2%)			
Hyperplasia, adenomatous	1 (2%)			
Liver	(50)	(50)	(50)	(50)
Angiectasis		1 (2%)	1 (2%)	
Basophilic focus		1 (2%)	1 (2%)	
Clear cell focus		2 (4%)	1 (2%)	
Congestion	1 (2%)			
Eosinophilic focus	4 (8%)	6 (12%)	5 (10%)	2 (4%)
Hematopoietic cell proliferation	2 (4%)	2 (4%)		
Hemorrhage		1 (2%)		
Hyperplasia, focal, lymphoid	1 (2%)		1 (2%)	
Inflammation, chronic	10 (20%)	6 (12%)	6 (12%)	6 (12%)
Mixed cell focus	2 (4%)	3 (6%)	2 (4%)	2 (4%)
Necrosis, focal	2 (4%)	2 (4%)	2 (4%)	3 (6%)
Vacuolization cytoplasmic	2 (4%)	6 (12%)	2 (4%)	3 (6%)
Bile duct, hyperplasia				1 (2%)
Centrilobular, necrosis	1 (2%)			
Hepatocyte, karyomegaly	1 (2%)		1 (2%)	1 (2%)
Mesentery	(10)	(12)	(9)	(10)
Hemorrhage	1 (10%)	2 (17%)		
Inflammation, chronic	1 (10%)	1 (8%)		
Fat, necrosis	7 (70%)	9 (75%)	5 (56%)	5 (50%)

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

TABLE H3
Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 2-Year Gavage Study of AZT/5,000 U α-Interferon A/D

	Vehicle Control	30 mg AZT/kg + 5,000 U α-IFN A/D	60 mg AZT/kg + 5,000 U α-IFN A/D	120 mg AZT/kg + 5,000 U α-IFN A/D
Alimentary System (continued)				
Pancreas	(48)	(50)	(50)	(49)
Inflammation, chronic			1 (2%)	
Necrosis	1 (2%)			
Acinus, atrophy, diffuse		1 (2%)		1 (2%)
Acinus, atrophy, focal			2 (4%)	1 (2%)
Duct, cyst		1 (2%)	1 (2%)	3 (6%)
Salivary glands	(50)	(49)	(50)	(48)
Inflammation, chronic			1 (2%)	
Stomach, forestomach	(50)	(50)	(49)	(48)
Cyst			1 (2%)	1 (2%)
Inflammation, chronic		1 (2%)	1 (2%)	
Epithelium, hyperplasia	3 (6%)	2 (4%)	1 (2%)	1 (2%)
Stomach, glandular	(49)	(50)	(48)	(49)
Edema	1 (2%)	1 (2%)		
Mineralization		1 (2%)		
Glands, degeneration, cystic, focal	5 (10%)	1 (2%)	8 (17%)	8 (16%)
Cardiovascular System				
Heart	(50)	(50)	(50)	(50)
Inflammation, chronic, focal	2 (4%)		1 (2%)	
Thrombosis	1 (2%)	1 (2%)		1 (2%)
Endocrine System				
Adrenal cortex	(50)	(49)	(50)	(49)
Accessory adrenal cortical nodule	1 (2%)		3 (6%)	
Cyst	1 (2%)	1 (2%)		
Hyperplasia, focal	3 (6%)	4 (8%)	1 (2%)	4 (8%)
Hypertrophy, focal			2 (4%)	2 (4%)
Islets, pancreatic	(48)	(49)	(50)	(48)
Hyperplasia	1 (2%)		1 (2%)	1 (2%)
Parathyroid gland	(43)	(43)	(45)	(46)
Cyst	1 (2%)			
Pituitary gland	(49)	(44)	(48)	(44)
Angiectasis	4 (8%)	1 (2%)	4 (8%)	3 (7%)
Pars distalis, cyst		1 (2%)	1 (2%)	3 (7%)
Pars distalis, cytoplasmic alteration, focal		2 (5%)	1 (2%)	
Pars distalis, hyperplasia, focal	8 (16%)	7 (16%)	8 (17%)	8 (18%)
Rathke's cleft, cyst	1 (2%)			3 (7%)
Thyroid gland	(49)	(50)	(50)	(50)
Degeneration, cystic, focal	19 (39%)	16 (32%)	14 (28%)	12 (24%)
Inflammation, chronic, focal	1 (2%)			
Follicle, cyst	7 (14%)	6 (12%)	9 (18%)	7 (14%)
Follicular cell, hyperplasia	21 (43%)	19 (38%)	17 (34%)	17 (34%)
General Body System				
None				

TABLE H3
Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 2-Year Gavage Study of AZT/5,000 U α-Interferon A/D

	Vehicle Control	30 mg AZT/kg + 5,000 U α-IFN A/D	60 mg AZT/kg + 5,000 U α-IFN A/D	120 mg AZT/kg + 5,000 U α-IFN A/D
Genital System				
Clitoral gland	(50)	(50)	(50)	(49)
Degeneration, cystic	3 (6%)	1 (2%)	3 (6%)	3 (6%)
Inflammation, chronic				1 (2%)
Ovary	(50)	(49)	(49)	(50)
Cyst	10 (20%)	6 (12%)	5 (10%)	13 (26%)
Hemorrhage		2 (4%)	1 (2%)	4 (8%)
Mineralization	1 (2%)	1 (2%)		
Thrombosis		1 (2%)		1 (2%)
Bilateral, cyst				1 (2%)
Uterus	(50)	(50)	(50)	(50)
Angiectasis			2 (4%)	
Cyst	1 (2%)	2 (4%)		
Hemorrhage		1 (2%)		1 (2%)
Hydrometra	19 (38%)	21 (42%)	13 (26%)	15 (30%)
Thrombosis	1 (2%)	1 (2%)		
Endometrium, hyperplasia, cystic	42 (84%)	37 (74%)	41 (82%)	45 (90%)
Vagina	(50)	(48)	(48)	(50)
Epithelium, hyperplasia	1 (2%)	3 (6%)	7 (15%)	12 (24%)
Epithelium, hyperplasia, atypical		1 (2%)	1 (2%)	3 (6%)
Hematopoietic System				
Bone marrow	(50)	(50)	(50)	(48)
Angiectasis				1 (2%)
Depletion cellular				2 (4%)
Hyperplasia	1 (2%)	4 (8%)	4 (8%)	4 (8%)
Lymph node	(8)	(7)	(4)	(6)
Iliac, hemorrhage	1 (13%)			
Renal, hemorrhage				1 (17%)
Lymph node, mandibular	(46)	(46)	(48)	(44)
Hemorrhage	1 (2%)		2 (4%)	
Hyperplasia, lymphoid	2 (4%)	1 (2%)	3 (6%)	1 (2%)
Infiltration cellular, mast cell			1 (2%)	
Lymph node, mesenteric	(48)	(49)	(48)	(49)
Ectasia		1 (2%)		2 (4%)
Hemorrhage	4 (8%)	2 (4%)	7 (15%)	6 (12%)
Hyperplasia, lymphoid	1 (2%)	2 (4%)		
Spleen	(49)	(49)	(49)	(49)
Depletion cellular			1 (2%)	1 (2%)
Fibrosis, focal				1 (2%)
Hematopoietic cell proliferation	23 (47%)	15 (31%)	12 (24%)	17 (35%)
Hyperplasia, lymphoid	5 (10%)	4 (8%)	8 (16%)	3 (6%)
Thymus	(47)	(46)	(48)	(48)
Atrophy		3 (7%)	1 (2%)	2 (4%)
Cyst	3 (6%)	4 (9%)	4 (8%)	2 (4%)
Hyperplasia, lymphoid	2 (4%)			
Inflammation, granulomatous		1 (2%)		
Necrosis		1 (2%)		

TABLE H3
Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 2-Year Gavage Study of AZT/5,000 U α-Interferon A/D

	Vehicle Control	30 mg AZT/kg + 5,000 U α-IFN A/D	60 mg AZT/kg + 5,000 U α-IFN A/D	120 mg AZT/kg + 5,000 U α-IFN A/D
Integumentary System				
Mammary gland	(50)	(50)	(49)	(50)
Ectasia	1 (2%)			
Hyperplasia		1 (2%)	1 (2%)	1 (2%)
Skin	(50)	(50)	(50)	(50)
Cyst epithelial inclusion	1 (2%)			
Edema		3 (6%)	3 (6%)	1 (2%)
Inflammation, chronic, focal		1 (2%)	1 (2%)	2 (4%)
Ulcer				1 (2%)
Subcutaneous tissue, inflammation, chronic active			1 (2%)	
Musculoskeletal System				
Bone	(50)	(50)	(50)	(50)
Fibrous osteodystrophy	2 (4%)			
Hyperostosis	48 (96%)	40 (80%)	36 (72%)	43 (86%)
Cranium, fibrous osteodystrophy			1 (2%)	
Femur, fibrous osteodystrophy		1 (2%)	2 (4%)	2 (4%)
Femur, osteopetrosis		1 (2%)		
Skeletal muscle	(47)	(50)	(49)	(50)
Hemorrhage, focal			1 (2%)	
Inflammation, suppurative				1 (2%)
Regeneration	2 (4%)			
Nervous System				
Brain	(50)	(50)	(50)	(50)
Atrophy, focal	2 (4%)	4 (8%)	1 (2%)	
Vacuolization cytoplasmic				1 (2%)
Meninges, inflammation, chronic	1 (2%)			1 (2%)
Spinal cord	(2)		(1)	(4)
Cyst epithelial inclusion	1 (50%)			1 (25%)
Hemorrhage, focal			1 (100%)	
Respiratory System				
Lung	(50)	(50)	(50)	(50)
Congestion	1 (2%)		2 (4%)	
Hemorrhage		3 (6%)	2 (4%)	3 (6%)
Hyperplasia, histiocytic	2 (4%)	3 (6%)	1 (2%)	1 (2%)
Metaplasia, osseous				1 (2%)
Pigmentation		1 (2%)	1 (2%)	
Alveolar epithelium, hyperplasia		2 (4%)	1 (2%)	2 (4%)
Mediastinum, inflammation, chronic			1 (2%)	
Nose	(50)	(50)	(50)	(50)
Inflammation, suppurative		1 (2%)	1 (2%)	
Mucosa, glands, dilatation, focal	3 (6%)			

TABLE H3
Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 2-Year Gavage Study of AZT/5,000 U α-Interferon A/D

	Vehicle Control	30 mg AZT/kg + 5,000 U α-IFN A/D	60 mg AZT/kg + 5,000 U α-IFN A/D	120 mg AZT/kg + 5,000 U α-IFN A/D
Special Senses System				
Eye	(2)		(1)	
Fibrosis	1 (50%)			
Cornea, inflammation, chronic			1 (100%)	
Harderian gland	(5)	(2)	(2)	(1)
Hyperplasia, focal	1 (20%)			
Inflammation, chronic, focal	1 (20%)			
Urinary System				
Kidney	(50)	(50)	(50)	(49)
Congestion				1 (2%)
Infarct	1 (2%)		1 (2%)	1 (2%)
Metaplasia, focal, osseous		3 (6%)	2 (4%)	
Nephropathy	35 (70%)	33 (66%)	39 (78%)	33 (67%)
Pelvis, dilatation			1 (2%)	1 (2%)
Renal tubule, accumulation, hyaline droplet		1 (2%)	1 (2%)	
Renal tubule, atrophy				1 (2%)
Renal tubule, dilatation	1 (2%)		1 (2%)	2 (4%)
Renal tubule, mineralization		1 (2%)	1 (2%)	
Renal tubule, necrosis		1 (2%)		
Renal tubule, pigmentation	1 (2%)			
Urinary bladder	(50)	(50)	(50)	(50)
Hyperplasia, lymphoid		1 (2%)	1 (2%)	

APPENDIX I
GENETIC TOXICOLOGY

GENETIC TOXICOLOGY

SALMONELLA MUTAGENICITY TEST PROTOCOL

Testing was performed as reported by Zeiger *et al*. (1992). 3′-Azido-3′-deoxythymidine (AZT) was sent to the laboratory as a coded aliquot from Radian Corporation (Austin, TX). It was incubated with the *Salmonella typhimurium* tester strains TA97, TA98, TA100, TA102, TA104, and TA1535 either in buffer or S9 mix (metabolic activation enzymes and cofactors from Aroclor 1254-induced male Sprague-Dawley rat or Syrian hamster liver) for 20 minutes at 37° C. Top agar supplemented with L-histidine and d-biotin was added, and the contents of the tubes were mixed and poured onto the surfaces of minimal glucose agar plates. Histidine-independent mutant colonies arising on these plates were counted following incubation for 2 days at 37° C.

Each trial consisted of triplicate plates of concurrent positive and negative controls and at least five doses of AZT. All positive trials were repeated under the conditions that elicited the positive response. The high dose was limited by toxicity.

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

CHINESE HAMSTER OVARY CELL CYTOGENETICS PROTOCOLS

Testing was performed as reported by Galloway *et al*. (1987). AZT was sent to the laboratory as a coded aliquot by Radian Corporation. It was tested in cultured Chinese hamster ovary (CHO) cells for induction of sister chromatid exchanges (SCEs) and chromosomal aberrations (Abs), both in the presence and absence of Aroclor 1254-induced male Sprague-Dawley rat liver S9 and cofactor mix. Cultures were handled under gold lights to prevent photolysis of bromodeoxyuridine-substituted DNA. Each test consisted of concurrent solvent and positive controls and of at least three doses of AZT; the high dose was limited by toxicity. A single flask per dose was used.

Sister Chromatid Exchange Test: In the SCE test without S9, CHO cells were incubated for 26 hours with AZT in McCoy's 5A medium. Bromodeoxyuridine (BrdU) was added 2 hours after culture initiation. After 26 hours, the medium containing AZT was removed and replaced with fresh medium plus BrdU and Colcemid, and incubation was continued for 2 hours. Cells were then harvested by mitotic shake-off, fixed, and stained with Hoechst 33258 and Giemsa. In the SCE test with S9, cells were incubated with AZT, serum-free medium, and S9 for 2 hours. The medium was then removed and replaced with medium containing serum and BrdU and no AZT, and incubation proceeded for an additional 26 hours with Colcemid present for the final 2 hours. Harvesting and staining were the same as for cells treated without S9. All slides were scored blind, and those from a single test were read by the same person. Fifty second-division metaphase cells were scored for frequency of SCEs/cell from each dose level, except for the 83 µg/mL dose without S9. At this dose, SCEs were so numerous that fewer cells were scored. Because significant AZT-induced cell cycle delay was seen at the 250 µg/mL dose without S9, incubation time was lengthened to 31 hours for these cultures to ensure a sufficient number of scorable (second-division metaphase) cells.

Statistical analyses were conducted on the slopes of the dose-response curves and the individual dose points (Galloway *et al.*, 1987). An SCE frequency 20% above the concurrent solvent control value was chosen as a statistically conservative positive response. The probability of this level of difference occurring by chance at one dose point is less than 0.01; the probability for such a chance occurrence at two dose points is less than 0.001. An increase of 20% or greater at any single dose was considered weak evidence of activity; increases at two or more doses resulted in a determination that the trial was positive. A statistically significant trend ($P < 0.005$) in the absence of any responses reaching 20% above background led to a call of equivocal.

Chromosomal Aberrations Test: In the Abs test without S9, cells were incubated in McCoy's 5A medium with AZT for 12.5 hours; Colcemid was added and incubation continued for 2 hours. The cells were then harvested by mitotic shake-off, fixed, and stained with Giemsa. For the Abs test with S9, cells were treated with AZT and S9 for 2 hours, after which the treatment medium was removed and the cells were incubated for 10 hours in fresh medium with Colcemid present for the final 2 hours. Cells were harvested in the same manner as for the treatment without S9.

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

Chromosomal aberration data are presented as percentage of cells with aberrations. To arrive at a statistical call for a trial, analyses were conducted on both the dose response curve and individual dose points. For a single trial, a statistically significant ($P \leq 0.05$) difference for one dose point and a significant trend ($P \leq 0.015$) were considered weak evidence for a positive response; significant differences for two or more doses indicated the trial was positive. A positive trend test in the absence of a statistically significant increase at any one dose resulted in an equivocal call (Galloway *et al.*, 1987). Ultimately, the trial calls were based on a consideration of the statistical analyses as well as the biological information available to the reviewers.

SHORT-TERM *IN VIVO* MOUSE BONE MARROW/ PERIPHERAL BLOOD MICRONUCLEUS TEST PROTOCOLS

Preliminary range-finding studies were performed. Factors affecting dose selection included chemical solubility, toxicity, and the extent of cell cycle delay induced by AZT exposure. The standard three-exposure protocol is described in detail by Phillips *et al.* (1991). Male $B6C3F_1$ mice were administered AZT dissolved in corn oil by gavage (0.3 mL per mouse) three times at 24-hour intervals. Solvent control animals received 0.3 mL of corn oil alone. The positive control mice received injections of dimethylbenzanthracene (12.5 mg/kg). Twenty-four hours after the final treatment, the mice were killed, and smears of the bone marrow cells obtained from the femurs were prepared. The data are shown in Table I4.

The data presented in Table I5 came from peripheral blood smears prepared from mice used in the initial range-finding study. These data were used to confirm the bone marrow micronucleus test results without the use of additional animals. For this analysis, the mice were killed 48 hours after the third treatment with AZT. The suitability of these samples for analysis is based on the well-known kinetics for polychromatic erythrocyte (PCE) formation and persistence in mouse bone marrow and peripheral blood (i.e., micronucleated PCE frequencies in bone marrow should be similar to frequencies in peripheral blood sampled 24 hours later) (MacGregor *et al.*, 1990). Because this was a range-finding study, there was no positive control group for this experiment.

Air-dried smears from both tissue types were fixed and stained with acridine orange; 2,000 PCEs per tissue per mouse were scored for frequency of micronucleated cells in each of 4 or 5 animals per dose group.

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

MOUSE PERIPHERAL BLOOD MICRONUCLEUS TEST PROTOCOL

A detailed discussion of this assay is presented in MacGregor *et al.* (1990). At the end of the 14-week toxicity study, peripheral blood samples were obtained from male and female mice, and smears were immediately prepared and fixed in absolute methanol. The methanol-fixed slides were stained with acridine orange and coded. Slides were scanned to determine the frequency of micronuclei in 1,000 PCEs and 1,000 NCEs in each of nine or ten animals per dose group. Data analysis was performed as described previously for the short-term *in vivo* micronucleus tests.

RESULTS

AZT is mutagenic. Positive results were obtained with AZT (0.003 to 3 µg/plate) in *S. typhimurium* strain TA102 without S9 activation enzymes and with 30% hamster liver S9; no mutagenic response was detected in strain TA97, TA98, TA100, TA104, or TA1535 (0.001 to 6 µg/plate), with or without hamster or rat liver S9 (Table I1). In cytogenetic tests with cultured CHO cells, AZT induced SCEs (Table I2), but not Abs (Table I3), with and without S9. The SCE response in the absence of S9 was much stronger and occurred at much lower doses than the response observed in the presence of S9. AZT, administered by gavage three times at 24-hour intervals at doses ranging from 200 to 2,000 mg/kg, induced increased frequencies of micronucleated PCEs in bone marrow (Table I4) and peripheral blood (Table I5) samples of male mice (Phillips *et al.*, 1991). The increased frequencies of micronuclei were very impressive, with the three treatment groups in the bone marrow analysis showing increases that were from three to nine times the level induced by the positive control, dimethylbenzanthracene (Table I4). The increases noted in peripheral blood (Table I5) were of similar or greater magnitude. Results of a 14-week peripheral blood micronucleus test with male mice showed significant increases in the frequencies of micronucleated PCEs and NCEs at doses of 100 and 1,000 mg AZT/kg body weight per day (Table I6). No increased frequency of micronucleated cells was noted at the lowest dose of 25 mg/kg per day.

TABLE I1
Mutagenicity of AZT in *Salmonella typhimurium*[a]

Strain	Dose (μg/plate)	Revertants/plate[b] S9 Trial 1	S9 Trial 2	S9 Trial 3	+30% hamster S9 Trial 1	+30% hamster S9 Trial 2	+30% hamster S9 Trial 3	+30% rat S9 Trial 1	+30% rat S9 Trial 2
TA102	0	191 ± 6.3	117 ± 6.9	183 ± 20.0	328 ± 20.3	282 ± 5.8	262 ± 1.5	355 ± 15.2	238 ± 17.0
	0.003	190 ± 8.7	145 ± 8.3		357 ± 10.7	306 ± 7.0		391 ± 4.1	
	0.01	187 ± 9.3	168 ± 10.4	193 ± 3.9	310 ± 16.8	305 ± 9.6	285 ± 7.1	391 ± 12.5	288 ± 7.5
	0.03	226 ± 2.5	190 ± 6.3	229 ± 11.2	357 ± 31.1	325 ± 3.5	277 ± 3.0	376 ± 14.7	289 ± 6.6
	0.1	334 ± 15.4	200 ± 5.5	300 ± 13.2	449 ± 9.2	374 ± 22.0	333 ± 8.0	394 ± 10.7	285 ± 12.0
	0.3	418 ± 9.5	212 ± 6.4	337 ± 15.1	482 ± 11.0	389 ± 20.6	360 ± 7.4	368 ± 25.7	295 ± 22.0
	0.6		207 ± 18.8	319 ± 20.7		456 ± 7.4	356 ± 6.3		293 ± 6.6
	1			333 ± 19.2			417 ± 14.6		250 ± 7.2
	3			34 ± 3.7[c]			228 ± 19.9		104 ± 14.4[c]
Trial summary		Positive	Positive	Positive	Positive	Positive	Weakly Positive	Negative	Negative
Positive control[d]		672 ± 72.5	541 ± 8.0	675 ± 22.0	501 ± 13.4	450 ± 10.9	636 ± 117.1	443 ± 0.3	554 ± 31.7

TA102 (continued)

Strain	Dose (μg/plate)	S9	+30% hamster S9	+30% rat S9
TA104	0	307 ± 12.4	343 ± 11.7	347 ± 5.8
	0.003	326 ± 11.2		
	0.01	326 ± 5.0	382 ± 12.1	376 ± 11.0
	0.03	344 ± 6.1	385 ± 22.4	404 ± 6.9
	0.1	347 ± 2.9	410 ± 15.4	390 ± 4.2
	0.3	277 ± 14.6	359 ± 10.7	372 ± 1.7
	1		289 ± 23.2	324 ± 26.5
Trial summary		Negative	Equivocal	Equivocal
Positive control		485 ± 2.9	852 ± 18.6	833 ± 18.5

TABLE I1
Mutagenicity of AZT in *Salmonella typhimurium*

Strain	Dose (μg/plate)	Revertants/plate				
		S9	+30% hamster S9		+30% rat S9	
			Trial 1	Trial 2	Trial 1	Trial 2
TA100	0	132 ± 5.2	128 ± 4.0	114 ± 6.4	158 ± 7.5	136 ± 5.1
	0.01			116 ± 5.5		132 ± 3.8
	0.03	128 ± 7.3		118 ± 4.7		137 ± 11.9
	0.1	121 ± 5.2	140 ± 8.0	111 ± 8.4	155 ± 11.0	135 ± 10.0
	0.3	107 ± 7.5	145 ± 2.8	111 ± 7.4	152 ± 9.4	137 ± 3.0
	1	81 ± 2.6	118 ± 12.3	122 ± 3.5	122 ± 2.9	120 ± 4.2
	3	6 ± 1.9[c]	25 ± 2.4		27 ± 1.7	
	6		1 ± 1.0		6 ± 2.1[c]	
Trial summary		Negative	Negative	Negative	Negative	
Positive control		465 ± 17.2	437 ± 41.9	453 ± 28.8	408 ± 13.7	427 ± 37.8

Strain	Dose (μg/plate)	S9	+30% hamster S9	+30% rat S9
TA1535	0	10 ± 1.2	10 ± 1.2	13 ± 1.5
	0.003	11 ± 1.2		
	0.01	10 ± 2.3	9 ± 0.9	17 ± 0.6
	0.03	8 ± 1.2	11 ± 4.3	12 ± 3.2
	0.1	9 ± 0.3	12 ± 1.5	13 ± 3.0
	0.3	9 ± 2.1	11 ± 0.9	13 ± 1.5
	1		10 ± 1.7	12 ± 1.2
Trial summary		Negative	Negative	
Positive control		454 ± 20.7	255 ± 2.1	102 ± 6.2

Strain	Dose (μg/plate)	S9	+30% hamster S9	+30% rat S9
TA97	0	177 ± 12.9	146 ± 9.2	194 ± 5.4
	0.003	204 ± 3.8		
	0.01	213 ± 2.4	144 ± 3.0	204 ± 14.9
	0.03	201 ± 7.0	143 ± 5.8	196 ± 7.8
	0.1	166 ± 15.2	143 ± 12.8	174 ± 1.2
	0.3	155 ± 2.1	130 ± 2.3	147 ± 13.6
	1		134 ± 7.5	170 ± 3.0
Trial summary		Negative	Negative	
Positive control		381 ± 15.2	499 ± 39.3	410 ± 19.7

TABLE I1
Mutagenicity of AZT in *Salmonella typhimurium*

Strain	Dose (µg/plate)	Revertants/plate		
		S9	+30% hamster S9	+30% rat S9
TA98	0	19 ± 1.8	26 ± 4.8	24 ± 2.3
	0.001	16 ± 1.0		22 ± 1.9
	0.003	20 ± 2.6	22 ± 3.4	21 ± 4.0
	0.01	22 ± 0.9	22 ± 2.2	18 ± 1.7
	0.03	26 ± 4.0	19 ± 2.3	25 ± 2.8
	0.1	22 ± 3.2	16 ± 2.8	17 ± 1.7
	0.3		17 ± 2.6	
Trial summary		Negative	Negative	
Positive control		416 ± 12.3	306 ± 6.4	92 ± 0.9

[a] Study was performed at SRI International. The detailed protocol is presented in Zeiger *et al*. (1992). 0 µg/plate was the solvent control.
[b] Revertants are presented as mean ± standard error from three plates.
[c] Slight toxicity
[d] The positive controls in the absence of metabolic activation were sodium azide (TA100 and TA1535), 9-aminoacridine (TA97), 4-nitro-*o*-phenylenediamine (TA98), mytomycin-C (TA102), and methyl methanesulfonate (TA104). The positive control for metabolic activation with all strains was 2-aminoanthracene.

TABLE I2
Induction of Sister Chromatid Exchanges in Chinese Hamster Ovary Cells by AZT[a]

Compound	Dose (µg/mL)	Total Cells Scored	No. of Chromo-somes	No. of SCEs	SCEs/ Chromo-some	SCEs/ Cell	Hrs in BrdU	Relative Change of SCEs/ Chromosome[b] (%)
S9								
Trial 1								
Summary: Positive								
Dimethylsulfoxide[c]		50	1,048	385	0.36	7.7	26.0	
Mitomycin-C[d]	0.001	50	1,047	687	0.65	13.7	26.0	78.61
	0.004	10	208	187	0.89	18.7	26.0	144.73
AZT	8.3	50	1,049	715	0.68	14.3	26.0	85.54*
	25	50	1,049	918	0.87	18.4	26.0	138.22*
	83	25	525	538	1.02	21.5	26.0	178.95*
	250	0					31.0[e]	
					P < 0.001[f]			
Trial 2								
Summary: Positive								
Dimethylsulfoxide		50	1,049	384	0.36	7.7	26.0	
Mitomycin-C	0.001	50	1,051	532	0.50	10.6	26.0	38.28
AZT	8.3	50	1,049	564	0.53	11.3	26.0	46.87*
	25	50	1,047	645	0.61	12.9	26.0	68.29*
	83	25	522	481	0.92	19.2	26.0	151.72*
	250	0					31.0[e]	
					P < 0.001			
+ S9								
Summary: Positive								
Dimethylsulfoxide		50	1,042	380	0.36	7.6	26.0	
Cyclophosphamide[d]	0.125	50	1,049	670	0.63	13.4	26.0	75.14
	0.5	10	210	204	0.97	20.4	26.0	166.38
AZT	250	50	1,050	443	0.42	8.9	26.0	15.69
	833	50	1,049	479	0.45	9.6	26.0	25.21*
	2,500	50	1,047	551	0.52	11.0	26.0	44.31*
					P < 0.001			

* Positive response ($P \leq 0.01$) versus the solvent control
[a] Study was performed at SITEK Research Laboratories. A detailed description of the protocol is presented in Galloway *et al*. (1987). SCE = sister chromatid exchange; BrdU = bromodeoxyuridine
[b] SCEs/chromosome in treated cells versus SCEs/chromosome in solvent control cells
[c] Solvent control
[d] Positive control
[e] Because AZT induced a delay in the cell division cycle, the harvest time was extended to maximize the number of second-division metaphase cells available for analysis.
[f] Significance of SCEs/chromosome tested by the linear regression trend test versus log of the dose

TABLE I3
Induction of Chromosomal Aberrations in Chinese Hamster Ovary Cells by AZT[a]

S9					+ S9				
Dose (µg/mL)	Total Cells Scored	No. of Abs	Abs/ Cell	Cells with Abs (%)	Dose (µg/mL)	Total Cells Scored	No. of Abs	Abs/ Cell	Cells with Abs (%)
Harvest time: 14.5 hours Summary: Negative					Harvest time: 12.0 hours Summary: Negative				
Dimethylsulfoxide[b]					Dimethylsulfoxide				
	200	3	0.02	1.5		200	6	0.03	3.0
Mitomycin-C[c]					Cyclophosphamide[c]				
0.4	25	22	0.88	52	20	25	31	1.24	48
AZT					AZT				
541	200	3	0.02	1.5	541	200	3	0.02	1.5
1,163	200	4	0.02	2.0	1,163	200	3	0.02	1.5
2,500	200	1	0.01	0.5	2,500	200	4	0.02	2.0
				P = 0.803[d]					P = 0.751

[a] Study was performed at SITEK Research Laboratories. The detailed protocol is presented in Galloway *et al*. (1987). Abs = aberrations
[b] Solvent control
[c] Positive control
[d] Significance of percent cells with aberrations tested by the linear regression trend test versus log of the dose

TABLE I4
Frequency of Micronuclei in Bone Marrow Polychromatic Erythrocytes of Male Mice Treated with AZT by Gavage for 3 Days[a]

Compound	Dose (mg/kg/day)	Number of Mice with Erythrocytes Scored	Micronucleated PCEs/1,000 PCEs[b]
Corn oil[c]			
	0	5	2.1 ± 0.71
Dimethylbenzanthracene[d]			
	12.5	5	4.0 ± 0.76
AZT			
	500	5	15.1 ± 3.13*
	1,000	5	13.0 ± 2.20*
	2,000	5	35.4 ± 3.34*
			P < 0.001[e]

* Significantly different from the solvent control (P≤0.001)
[a] Study was performed at Integrated Laboratory Systems. The detailed protocol and these data are presented in Phillips *et al*. (1991). PCE = polychromatic erythrocyte
[b] Mean ± standard error
[c] Solvent control
[d] Positive control
[e] Significance of micronucleated PCEs/1,000 PCEs tested by the one-tailed trend test; significant at P≤0.025 (Margolin *et al.*, 1990)

TABLE I5
Frequency of Micronuclei in Peripheral Blood Erythrocytes of Male Mice Treated with AZT by Gavage for 3 Days[a]

Compound	Dose (mg/kg/day)	Number of Mice with Erythrocytes Scored	Micronucleated PCEs/1,000 PCEs[b]
Corn oil[c]	0	5	2.6 ± 0.19
AZT	200	5	15.2 ± 1.10*
	1,000	4	18.1 ± 2.75*
	2,000	5	53.4 ± 12.75*
			P < 0.001[d]

* Significantly different from the solvent control (P≤0.001)
[a] Study was performed at Integrated Laboratory Systems. The protocol and these data are presented in Phillips *et al*. (1991). PCE = polychromatic erythrocyte
[b] Mean ± standard error
[c] Solvent control
[d] Significance of micronucleated PCEs/1,000 PCEs tested by the one-tailed trend test; significant at P≤0.025 (Margolin *et al.*, 1990)

TABLE I6
Frequency of Micronuclei in Peripheral Blood Erythrocytes of Male Mice Treated with AZT by Gavage for 14 Weeks[a]

Compound	Dose (mg/kg/day)	Number of Mice with Erythrocytes Scored	Micronucleated Cells/1,000 Cells[b]	
			PCEs	NCEs
Corn oil[c]	0	10	2.1 ± 0.31	2.5 ± 0.27
AZT	25	9	2.7 ± 0.41	2.8 ± 0.32
	100	9	12.9 ± 1.57*	5.9 ± 0.48*
	1,000	9	57.6 ± 4.03*	55.3 ± 2.67*
			P < 0.001[d]	P < 0.001

* Significantly different from the solvent control (P≤0.001)
[a] Study was performed at Integrated Laboratory Systems. The detailed protocol and these data are presented in Phillips *et al*. (1991). PCE = polychromatic erythrocyte; NCE = normochromatic erythrocyte
[b] Mean ± standard error
[c] Solvent control
[d] Significance of micronucleated cells/1,000 cells tested by the one-tailed trend test; significant at P≤0.025 (Margolin *et al.*, 1990)

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

TABLE J1
Organ Weights and Organ-Weight-to-Body-Weight Ratios for Mice in the 14-Week Gavage Study of AZT[a]

	Vehicle Control	50 mg/kg	100 mg/kg	200 mg/kg	800 mg/kg	2,000 mg/kg
Male						
Core Study						
n	10	10	10	10	10	10
Necropsy body wt	32.4 ± 0.6	34.0 ± 0.7	35.1 ± 1.1	34.6 ± 0.9	33.8 ± 0.7	32.0 ± 0.6
Heart						
Absolute	0.138 ± 0.004	0.158 ± 0.004**	0.147 ± 0.004	0.152 ± 0.004	0.142 ± 0.002	0.137 ± 0.004
Relative	4.26 ± 0.09	4.68 ± 0.21	4.20 ± 0.09	4.42 ± 0.16	4.21 ± 0.07	4.29 ± 0.13
L. Kidney						
Absolute	0.282 ± 0.008	0.295 ± 0.011	0.289 ± 0.009	0.324 ± 0.008**	0.281 ± 0.005	0.276 ± 0.006
Relative	8.71 ± 0.22	8.71 ± 0.36	8.28 ± 0.31	9.42 ± 0.30	8.34 ± 0.19	8.64 ± 0.20
R. Kidney						
Absolute	0.283 ± 0.007	0.306 ± 0.007	0.307 ± 0.008	0.327 ± 0.007**	0.292 ± 0.009	0.282 ± 0.007
Relative	8.75 ± 0.23	9.02 ± 0.20	8.78 ± 0.23	9.49 ± 0.23	8.64 ± 0.24	8.82 ± 0.23
Liver						
Absolute	1.287 ± 0.039	1.572 ± 0.048**	1.344 ± 0.054	1.607 ± 0.034**	1.338 ± 0.063	1.297 ± 0.031
Relative	39.74 ± 0.95	46.26 ± 1.09**	38.31 ± 1.22	46.61 ± 0.75**	39.46 ± 1.21	40.60 ± 1.16
Lung						
Absolute	0.175 ± 0.006	0.182 ± 0.006[b]	0.182 ± 0.005	0.176 ± 0.004	0.178 ± 0.009	0.172 ± 0.003
Relative	5.42 ± 0.22	5.39 ± 0.19[b]	5.19 ± 0.10	5.12 ± 0.17	5.27 ± 0.24	5.39 ± 0.16
R. Testis						
Absolute	0.114 ± 0.003	0.115 ± 0.003	0.121 ± 0.003	0.116 ± 0.002	0.119 ± 0.002	0.104 ± 0.002*
Relative	3.52 ± 0.11	3.38 ± 0.08	3.47 ± 0.10	3.38 ± 0.09	3.53 ± 0.07	3.25 ± 0.10
Thymus						
Absolute	0.031 ± 0.002	0.042 ± 0.002**[b]	0.038 ± 0.003	0.034 ± 0.002	0.035 ± 0.002	0.030 ± 0.001
Relative	0.97 ± 0.05	1.24 ± 0.06*[b]	1.09 ± 0.08	0.99 ± 0.05	1.03 ± 0.07	0.93 ± 0.05
Recovery Study						
n	10	—	10	—	10	10
Necropsy body wt	37.1 ± 1.0		39.7 ± 0.6		40.0 ± 1.2	37.1 ± 0.9
Heart						
Absolute	0.152 ± 0.004		0.159 ± 0.003		0.165 ± 0.005*	0.151 ± 0.003
Relative	4.12 ± 0.11		4.01 ± 0.09		4.14 ± 0.13	4.08 ± 0.07
L. Kidney						
Absolute	0.315 ± 0.006		0.318 ± 0.004		0.319 ± 0.008	0.305 ± 0.007
Relative	8.53 ± 0.20		8.03 ± 0.17		8.00 ± 0.19	8.25 ± 0.21
R. Kidney						
Absolute	0.328 ± 0.011		0.333 ± 0.004		0.347 ± 0.010	0.326 ± 0.009
Relative	8.88 ± 0.29		8.40 ± 0.14		8.69 ± 0.19	8.80 ± 0.22
Liver						
Absolute	1.675 ± 0.051		1.754 ± 0.029		1.763 ± 0.054	1.721 ± 0.061
Relative	45.23 ± 0.96		44.25 ± 0.98		44.21 ± 1.28	46.30 ± 0.79
Lung						
Absolute	0.183 ± 0.005		0.187 ± 0.003		0.193 ± 0.006	0.178 ± 0.005
Relative	4.96 ± 0.15		4.72 ± 0.09		4.85 ± 0.17	4.84 ± 0.25
R. Testis						
Absolute	0.122 ± 0.002		0.122 ± 0.003		0.121 ± 0.003	0.116 ± 0.002
Relative	3.30 ± 0.10		3.06 ± 0.08		3.03 ± 0.10	3.13 ± 0.10
Thymus						
Absolute	0.033 ± 0.002		0.034 ± 0.002		0.038 ± 0.002	0.038 ± 0.002
Relative	0.89 ± 0.06		0.86 ± 0.05		0.94 ± 0.05	1.04 ± 0.05

TABLE J1
Organ Weights and Organ-Weight-to-Body-Weight Ratios for Mice in the 14-Week Gavage Study of AZT

	Vehicle Control	50 mg/kg	100 mg/kg	200 mg/kg	800 mg/kg	2,000 mg/kg
Female						
Core Study						
n	10	10	9	8	10	9
Necropsy body wt	28.8 ± 1.2	29.1 ± 0.6	27.4 ± 0.5	26.8 ± 0.7	27.3 ± 0.6	26.8 ± 1.1
Heart						
Absolute	0.115 ± 0.003	0.120 ± 0.003	0.116 ± 0.003	0.121 ± 0.006	0.113 ± 0.003	0.113 ± 0.004
Relative	4.04 ± 0.18	4.14 ± 0.13	4.22 ± 0.10	4.55 ± 0.26	4.15 ± 0.11	4.28 ± 0.19
L. Kidney						
Absolute	0.186 ± 0.006	0.180 ± 0.005	0.182 ± 0.004	0.179 ± 0.003	0.176 ± 0.003	0.186 ± 0.003
Relative	6.51 ± 0.23	6.19 ± 0.14	6.64 ± 0.10	6.70 ± 0.10	6.46 ± 0.10	7.01 ± 0.28
R. Kidney						
Absolute	0.192 ± 0.005	0.188 ± 0.004	0.193 ± 0.006	0.191 ± 0.005	0.190 ± 0.004	0.196 ± 0.005
Relative	6.71 ± 0.16	6.47 ± 0.10	7.05 ± 0.14	7.16 ± 0.18	6.97 ± 0.07	7.35 ± 0.19**
Liver						
Absolute	1.285 ± 0.045	1.322 ± 0.038	1.262 ± 0.050	1.244 ± 0.040	1.279 ± 0.030	1.274 ± 0.054
Relative	44.85 ± 1.06	45.58 ± 1.39	45.94 ± 1.41	46.56 ± 1.26	46.91 ± 0.59	47.72 ± 1.26
Lung						
Absolute	0.171 ± 0.007	0.178 ± 0.009	0.172 ± 0.008	0.179 ± 0.013	0.180 ± 0.019	0.174 ± 0.007
Relative	5.99 ± 0.27	6.15 ± 0.35	6.26 ± 0.24	6.72 ± 0.53	6.54 ± 0.58	6.59 ± 0.35
Thymus						
Absolute	0.049 ± 0.003	0.056 ± 0.003	0.047 ± 0.002	0.050 ± 0.002	0.044 ± 0.002	0.040 ± 0.002**
Relative	1.72 ± 0.09	1.93 ± 0.10	1.71 ± 0.07	1.86 ± 0.06	1.59 ± 0.06	1.50 ± 0.07
Recovery Study						
n	10	—	10	—	10	9
Necropsy body wt	30.8 ± 1.5		32.2 ± 0.7		33.3 ± 1.1	29.8 ± 1.1
Heart						
Absolute	0.119 ± 0.005		0.127 ± 0.005		0.123 ± 0.004	0.128 ± 0.004
Relative	3.93 ± 0.24		3.94 ± 0.13		3.71 ± 0.12	4.35 ± 0.26
L. Kidney						
Absolute	0.196 ± 0.005		0.205 ± 0.007		0.205 ± 0.009	0.213 ± 0.010
Relative	6.43 ± 0.23		6.36 ± 0.15		6.19 ± 0.27	7.26 ± 0.48
R. Kidney						
Absolute	0.203 ± 0.006		0.213 ± 0.006		0.218 ± 0.008	0.230 ± 0.011
Relative	6.66 ± 0.23		6.60 ± 0.11		6.60 ± 0.27	7.82 ± 0.50*
Liver						
Absolute	1.319 ± 0.048		1.399 ± 0.040		1.460 ± 0.047[b]	1.419 ± 0.059
Relative	43.08 ± 1.24		43.41 ± 0.79		44.16 ± 0.92[b]	47.64 ± 1.14**
Lung						
Absolute	0.175 ± 0.009		0.184 ± 0.008		0.172 ± 0.004	0.190 ± 0.016
Relative	5.76 ± 0.37		5.72 ± 0.23		5.21 ± 0.17	6.39 ± 0.45
Thymus						
Absolute	0.050 ± 0.003		0.048 ± 0.005		0.044 ± 0.003	0.050 ± 0.003
Relative	1.63 ± 0.11		1.50 ± 0.14		1.34 ± 0.09	1.69 ± 0.11

* Significantly different ($P \leq 0.05$) from the control group by Williams' or Dunnett's test
** $P \leq 0.01$
[a] Organ weights and body weights are given in grams; organ-weight-to-body-weight ratios (relative weights) are given as mg organ weight/g body weight (mean ± standard error). The recovery study only included animals in the vehicle control, 100, 800, and 2,000 mg/kg groups.
[b] n = 9

APPENDIX K
HEMATOLOGY AND
BONE MARROW ANALYSES

TABLE K1
Hematology and Bone Marrow Data for Mice in the 14-Week Gavage Study of AZT[a]

	Vehicle Control	50 mg/kg	100 mg/kg	200 mg/kg	800 mg/kg	2,000 mg/kg
Male						
Hematology						
Core Study						
n						
Day 5	9	10	10	9	10	10
Day 23	10	9	10	8	10	9
Week 14	10	10	10	10	10	10
Hematocrit (%)						
Day 5	45.2 ± 0.7	44.3 ± 0.3	43.7 ± 0.5	43.8 ± 0.3	43.8 ± 0.6	43.0 ± 0.6*
Day 23	48.2 ± 0.6	48.2 ± 0.6	47.1 ± 0.4	45.0 ± 1.1**	43.5 ± 0.4**	41.5 ± 0.5**
Week 14	50.6 ± 0.8	49.5 ± 0.5	49.7 ± 0.5	50.6 ± 0.8	47.7 ± 0.6**	44.9 ± 0.3**
Hemoglobin (g/dL)						
Day 5	15.4 ± 0.3	15.2 ± 0.1	15.0 ± 0.2	15.0 ± 0.1	15.0 ± 0.2	14.7 ± 0.2
Day 23	15.8 ± 0.2	15.9 ± 0.1	15.4 ± 0.1	15.0 ± 0.1**[b]	14.3 ± 0.1**	13.8 ± 0.2**
Week 14	16.2 ± 0.1	16.0 ± 0.1	16.1 ± 0.1	16.0 ± 0.1	15.1 ± 0.1**	14.1 ± 0.1**
Erythrocytes (10^6/μL)						
Day 5	9.48 ± 0.14	9.26 ± 0.06	9.19 ± 0.11	9.18 ± 0.05	9.17 ± 0.13	8.96 ± 0.12**
Day 23	9.75 ± 0.11	9.55 ± 0.12	9.16 ± 0.08**	8.70 ± 0.20**	8.09 ± 0.07**	7.62 ± 0.12**
Week 14	10.12 ± 0.16	9.48 ± 0.09**	9.29 ± 0.08**	8.98 ± 0.11**	7.85 ± 0.08**	6.71 ± 0.06**
Reticulocytes (10^6/μL)						
Day 5	0.23 ± 0.02	0.17 ± 0.02	0.17 ± 0.02	0.14 ± 0.02*	0.07 ± 0.01**	0.04 ± 0.01**
Day 23	0.14 ± 0.02	0.14 ± 0.01	0.16 ± 0.02	0.12 ± 0.01	0.14 ± 0.01	0.11 ± 0.01
Week 14	0.35 ± 0.04	0.38 ± 0.03	0.29 ± 0.03	0.40 ± 0.03[c]	0.21 ± 0.02*[c]	0.21 ± 0.02**
Nucleated erythrocytes (10^3/μL)						
Day 5	0.02 ± 0.02	0.01 ± 0.01	0.00 ± 0.00	0.01 ± 0.01	0.01 ± 0.01	0.02 ± 0.01
Day 23	0.01 ± 0.01	0.00 ± 0.00	0.00 ± 0.00	0.01 ± 0.01	0.01 ± 0.01	0.00 ± 0.00
Week 14	0.00 ± 0.00[c]	0.00 ± 0.00[c]	0.00 ± 0.00[c]	0.03 ± 0.03	0.00 ± 0.00	0.00 ± 0.00
Mean cell volume (fL)						
Day 5	47.8 ± 0.2	47.8 ± 0.2	47.6 ± 0.3	47.7 ± 0.2	47.7 ± 0.2	48.0 ± 0.3
Day 23	49.4 ± 0.3	50.6 ± 0.2**	51.4 ± 0.2**	51.8 ± 0.3**	54.1 ± 0.3**	54.6 ± 0.3**
Week 14	50.0 ± 0.3	52.2 ± 0.2**	53.6 ± 0.4**	56.5 ± 0.4**	60.9 ± 0.4**	67.1 ± 0.4**
Mean cell hemoglobin (pg)						
Day 5	16.3 ± 0.1	16.4 ± 0.1	16.4 ± 0.1	16.3 ± 0.1	16.3 ± 0.1	16.4 ± 0.1
Day 23	16.2 ± 0.1	16.6 ± 0.1**	16.8 ± 0.0**	16.9 ± 0.2**[b]	17.8 ± 0.1**	18.1 ± 0.1**
Week 14	16.1 ± 0.2	16.9 ± 0.2**	17.3 ± 0.2**	17.8 ± 0.1**	19.3 ± 0.1**	21.0 ± 0.1**
Mean cell hemoglobin concentration (g/dL)						
Day 5	34.1 ± 0.2	34.3 ± 0.1	34.4 ± 0.1	34.3 ± 0.2	34.3 ± 0.2	34.2 ± 0.1
Day 23	32.7 ± 0.2	33.0 ± 0.2	32.8 ± 0.2	32.6 ± 0.3[b]	32.9 ± 0.2	33.2 ± 0.1
Week 14	32.1 ± 0.4	32.4 ± 0.3	32.4 ± 0.4	31.7 ± 0.3	31.7 ± 0.3	31.4 ± 0.2
Platelets (10^3/μL)						
Day 5	1,111.0 ± 53.8	1,033.8 ± 43.7	1,137.8 ± 36.7	1,043.0 ± 54.5	1,014.8 ± 33.8	1,103.3 ± 28.7
Day 23	878.5 ± 45.0	828.3 ± 43.8	919.3 ± 42.1	1,010.8 ± 45.9	1,052.1 ± 43.3*	1,302.3 ± 44.3**
Week 14	1,111.1 ± 25.5	1,183.0 ± 35.6	1,231.6 ± 40.7*	1,160.0 ± 57.8	1,206.6 ± 43.8	1,297.6 ± 37.5**
Leukocytes (10^3/μL)						
Day 5	6.23 ± 0.21	6.41 ± 0.21	6.08 ± 0.14	6.09 ± 0.28	6.40 ± 0.19	5.91 ± 0.31
Day 23	7.45 ± 0.44	6.39 ± 0.30	7.04 ± 0.36	6.93 ± 0.34	6.34 ± 0.29	6.26 ± 0.22
Week 14	2.57 ± 0.37	3.09 ± 0.46	4.62 ± 0.67	4.80 ± 0.88	3.82 ± 0.56	2.78 ± 0.41
Segmented neutrophils (10^3/μL)						
Day 5	0.73 ± 0.09	0.73 ± 0.06	0.90 ± 0.08	0.78 ± 0.14	0.70 ± 0.09	0.56 ± 0.08
Day 23	0.94 ± 0.16	0.90 ± 0.12	0.77 ± 0.13	0.70 ± 0.07	0.49 ± 0.05	0.68 ± 0.11
Week 14	0.66 ± 0.08[c]	0.88 ± 0.17[c]	0.74 ± 0.11[c]	0.99 ± 0.12	0.89 ± 0.12	0.70 ± 0.12
Lymphocytes (10^3/μL)						
Day 5	5.21 ± 0.19	5.56 ± 0.17	5.02 ± 0.18	5.19 ± 0.24	5.55 ± 0.20	5.19 ± 0.30
Day 23	6.38 ± 0.32	5.41 ± 0.34	6.12 ± 0.28	6.08 ± 0.34	5.70 ± 0.30	5.42 ± 0.21
Week 14	1.73 ± 0.33[c]	2.09 ± 0.42[c]	3.43 ± 0.60[c]	3.58 ± 0.82	2.80 ± 0.49	1.97 ± 0.28

TABLE K1
Hematology and Bone Marrow Data for Mice in the 14-Week Gavage Study of AZT

	Vehicle Control	50 mg/kg	100 mg/kg	200 mg/kg	800 mg/kg	2,000 mg/kg
Male (continued)						
Hematology (continued)						
Core Study (continued)						
n						
Day 5	9	10	10	9	10	10
Day 23	10	9	10	8	10	9
Week 14	10	10	10	10	10	10
Atypical lymphocytes (10^3/μL)						
Day 5	0.00 ± 0.00	0.02 ± 0.01	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00
Day 23	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00
Week 14	0.00 ± 0.00[c]	0.00 ± 0.00[c]	0.00 ± 0.00[c]	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00
Monocytes (10^3/μL)						
Day 5	0.08 ± 0.02	0.05 ± 0.02	0.05 ± 0.02	0.06 ± 0.02	0.04 ± 0.02	0.05 ± 0.02
Day 23	0.04 ± 0.03	0.01 ± 0.01	0.01 ± 0.01	0.00 ± 0.00	0.04 ± 0.02	0.03 ± 0.02
Week 14	0.03 ± 0.02[c]	0.01 ± 0.01[c]	0.03 ± 0.02[c]	0.02 ± 0.01	0.01 ± 0.01	0.01 ± 0.01
Eosinophils (10^3/μL)						
Day 5	0.21 ± 0.03	0.10 ± 0.03	0.11 ± 0.04	0.07 ± 0.02*	0.12 ± 0.02	0.13 ± 0.04
Day 23	0.10 ± 0.03	0.09 ± 0.02	0.13 ± 0.03	0.11 ± 0.02	0.12 ± 0.03	0.16 ± 0.04
Week 14	0.04 ± 0.02[c]	0.12 ± 0.04[c]	0.13 ± 0.04[c]	0.19 ± 0.05	0.11 ± 0.03	0.12 ± 0.03
Recovery Study						
n	10	—	10	—	10	10
Hematocrit (%)						
Week 14	48.0 ± 0.3		47.9 ± 0.5		45.9 ± 0.3**	43.4 ± 0.7**
Week 17	50.2 ± 0.6		48.6 ± 0.4		49.3 ± 0.4	48.5 ± 0.5
Hemoglobin (g/dL)						
Week 14	15.9 ± 0.1		15.6 ± 0.1		14.4 ± 0.1**	13.4 ± 0.2**
Week 17	16.8 ± 0.1		16.5 ± 0.1*		16.5 ± 0.1*	16.2 ± 0.2**
Erythrocytes (10^6/μL)						
Week 14	9.61 ± 0.07		8.92 ± 0.11**		7.51 ± 0.08**	6.45 ± 0.13**
Week 17	10.27 ± 0.11		9.75 ± 0.06**		9.59 ± 0.08**	9.43 ± 0.13**
Reticulocytes (10^6/μL)						
Week 14	0.08 ± 0.01		0.08 ± 0.01		0.07 ± 0.02	0.05 ± 0.01
Week 17	0.11 ± 0.02[e]		0.09 ± 0.02		0.12 ± 0.02	0.13 ± 0.02
Nucleated erythrocytes (10^3/μL)						
Week 14	0.00 ± 0.00		0.00 ± 0.00		0.00 ± 0.00	0.00 ± 0.00
Week 17	0.00 ± 0.00		0.00 ± 0.00[c]		0.01 ± 0.01	0.01 ± 0.01
Mean cell volume (fL)						
Week 14	50.1 ± 0.2		53.8 ± 0.2**		61.1 ± 0.4**	67.4 ± 0.5**
Week 17	49.1 ± 0.3		49.7 ± 0.2*		51.5 ± 0.3**	51.4 ± 0.3**
Mean cell hemoglobin (pg)						
Week 14	16.6 ± 0.1		17.5 ± 0.1**		19.1 ± 0.1**	20.8 ± 0.2**
Week 17	16.4 ± 0.1		16.9 ± 0.1**		17.2 ± 0.1**	17.2 ± 0.2**
Mean cell hemoglobin concentration (g/dL)						
Week 14	33.2 ± 0.2		32.6 ± 0.2		31.3 ± 0.2**	31.0 ± 0.3**
Week 17	33.6 ± 0.3		33.9 ± 0.2		33.4 ± 0.2	33.4 ± 0.3
Platelets (10^3/μL)						
Week 14	1,086.8 ± 48.3		1,173.6 ± 22.8		1,245.6 ± 27.4**	1,554.2 ± 55.8**
Week 17	1,112.0 ± 44.9		1,152.7 ± 19.1		1,172.0 ± 41.1	1,215.6 ± 28.4
Leukocytes (10^3/μL)						
Week 14	8.37 ± 0.57		8.44 ± 0.50		8.35 ± 0.51	7.37 ± 0.25
Week 17	6.78 ± 0.34		6.07 ± 0.58[c]		5.92 ± 0.41	5.84 ± 0.44

TABLE K1
Hematology and Bone Marrow Data for Mice in the 14-Week Gavage Study of AZT

	Vehicle Control	50 mg/kg	100 mg/kg	200 mg/kg	800 mg/kg	2,000 mg/kg
Male (continued)						
Hematology (continued)						
Recovery Study (continued)						
n	10	—	10	—	10	10
Segmented neutrophils (10^3/μL)						
Week 14	1.36 ± 0.17		1.71 ± 0.17		1.32 ± 0.20	1.03 ± 0.12
Week 17	1.05 ± 0.16		0.89 ± 0.10[c]		0.86 ± 0.05	0.84 ± 0.13
Lymphocytes (10^3/μL)						
Week 14	6.79 ± 0.43		6.51 ± 0.38		6.69 ± 0.36	6.05 ± 0.26
Week 17	5.50 ± 0.28		5.04 ± 0.53[c]		4.83 ± 0.36	4.83 ± 0.34
Atypical lymphocytes (10^3/μL)						
Week 14	0.00 ± 0.00		0.00 ± 0.00		0.00 ± 0.00	0.00 ± 0.00
Week 17	0.00 ± 0.00		0.00 ± 0.00[c]		0.00 ± 0.00	0.00 ± 0.00
Monocytes (10^3/μL)						
Week 14	0.07 ± 0.03		0.03 ± 0.02		0.01 ± 0.01	0.06 ± 0.02
Week 17	0.05 ± 0.02		0.04 ± 0.02[c]		0.03 ± 0.02	0.06 ± 0.02
Eosinophils (10^3/μL)						
Week 14	0.16 ± 0.03		0.23 ± 0.06		0.23 ± 0.05[c]	0.22 ± 0.04
Week 17	0.17 ± 0.03		0.11 ± 0.03[c]		0.18 ± 0.05	0.10 ± 0.02
Bone Marrow Analyses						
Core Study						
n	10	—	9	—	9	8
Total femoral count (10^6/femur)	20.17 ± 1.29		19.84 ± 0.84		17.88 ± 0.97	15.18 ± 1.10*
M:E ratio	2.34 ± 0.11		2.05 ± 0.11[d]		3.36 ± 0.26*[d]	3.50 ± 0.23**[d]
Rubriblasts (10^6)	0.38 ± 0.05		0.51 ± 0.06		0.40 ± 0.07	0.50 ± 0.05
Prorubricytes (10^6)	0.63 ± 0.06		0.64 ± 0.08		0.41 ± 0.06	0.44 ± 0.05
Rubricytes (10^6)	2.30 ± 0.24		2.54 ± 0.18		1.59 ± 0.19	1.28 ± 0.08**
Metarubricytes (10^6)	1.42 ± 0.14		1.30 ± 0.06		0.71 ± 0.13**	0.51 ± 0.10**
Myeloblasts (10^6)	0.42 ± 0.05		0.31 ± 0.04		0.35 ± 0.05	0.36 ± 0.06
Promyelocytes (10^6)	0.77 ± 0.06		0.66 ± 0.04		0.60 ± 0.07	0.74 ± 0.09
Neutrophilic myelocytes (10^6)	2.05 ± 0.19		1.88 ± 0.27		1.61 ± 0.12	1.58 ± 0.14
Neutrophilic metamyelocytes (10^6)	0.73 ± 0.15		0.67 ± 0.11		0.53 ± 0.12	0.62 ± 0.11
Neutrophilic bands (10^6)	1.84 ± 0.24		1.58 ± 0.13		1.52 ± 0.09	1.25 ± 0.18
Neutrophilic segments (10^6)	4.73 ± 0.23		4.66 ± 0.26		5.34 ± 0.29	4.31 ± 0.47
Eosinophilic metamyelocytes (10^6)	0.06 ± 0.01		0.08 ± 0.01		0.09 ± 0.01	0.11 ± 0.03
Eosinophilic bands (10^6)	0.10 ± 0.02		0.18 ± 0.03*		0.13 ± 0.02	0.14 ± 0.03
Eosinophilic myelocytes (10^6)	0.072 ± 0.027		0.096 ± 0.029		0.079 ± 0.021	0.060 ± 0.025
Eosinophilic segments (10^6)	0.048 ± 0.013		0.042 ± 0.012		0.050 ± 0.014	0.058 ± 0.013
Basophilic myelocytes (10^6)	0.000 ± 0.000		0.000 ± 0.000		0.000 ± 0.000	0.000 ± 0.000
Basophilic metamyelocytes (10^6)	0.000 ± 0.000		0.000 ± 0.000		0.000 ± 0.000	0.000 ± 0.000
Basophilic bands (10^6)	0.000 ± 0.000		0.000 ± 0.000		0.000 ± 0.000	0.000 ± 0.000
Basophilic segments (10^6)	0.000 ± 0.000		0.000 ± 0.000		0.000 ± 0.000	0.000 ± 0.000
Bone marrow lymphocytes (10^6)	3.70 ± 0.29		3.92 ± 0.33		3.37 ± 0.23	2.31 ± 0.15**
Bone marrow macrophages (10^6)	0.043 ± 0.011		0.049 ± 0.013		0.067 ± 0.020	0.081 ± 0.024
Bone marrow monocytes (10^6)	0.000 ± 0.000		0.000 ± 0.000		0.000 ± 0.000	0.000 ± 0.000

TABLE K1
Hematology and Bone Marrow Data for Mice in the 14-Week Gavage Study of AZT

	Vehicle Control	50 mg/kg	100 mg/kg	200 mg/kg	800 mg/kg	2,000 mg/kg
Male (continued)						
Bone Marrow Analyses (continued)						
Core Study (continued)						
n	10	—	9	—	9	8
Megakaryo cells (10^6)	0.019 ± 0.014		0.024 ± 0.011		0.031 ± 0.012	0.025 ± 0.011
Plasma cells (10^6)	0.011 ± 0.006		0.020 ± 0.010		0.009 ± 0.006	0.031 ± 0.012
Mitotic figures (10^6)	0.29 ± 0.03		0.20 ± 0.04		0.28 ± 0.04	0.26 ± 0.03
Fat cells (10^6)	0.000 ± 0.000		0.000 ± 0.000		0.000 ± 0.000	0.000 ± 0.000
Mast cells (10^6)	0.000 ± 0.000		0.000 ± 0.000		0.000 ± 0.000	0.000 ± 0.000
Smudge cells (10^6)	0.58 ± 0.14		0.45 ± 0.10		0.70 ± 0.33	0.51 ± 0.09
Osteoblasts (10^6)	0.000 ± 0.000		0.000 ± 0.000		0.000 ± 0.000	0.000 ± 0.000
Osteoclasts (10^6)	0.000 ± 0.000		0.000 ± 0.000		0.000 ± 0.000	0.000 ± 0.000
Other bone marrow cells (10^6)	0.000 ± 0.000		0.000 ± 0.000		0.000 ± 0.000	0.000 ± 0.000
Recovery Study						
n	10	—	10	—	10	10
Total femoral count (10^6/femur)	24.3 ± 1.4		25.1 ± 1.0		25.2 ± 0.7	27.0 ± 0.8
M:E ratio	1.81 ± 0.12		1.83 ± 0.09		1.67 ± 0.07	1.50 ± 0.10
Rubriblasts (10^6)	0.45 ± 0.03		0.47 ± 0.06		0.44 ± 0.05	0.50 ± 0.06
Prorubricytes (10^6)	0.46 ± 0.08		0.42 ± 0.05		0.42 ± 0.07	0.48 ± 0.06
Rubricytes (10^6)	2.81 ± 0.29		2.91 ± 0.24		3.35 ± 0.26	3.74 ± 0.27*
Metarubricytes (10^6)	2.51 ± 0.19		2.52 ± 0.25		2.52 ± 0.38	3.07 ± 0.44
Myeloblasts (10^6)	0.35 ± 0.04		0.39 ± 0.06		0.37 ± 0.04	0.38 ± 0.04
Promyelocytes (10^6)	0.70 ± 0.07		0.62 ± 0.05		0.63 ± 0.08	0.81 ± 0.10
Neutrophilic myelocytes (10^6)	3.11 ± 0.34		3.26 ± 0.17		3.09 ± 0.25	3.13 ± 0.25
Neutrophilic metamyelocytes (10^6)	0.039 ± 0.016		0.069 ± 0.033		0.036 ± 0.017	0.091 ± 0.020
Neutrophilic bands (10^6)	0.35 ± 0.07		0.42 ± 0.07		0.26 ± 0.05	0.34 ± 0.04
Neutrophilic segments (10^6)	6.17 ± 0.44		6.18 ± 0.35		6.37 ± 0.27	6.20 ± 0.27
Eosinophilic myelocytes (10^6)	0.14 ± 0.02		0.18 ± 0.03		0.19 ± 0.03	0.20 ± 0.03
Eosinophilic metamyelocytes (10^6)	0.07 ± 0.02		0.12 ± 0.03		0.09 ± 0.02	0.06 ± 0.01
Eosinophilic bands (10^6)	0.041 ± 0.011		0.045 ± 0.016		0.036 ± 0.014	0.043 ± 0.011
Eosinophilic segments (10^6)	0.066 ± 0.016		0.103 ± 0.025		0.076 ± 0.025	0.081 ± 0.018
Basophilic myelocytes (10^6)	0.000 ± 0.000		0.000 ± 0.000		0.000 ± 0.000	0.000 ± 0.000
Basophilic metamyelocytes (10^6)	0.000 ± 0.000		0.000 ± 0.000		0.000 ± 0.000	0.000 ± 0.000
Basophilic bands (10^6)	0.000 ± 0.000		0.000 ± 0.000		0.000 ± 0.000	0.000 ± 0.000
Basophilic segments (10^6)	0.000 ± 0.000		0.000 ± 0.000		0.000 ± 0.000	0.000 ± 0.000
Bone marrow lymphocytes (10^6)	4.17 ± 0.35		4.58 ± 0.36		4.56 ± 0.19	4.63 ± 0.25
Bone marrow macrophages (10^6)	0.11 ± 0.03		0.06 ± 0.02		0.09 ± 0.02	0.09 ± 0.02
Bone marrow monocytes (10^6)	0.000 ± 0.000		0.000 ± 0.000		0.000 ± 0.000	0.000 ± 0.000
Megakaryo cells (10^6)	0.028 ± 0.008		0.026 ± 0.009		0.042 ± 0.011	0.042 ± 0.017
Plasma cells (10^6)	0.020 ± 0.009		0.045 ± 0.016		0.070 ± 0.021	0.052 ± 0.014
Mitotic figures (10^6)	0.27 ± 0.05		0.29 ± 0.03		0.34 ± 0.04	0.29 ± 0.04
Fat cells (10^6)	0.000 ± 0.000		0.000 ± 0.000		0.000 ± 0.000	0.000 ± 0.000
Mast cells (10^6)	0.000 ± 0.000		0.000 ± 0.000		0.000 ± 0.000	0.000 ± 0.000
Smudge cells (10^6)	2.48 ± 0.31		2.35 ± 0.15		2.26 ± 0.16	2.76 ± 0.24
Osteoblasts (10^6)	0.000 ± 0.000		0.000 ± 0.000		0.000 ± 0.000	0.000 ± 0.000
Osteoclasts (10^6)	0.000 ± 0.000		0.000 ± 0.000		0.000 ± 0.000	0.000 ± 0.000
Other bone marrow cells (10^6)	0.000 ± 0.000		0.000 ± 0.000		0.000 ± 0.000	0.000 ± 0.000

TABLE K1
Hematology and Bone Marrow Data for Mice in the 14-Week Gavage Study of AZT

	Vehicle Control	50 mg/kg	100 mg/kg	200 mg/kg	800 mg/kg	2,000 mg/kg
Female						
Hematology						
Core Study						
n						
Day 5	10	10	9	8	10	10
Day 23	10	10	9	8	10	10
Week 14	10	10	9	8	10	9
Hematocrit (%)						
Day 5	47.1 ± 0.6	47.7 ± 0.7	46.0 ± 0.6	47.2 ± 0.9	45.1 ± 0.7	45.2 ± 0.5
Day 23	46.7 ± 0.5	44.6 ± 0.6*	45.2 ± 0.5	43.5 ± 0.4**	42.3 ± 0.4**	40.6 ± 1.1**
Week 14	48.3 ± 0.6	48.5 ± 0.6	47.6 ± 0.6	47.9 ± 0.6	45.7 ± 0.4**	43.4 ± 0.4**
Hemoglobin (g/dL)						
Day 5	15.3 ± 0.2	15.6 ± 0.3	15.0 ± 0.2	15.6 ± 0.3	14.7 ± 0.2	14.8 ± 0.2
Day 23	16.0 ± 0.2	15.3 ± 0.2*	15.6 ± 0.2	15.0 ± 0.2**	14.6 ± 0.1**	13.9 ± 0.4**
Week 14	16.3 ± 0.2	16.3 ± 0.2	15.8 ± 0.1*	15.9 ± 0.2	15.0 ± 0.1**	14.0 ± 0.1**
Erythrocytes (10^6/μL)						
Day 5	9.56 ± 0.15	9.61 ± 0.16	9.36 ± 0.13	9.67 ± 0.20	9.04 ± 0.16*	9.08 ± 0.11*
Day 23	9.83 ± 0.11	9.13 ± 0.10**	9.13 ± 0.11**	8.64 ± 0.10**	8.07 ± 0.08**	7.80 ± 0.19**
Week 14	9.62 ± 0.10	9.03 ± 0.10**	8.66 ± 0.09**	8.39 ± 0.12**	7.36 ± 0.08**	6.50 ± 0.09**
Reticulocytes (10^6/μL)						
Day 5	0.16 ± 0.02	0.16 ± 0.02[c]	0.13 ± 0.03[b]	0.10 ± 0.01*[b]	0.06 ± 0.01**[e]	0.04 ± 0.00**[c]
Day 23	0.17 ± 0.02	0.19 ± 0.02	0.17 ± 0.02	0.15 ± 0.02[b]	0.17 ± 0.02	0.22 ± 0.04
Week 14	0.11 ± 0.01	0.11 ± 0.02	0.05 ± 0.01**	0.07 ± 0.01**	0.05 ± 0.01**	0.04 ± 0.01**
Nucleated erythrocytes (10^3/μL)						
Day 5	0.07 ± 0.03	0.04 ± 0.02	0.06 ± 0.02	0.10 ± 0.03	0.01 ± 0.01	0.03 ± 0.02
Day 23	0.00 ± 0.00	0.01 ± 0.01	0.02 ± 0.01[d]	0.01 ± 0.01[b]	0.00 ± 0.00	0.01 ± 0.01
Week 14	0.00 ± 0.00	0.01 ± 0.01	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.01 ± 0.01
Mean cell volume (fL)						
Day 5	49.4 ± 0.2	49.8 ± 0.2	49.2 ± 0.3	48.8 ± 0.3	49.8 ± 0.2	49.8 ± 0.3
Day 23	47.4 ± 0.3	48.8 ± 0.3**	49.6 ± 0.2**	50.5 ± 0.3**	52.4 ± 0.2**	52.1 ± 0.5**
Week 14	50.3 ± 0.4	53.7 ± 0.3**	55.0 ± 0.3**	57.1 ± 0.4**	62.3 ± 0.6**	67.0 ± 0.7**
Mean cell hemoglobin (pg)						
Day 5	16.0 ± 0.1	16.2 ± 0.0	16.1 ± 0.1	16.2 ± 0.1	16.3 ± 0.1	16.3 ± 0.1
Day 23	16.3 ± 0.1	16.8 ± 0.1**	17.0 ± 0.1**	17.3 ± 0.1**	18.1 ± 0.1**	17.8 ± 0.2**
Week 14	17.0 ± 0.1	18.0 ± 0.1**	18.3 ± 0.1**	18.9 ± 0.2**	20.4 ± 0.1**	21.5 ± 0.1**
Mean cell hemoglobin concentration (g/dL)						
Day 5	32.5 ± 0.2	32.7 ± 0.2	32.7 ± 0.1	33.1 ± 0.2	32.7 ± 0.2	32.8 ± 0.1
Day 23	34.3 ± 0.1	34.3 ± 0.2	34.4 ± 0.2	34.4 ± 0.1	34.4 ± 0.1	34.3 ± 0.1
Week 14	33.8 ± 0.4	33.6 ± 0.3	33.3 ± 0.3	33.2 ± 0.2	32.8 ± 0.3*	32.3 ± 0.3**
Platelets (10^3/μL)						
Day 5	825.7 ± 64.6	793.6 ± 53.1	972.4 ± 31.0	868.6 ± 45.0	768.9 ± 38.7	871.4 ± 69.3
Day 23	745.1 ± 21.8	808.6 ± 60.6	838.8 ± 32.3**	895.5 ± 41.4**	990.8 ± 36.6**	1,130.7 ± 54.9**
Week 14	831.0 ± 29.1	913.6 ± 43.6	893.7 ± 49.9	874.8 ± 56.8	880.5 ± 26.3	878.7 ± 35.3
Leukocytes (10^3/μL)						
Day 5	5.98 ± 0.31	6.17 ± 0.32	5.94 ± 0.23	6.51 ± 0.46	5.67 ± 0.39	5.74 ± 0.37
Day 23	6.92 ± 0.41	5.72 ± 0.18	6.12 ± 0.30	6.35 ± 0.48	5.90 ± 0.21	6.67 ± 0.71
Week 14	6.37 ± 0.34	6.86 ± 0.32	7.03 ± 0.53	6.96 ± 0.54	6.21 ± 0.39	6.44 ± 0.30
Segmented neutrophils (10^3/μL)						
Day 5	0.81 ± 0.11	0.94 ± 0.21	0.78 ± 0.11	0.64 ± 0.13	0.38 ± 0.09**	0.68 ± 0.21*
Day 23	0.72 ± 0.14	0.84 ± 0.16	0.73 ± 0.14	0.58 ± 0.07	0.50 ± 0.04	0.44 ± 0.06
Week 14	0.70 ± 0.13	0.81 ± 0.11	0.86 ± 0.04	1.03 ± 0.22	0.71 ± 0.09	0.80 ± 0.10
Lymphocytes (10^3/μL)						
Day 5	4.95 ± 0.24	5.08 ± 0.21	4.96 ± 0.19	5.61 ± 0.39	5.14 ± 0.32	4.90 ± 0.29
Day 23	6.07 ± 0.36	4.81 ± 0.13**	5.23 ± 0.21	5.74 ± 0.49	5.24 ± 0.18	6.16 ± 0.70
Week 14	5.51 ± 0.36	5.77 ± 0.28	5.91 ± 0.48	5.71 ± 0.47	5.34 ± 0.31	5.41 ± 0.33

TABLE K1
Hematology and Bone Marrow Data for Mice in the 14-Week Gavage Study of AZT

	Vehicle Control	50 mg/kg	100 mg/kg	200 mg/kg	800 mg/kg	2,000 mg/kg
Female (continued)						
Hematology (continued)						
Core Study (continued)						
n						
Day 5	10	10	9	8	10	10
Day 23	10	10	9	8	10	10
Week 14	10	10	9	8	10	9
Atypical lymphocytes (10^3/μL)						
Day 5	0.01 ± 0.01	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.01 ± 0.01	0.00 ± 0.00
Day 23	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00
Week 14	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00
Monocytes (10^3/μL)						
Day 5	0.07 ± 0.03	0.03 ± 0.02	0.08 ± 0.03	0.03 ± 0.02	0.05 ± 0.02	0.07 ± 0.03
Day 23	0.02 ± 0.01	0.02 ± 0.01	0.02 ± 0.02	0.00 ± 0.00	0.01 ± 0.01	0.03 ± 0.02
Week 14	0.08 ± 0.03	0.08 ± 0.03	0.09 ± 0.04	0.06 ± 0.02	0.07 ± 0.03	0.10 ± 0.03
Eosinophils (10^3/μL)						
Day 5	0.15 ± 0.05	0.13 ± 0.03	0.12 ± 0.04	0.21 ± 0.04	0.13 ± 0.04	0.09 ± 0.02
Day 23	0.12 ± 0.02	0.05 ± 0.02	0.16 ± 0.04	0.06 ± 0.02	0.12 ± 0.03	0.07 ± 0.03
Week 14	0.09 ± 0.03	0.21 ± 0.04	0.21 ± 0.05	0.14 ± 0.05	0.10 ± 0.03	0.13 ± 0.02
Recovery Study						
n	10	—	10	—	10	9
Hematocrit (%)						
Week 14	47.5 ± 0.4		44.8 ± 0.6**		43.5 ± 0.8**	38.4 ± 0.6**
Week 17	49.1 ± 0.7		49.2 ± 0.5		48.3 ± 0.5	47.2 ± 0.6
Hemoglobin (g/dL)						
Week 14	15.9 ± 0.1		15.0 ± 0.2**		14.6 ± 0.3**	12.8 ± 0.2**
Week 17	16.6 ± 0.2		16.6 ± 0.1		16.2 ± 0.1	15.8 ± 0.1**
Erythrocytes (10^6/μL)						
Week 14	9.97 ± 0.07		8.64 ± 0.13**		7.47 ± 0.14**	6.33 ± 0.12**
Week 17	10.09 ± 0.12		9.93 ± 0.04		9.61 ± 0.13**	9.40 ± 0.10**
Reticulocytes (10^6/μL)						
Week 14	0.13 ± 0.01		0.14 ± 0.01		0.14 ± 0.01	0.15 ± 0.03
Week 17	0.15 ± 0.02		0.11 ± 0.03		0.13 ± 0.01	0.13 ± 0.02
Nucleated erythrocytes (10^3/μL)						
Week 14	0.00 ± 0.00		0.00 ± 0.00		0.00 ± 0.00[c]	0.00 ± 0.00
Week 17	0.01 ± 0.01		0.01 ± 0.01		0.01 ± 0.01	0.01 ± 0.01
Mean cell volume (fL)						
Week 14	47.6 ± 0.2		51.8 ± 0.2**		58.2 ± 0.2**	60.7 ± 0.4**
Week 17	48.7 ± 0.3		49.5 ± 0.4		50.4 ± 0.3**	50.3 ± 0.4**
Mean cell hemoglobin (pg)						
Week 14	16.0 ± 0.1		17.4 ± 0.1**		19.6 ± 0.1**	20.2 ± 0.1**
Week 17	16.4 ± 0.1		16.7 ± 0.1		17.0 ± 0.1**	16.8 ± 0.1*
Mean cell hemoglobin concentration (g/dL)						
Week 14	33.5 ± 0.1		33.5 ± 0.1		33.6 ± 0.1	33.2 ± 0.2
Week 17	33.8 ± 0.3		33.7 ± 0.2		33.7 ± 0.3	33.6 ± 0.2
Platelets (10^3/μL)						
Week 14	738.7 ± 32.6		924.5 ± 22.5**		1,015.7 ± 42.0**	1,337.4 ± 87.3**
Week 17	918.4 ± 42.6		887.5 ± 49.9		916.7 ± 40.7	838.6 ± 49.6
Leukocytes (10^3/μL)						
Week 14	7.40 ± 0.47		7.18 ± 0.17		7.08 ± 0.42	6.38 ± 0.29
Week 17	6.25 ± 0.29		7.04 ± 0.39		6.30 ± 0.31	5.74 ± 0.32

TABLE K1
Hematology and Bone Marrow Data for Mice in the 14-Week Gavage Study of AZT

	Vehicle Control	50 mg/kg	100 mg/kg	200 mg/kg	800 mg/kg	2,000 mg/kg
Female (continued)						
Hematology (continued)						
Recovery Study (continued)						
n	10	—	10	—	10	9
Segmented neutrophils (10^3/μL)						
Week 14	0.76 ± 0.15		0.68 ± 0.09		0.56 ± 0.07	0.54 ± 0.09
Week 17	1.02 ± 0.10		1.03 ± 0.10		1.01 ± 0.11	0.90 ± 0.14
Lymphocytes (10^3/μL)						
Week 14	6.44 ± 0.38		6.35 ± 0.19		6.34 ± 0.37	5.69 ± 0.18
Week 17	5.16 ± 0.24		5.84 ± 0.28		5.20 ± 0.23	4.73 ± 0.20
Atypical lymphocytes (10^3/μL)						
Week 14	0.00 ± 0.00		0.00 ± 0.00		0.00 ± 0.00	0.00 ± 0.00
Week 17	0.00 ± 0.00		0.00 ± 0.00		0.00 ± 0.00	0.00 ± 0.00
Monocytes (10^3/μL)						
Week 14	0.03 ± 0.02		0.03 ± 0.02		0.01 ± 0.01	0.01 ± 0.01
Week 17	0.02 ± 0.01		0.02 ± 0.01		0.03 ± 0.02	0.02 ± 0.02
Eosinophils (10^3/μL)						
Week 14	0.18 ± 0.03		0.14 ± 0.04		0.17 ± 0.04	0.17 ± 0.04
Week 17	0.08 ± 0.02		0.17 ± 0.03		0.09 ± 0.02	0.10 ± 0.03
Bone Marrow Analyses						
Core Study						
n	10	—	9	—	10	9
Total femoral count (10^6/femur)	18.10 ± 1.43		10.16 ± 1.58**		9.65 ± 0.93**	7.60 ± 0.50**
M:E ratio	1.40 ± 0.06		2.11 ± 0.17**		3.04 ± 0.44**	2.57 ± 0.28**
Rubriblasts (10^6)	0.26 ± 0.06		0.08 ± 0.03*		0.07 ± 0.02*	0.09 ± 0.02
Prorubricytes (10^6)	0.86 ± 0.14		0.30 ± 0.06**		0.33 ± 0.05*	0.30 ± 0.03*
Rubricytes (10^6)	3.03 ± 0.35		1.58 ± 0.33*		1.24 ± 0.22**	0.98 ± 0.12**
Metarubricytes (10^6)	1.30 ± 0.23		0.40 ± 0.04**		0.32 ± 0.05**	0.19 ± 0.04**
Myeloblasts (10^6)	0.14 ± 0.03		0.09 ± 0.02		0.08 ± 0.01	0.08 ± 0.01
Promyelocytes (10^6)	0.17 ± 0.03		0.12 ± 0.02		0.13 ± 0.01	0.12 ± 0.02
Neutrophilic myelocytes (10^6)	0.28 ± 0.03		0.25 ± 0.04		0.29 ± 0.04	0.24 ± 0.03
Neutrophilic metamyelocytes (10^6)	0.74 ± 0.11		0.48 ± 0.13		0.41 ± 0.09*	0.30 ± 0.05**
Neutrophilic bands (10^6)	1.27 ± 0.14		1.00 ± 0.24		0.93 ± 0.14	0.60 ± 0.07*
Neutrophilic segments (10^6)	4.48 ± 0.38		2.69 ± 0.49*		3.02 ± 0.37*	2.19 ± 0.20**
Eosinophilic metamyelocytes (10^6)	0.17 ± 0.04		0.11 ± 0.03		0.07 ± 0.01*	0.06 ± 0.01*
Eosinophilic bands (10^6)	0.11 ± 0.03		0.14 ± 0.04		0.10 ± 0.01	0.10 ± 0.02
Eosinophilic myelocytes (10^6)	0.054 ± 0.018		0.049 ± 0.013		0.039 ± 0.011	0.033 ± 0.007
Eosinophilic segments (10^6)	0.117 ± 0.019		0.106 ± 0.035		0.083 ± 0.017	0.080 ± 0.012
Basophilic myelocytes (10^6)	0.004 ± 0.004		0.000 ± 0.000		0.000 ± 0.000	0.000 ± 0.000
Basophilic metamyelocytes (10^6)	0.000 ± 0.000		0.004 ± 0.004		0.000 ± 0.000	0.000 ± 0.000
Basophilic bands (10^6)	0.000 ± 0.000		0.000 ± 0.000		0.004 ± 0.004	0.003 ± 0.002
Basophilic segments (10^6)	0.003 ± 0.003		0.008 ± 0.005		0.003 ± 0.002	0.000 ± 0.000
Bone marrow lymphocytes (10^6)	2.32 ± 0.16		1.63 ± 0.16*		1.34 ± 0.14**	1.11 ± 0.13**
Bone marrow macrophages (10^6)	0.102 ± 0.017		0.089 ± 0.025		0.078 ± 0.020	0.056 ± 0.014
Bone marrow monocytes (10^6)	0.134 ± 0.024		0.081 ± 0.024		0.062 ± 0.013*	0.048 ± 0.011**
Megakaryo cells (10^6)	0.033 ± 0.012		0.031 ± 0.011		0.031 ± 0.008	0.020 ± 0.005
Plasma cells (10^6)	0.061 ± 0.022		0.034 ± 0.009		0.045 ± 0.022	0.036 ± 0.012
Mitotic figures (10^6)	0.24 ± 0.04		0.13 ± 0.02		0.16 ± 0.03	0.12 ± 0.02*

TABLE K1
Hematology and Bone Marrow Data for Mice in the 14-Week Gavage Study of AZT

	Vehicle Control	50 mg/kg	100 mg/kg	200 mg/kg	800 mg/kg	2,000 mg/kg
Female (continued)						
Bone Marrow Analyses (continued)						
Core Study (continued)						
n	10	—	9	—	10	9
Fat cells (10^6)	0.000 ± 0.000		0.000 ± 0.000		0.000 ± 0.000	0.000 ± 0.000
Mast cells (10^6)	0.003 ± 0.003		0.000 ± 0.000		0.000 ± 0.000	0.001 ± 0.001
Smudge cells (10^6)	2.19 ± 0.26		0.76 ± 0.07**		0.80 ± 0.08**	0.76 ± 0.04**
Osteoblasts (10^6)	0.016 ± 0.012		0.002 ± 0.002		0.000 ± 0.000	0.001 ± 0.001
Osteoclasts (10^6)	0.003 ± 0.003		0.000 ± 0.000		0.004 ± 0.003	0.006 ± 0.003
Other bone marrow cells (10^6)	0.012 ± 0.012		0.014 ± 0.012		0.024 ± 0.010	0.052 ± 0.020
Recovery Study						
n	10	—	10	—	10	9
Total femoral count (10^6/femur)	18.9 ± 0.5		18.6 ± 1.0		20.5 ± 0.8	22.3 ± 0.9**
M:E ratio	1.86 ± 0.19		1.91 ± 0.13		1.80 ± 0.12	1.98 ± 0.20
Rubriblasts (10^6)	0.22 ± 0.03		0.14 ± 0.02		0.26 ± 0.05	0.22 ± 0.04
Prorubricytes (10^6)	0.64 ± 0.08		0.75 ± 0.12		0.79 ± 0.07	0.63 ± 0.05
Rubricytes (10^6)	2.73 ± 0.22		2.40 ± 0.16		3.08 ± 0.19	3.28 ± 0.27
Metarubricytes (10^6)	1.24 ± 0.15		1.25 ± 0.14		1.24 ± 0.19	1.26 ± 0.10
Myeloblasts (10^6)	0.27 ± 0.03		0.28 ± 0.03		0.32 ± 0.03	0.39 ± 0.04
Promyelocytes (10^6)	0.62 ± 0.09		0.53 ± 0.07		0.68 ± 0.11	0.70 ± 0.08
Neutrophilic myelocytes (10^6)	1.56 ± 0.10		1.31 ± 0.19		1.52 ± 0.09	1.72 ± 0.24
Neutrophilic metamyelocytes (10^6)	0.523 ± 0.066		0.436 ± 0.078		0.594 ± 0.053	0.563 ± 0.072
Neutrophilic bands (10^6)	1.55 ± 0.11		1.63 ± 0.12		1.85 ± 0.11	1.88 ± 0.20
Neutrophilic segments (10^6)	3.58 ± 0.16		3.84 ± 0.27		4.02 ± 0.37	4.26 ± 0.31
Eosinophilic myelocytes (10^6)	0.17 ± 0.04		0.17 ± 0.03		0.23 ± 0.02	0.20 ± 0.04
Eosinophilic metamyelocytes (10^6)	0.07 ± 0.01		0.06 ± 0.01		0.07 ± 0.02	0.09 ± 0.02
Eosinophilic bands (10^6)	0.120 ± 0.019		0.162 ± 0.030		0.130 ± 0.018	0.308 ± 0.035**
Eosinophilic segments (10^6)	0.016 ± 0.007		0.030 ± 0.009		0.040 ± 0.017	0.029 ± 0.010
Basophilic myelocytes (10^6)	0.000 ± 0.000		0.000 ± 0.000		0.000 ± 0.000	0.000 ± 0.000
Basophilic metamyelocytes (10^6)	0.000 ± 0.000		0.000 ± 0.000		0.000 ± 0.000	0.000 ± 0.000
Basophilic bands (10^6)	0.000 ± 0.000		0.000 ± 0.000		0.000 ± 0.000	0.000 ± 0.000
Basophilic segments (10^6)	0.000 ± 0.000		0.000 ± 0.000		0.000 ± 0.000	0.000 ± 0.000
Bone marrow lymphocytes (10^6)	3.71 ± 0.24		3.40 ± 0.21		4.09 ± 0.28	4.29 ± 0.31
Bone marrow macrophages (10^6)	0.29 ± 0.03		0.29 ± 0.06		0.32 ± 0.08	0.31 ± 0.09
Bone marrow monocytes (10^6)	0.000 ± 0.000		0.000 ± 0.000		0.000 ± 0.000	0.000 ± 0.000
Megakaryo cells (10^6)	0.019 ± 0.011		0.019 ± 0.008		0.046 ± 0.016	0.026 ± 0.014
Plasma cells (10^6)	0.053 ± 0.032		0.059 ± 0.016		0.037 ± 0.015	0.039 ± 0.018
Mitotic figures (10^6)	0.27 ± 0.04		0.37 ± 0.05		0.35 ± 0.06	0.29 ± 0.05
Fat cells (10^6)	0.000 ± 0.000		0.000 ± 0.000		0.000 ± 0.000	0.000 ± 0.000
Mast cells (10^6)	0.000 ± 0.000		0.000 ± 0.000		0.000 ± 0.000	0.000 ± 0.000
Smudge cells (10^6)	1.27 ± 0.27		1.51 ± 0.30		0.88 ± 0.30	1.81 ± 0.55
Osteoblasts (10^6)	0.000 ± 0.000		0.000 ± 0.000		0.000 ± 0.000	0.000 ± 0.000
Osteoclasts (10^6)	0.000 ± 0.000		0.000 ± 0.000		0.000 ± 0.000	0.000 ± 0.000
Other bone marrow cells (10^6)	0.000 ± 0.000		0.000 ± 0.000		0.000 ± 0.000	0.000 ± 0.000

* Significantly different ($P \le 0.05$) from the control group by Dunn's or Shirley's test
** $P \le 0.01$
[a] Mean ± standard error. Statistical tests were performed on unrounded data. Bone marrow analyses were not performed on core study animals receiving 50 or 200 mg/kg. The recovery study only included animals in the vehicle control, 100, 800, and 2,000 mg/kg groups.
[b] n = 7
[c] n = 9
[d] n = 10
[e] n = 8

TABLE K2
Hematology and Bone Marrow Data for Mice in the 2-Year Gavage Study of AZT[a]

	Vehicle Control	30 mg/kg	60 mg/kg	120 mg/kg
Male				
Hematology				
Clinical Pathology Groups				
n				
Week 14	10	10	9	10
Week 27	10	10	10	10
Week 40	10	9	10	9
Week 54	10	10	10	10
Week 66	9	10	10	9
Week 80	10	9	8	10
Hematocrit (%)				
Week 14	46.6 ± 0.4	45.6 ± 0.6	45.0 ± 0.9	45.5 ± 0.8
Week 27	46.7 ± 0.6	44.6 ± 0.2*	45.5 ± 0.3	45.4 ± 0.5
Week 40	43.1 ± 0.6	43.7 ± 0.8	43.7 ± 0.9	42.6 ± 1.2
Week 54	40.4 ± 0.8	41.1 ± 0.6	40.5 ± 0.5	42.2 ± 1.2
Week 66	44.4 ± 1.7	42.0 ± 1.1	42.6 ± 1.4	41.6 ± 0.5
Week 80	44.9 ± 1.2	49.2 ± 3.3	41.5 ± 1.2	43.5 ± 2.3
Hemoglobin (g/dL)				
Week 14	15.4 ± 0.1	15.0 ± 0.2	14.6 ± 0.2*	14.9 ± 0.2
Week 27	15.5 ± 0.2	14.7 ± 0.1**	15.0 ± 0.1	15.1 ± 0.2
Week 40	14.2 ± 0.2	14.4 ± 0.3	14.3 ± 0.3	14.2 ± 0.3
Week 54	13.6 ± 0.3	13.9 ± 0.3	13.8 ± 0.2	14.1 ± 0.4
Week 66	14.6 ± 0.6	13.9 ± 0.3	14.1 ± 0.5	13.9 ± 0.2
Week 80	14.9 ± 0.4	16.3 ± 1.1	14.0 ± 0.3	14.5 ± 0.8
Erythrocytes (10^6/µL)				
Week 14	10.24 ± 0.09	9.70 ± 0.11**	9.35 ± 0.14**	9.29 ± 0.15**
Week 27	10.33 ± 0.14	9.58 ± 0.07**	9.71 ± 0.07**	9.59 ± 0.11**
Week 40	9.55 ± 0.10	9.18 ± 0.15	8.99 ± 0.15**	8.67 ± 0.19**
Week 54	9.33 ± 0.17	8.89 ± 0.09*	8.68 ± 0.10**	8.89 ± 0.33**
Week 66	9.87 ± 0.52	8.88 ± 0.37*	8.58 ± 0.34**	8.12 ± 0.11**
Week 80	9.86 ± 0.40	10.41 ± 0.86	8.22 ± 0.20**	8.30 ± 0.50**
Reticulocytes (10^6/µL)				
Week 14	0.16 ± 0.01[b]	0.16 ± 0.01[b]	0.15 ± 0.01	0.10 ± 0.01**[b]
Week 27	0.12 ± 0.01	0.10 ± 0.01	0.11 ± 0.01	0.10 ± 0.02
Week 40	0.27 ± 0.02[b]	0.22 ± 0.02	0.24 ± 0.01	0.21 ± 0.02
Week 54	0.23 ± 0.04	0.21 ± 0.03	0.18 ± 0.03	0.24 ± 0.04
Week 66	0.33 ± 0.02	0.32 ± 0.02	0.31 ± 0.01	0.29 ± 0.01
Week 80	0.20 ± 0.03	0.24 ± 0.03	0.18 ± 0.02	0.15 ± 0.03
Nucleated erythrocytes (10^3/µL)				
Week 14	0.01 ± 0.01	0.01 ± 0.01	0.02 ± 0.01	0.03 ± 0.01[b]
Week 27	0.01 ± 0.01	0.06 ± 0.02*	0.02 ± 0.01	0.04 ± 0.01
Week 40	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00
Week 54	0.01 ± 0.01	0.01 ± 0.01	0.00 ± 0.00	0.00 ± 0.00
Week 66	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00
Week 80	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00
Mean cell volume (fL)				
Week 14	45.5 ± 0.3	47.0 ± 0.2**	48.1 ± 0.3**	49.0 ± 0.3**
Week 27	45.2 ± 0.2	46.6 ± 0.2**	46.8 ± 0.2**	47.3 ± 0.2**
Week 40	45.1 ± 0.5	47.6 ± 0.4**	48.6 ± 0.4*	49.1 ± 0.3**
Week 54	43.4 ± 0.8	46.2 ± 0.6**	46.7 ± 0.4**	47.7 ± 0.6**
Week 66	45.3 ± 1.0	47.6 ± 0.9*	49.8 ± 0.4**	51.2 ± 0.3**
Week 80	45.8 ± 0.7	47.7 ± 0.9	50.4 ± 0.5**	52.6 ± 0.4**

TABLE K2
Hematology and Bone Marrow Data for Mice in the 2-Year Gavage Study of AZT

	Vehicle Control	30 mg/kg	60 mg/kg	120 mg/kg
Male (continued)				
Hematology (continued)				
Clinical Pathology Groups (continued)				
n				
Week 14	10	10	9	10
Week 27	10	10	10	10
Week 40	10	9	10	9
Week 54	10	10	10	10
Week 66	9	10	10	9
Week 80	10	9	8	10
Mean cell hemoglobin (pg)				
Week 14	15.0 ± 0.1	15.4 ± 0.1**	15.6 ± 0.1**	16.0 ± 0.1**
Week 27	15.0 ± 0.1	15.4 ± 0.1**	15.5 ± 0.1**	15.8 ± 0.1**
Week 40	14.8 ± 0.2	15.7 ± 0.1**	15.9 ± 0.1**	16.4 ± 0.1**
Week 54	14.6 ± 0.3	15.7 ± 0.3*	15.9 ± 0.2**	15.9 ± 0.3**
Week 66	14.9 ± 0.4	15.7 ± 0.3	16.5 ± 0.2**	17.1 ± 0.1**
Week 80	15.2 ± 0.3	15.8 ± 0.3	17.0 ± 0.2**	17.5 ± 0.2**
Mean cell hemoglobin concentration (g/dL)				
Week 14	33.0 ± 0.2	32.8 ± 0.2	32.6 ± 0.3	32.7 ± 0.1
Week 27	33.3 ± 0.2	33.0 ± 0.2	33.1 ± 0.1	33.4 ± 0.1
Week 40	32.9 ± 0.3	32.9 ± 0.2	32.7 ± 0.2	33.3 ± 0.2
Week 54	33.7 ± 0.2	33.8 ± 0.2	34.1 ± 0.2	33.3 ± 0.3
Week 66	32.9 ± 0.2	33.1 ± 0.3	33.0 ± 0.3	33.3 ± 0.3
Week 80	33.2 ± 0.2	33.2 ± 0.1	33.8 ± 0.3	33.3 ± 0.2
Platelets (10^3/μL)				
Week 14	1,163.9 ± 52.5	1,215.3 ± 70.0	1,257.8 ± 70.8	1,249.2 ± 52.3
Week 27	1,091.9 ± 60.9	1,270.0 ± 43.0	1,139.9 ± 48.8	1,136.6 ± 76.5
Week 40	1,451.6 ± 40.3	1,557.6 ± 74.7	1,353.1 ± 69.6	1,450.4 ± 35.1
Week 54	1,623.5 ± 201.3	1,458.7 ± 77.7	1,454.5 ± 73.8	1,574.0 ± 108.3
Week 66	1,706.8 ± 108.2	1,806.5 ± 134.6	1,657.6 ± 53.9	1,802.3 ± 57.7
Week 80	1,709.6 ± 94.2	1,694.0 ± 161.6	1,807.4 ± 120.6	1,674.6 ± 121.7
Leukocytes (10^3/μL)				
Week 14	6.28 ± 0.36	6.47 ± 0.46	6.71 ± 0.64	6.09 ± 0.29
Week 27	7.33 ± 0.25	8.25 ± 0.54	8.31 ± 0.33	7.65 ± 0.23
Week 40	8.57 ± 0.53	8.13 ± 0.62	7.34 ± 0.63	7.05 ± 0.44
Week 54	10.82 ± 0.88	8.92 ± 0.72	9.40 ± 0.59	9.15 ± 0.91
Week 66	10.64 ± 1.11	10.90 ± 0.77	9.30 ± 0.85	7.56 ± 0.84*
Week 80	10.15 ± 0.96	9.56 ± 0.91	9.08 ± 0.89	8.14 ± 0.79
Segmented neutrophils (10^3/μL)				
Week 14	0.76 ± 0.10	0.82 ± 0.07	0.71 ± 0.13	0.72 ± 0.14[b]
Week 27	1.62 ± 0.08	1.90 ± 0.22	1.72 ± 0.15	1.48 ± 0.19
Week 40	2.09 ± 0.20	1.97 ± 0.28	1.61 ± 0.26	1.50 ± 0.21
Week 54	3.18 ± 0.42	2.27 ± 0.27	2.04 ± 0.21	2.32 ± 0.38
Week 66	2.01 ± 0.23	2.08 ± 0.18	1.84 ± 0.22	1.34 ± 0.12*
Week 80	2.43 ± 0.42	2.40 ± 0.23	2.21 ± 0.62	1.73 ± 0.28
Lymphocytes (10^3/μL)				
Week 14	5.44 ± 0.32	5.55 ± 0.43	5.87 ± 0.56	5.31 ± 0.20[b]
Week 27	5.38 ± 0.21	5.86 ± 0.35	6.18 ± 0.29	5.82 ± 0.29
Week 40	6.35 ± 0.41	5.92 ± 0.41	5.59 ± 0.42	5.40 ± 0.24
Week 54	7.14 ± 0.58	6.35 ± 0.52	6.99 ± 0.44	6.66 ± 0.67
Week 66	8.09 ± 0.97	8.19 ± 0.56	7.04 ± 0.64	5.86 ± 0.66
Week 80	7.60 ± 0.68	6.91 ± 0.78	6.79 ± 0.57	6.31 ± 0.59

TABLE K2
Hematology and Bone Marrow Data for Mice in the 2-Year Gavage Study of AZT

	Vehicle Control	30 mg/kg	60 mg/kg	120 mg/kg
Male (continued)				
Hematology (continued)				
Clinical Pathology Groups (continued)				
n				
Week 14	10	10	9	10
Week 27	10	10	10	10
Week 40	10	9	10	9
Week 54	10	10	10	10
Week 66	9	10	10	9
Week 80	10	9	8	10
Atypical lymphocytes (10^3/μL)				
Week 14	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00[b]
Week 27	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00
Week 40	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00
Week 54	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00
Week 66	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00
Week 80	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00
Monocytes (10^3/μL)				
Week 14	0.04 ± 0.01	0.04 ± 0.02	0.09 ± 0.03	0.02 ± 0.01[b]
Week 27	0.18 ± 0.05	0.22 ± 0.06	0.17 ± 0.06	0.16 ± 0.04
Week 40	0.05 ± 0.02	0.04 ± 0.02	0.03 ± 0.02	0.03 ± 0.02
Week 54	0.24 ± 0.11	0.11 ± 0.04	0.24 ± 0.07	0.08 ± 0.03
Week 66	0.44 ± 0.07	0.51 ± 0.08	0.30 ± 0.05	0.22 ± 0.06*
Week 80	0.08 ± 0.04	0.18 ± 0.06	0.05 ± 0.03	0.04 ± 0.02
Eosinophils (10^3/μL)				
Week 14	0.04 ± 0.01	0.06 ± 0.02	0.05 ± 0.02	0.02 ± 0.02[b]
Week 27	0.15 ± 0.02	0.27 ± 0.09	0.23 ± 0.04	0.20 ± 0.03
Week 40	0.09 ± 0.02	0.20 ± 0.06	0.12 ± 0.03	0.11 ± 0.03
Week 54	0.25 ± 0.09	0.19 ± 0.09	0.12 ± 0.04	0.10 ± 0.03
Week 66	0.10 ± 0.04	0.13 ± 0.03	0.12 ± 0.03	0.14 ± 0.03
Week 80	0.03 ± 0.01	0.07 ± 0.03	0.04 ± 0.02	0.05 ± 0.02
Core Groups				
n	10	10	6	10
Hematocrit (%)	38.1 ± 0.8	40.0 ± 2.1	35.3 ± 1.8	45.4 ± 3.8
Hemoglobin (g/dL)	13.2 ± 0.4	13.6 ± 0.7	12.0 ± 0.8	15.1 ± 1.3
Erythrocytes (10^6/μL)	8.48 ± 0.30	8.94 ± 0.61	7.14 ± 0.58	9.09 ± 0.79
Reticulocytes (10^6/μL)	0.25 ± 0.04	0.34 ± 0.07	0.23 ± 0.05	0.35 ± 0.07
Nucleated erythrocytes (10^3/μL)	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00
Mean cell volume (fL)	45.2 ± 0.7	45.2 ± 0.8	50.4 ± 2.5*	50.0 ± 0.7**
Mean cell hemoglobin (pg)	15.6 ± 0.2	15.4 ± 0.3	17.0 ± 0.6*	16.7 ± 0.2**
Mean cell hemoglobin concentration (g/dL)	34.6 ± 0.3	34.1 ± 0.3	33.8 ± 0.6	33.4 ± 0.3**
Platelets (10^3/μL)	1,753.6 ± 77.7	2,045.9 ± 107.6*	2,106.2 ± 149.2*	2,349.7 ± 191.1**
Leukocytes (10^3/μL)	7.35 ± 0.75	9.86 ± 0.55	8.61 ± 1.54	10.36 ± 0.81*
Segmented neutrophils (10^3/μL)	2.44 ± 0.25	3.12 ± 0.23	2.22 ± 0.29	3.71 ± 0.67
Lymphocytes (10^3/μL)	4.57 ± 0.53	6.27 ± 0.54	5.88 ± 1.28	5.90 ± 0.48
Atypical lymphocytes (10^3/μL)	0.01 ± 0.01	0.00 ± 0.00	0.09 ± 0.09	0.00 ± 0.00
Monocytes (10^3/μL)	0.25 ± 0.06	0.42 ± 0.05	0.33 ± 0.09	0.58 ± 0.18
Eosinophils (10^3/μL)	0.07 ± 0.02	0.06 ± 0.03	0.09 ± 0.04	0.17 ± 0.05

TABLE K2
Hematology and Bone Marrow Data for Mice in the 2-Year Gavage Study of AZT

	Vehicle Control	30 mg/kg	60 mg/kg	120 mg/kg
Male (continued)				
Bone Marrow Analyses				
Clinical Pathology Groups				
n				
Week 54	10	10	10	10
Week 66	9	10	9	8
Week 80	10	9	8	10
Total femoral count (10^6/femur)				
Week 54	32.1 ± 1.7	28.4 ± 1.6	29.1 ± 1.2	29.2 ± 1.4
Week 66	34.1 ± 2.1	34.9 ± 1.4	32.9 ± 0.9	33.5 ± 1.5
Week 80	35.7 ± 1.6	34.4 ± 1.4	32.0 ± 1.2	32.2 ± 1.3
M:E ratio				
Week 54	1.59 ± 0.21	1.87 ± 0.12	2.06 ± 0.23	1.97 ± 0.07
Week 66	2.20 ± 0.20	2.13 ± 0.19	2.04 ± 0.19	2.21 ± 0.13
Week 80	2.84 ± 0.23	2.72 ± 0.22	3.29 ± 0.42	3.00 ± 0.36
Rubriblasts (10^6)				
Week 54	0.80 ± 0.08	0.69 ± 0.12	0.70 ± 0.07	0.85 ± 0.07
Week 66	0.58 ± 0.08	0.57 ± 0.06	0.71 ± 0.10	0.74 ± 0.07
Week 80	0.31 ± 0.05	0.26 ± 0.03	0.24 ± 0.04	0.34 ± 0.04
Prorubricytes (10^6)				
Week 54	0.53 ± 0.11	0.63 ± 0.09	0.53 ± 0.05	0.79 ± 0.09
Week 66	0.48 ± 0.08	0.57 ± 0.07	0.67 ± 0.13	0.31 ± 0.03
Week 80	0.93 ± 0.10	0.97 ± 0.13	0.87 ± 0.14	0.87 ± 0.11
Rubricytes (10^6)				
Week 54	5.73 ± 0.49	4.17 ± 0.28*	3.57 ± 0.41**	3.47 ± 0.27**
Week 66	3.74 ± 0.28	4.13 ± 0.31	3.73 ± 0.32	3.82 ± 0.42
Week 80	3.66 ± 0.32	3.92 ± 0.51	3.27 ± 0.49	3.44 ± 0.39
Metarubricytes (10^6)				
Week 54	2.87 ± 0.24	1.55 ± 0.20**	1.95 ± 0.24*	1.85 ± 0.16*
Week 66	2.37 ± 0.18	2.28 ± 0.20	2.47 ± 0.19	2.18 ± 0.20
Week 80	1.85 ± 0.18	1.80 ± 0.08	1.15 ± 0.08*	1.42 ± 0.21
Myeloblasts (10^6)				
Week 54	1.12 ± 0.12	0.36 ± 0.06**	0.33 ± 0.04**	0.27 ± 0.05**
Week 66	0.63 ± 0.08	0.72 ± 0.09	0.56 ± 0.07	0.65 ± 0.07
Week 80	0.56 ± 0.06	0.54 ± 0.06	0.40 ± 0.08	0.66 ± 0.07
Promyelocytes (10^6)				
Week 54	0.52 ± 0.09	0.76 ± 0.13	0.71 ± 0.08	0.58 ± 0.09
Week 66	0.46 ± 0.06	0.42 ± 0.09	0.42 ± 0.09	0.59 ± 0.12
Week 80	0.68 ± 0.09	0.66 ± 0.09	0.69 ± 0.08	0.89 ± 0.09
Neutrophilic myelocytes (10^6)				
Week 54	1.06 ± 0.16	0.96 ± 0.12	0.95 ± 0.07	1.23 ± 0.10
Week 66	1.75 ± 0.15	1.57 ± 0.14	1.27 ± 0.07**	1.14 ± 0.12**
Week 80	1.17 ± 0.21	1.04 ± 0.12	1.45 ± 0.18	1.31 ± 0.17
Neutrophilic metamyelocytes (10^6)				
Week 54	5.40 ± 0.55	4.23 ± 0.21	4.41 ± 0.30	4.65 ± 0.38
Week 66	4.07 ± 0.49	4.42 ± 0.38	4.12 ± 0.32	4.30 ± 0.33
Week 80	1.49 ± 0.25	1.31 ± 0.17	0.78 ± 0.21	1.04 ± 0.18
Neutrophilic bands (10^6)				
Week 54	0.41 ± 0.05	0.31 ± 0.08	0.44 ± 0.06	0.34 ± 0.05
Week 66	0.39 ± 0.10	0.48 ± 0.05	0.45 ± 0.07	0.51 ± 0.07
Week 80	1.86 ± 0.40	1.44 ± 0.31	1.33 ± 0.30	1.15 ± 0.24

TABLE K2
Hematology and Bone Marrow Data for Mice in the 2-Year Gavage Study of AZT

	Vehicle Control	30 mg/kg	60 mg/kg	120 mg/kg
Male (continued)				
Bone Marrow Analyses (continued)				
Clinical Pathology Groups (continued)				
n				
Week 54	10	10	10	10
Week 66	9	10	9	8
Week 80	10	9	8	10
Neutrophilic segments (10^6)				
Week 54	5.54 ± 0.47	5.65 ± 0.47	5.51 ± 0.22	6.02 ± 0.32
Week 66	7.50 ± 0.86	7.26 ± 0.53	7.52 ± 0.38	7.44 ± 0.36
Week 80	12.05 ± 0.63	12.30 ± 0.77	11.63 ± 0.89	11.06 ± 0.35
Eosinophilic myelocytes (10^6)				
Week 54	0.129 ± 0.034	0.058 ± 0.024	0.061 ± 0.026	0.077 ± 0.021
Week 66	0.086 ± 0.050	0.055 ± 0.025	0.022 ± 0.011	0.044 ± 0.013
Week 80	0.023 ± 0.012	0.062 ± 0.018	0.049 ± 0.016	0.048 ± 0.024
Eosinophilic metamyelocytes (10^6)				
Week 54	0.23 ± 0.05	0.22 ± 0.07	0.21 ± 0.05	0.25 ± 0.04
Week 66	0.25 ± 0.04	0.19 ± 0.05	0.17 ± 0.03	0.18 ± 0.03
Week 80	0.08 ± 0.03	0.09 ± 0.03	0.03 ± 0.01	0.04 ± 0.01
Eosinophilic bands (10^6)				
Week 54	0.12 ± 0.03	0.16 ± 0.05	0.10 ± 0.04	0.11 ± 0.03
Week 66	0.14 ± 0.04	0.11 ± 0.02	0.16 ± 0.04	0.11 ± 0.02
Week 80	0.27 ± 0.04	0.21 ± 0.05	0.16 ± 0.02	0.19 ± 0.05
Eosinophilic segments (10^6)				
Week 54	0.11 ± 0.04	0.10 ± 0.03	0.13 ± 0.03	0.09 ± 0.03
Week 66	0.27 ± 0.07	0.13 ± 0.03	0.22 ± 0.04	0.22 ± 0.08
Week 80	0.22 ± 0.04	0.26 ± 0.05	0.21 ± 0.04	0.23 ± 0.04
Basophilic myelocytes (10^6)				
Week 54	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000
Week 66	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000
Week 80	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000
Basophilic metamyelocytes (10^6)				
Week 54	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000
Week 66	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000
Week 80	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000
Basophilic bands (10^6)				
Week 54	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000
Week 66	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000
Week 80	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000
Basophilic segments (10^6)				
Week 54	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000
Week 66	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000
Week 80	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000
Bone marrow lymphocytes (10^6)				
Week 54	3.43 ± 0.51	3.88 ± 0.21	4.36 ± 0.53	4.03 ± 0.45
Week 66	4.57 ± 0.55	4.93 ± 0.37	3.95 ± 0.28	4.52 ± 0.31
Week 80	4.58 ± 0.64	3.95 ± 0.25	4.21 ± 0.29	4.43 ± 0.50
Bone marrow macrophages (10^6)				
Week 54	0.19 ± 0.07	0.14 ± 0.03	0.12 ± 0.03	0.14 ± 0.03
Week 66	0.27 ± 0.04	0.21 ± 0.05	0.19 ± 0.02	0.31 ± 0.04
Week 80	0.18 ± 0.04	0.20 ± 0.05	0.19 ± 0.05	0.22 ± 0.02
Bone marrow monocytes (10^6)				
Week 54	0.00 ± 0.00	0.00 ± 0.00	0.01 ± 0.01	0.00 ± 0.00
Week 66	0.00 ± 0.00	0.00 ± 0.00	0.01 ± 0.01	0.00 ± 0.00
Week 80	0.33 ± 0.06	0.21 ± 0.05	0.19 ± 0.05	0.21 ± 0.03

TABLE K2
Hematology and Bone Marrow Data for Mice in the 2-Year Gavage Study of AZT

	Vehicle Control	30 mg/kg	60 mg/kg	120 mg/kg
Male (continued)				
Bone Marrow Analyses (continued)				
Clinical Pathology Groups (continued)				
n				
Week 54	10	10	10	10
Week 66	9	10	9	8
Week 80	10	9	8	10
Megakaryo cells (10^6)				
Week 54	0.064 ± 0.018	0.040 ± 0.017	0.045 ± 0.015	0.054 ± 0.011
Week 66	0.15 ± 0.03	0.13 ± 0.03	0.09 ± 0.02	0.16 ± 0.04
Week 80	0.11 ± 0.03	0.08 ± 0.02	0.13 ± 0.03	0.15 ± 0.04
Plasma cells (10^6)				
Week 54	0.13 ± 0.05	0.12 ± 0.01	0.25 ± 0.05*	0.13 ± 0.02
Week 66	0.16 ± 0.04	0.21 ± 0.03	0.21 ± 0.03	0.20 ± 0.03
Week 80	0.33 ± 0.07	0.28 ± 0.05	0.38 ± 0.08	0.33 ± 0.11
Mitotic figures (10^6)				
Week 54	0.31 ± 0.06	0.49 ± 0.07*	0.54 ± 0.09*	0.65 ± 0.07**
Week 66	0.24 ± 0.04	0.26 ± 0.05	0.21 ± 0.06	0.27 ± 0.06
Week 80	0.18 ± 0.05	0.11 ± 0.03	0.17 ± 0.04	0.20 ± 0.03
Fat cells (10^6)				
Week 54	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000
Week 66	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000
Week 80	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000
Mast cells (10^6)				
Week 54	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.006 ± 0.006
Week 66	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000
Week 80	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000
Smudge cells (10^6)				
Week 54	3.43 ± 0.27	3.88 ± 0.29	4.18 ± 0.34	3.66 ± 0.31
Week 66	6.01 ± 0.56	6.24 ± 0.27	5.74 ± 0.41	5.73 ± 0.48
Week 80	4.82 ± 0.27	4.71 ± 0.32	4.45 ± 0.25	4.01 ± 0.25
Osteoblasts (10^6)				
Week 54	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000
Week 66	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000
Week 80	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000
Osteoclasts (10^6)				
Week 54	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.012 ± 0.008
Week 66	0.033 ± 0.013	0.044 ± 0.017	0.028 ± 0.015	0.033 ± 0.012
Week 80	0.000 ± 0.000	0.006 ± 0.006	0.000 ± 0.000	0.000 ± 0.000
Other bone marrow cells (10^6)				
Week 54	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000
Week 66	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000
Week 80	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000
Neutrophilic hypersegments (10^6)				
Week 54	0.11 ± 0.04	0.13 ± 0.05	0.13 ± 0.03	0.25 ± 0.04*
Week 66	0.35 ± 0.06	0.20 ± 0.04	0.42 ± 0.07	0.29 ± 0.06
Week 80	0.11 ± 0.08	0.25 ± 0.15	0.21 ± 0.06	0.13 ± 0.04

TABLE K2
Hematology and Bone Marrow Data for Mice in the 2-Year Gavage Study of AZT

	Vehicle Control	30 mg/kg	60 mg/kg	120 mg/kg
Male (continued)				
Bone Marrow Analyses (continued)				
Core Groups				
n	10	9	6	8
Total femoral count (10^6/femur)	31.4 ± 2.3	28.7 ± 2.2	30.2 ± 2.9	29.3 ± 1.5
M:E ratio	2.59 ± 0.36	1.81 ± 0.23	2.53 ± 0.48	2.31 ± 0.29
Rubriblasts (10^6)	0.39 ± 0.03	0.42 ± 0.08	0.41 ± 0.08	0.40 ± 0.08
Prorubricytes (10^6)	0.84 ± 0.09	1.31 ± 0.26	1.17 ± 0.28	1.26 ± 0.09
Rubricytes (10^6)	4.10 ± 0.34	4.33 ± 0.36	3.86 ± 0.96	3.86 ± 0.45
Metarubricytes (10^6)	1.59 ± 0.28	2.23 ± 0.37	2.00 ± 0.45	1.51 ± 0.15
Myeloblasts (10^6)	0.33 ± 0.03	0.37 ± 0.04	0.36 ± 0.06	0.25 ± 0.03
Promyelocytes (10^6)	0.54 ± 0.07	0.50 ± 0.07	0.57 ± 0.09	0.46 ± 0.06
Neutrophilic myelocytes (10^6)	1.55 ± 0.23	1.29 ± 0.18	1.45 ± 0.16	1.43 ± 0.27
Neutrophilic metamyelocytes (10^6)	1.18 ± 0.24	0.95 ± 0.18	0.86 ± 0.16	1.21 ± 0.12
Neutrophilic bands (10^6)	3.66 ± 0.42	3.15 ± 0.42	4.48 ± 0.69	3.87 ± 0.45
Neutrophilic segments (10^6)	8.55 ± 0.98	7.44 ± 0.94	6.95 ± 0.49	7.65 ± 0.98
Eosinophilic myelocytes (10^6)	0.076 ± 0.030	0.027 ± 0.011	0.058 ± 0.025	0.056 ± 0.016
Eosinophilic metamyelocytes (10^6)	0.067 ± 0.025	0.084 ± 0.032	0.025 ± 0.018	0.068 ± 0.015
Eosinophilic bands (10^6)	0.23 ± 0.05	0.17 ± 0.03	0.20 ± 0.07	0.27 ± 0.05
Eosinophilic segments (10^6)	0.13 ± 0.05	0.13 ± 0.04	0.12 ± 0.03	0.13 ± 0.04
Basophilic myelocytes (10^6)	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000
Basophilic metamyelocytes (10^6)	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000
Basophilic bands (10^6)	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000
Basophilic segments (10^6)	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000
Bone marrow lymphocytes (10^6)	4.14 ± 0.60	2.82 ± 0.60	3.59 ± 0.47	2.32 ± 0.26
Bone marrow macrophages (10^6)	0.28 ± 0.05	0.15 ± 0.04	0.13 ± 0.02	0.26 ± 0.06
Bone marrow monocytes (10^6)	0.52 ± 0.17	0.24 ± 0.05	0.38 ± 0.06	0.32 ± 0.07
Megakaryo cells (10^6)	0.06 ± 0.01	0.09 ± 0.02	0.06 ± 0.02	0.14 ± 0.04
Plasma cells (10^6)	0.33 ± 0.07	0.36 ± 0.09	0.36 ± 0.12	0.50 ± 0.13
Mitotic figures (10^6)	0.23 ± 0.04	0.14 ± 0.03	0.24 ± 0.10	0.16 ± 0.04
Fat cells (10^6)	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000
Mast cells (10^6)	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000
Smudge cells (10^6)	2.56 ± 0.20	2.48 ± 0.42	2.87 ± 0.63	3.12 ± 0.36
Osteoblasts (10^6)	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000
Osteoclasts (10^6)	0.000 ± 0.000	0.003 ± 0.003	0.000 ± 0.000	0.008 ± 0.008
Other bone marrow cells (10^6)	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000

TABLE K2
Hematology and Bone Marrow Data for Mice in the 2-Year Gavage Study of AZT

	Vehicle Control	30 mg/kg	60 mg/kg	120 mg/kg
Female				
Hematology				
Clinical Pathology Groups				
n				
Week 14	10	10	9	9
Week 27	10	9	10	9
Week 40	10	10	10	9
Week 54	10	10	10	10
Week 66	10	9	10	10
Week 80	10	9	9	9
Hematocrit (%)				
Week 14	46.0 ± 0.7	44.9 ± 0.5	44.8 ± 0.6	44.0 ± 0.6
Week 27	46.5 ± 0.5	46.1 ± 0.4	45.3 ± 0.5	46.6 ± 0.4
Week 40	45.5 ± 0.6	44.3 ± 0.3	44.2 ± 0.4	43.6 ± 0.7
Week 54	44.0 ± 0.3	44.2 ± 0.3	42.4 ± 0.2**	43.0 ± 0.6
Week 66	43.1 ± 2.8	43.5 ± 0.7	44.7 ± 1.0	42.8 ± 0.3**
Week 80	48.3 ± 2.3	48.3 ± 3.2	44.8 ± 0.3**	43.6 ± 0.6**
Hemoglobin (g/dL)				
Week 14	15.2 ± 0.2	14.9 ± 0.1	14.8 ± 0.2	14.6 ± 0.2*
Week 27	15.4 ± 0.1	15.2 ± 0.1	15.0 ± 0.2	15.3 ± 0.1
Week 40	15.0 ± 0.2	14.7 ± 0.1	14.7 ± 0.1	14.3 ± 0.2*
Week 54	14.8 ± 0.1	14.9 ± 0.1	14.5 ± 0.1	14.3 ± 0.2*
Week 66	14.3 ± 0.9	14.3 ± 0.2	14.6 ± 0.3	14.0 ± 0.1**
Week 80	16.2 ± 0.7	16.1 ± 1.1	14.9 ± 0.1**	14.3 ± 0.2**
Erythrocytes (10^6/µL)				
Week 14	10.03 ± 0.13	9.30 ± 0.09**	9.13 ± 0.11**	8.80 ± 0.12**
Week 27	10.24 ± 0.09	9.97 ± 0.09*	9.73 ± 0.10**	9.76 ± 0.06**
Week 40	9.75 ± 0.10	9.10 ± 0.08**	8.92 ± 0.09**	8.65 ± 0.14**
Week 54	9.67 ± 0.07	9.21 ± 0.07**	8.76 ± 0.06**	8.58 ± 0.09**
Week 66	8.91 ± 0.51	8.46 ± 0.13**	8.56 ± 0.19**	8.00 ± 0.07**
Week 80	9.96 ± 0.66	9.24 ± 0.60*	8.49 ± 0.04**	8.18 ± 0.11**
Reticulocytes (10^6/µL)				
Week 14	0.20 ± 0.02[b]	0.19 ± 0.01	0.17 ± 0.01	0.17 ± 0.01
Week 27	0.15 ± 0.02	0.15 ± 0.01[c]	0.13 ± 0.01	0.16 ± 0.02
Week 40	0.23 ± 0.01	0.25 ± 0.02	0.30 ± 0.03*	0.36 ± 0.02**
Week 54	0.24 ± 0.03	0.24 ± 0.02	0.13 ± 0.01**	0.18 ± 0.02
Week 66	0.25 ± 0.02	0.27 ± 0.02	0.27 ± 0.02	0.28 ± 0.01
Week 80	0.22 ± 0.04	0.19 ± 0.03	0.18 ± 0.02	0.19 ± 0.02
Nucleated erythrocytes (10^3/µL)				
Week 14	0.03 ± 0.01[b]	0.02 ± 0.01	0.03 ± 0.01	0.04 ± 0.02
Week 27	0.01 ± 0.01	0.00 ± 0.00	0.01 ± 0.01	0.00 ± 0.00
Week 40	0.01 ± 0.01	0.00 ± 0.00	0.00 ± 0.00	0.01 ± 0.01
Week 54	0.01 ± 0.01	0.00 ± 0.00	0.01 ± 0.01	0.01 ± 0.01
Week 66	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00
Week 80	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00
Mean cell volume (fL)				
Week 14	45.9 ± 0.3	48.3 ± 0.2**	49.1 ± 0.2**	50.0 ± 0.2**
Week 27	45.4 ± 0.3	46.2 ± 0.4	46.6 ± 0.3*	47.8 ± 0.3**
Week 40	46.7 ± 0.3	48.7 ± 0.3**	49.5 ± 0.2**	50.4 ± 0.3**
Week 54	45.4 ± 0.1	48.0 ± 0.2**	48.5 ± 0.2**	50.2 ± 0.3**
Week 66	48.1 ± 0.7	51.5 ± 0.3**	52.3 ± 0.4**	53.5 ± 0.4**
Week 80	48.9 ± 0.7	52.2 ± 0.3**	52.7 ± 0.3**	53.3 ± 0.6**

TABLE K2
Hematology and Bone Marrow Data for Mice in the 2-Year Gavage Study of AZT

	Vehicle Control	30 mg/kg	60 mg/kg	120 mg/kg
Female (continued)				
Hematology (continued)				
Clinical Pathology Groups (continued)				
n				
Week 14	10	10	9	9
Week 27	10	9	10	9
Week 40	10	10	10	9
Week 54	10	10	10	10
Week 66	10	9	10	10
Week 80	10	9	9	9
Mean cell hemoglobin (pg)				
Week 14	15.1 ± 0.1	16.0 ± 0.1**	16.2 ± 0.1**	16.6 ± 0.1**
Week 27	15.1 ± 0.1	15.2 ± 0.1	15.4 ± 0.1*	15.7 ± 0.1**
Week 40	15.4 ± 0.1	16.1 ± 0.0**	16.5 ± 0.0**	16.6 ± 0.1**
Week 54	15.3 ± 0.1	16.2 ± 0.1**	16.5 ± 0.1**	16.7 ± 0.1**
Week 66	15.9 ± 0.2	16.9 ± 0.1**	17.1 ± 0.1**	17.6 ± 0.1**
Week 80	16.4 ± 0.3	17.4 ± 0.1**	17.6 ± 0.1**	17.4 ± 0.2**
Mean cell hemoglobin concentration (g/dL)				
Week 14	33.1 ± 0.2	33.1 ± 0.2	33.0 ± 0.1	33.2 ± 0.1
Week 27	33.2 ± 0.2	33.0 ± 0.2	33.0 ± 0.1	32.7 ± 0.2
Week 40	33.0 ± 0.2	33.1 ± 0.2	33.2 ± 0.1	32.9 ± 0.2
Week 54	33.7 ± 0.1	33.7 ± 0.1	34.1 ± 0.1	33.2 ± 0.1
Week 66	33.2 ± 0.1	32.8 ± 0.1	32.7 ± 0.1	32.8 ± 0.2
Week 80	33.5 ± 0.2	33.4 ± 0.1	33.4 ± 0.2	32.7 ± 0.2*
Platelets (10^3/µL)				
Week 14	980.5 ± 45.4	1,088.9 ± 47.7	1,075.0 ± 40.6	1,178.2 ± 78.1
Week 27	883.7 ± 54.6	953.7 ± 43.3	1,069.1 ± 71.3	1,020.4 ± 43.6
Week 40	1,158.3 ± 52.6	1,221.8 ± 40.7	1,302.7 ± 33.7*	1,409.1 ± 71.3**
Week 54	1,095.2 ± 51.2	1,118.4 ± 58.7	1,175.9 ± 65.2	1,268.0 ± 103.2
Week 66	1,132.2 ± 70.2	1,343.9 ± 84.0	1,361.6 ± 49.7*	1,416.5 ± 42.2**
Week 80	1,096.2 ± 60.8	1,185.2 ± 106.5	1,182.8 ± 26.6	1,478.6 ± 97.2**
Leukocytes (10^3/µL)				
Week 14	5.79 ± 0.29	5.81 ± 0.36	6.00 ± 0.41	5.32 ± 0.39
Week 27	6.06 ± 0.32	6.88 ± 0.29	6.36 ± 0.55	5.86 ± 0.61
Week 40	6.88 ± 0.41	4.97 ± 0.40**	6.36 ± 0.27	5.56 ± 0.27
Week 54	6.65 ± 0.33	6.59 ± 0.35	6.44 ± 0.24	6.34 ± 0.31
Week 66	4.60 ± 0.33	4.49 ± 0.25	4.50 ± 0.23	4.60 ± 0.20
Week 80	6.94 ± 0.46	5.68 ± 0.37	5.98 ± 0.54	6.09 ± 0.52
Segmented neutrophils (10^3/µL)				
Week 14	1.22 ± 0.16[b]	1.10 ± 0.15	0.82 ± 0.08	0.85 ± 0.11
Week 27	1.27 ± 0.15	1.22 ± 0.16	1.33 ± 0.21	1.05 ± 0.14
Week 40	1.34 ± 0.19	0.98 ± 0.10	1.17 ± 0.16	1.04 ± 0.09
Week 54	1.65 ± 0.18	1.42 ± 0.13	1.61 ± 0.08	1.61 ± 0.17
Week 66	1.14 ± 0.21	0.87 ± 0.06	0.91 ± 0.08	0.90 ± 0.10
Week 80	1.31 ± 0.11	2.09 ± 0.39	1.21 ± 0.25	1.11 ± 0.18
Lymphocytes (10^3/µL)				
Week 14	4.37 ± 0.23[b]	4.59 ± 0.30	4.99 ± 0.37	4.31 ± 0.36
Week 27	4.60 ± 0.23	5.46 ± 0.32	4.81 ± 0.42	4.63 ± 0.46
Week 40	5.42 ± 0.29	3.85 ± 0.34**	5.07 ± 0.22	4.42 ± 0.24
Week 54	4.53 ± 0.28	4.91 ± 0.34	4.48 ± 0.25	4.31 ± 0.27
Week 66	3.25 ± 0.36	3.42 ± 0.20	3.36 ± 0.16	3.49 ± 0.15
Week 80	5.47 ± 0.51	3.34 ± 0.50*	4.62 ± 0.49	4.83 ± 0.42

TABLE K2
Hematology and Bone Marrow Data for Mice in the 2-Year Gavage Study of AZT

	Vehicle Control	30 mg/kg	60 mg/kg	120 mg/kg
Female (continued)				
Hematology (continued)				
Clinical Pathology Groups (continued)				
n				
Week 14	10	10	9	9
Week 27	10	9	10	9
Week 40	10	10	10	9
Week 54	10	10	10	10
Week 66	10	9	10	10
Week 80	10	9	9	9
Atypical lymphocytes (10^3/μL)				
Week 14	0.00 ± 0.00[b]	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00
Week 27	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00
Week 40	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00
Week 54	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00
Week 66	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00
Week 80	0.00 ± 0.00	0.01 ± 0.01	0.00 ± 0.00	0.00 ± 0.00
Monocytes (10^3/μL)				
Week 14	0.06 ± 0.02[b]	0.08 ± 0.01	0.11 ± 0.03	0.07 ± 0.02
Week 27	0.12 ± 0.04	0.04 ± 0.02	0.08 ± 0.03	0.08 ± 0.03
Week 40	0.02 ± 0.01	0.01 ± 0.01	0.01 ± 0.01	0.03 ± 0.02
Week 54	0.22 ± 0.03	0.11 ± 0.03	0.17 ± 0.04	0.17 ± 0.04
Week 66	0.11 ± 0.03	0.08 ± 0.03	0.11 ± 0.03	0.12 ± 0.02
Week 80	0.04 ± 0.02	0.12 ± 0.02*	0.05 ± 0.02	0.05 ± 0.03
Eosinophils (10^3/μL)				
Week 14	0.09 ± 0.04[b]	0.04 ± 0.02	0.08 ± 0.03	0.10 ± 0.04
Week 27	0.07 ± 0.02	0.16 ± 0.06	0.14 ± 0.03	0.11 ± 0.02
Week 40	0.11 ± 0.03	0.13 ± 0.06	0.11 ± 0.03	0.07 ± 0.01
Week 54	0.25 ± 0.05	0.14 ± 0.03	0.18 ± 0.03	0.25 ± 0.05
Week 66	0.10 ± 0.02	0.11 ± 0.03	0.12 ± 0.01	0.09 ± 0.02
Week 80	0.10 ± 0.03	0.12 ± 0.02	0.09 ± 0.04	0.08 ± 0.03
Core Groups				
n	8	8	8	8
Hematocrit (%)	46.8 ± 2.9	40.4 ± 1.0**	41.7 ± 0.6**	38.2 ± 1.6**
Hemoglobin (g/dL)	15.6 ± 0.9	13.3 ± 0.4**	13.9 ± 0.2**	12.6 ± 0.5**
Erythrocytes (10^6/μL)	9.88 ± 0.65	8.00 ± 0.19**	8.00 ± 0.12**	7.18 ± 0.31**
Reticulocytes (10^6/μL)	0.24 ± 0.03	0.19 ± 0.04	0.19 ± 0.04	0.16 ± 0.03
Nucleated erythrocytes (10^3/μL)	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00
Mean cell volume (fL)	47.5 ± 0.6	50.6 ± 0.6**	52.1 ± 0.3**	53.1 ± 0.5**
Mean cell hemoglobin (pg)	15.8 ± 0.3	16.7 ± 0.2*	17.4 ± 0.1**	17.5 ± 0.1**
Mean cell hemoglobin concentration (g/dL)	33.4 ± 0.2	33.0 ± 0.2	33.4 ± 0.2	33.0 ± 0.3
Platelets (10^3/μL)	1,193.3 ± 61.3	1,125.4 ± 110.1	1,230.6 ± 61.0	1,266.3 ± 154.2
Leukocytes (10^3/μL)	5.85 ± 0.51	4.73 ± 0.54	5.11 ± 0.48	4.94 ± 0.28
Segmented neutrophils (10^3/μL)	1.52 ± 0.16	1.39 ± 0.09	1.28 ± 0.17	1.76 ± 0.23
Lymphocytes (10^3/μL)	3.90 ± 0.49	2.95 ± 0.45	3.44 ± 0.48	2.73 ± 0.25
Atypical lymphocytes (10^3/μL)	0.09 ± 0.04	0.09 ± 0.04	0.09 ± 0.03	0.04 ± 0.01
Monocytes (10^3/μL)	0.23 ± 0.03	0.18 ± 0.03	0.18 ± 0.03	0.28 ± 0.06
Eosinophils (10^3/μL)	0.10 ± 0.02	0.11 ± 0.02	0.09 ± 0.02	0.10 ± 0.02

TABLE K2
Hematology and Bone Marrow Data for Mice in the 2-Year Gavage Study of AZT

	Vehicle Control	30 mg/kg	60 mg/kg	120 mg/kg
Female (continued)				
Bone Marrow Analyses				
Clinical Pathology Groups				
n				
Week 54	10	10	10	10
Week 66	9	9	10	10
Week 80	10	9	9	9
Total femoral count (10^6/femur)				
Week 54	25.5 ± 1.0	24.9 ± 1.0	24.3 ± 2.0	22.3 ± 1.3
Week 66	28.1 ± 1.4	29.1 ± 1.5	27.7 ± 1.2	26.5 ± 0.8
Week 80	28.2 ± 0.6	29.7 ± 1.6	25.6 ± 2.0	26.0 ± 1.2
M:E ratio				
Week 54	1.45 ± 0.09	2.05 ± 0.13**	2.57 ± 0.25**	3.00 ± 0.17**
Week 66	1.90 ± 0.29	1.44 ± 0.06	1.67 ± 0.25	1.63 ± 0.11
Week 80	2.04 ± 0.17	2.28 ± 0.24	2.39 ± 0.35	2.82 ± 0.37
Rubriblasts (10^6)				
Week 54	0.72 ± 0.06	0.65 ± 0.08	0.38 ± 0.06**	0.42 ± 0.09**
Week 66	0.56 ± 0.06	0.48 ± 0.04	0.47 ± 0.08	0.71 ± 0.10
Week 80	0.33 ± 0.04	0.33 ± 0.04	0.32 ± 0.05	0.36 ± 0.04
Prorubricytes (10^6)				
Week 54	0.66 ± 0.05	0.48 ± 0.07	0.41 ± 0.06*	0.52 ± 0.06
Week 66	0.43 ± 0.09	0.62 ± 0.12	0.51 ± 0.06	0.52 ± 0.08
Week 80	1.03 ± 0.13	1.19 ± 0.18	1.32 ± 0.32	0.89 ± 0.13
Rubricytes (10^6)				
Week 54	3.46 ± 0.31	3.15 ± 0.17	2.67 ± 0.27*	2.16 ± 0.23**
Week 66	4.67 ± 0.39	4.96 ± 0.31	4.65 ± 0.32	3.64 ± 0.24
Week 80	3.49 ± 0.29	3.72 ± 0.25	3.34 ± 0.45	3.02 ± 0.33
Metarubricytes (10^6)				
Week 54	2.28 ± 0.16	1.19 ± 0.13**	1.06 ± 0.11**	0.75 ± 0.10**
Week 66	1.27 ± 0.16	2.10 ± 0.14**	1.89 ± 0.17**	2.35 ± 0.23**
Week 80	1.18 ± 0.10	1.16 ± 0.09	0.88 ± 0.16	0.63 ± 0.12**
Myeloblasts (10^6)				
Week 54	0.31 ± 0.06	0.29 ± 0.06	0.33 ± 0.07	0.22 ± 0.04
Week 66	0.60 ± 0.14	0.41 ± 0.08	0.44 ± 0.06	0.62 ± 0.08
Week 80	0.45 ± 0.08	0.46 ± 0.06	0.54 ± 0.09	0.53 ± 0.06
Promyelocytes (10^6)				
Week 54	0.42 ± 0.06	0.29 ± 0.04	0.25 ± 0.03*	0.18 ± 0.03**
Week 66	0.25 ± 0.05	0.54 ± 0.12*	0.34 ± 0.06	0.39 ± 0.03
Week 80	0.62 ± 0.07	0.71 ± 0.10	0.71 ± 0.12	0.82 ± 0.09
Neutrophilic myelocytes (10^6)				
Week 54	0.87 ± 0.11	1.14 ± 0.09	1.11 ± 0.11	1.09 ± 0.13
Week 66	1.17 ± 0.20	0.83 ± 0.08	0.92 ± 0.12	1.02 ± 0.09
Week 80	1.13 ± 0.15	1.27 ± 0.25	0.87 ± 0.14	1.19 ± 0.17
Neutrophilic metamyelocytes (10^6)				
Week 54	3.18 ± 0.16	3.17 ± 0.30	3.49 ± 0.37	3.22 ± 0.23
Week 66	3.64 ± 0.25	3.93 ± 0.33	3.76 ± 0.53	3.62 ± 0.20
Week 80	0.67 ± 0.11	0.98 ± 0.12	0.97 ± 0.24	1.03 ± 0.12
Neutrophilic bands (10^6)				
Week 54	0.26 ± 0.03	0.23 ± 0.03	0.27 ± 0.05	0.23 ± 0.03
Week 66	0.40 ± 0.08	0.38 ± 0.07	0.30 ± 0.03	0.40 ± 0.06
Week 80	1.00 ± 0.16	1.48 ± 0.29	0.93 ± 0.13	1.29 ± 0.27

TABLE K2
Hematology and Bone Marrow Data for Mice in the 2-Year Gavage Study of AZT

	Vehicle Control	30 mg/kg	60 mg/kg	120 mg/kg
Female (continued)				
Bone Marrow Analyses (continued)				
Clinical Pathology Groups (continued)				
n				
Week 54	10	10	10	10
Week 66	9	9	10	10
Week 80	10	9	9	9
Neutrophilic segments (10^6)				
Week 54	4.47 ± 0.32	5.24 ± 0.34	5.44 ± 0.50	5.57 ± 0.42
Week 66	5.77 ± 0.68	5.17 ± 0.44	5.61 ± 0.52	4.65 ± 0.24
Week 80	7.49 ± 0.54	8.35 ± 0.88	7.64 ± 1.14	7.18 ± 0.57
Eosinophilic myelocytes (10^6)				
Week 54	0.106 ± 0.023	0.079 ± 0.024	0.011 ± 0.008**	0.061 ± 0.017
Week 66	0.048 ± 0.011	0.078 ± 0.016	0.016 ± 0.008	0.037 ± 0.008
Week 80	0.098 ± 0.022	0.094 ± 0.042	0.061 ± 0.025	0.063 ± 0.018
Eosinophilic metamyelocytes (10^6)				
Week 54	0.21 ± 0.04	0.23 ± 0.06	0.21 ± 0.07	0.34 ± 0.07
Week 66	0.26 ± 0.03	0.23 ± 0.02	0.24 ± 0.05	0.24 ± 0.04
Week 80	0.075 ± 0.015	0.163 ± 0.060	0.119 ± 0.018	0.064 ± 0.012
Eosinophilic bands (10^6)				
Week 54	0.06 ± 0.02	0.05 ± 0.02	0.08 ± 0.02	0.11 ± 0.02
Week 66	0.14 ± 0.03	0.18 ± 0.04	0.12 ± 0.03	0.24 ± 0.04
Week 80	0.19 ± 0.03	0.27 ± 0.07	0.23 ± 0.06	0.23 ± 0.03
Eosinophilic segments (10^6)				
Week 54	0.14 ± 0.03	0.24 ± 0.04	0.28 ± 0.08	0.29 ± 0.05
Week 66	0.17 ± 0.03	0.14 ± 0.04	0.17 ± 0.03	0.20 ± 0.03
Week 80	0.12 ± 0.03	0.27 ± 0.05*	0.26 ± 0.07	0.23 ± 0.04
Basophilic myelocytes (10^6)				
Week 54	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000
Week 66	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000
Week 80	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000
Basophilic metamyelocytes (10^6)				
Week 54	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000
Week 66	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000
Week 80	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000
Basophilic bands (10^6)				
Week 54	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000
Week 66	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000
Week 80	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000
Basophilic segments (10^6)				
Week 54	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000
Week 66	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000
Week 80	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000
Bone marrow lymphocytes (10^6)				
Week 54	3.68 ± 0.60	4.21 ± 0.36	4.39 ± 0.55	3.20 ± 0.40
Week 66	3.71 ± 0.42	3.40 ± 0.40	3.27 ± 0.22	3.51 ± 0.12
Week 80	5.44 ± 0.47	4.19 ± 0.51	3.44 ± 0.32**	4.09 ± 0.27
Bone marrow macrophages (10^6)				
Week 54	0.08 ± 0.02	0.08 ± 0.02	0.09 ± 0.03	0.08 ± 0.03
Week 66	0.15 ± 0.04	0.17 ± 0.05	0.24 ± 0.04	0.22 ± 0.03
Week 80	0.21 ± 0.04	0.28 ± 0.07	0.17 ± 0.06	0.19 ± 0.04

TABLE K2
Hematology and Bone Marrow Data for Mice in the 2-Year Gavage Study of AZT

	Vehicle Control	30 mg/kg	60 mg/kg	120 mg/kg
Female (continued)				
Bone Marrow Analyses (continued)				
Clinical Pathology Groups (continued)				
n				
Week 54	10	10	10	10
Week 66	9	9	10	10
Week 80	10	9	9	9
Bone marrow monocytes (10^6)				
Week 54	0.000 ± 0.000	0.005 ± 0.005	0.000 ± 0.000	0.000 ± 0.000
Week 66	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000
Week 80	0.18 ± 0.03	0.30 ± 0.06	0.26 ± 0.07	0.24 ± 0.05
Megakaryo cells (10^6)				
Week 54	0.041 ± 0.015	0.032 ± 0.012	0.028 ± 0.015	0.051 ± 0.016
Week 66	0.13 ± 0.04	0.14 ± 0.04	0.10 ± 0.02	0.07 ± 0.02
Week 80	0.11 ± 0.02	0.10 ± 0.02	0.10 ± 0.03	0.09 ± 0.02
Plasma cells (10^6)				
Week 54	0.18 ± 0.03	0.19 ± 0.05	0.14 ± 0.02	0.18 ± 0.03
Week 66	0.13 ± 0.04	0.18 ± 0.04	0.18 ± 0.03	0.22 ± 0.04
Week 80	0.25 ± 0.04	0.36 ± 0.07	0.20 ± 0.03	0.30 ± 0.07
Mitotic figures (10^6)				
Week 54	0.51 ± 0.06	0.38 ± 0.04	0.38 ± 0.06	0.27 ± 0.04**
Week 66	0.23 ± 0.02	0.30 ± 0.05	0.25 ± 0.03	0.25 ± 0.05
Week 80	0.08 ± 0.02	0.14 ± 0.04	0.07 ± 0.02	0.12 ± 0.02
Fat cells (10^6)				
Week 54	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000
Week 66	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000
Week 80	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000
Mast cells (10^6)				
Week 54	0.006 ± 0.006	0.000 ± 0.000	0.009 ± 0.009	0.000 ± 0.000
Week 66	0.000 ± 0.000	0.004 ± 0.004	0.005 ± 0.005	0.000 ± 0.000
Week 80	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000
Smudge cells (10^6)				
Week 54	3.82 ± 0.16	3.60 ± 0.26	3.25 ± 0.28	3.37 ± 0.23
Week 66	4.34 ± 0.25	4.81 ± 0.49	4.23 ± 0.25	3.53 ± 0.29
Week 80	4.05 ± 0.37	3.87 ± 0.30	3.17 ± 0.30	3.43 ± 0.27
Osteoblasts (10^6)				
Week 54	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000
Week 66	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000
Week 80	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000
Osteoclasts (10^6)				
Week 54	0.016 ± 0.008	0.005 ± 0.005	0.017 ± 0.009	0.000 ± 0.000
Week 66	0.014 ± 0.010	0.019 ± 0.013	0.023 ± 0.009	0.031 ± 0.011
Week 80	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000
Other bone marrow cells (10^6)				
Week 54	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000
Week 66	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000
Week 80	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000
Neutrophilic hypersegments (10^6)				
Week 54	0.30 ± 0.09	0.50 ± 0.11	0.45 ± 0.09	0.46 ± 0.08
Week 66	0.08 ± 0.04	0.09 ± 0.04	0.12 ± 0.04	0.27 ± 0.05**
Week 80	0.05 ± 0.02	0.13 ± 0.07	0.10 ± 0.05	0.15 ± 0.05

TABLE K2
Hematology and Bone Marrow Data for Mice in the 2-Year Gavage Study of AZT

	Vehicle Control	30 mg/kg	60 mg/kg	120 mg/kg
Female (continued)				
Bone Marrow Analyses (continued)				
Core Groups				
n	9	9	8	8
Total femoral count (10^6/femur)	19.3 ± 0.9	24.8 ± 2.1	24.1 ± 2.7	21.7 ± 1.3
M:E ratio	2.01 ± 0.22	2.38 ± 0.29	3.98 ± 1.14	5.63 ± 1.23*
Rubriblasts (10^6)	0.38 ± 0.03	0.39 ± 0.07	0.38 ± 0.06	0.36 ± 0.07
Prorubricytes (10^6)	0.91 ± 0.14	0.90 ± 0.21	0.86 ± 0.16	0.68 ± 0.17
Rubricytes (10^6)	2.64 ± 0.29	3.20 ± 0.47	2.17 ± 0.34	1.83 ± 0.52
Metarubricytes (10^6)	1.10 ± 0.14	1.17 ± 0.22	1.14 ± 0.33	0.49 ± 0.15
Myeloblasts (10^6)	0.28 ± 0.03	0.39 ± 0.07	0.54 ± 0.14	0.34 ± 0.04
Promyelocytes (10^6)	0.29 ± 0.06	0.60 ± 0.08*	0.51 ± 0.12	0.48 ± 0.17
Neutrophilic myelocytes (10^6)	0.61 ± 0.07	0.74 ± 0.07	0.97 ± 0.12	0.92 ± 0.20
Neutrophilic metamyelocytes (10^6)	0.77 ± 0.12	1.15 ± 0.24	0.92 ± 0.24	0.84 ± 0.19
Neutrophilic bands (10^6)	2.97 ± 0.40	2.95 ± 0.62	2.61 ± 0.39	2.82 ± 0.66
Neutrophilic segments (10^6)	4.08 ± 0.26	5.51 ± 0.47*	7.72 ± 1.06**	6.84 ± 0.73**
Eosinophilic myelocytes (10^6)	0.026 ± 0.007	0.069 ± 0.018	0.009 ± 0.009	0.054 ± 0.019
Eosinophilic metamyelocytes (10^6)	0.071 ± 0.037	0.039 ± 0.011	0.050 ± 0.017	0.019 ± 0.007
Eosinophilic bands (10^6)	0.17 ± 0.02	0.29 ± 0.06	0.21 ± 0.06	0.20 ± 0.05
Eosinophilic segments (10^6)	0.14 ± 0.03	0.20 ± 0.05	0.19 ± 0.05	0.21 ± 0.05
Basophilic myelocytes (10^6)	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000
Basophilic metamyelocytes (10^6)	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000
Basophilic bands (10^6)	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000
Basophilic segments (10^6)	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000
Bone marrow lymphocytes (10^6)	2.77 ± 0.29	3.87 ± 0.57	3.04 ± 0.46	2.54 ± 0.29
Bone marrow macrophages (10^6)	0.11 ± 0.02	0.25 ± 0.06	0.09 ± 0.02	0.15 ± 0.03
Bone marrow monocytes (10^6)	0.18 ± 0.04	0.33 ± 0.07	0.31 ± 0.06	0.22 ± 0.05
Megakaryo cells (10^6)	0.06 ± 0.02	0.09 ± 0.03	0.09 ± 0.02	0.09 ± 0.02
Plasma cells (10^6)	0.28 ± 0.04	0.48 ± 0.08	0.57 ± 0.17	0.52 ± 0.07*
Mitotic figures (10^6)	0.14 ± 0.02	0.18 ± 0.04	0.11 ± 0.03	0.13 ± 0.04
Fat cells (10^6)	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000
Mast cells (10^6)	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000
Smudge cells (10^6)	1.36 ± 0.29	1.72 ± 0.31	1.65 ± 0.19	2.02 ± 0.27
Osteoblasts (10^6)	0.000 ± 0.000	0.201 ± 0.201	0.000 ± 0.000	0.000 ± 0.000
Osteoclasts (10^6)	0.000 ± 0.000	0.014 ± 0.010	0.004 ± 0.004	0.000 ± 0.000
Other bone marrow cells (10^6)	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000
Neutrophilic hypersegments (10^6)	0.06 ± 0.03	0.14 ± 0.04	0.32 ± 0.06**	0.22 ± 0.06**

* Significantly different ($P \leq 0.05$) from the control group by Dunn's or Shirley's test
** $P \leq 0.01$
[a] Mean ± standard error. Statistical tests were performed on unrounded data.
[b] n = 9
[c] n = 8

TABLE K3
Hematology and Bone Marrow Data for Mice in the 2-Year Subcutaneous Study of α-Interferon A/D[a]

	Vehicle Control	5,000 U α-IFN A	500 U α-IFN A/D	5,000 U α-IFN A/D
Male				
Hematology				
Clinical Pathology Groups				
n				
Week 14	8	10	9	10
Week 27	10	10	10	10
Week 40	10	10	9	9
Week 54	9	10	10	10
Week 66	10	10	10	10
Week 79	10	9	8	9
Hematocrit (%)				
Week 14	45.2 ± 0.3	46.3 ± 0.6	45.7 ± 0.3	45.5 ± 0.3
Week 27	46.1 ± 0.4	44.5 ± 0.7	46.3 ± 0.5	47.0 ± 0.8
Week 40	42.0 ± 0.6	43.1 ± 0.4	43.3 ± 0.4	42.2 ± 0.4
Week 54	43.3 ± 0.5	43.7 ± 0.7	45.0 ± 0.6	43.0 ± 0.9
Week 66	46.2 ± 1.4	43.6 ± 1.0	45.6 ± 1.6	43.1 ± 0.9
Week 79	44.5 ± 1.3	44.6 ± 1.4	43.6 ± 0.7	43.3 ± 1.3
Hemoglobin (g/dL)				
Week 14	15.1 ± 0.1	15.3 ± 0.2	15.1 ± 0.1	15.1 ± 0.1
Week 27	15.5 ± 0.1	15.0 ± 0.3	15.4 ± 0.1	15.5 ± 0.3
Week 40	14.0 ± 0.2	14.4 ± 0.1	14.5 ± 0.2	14.1 ± 0.2
Week 54	14.4 ± 0.2	14.6 ± 0.3	15.0 ± 0.2	14.2 ± 0.3
Week 66	15.5 ± 0.5	14.7 ± 0.4	15.3 ± 0.5	14.2 ± 0.3
Week 79	14.6 ± 0.4	14.8 ± 0.5	14.5 ± 0.3	14.3 ± 0.5
Erythrocytes (10^6/μL)				
Week 14	9.63 ± 0.07	9.79 ± 0.11	9.65 ± 0.08	9.70 ± 0.06
Week 27	10.12 ± 0.08	9.82 ± 0.14	10.18 ± 0.10	10.24 ± 0.16
Week 40	9.04 ± 0.10	9.27 ± 0.09	9.17 ± 0.11	9.11 ± 0.10
Week 54	9.41 ± 0.08	9.42 ± 0.15	9.66 ± 0.11	9.25 ± 0.17
Week 66	9.90 ± 0.53	9.22 ± 0.20	9.52 ± 0.44	9.29 ± 0.16
Week 79	9.57 ± 0.44	9.46 ± 0.44	8.92 ± 0.12	9.29 ± 0.49
Reticulocytes (10^6/μL)				
Week 14	0.18 ± 0.03	0.18 ± 0.02	0.17 ± 0.02	0.19 ± 0.01
Week 27	0.23 ± 0.01	0.20 ± 0.02	0.17 ± 0.01*	0.19 ± 0.01
Week 40	0.27 ± 0.02[b]	0.27 ± 0.02	0.22 ± 0.01	0.21 ± 0.01*
Week 54	0.25 ± 0.02	0.22 ± 0.02	0.22 ± 0.02	0.23 ± 0.02
Week 66	0.18 ± 0.02	0.14 ± 0.01	0.15 ± 0.01	0.19 ± 0.01
Week 79	0.12 ± 0.01	0.12 ± 0.01	0.10 ± 0.01	0.12 ± 0.02
Nucleated erythrocytes (10^3/μL)				
Week 14	0.02 ± 0.01	0.00 ± 0.00	0.01 ± 0.01	0.00 ± 0.00
Week 27	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00
Week 40	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00
Week 54	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00
Week 66	0.00 ± 0.00	0.00 ± 0.00	0.01 ± 0.01	0.00 ± 0.00
Week 79	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00
Mean cell volume (fL)				
Week 14	46.9 ± 0.2	47.3 ± 0.2	47.4 ± 0.3	47.0 ± 0.3
Week 27	45.6 ± 0.3	45.3 ± 0.3	45.4 ± 0.2	45.9 ± 0.3
Week 40	46.4 ± 0.5	46.5 ± 0.3	47.3 ± 0.4	46.3 ± 0.5
Week 54	46.0 ± 0.3	46.4 ± 0.3	46.6 ± 0.3	46.4 ± 0.4
Week 66	47.1 ± 1.1	47.3 ± 0.7	48.1 ± 0.5	46.4 ± 0.8
Week 79	46.9 ± 1.0	47.4 ± 0.8	48.9 ± 0.8	47.0 ± 1.1

TABLE K3
Hematology and Bone Marrow Data for Mice in the 2-Year Subcutaneous Study of α-Interferon A/D

	Vehicle Control	5,000 U α-IFN A	500 U α-IFN A/D	5,000 U α-IFN A/D
Male (continued)				
Hematology (continued)				
Clinical Pathology Groups (continued)				
n				
Week 14	8	10	9	10
Week 27	10	10	10	10
Week 40	10	10	9	9
Week 54	9	10	10	10
Week 66	10	10	10	10
Week 79	10	9	8	9
Mean cell hemoglobin (pg)				
Week 14	15.7 ± 0.1	15.6 ± 0.1	15.6 ± 0.1	15.5 ± 0.1
Week 27	15.3 ± 0.1	15.2 ± 0.1	15.2 ± 0.1	15.2 ± 0.1
Week 40	15.4 ± 0.1	15.5 ± 0.1	15.8 ± 0.1	15.4 ± 0.1
Week 54	15.3 ± 0.2	15.4 ± 0.1	15.5 ± 0.1	15.3 ± 0.1
Week 66	15.8 ± 0.4	15.9 ± 0.3	16.2 ± 0.2	15.3 ± 0.3
Week 79	15.4 ± 0.3	15.7 ± 0.3	16.3 ± 0.3	15.5 ± 0.4
Mean cell hemoglobin concentration (g/dL)				
Week 14	33.4 ± 0.2	33.0 ± 0.1	32.9 ± 0.1	33.1 ± 0.1
Week 27	33.5 ± 0.1	33.6 ± 0.2	33.4 ± 0.2	33.1 ± 0.2
Week 40	33.2 ± 0.2	33.3 ± 0.2	33.4 ± 0.2	33.4 ± 0.2
Week 54	33.2 ± 0.3	33.2 ± 0.3	33.3 ± 0.2	32.9 ± 0.2
Week 66	33.6 ± 0.3	33.7 ± 0.2	33.6 ± 0.2	32.9 ± 0.2
Week 79	32.9 ± 0.2	33.2 ± 0.2	33.3 ± 0.2	33.1 ± 0.2
Platelets (10^3/μL)				
Week 14	1,334.1 ± 40.0	1,229.4 ± 38.5	1,356.3 ± 34.5	1,369.4 ± 45.4
Week 27	1,050.6 ± 52.2	1,205.8 ± 72.0	1,115.1 ± 37.7	1,120.2 ± 60.5
Week 40	1,308.2 ± 44.2	1,350.9 ± 47.0	1,435.7 ± 30.5	1,528.4 ± 62.7*
Week 54	1,376.8 ± 44.7	1,235.3 ± 58.6	1,258.4 ± 37.5	1,376.6 ± 170.2
Week 66	1,665.0 ± 170.7	1,348.2 ± 83.7	1,295.0 ± 73.4	1,484.2 ± 72.2
Week 79	1,669.6 ± 103.6	1,633.0 ± 69.7	1,556.0 ± 109.6	1,765.4 ± 100.5
Leukocytes (10^3/μL)				
Week 14	8.21 ± 0.63	8.18 ± 0.45	7.38 ± 0.49	7.72 ± 0.48
Week 27	7.95 ± 0.51	8.60 ± 0.50	8.31 ± 0.41	7.90 ± 0.40
Week 40	8.35 ± 0.43	8.04 ± 0.64	7.00 ± 0.38	8.67 ± 0.57
Week 54	8.14 ± 0.92	7.24 ± 0.58	6.41 ± 0.80	6.71 ± 0.99
Week 66	10.29 ± 0.84	10.73 ± 1.15	8.55 ± 0.83	11.54 ± 1.03
Week 79	11.66 ± 0.84	12.12 ± 1.19	9.06 ± 0.64	11.75 ± 0.95
Segmented neutrophils (10^3/μL)				
Week 14	1.83 ± 0.27	1.65 ± 0.18	1.56 ± 0.23	1.97 ± 0.12
Week 27	1.33 ± 0.20	1.45 ± 0.17	1.69 ± 0.18	1.49 ± 0.12
Week 40	2.08 ± 0.33	1.89 ± 0.24	1.46 ± 0.17	1.91 ± 0.20
Week 54	1.69 ± 0.42	1.50 ± 0.21	1.13 ± 0.20	1.11 ± 0.13
Week 66	2.18 ± 0.29	2.35 ± 0.50	1.99 ± 0.40	2.12 ± 0.21
Week 79	2.50 ± 0.31	2.59 ± 0.35	2.91 ± 0.68	2.72 ± 0.38
Lymphocytes (10^3/μL)				
Week 14	6.18 ± 0.37	6.29 ± 0.36	5.62 ± 0.32	5.46 ± 0.43
Week 27	6.40 ± 0.29	6.81 ± 0.39	6.35 ± 0.33	6.12 ± 0.36
Week 40	6.18 ± 0.24	6.06 ± 0.46	5.39 ± 0.30	6.56 ± 0.39
Week 54	6.16 ± 0.62	5.50 ± 0.43	5.11 ± 0.59	5.39 ± 0.88
Week 66	7.61 ± 0.60	7.90 ± 0.80	6.13 ± 0.56	8.76 ± 0.79
Week 79	9.03 ± 0.65	9.38 ± 0.91	6.06 ± 0.17**	8.88 ± 0.68

TABLE K3
Hematology and Bone Marrow Data for Mice in the 2-Year Subcutaneous Study of α-Interferon A/D

	Vehicle Control	5,000 U α-IFN A	500 U α-IFN A/D	5,000 U α-IFN A/D
Male (continued)				
Hematology (continued)				
Clinical Pathology Groups (continued)				
n				
Week 14	8	10	9	10
Week 27	10	10	10	10
Week 40	10	10	9	9
Week 54	9	10	10	10
Week 66	10	10	10	10
Week 79	10	9	8	9
Atypical lymphocytes (10^3/μL)				
Week 14	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00
Week 27	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00
Week 40	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00
Week 54	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00
Week 66	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00
Week 79	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00
Monocytes (10^3/μL)				
Week 14	0.06 ± 0.03	0.03 ± 0.01	0.01 ± 0.01	0.07 ± 0.03
Week 27	0.05 ± 0.02	0.10 ± 0.05	0.10 ± 0.04	0.10 ± 0.05
Week 40	0.03 ± 0.02	0.03 ± 0.03	0.02 ± 0.01	0.02 ± 0.02
Week 54	0.15 ± 0.07	0.07 ± 0.03	0.07 ± 0.02	0.11 ± 0.04
Week 66	0.39 ± 0.08	0.33 ± 0.07	0.29 ± 0.03	0.50 ± 0.08
Week 79	0.10 ± 0.04	0.06 ± 0.02	0.06 ± 0.04	0.10 ± 0.03
Eosinophils (10^3/μL)				
Week 14	0.14 ± 0.04	0.21 ± 0.05	0.18 ± 0.06	0.22 ± 0.04
Week 27	0.17 ± 0.06	0.23 ± 0.05	0.17 ± 0.04	0.19 ± 0.06
Week 40	0.07 ± 0.03	0.07 ± 0.03	0.13 ± 0.06	0.17 ± 0.06
Week 54	0.13 ± 0.03	0.17 ± 0.04	0.10 ± 0.03	0.11 ± 0.03
Week 66	0.11 ± 0.03	0.15 ± 0.05	0.13 ± 0.02	0.15 ± 0.03
Week 79	0.05 ± 0.03	0.08 ± 0.05	0.02 ± 0.02	0.04 ± 0.02
Core Groups				
n	10	10	10	10
Hematocrit (%)	37.9 ± 1.3	39.3 ± 2.4	42.1 ± 2.4	39.8 ± 1.8
Hemoglobin (g/dL)	12.6 ± 0.5	13.5 ± 0.8	14.3 ± 0.9	13.7 ± 0.6
Erythrocytes (10^6/μL)	8.10 ± 0.42	8.83 ± 0.5	9.28 ± 0.62	8.91 ± 0.395
Reticulocytes (10^6/μL)	0.30 ± 0.04	0.24 ± 0.0	0.38 ± 0.07	0.24 ± 0.043
Nucleated erythrocytes (10^3/μL)	0.00 ± 0.00	0.00 ± 0.0	0.00 ± 0.00	0.00 ± 0.00
Mean cell volume (fL)	47.3 ± 1.4	44.6 ± 0.6	45.8 ± 1.3	44.7 ± 0.7
Mean cell hemoglobin (pg)	15.8 ± 0.4	15.3 ± 0.2	15.5 ± 0.3	15.4 ± 0.2
Mean cell hemoglobin concentration (g/dL)	33.4 ± 0.3	34.2 ± 0.2	34.0 ± 0.4	34.3 ± 0.1
Platelets (10^3/μL)	1,915.1 ± 231.1	1,819.3 ± 100.2	1,937.4 ± 152.8	1,579.1 ± 104.3
Leukocytes (10^3/μL)	9.15 ± 0.89	9.75 ± 0.73	9.11 ± 0.71	8.93 ± 0.74
Segmented neutrophils (10^3/μL)	2.83 ± 0.47	3.96 ± 0.58	3.21 ± 0.45	3.29 ± 0.51
Lymphocytes (10^3/μL)	5.49 ± 0.67	4.99 ± 0.44	5.11 ± 0.63	4.98 ± 0.42
Atypical lymphocytes (10^3/μL)	0.12 ± 0.04	0.18 ± 0.12	0.12 ± 0.05	0.03 ± 0.02
Monocytes (10^3/μL)	0.58 ± 0.10	0.51 ± 0.09	0.52 ± 0.08	0.48 ± 0.05
Eosinophils (10^3/μL)	0.09 ± 0.01	0.08 ± 0.02	0.09 ± 0.02	0.09 ± 0.03

TABLE K3
Hematology and Bone Marrow Data for Mice in the 2-Year Subcutaneous Study of α-Interferon A/D

	Vehicle Control	5,000 U α-IFN A	500 U α-IFN A/D	5,000 U α-IFN A/D
Male (continued)				
Bone Marrow Analyses				
Clinical Pathology Groups				
n				
Week 54	9	9	9	10
Week 66	10	9	10	10
Week 79	10	9	8	9
Total femoral count (10^6/femur)				
Week 54	30.6 ± 1.4	28.1 ± 1.5	29.4 ± 1.0	27.3 ± 1.2
Week 66	34.2 ± 1.4	33.9 ± 1.4	30.9 ± 1.9	34.7 ± 1.5
Week 79	38.7 ± 1.6	37.5 ± 1.9	37.2 ± 1.4	36.5 ± 1.6
M:E ratio				
Week 54	2.84 ± 0.22	2.93 ± 0.19[c]	2.91 ± 0.52	2.88 ± 0.34
Week 66	3.61 ± 0.24	3.26 ± 0.33	4.55 ± 0.84	3.13 ± 0.36
Week 79	2.87 ± 0.25	3.14 ± 0.23	4.35 ± 0.71	3.32 ± 0.26
Rubriblasts (10^6)				
Week 54	0.38 ± 0.06	0.36 ± 0.07	0.41 ± 0.07	0.34 ± 0.04
Week 66	0.14 ± 0.03	0.25 ± 0.05	0.12 ± 0.03	0.22 ± 0.03
Week 79	0.49 ± 0.04	0.38 ± 0.04	0.40 ± 0.04	0.34 ± 0.03*
Prorubricytes (10^6)				
Week 54	0.22 ± 0.04	0.20 ± 0.03	0.20 ± 0.03	0.14 ± 0.02
Week 66	0.16 ± 0.04	0.13 ± 0.02	0.12 ± 0.03	0.20 ± 0.03
Week 79	0.61 ± 0.10	0.78 ± 0.10	0.56 ± 0.09	0.72 ± 0.15
Rubricytes (10^6)				
Week 54	3.07 ± 0.19	2.77 ± 0.18	3.48 ± 0.27	3.10 ± 0.40
Week 66	3.38 ± 0.30	3.39 ± 0.25	2.91 ± 0.40	3.54 ± 0.40
Week 79	4.56 ± 0.30	3.35 ± 0.37	3.54 ± 0.51	3.33 ± 0.28
Metarubricytes (10^6)				
Week 54	1.91 ± 0.21	1.60 ± 0.18	1.72 ± 0.28	1.75 ± 0.32
Week 66	1.35 ± 0.17	1.68 ± 0.16	1.21 ± 0.15	1.99 ± 0.15*
Week 79	1.53 ± 0.20	1.45 ± 0.23	0.88 ± 0.17	1.23 ± 0.18
Myeloblasts (10^6)				
Week 54	0.53 ± 0.07	0.59 ± 0.07	0.55 ± 0.07	0.59 ± 0.13
Week 66	0.25 ± 0.03	0.35 ± 0.04	0.39 ± 0.06	0.41 ± 0.05*
Week 79	0.72 ± 0.09	0.64 ± 0.10	0.63 ± 0.09	0.67 ± 0.09
Promyelocytes (10^6)				
Week 54	0.44 ± 0.09	0.46 ± 0.07	0.40 ± 0.05	0.34 ± 0.03
Week 66	0.34 ± 0.05	0.41 ± 0.11	0.34 ± 0.04	0.31 ± 0.04
Week 79	0.92 ± 0.14	0.87 ± 0.18	0.93 ± 0.14	0.75 ± 0.08
Neutrophilic myelocytes (10^6)				
Week 54	0.57 ± 0.05	0.75 ± 0.13	0.63 ± 0.08	0.67 ± 0.05
Week 66	0.76 ± 0.08	0.95 ± 0.35	0.73 ± 0.08	0.68 ± 0.06
Week 79	1.22 ± 0.13	1.26 ± 0.23	1.15 ± 0.10	1.29 ± 0.30
Neutrophilic metamyelocytes (10^6)				
Week 54	2.97 ± 0.25	3.14 ± 0.32	3.39 ± 0.25	3.31 ± 0.31
Week 66	3.55 ± 0.19	3.22 ± 0.32	3.66 ± 0.22	3.68 ± 0.23
Week 79	3.16 ± 0.28	1.23 ± 0.30**	3.52 ± 0.65	1.99 ± 0.46*
Neutrophilic bands (10^6)				
Week 54	0.52 ± 0.07	0.43 ± 0.06	0.52 ± 0.13	0.36 ± 0.07
Week 66	0.68 ± 0.09	0.49 ± 0.08	0.54 ± 0.12	0.31 ± 0.07*
Week 79	2.50 ± 0.17	3.17 ± 0.37	1.67 ± 0.23	2.03 ± 0.42

TABLE K3
Hematology and Bone Marrow Data for Mice in the 2-Year Subcutaneous Study of α-Interferon A/D

	Vehicle Control	5,000 U α-IFN A	500 U α-IFN A/D	5,000 U α-IFN A/D
Male (continued)				
Bone Marrow Analyses (continued)				
Clinical Pathology Groups (continued)				
n				
Week 54	9	9	9	10
Week 66	10	9	10	10
Week 79	10	9	8	9
Neutrophilic segments (10^6)				
Week 54	9.72 ± 0.83	8.19 ± 0.65	8.66 ± 0.61	7.64 ± 0.44
Week 66	11.15 ± 0.64	10.72 ± 0.82	10.25 ± 0.90	10.74 ± 0.43
Week 79	10.38 ± 0.64	10.29 ± 0.88	11.88 ± 0.83	10.69 ± 0.84
Eosinophilic myelocytes (10^6)				
Week 54	0.120 ± 0.037	0.051 ± 0.016	0.046 ± 0.019	0.037 ± 0.013
Week 66	0.069 ± 0.025	0.073 ± 0.014	0.039 ± 0.014	0.083 ± 0.025
Week 79	0.102 ± 0.023	0.014 ± 0.014**	0.035 ± 0.013	0.012 ± 0.008**
Eosinophilic metamyelocytes (10^6)				
Week 54	0.00 ± 0.00	0.03 ± 0.02	0.00 ± 0.00	0.02 ± 0.01
Week 66	0.12 ± 0.02	0.07 ± 0.02	0.06 ± 0.02	0.09 ± 0.02
Week 79	0.09 ± 0.02	0.06 ± 0.03	0.03 ± 0.01	0.09 ± 0.04
Eosinophilic bands (10^6)				
Week 54	0.03 ± 0.01	0.01 ± 0.01	0.04 ± 0.02	0.01 ± 0.01
Week 66	0.03 ± 0.01	0.07 ± 0.02	0.03 ± 0.01	0.08 ± 0.02
Week 79	0.17 ± 0.04	0.24 ± 0.09	0.17 ± 0.05	0.10 ± 0.03
Eosinophilic segments (10^6)				
Week 54	0.57 ± 0.08	0.40 ± 0.03	0.59 ± 0.07	0.55 ± 0.08
Week 66	0.62 ± 0.07	0.55 ± 0.11	0.43 ± 0.06	0.68 ± 0.08
Week 79	0.28 ± 0.04	0.23 ± 0.05	0.42 ± 0.07	0.33 ± 0.05
Basophilic myelocytes (10^6)				
Week 54	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000
Week 66	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000
Week 79	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000
Basophilic metamyelocytes (10^6)				
Week 54	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000
Week 66	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000
Week 79	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000
Basophilic bands (10^6)				
Week 54	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000
Week 66	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000
Week 79	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000
Basophilic segments (10^6)				
Week 54	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000
Week 66	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000
Week 79	0.007 ± 0.007	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000
Bone marrow lymphocytes (10^6)				
Week 54	3.94 ± 0.29	4.10 ± 0.38	3.84 ± 0.33	3.52 ± 0.39
Week 66	5.23 ± 0.21	5.23 ± 0.54	4.53 ± 0.56	5.32 ± 0.56
Week 79	7.04 ± 0.58	8.08 ± 1.04	5.08 ± 0.47	6.01 ± 0.66
Bone marrow macrophages (10^6)				
Week 54	0.12 ± 0.04	0.07 ± 0.03	0.10 ± 0.03	0.03 ± 0.01
Week 66	0.12 ± 0.03	0.16 ± 0.04	0.08 ± 0.02	0.12 ± 0.04
Week 79	0.19 ± 0.04	0.21 ± 0.05	0.14 ± 0.02	0.12 ± 0.01

TABLE K3
Hematology and Bone Marrow Data for Mice in the 2-Year Subcutaneous Study of α-Interferon A/D

	Vehicle Control	5,000 U α-IFN A	500 U α-IFN A/D	5,000 U α-IFN A/D
Male (continued)				
Bone Marrow Analyses (continued)				
Clinical Pathology Groups (continued)				
n				
Week 54	9	9	9	10
Week 66	10	9	10	10
Week 79	10	9	8	9
Bone marrow monocytes (10^6)				
Week 54	0.33 ± 0.12	0.31 ± 0.10	0.16 ± 0.05	0.24 ± 0.05
Week 66	0.13 ± 0.04	0.15 ± 0.06	0.09 ± 0.03	0.08 ± 0.02
Week 79	0.67 ± 0.10	0.31 ± 0.04**	0.53 ± 0.05	0.42 ± 0.09
Megakaryo cells (10^6)				
Week 54	0.09 ± 0.02	0.09 ± 0.02	0.05 ± 0.02	0.11 ± 0.04
Week 66	0.11 ± 0.03	0.09 ± 0.02	0.12 ± 0.02	0.16 ± 0.02
Week 79	0.09 ± 0.02	0.22 ± 0.03*	0.09 ± 0.02	0.12 ± 0.03
Plasma cells (10^6)				
Week 54	0.26 ± 0.03	0.18 ± 0.03	0.19 ± 0.07	0.16 ± 0.02
Week 66	0.21 ± 0.04	0.19 ± 0.03	0.22 ± 0.04	0.21 ± 0.04
Week 79	0.33 ± 0.10	0.33 ± 0.09	0.19 ± 0.04	0.51 ± 0.16
Mitotic figures (10^6)				
Week 54	0.46 ± 0.09	0.40 ± 0.06	0.49 ± 0.08	0.30 ± 0.05
Week 66	0.34 ± 0.07	0.33 ± 0.07	0.27 ± 0.05	0.26 ± 0.03
Week 79	0.06 ± 0.01	0.25 ± 0.05**	0.08 ± 0.02	0.22 ± 0.04**
Fat cells (10^6)				
Week 54	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000
Week 66	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000
Week 79	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000
Mast cells (10^6)				
Week 54	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000
Week 66	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000
Week 79	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000
Smudge cells (10^6)				
Week 54	4.32 ± 0.25	3.94 ± 0.26	3.98 ± 0.20	4.03 ± 0.18
Week 66	5.45 ± 0.28	5.40 ± 0.34	4.78 ± 0.38	5.50 ± 0.31
Week 79	3.59 ± 0.23	4.15 ± 0.22	5.32 ± 0.22**	5.46 ± 0.41**
Osteoblasts (10^6)				
Week 54	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000
Week 66	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000
Week 79	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000
Osteoclasts (10^6)				
Week 54	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000
Week 66	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000
Week 79	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.007 ± 0.007
Other bone marrow cells (10^6)				
Week 54	0.019 ± 0.014	0.000 ± 0.000	0.008 ± 0.008	0.012 ± 0.008
Week 66	0.016 ± 0.016	0.007 ± 0.007	0.000 ± 0.000	0.012 ± 0.012
Week 79	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000
Neutrophilic hypersegments (10^6)				
Week 54	0.01 ± 0.01	0.06 ± 0.02*	0.00 ± 0.00	0.08 ± 0.02**
Week 66	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00
Week 79	0.05 ± 0.03	0.19 ± 0.05*	0.15 ± 0.07	0.15 ± 0.06

TABLE K3
Hematology and Bone Marrow Data for Mice in the 2-Year Subcutaneous Study of α-Interferon A/D

	Vehicle Control	5,000 U α-IFN A	500 U α-IFN A/D	5,000 U α-IFN A/D
Male (continued)				
Bone Marrow Analyses (continued)				
Core Groups				
n	10	10	10	10
Total femoral count (10^6/femur)	28.0 ± 0.7	29.3 ± 2.8	28.1 ± 1.3	29.6 ± 1.2
M:E ratio	1.59 ± 0.18	2.45 ± 0.34	2.03 ± 0.26	1.92 ± 0.11
Rubriblasts (10^6)	0.41 ± 0.06	0.31 ± 0.08	0.35 ± 0.05	0.40 ± 0.05
Prorubricytes (10^6)	0.93 ± 0.14	1.00 ± 0.14	1.12 ± 0.22	0.73 ± 0.14
Rubricytes (10^6)	6.14 ± 0.41	4.84 ± 0.96	5.76 ± 0.70	5.67 ± 0.59
Metarubricytes (10^6)	1.80 ± 0.41	1.66 ± 0.34	1.18 ± 0.22	1.59 ± 0.20
Myeloblasts (10^6)	0.42 ± 0.06	0.44 ± 0.07	0.46 ± 0.06	0.55 ± 0.08
Promyelocytes (10^6)	0.47 ± 0.08	0.57 ± 0.09	0.53 ± 0.09	0.50 ± 0.11
Neutrophilic myelocytes (10^6)	1.45 ± 0.19	1.17 ± 0.20	0.73 ± 0.13*	1.34 ± 0.21
Neutrophilic metamyelocytes (10^6)	1.02 ± 0.17	1.21 ± 0.25	0.84 ± 0.14	1.19 ± 0.16
Neutrophilic bands (10^6)	3.32 ± 0.40	3.94 ± 0.75	3.21 ± 0.46	3.93 ± 0.65
Neutrophilic segments (10^6)	6.70 ± 0.61	8.73 ± 0.77	9.11 ± 0.65*	7.73 ± 0.48
Eosinophilic myelocytes (10^6)	0.010 ± 0.010	0.070 ± 0.017**	0.009 ± 0.009	0.011 ± 0.011
Eosinophilic metamyelocytes (10^6)	0.032 ± 0.016	0.085 ± 0.033	0.034 ± 0.018	0.013 ± 0.009
Eosinophilic bands (10^6)	0.12 ± 0.04	0.16 ± 0.03	0.11 ± 0.04	0.13 ± 0.02
Eosinophilic segments (10^6)	0.18 ± 0.02	0.19 ± 0.05	0.16 ± 0.06	0.12 ± 0.03
Basophilic myelocytes (10^6)	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000
Basophilic metamyelocytes (10^6)	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000
Basophilic bands (10^6)	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000
Basophilic segments (10^6)	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000
Bone marrow lymphocytes (10^6)	2.10 ± 0.18	1.93 ± 0.27	1.64 ± 0.35	2.58 ± 0.49
Bone marrow macrophages (10^6)	0.28 ± 0.08	0.21 ± 0.04	0.18 ± 0.05	0.21 ± 0.07
Bone marrow monocytes (10^6)	0.27 ± 0.06	0.35 ± 0.11	0.26 ± 0.05	0.31 ± 0.08
Megakaryo cells (10^6)	0.12 ± 0.02	0.13 ± 0.02	0.08 ± 0.02	0.14 ± 0.03
Plasma cells (10^6)	0.41 ± 0.15	0.40 ± 0.10	0.45 ± 0.09	0.62 ± 0.14
Mitotic figures (10^6)	0.24 ± 0.05	0.21 ± 0.06	0.21 ± 0.04	0.24 ± 0.05
Fat cells (10^6)	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000
Mast cells (10^6)	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000
Smudge cells (10^6)	1.59 ± 0.21	1.67 ± 0.30	1.67 ± 0.28	1.63 ± 0.18
Osteoblasts (10^6)	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000
Osteoclasts (10^6)	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000
Other bone marrow cells (10^6)	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000
Neutrophilic hypersegments (10^6)	0.05 ± 0.03	0.03 ± 0.02	0.05 ± 0.04	0.10 ± 0.04

TABLE K3
Hematology and Bone Marrow Data for Mice in the 2-Year Subcutaneous Study of α-Interferon A/D

	Vehicle Control	5,000 U α-IFN A	500 U α-IFN A/D	5,000 U α-IFN A/D
Female				
Hematology				
Clinical Pathology Groups				
n				
Week 14	10	9	10	9
Week 27	10	10	10	10
Week 40	9	10	10	9
Week 54	10	10	10	9
Week 66	10	10	9	10
Week 79	9	9	10	7
Hematocrit (%)				
Week 14	45.9 ± 0.3	45.8 ± 0.4	45.4 ± 0.6	45.2 ± 0.5
Week 27	45.6 ± 0.1	45.7 ± 0.4	45.4 ± 0.5	45.9 ± 0.3
Week 40	44.7 ± 0.6	43.9 ± 0.3	44.5 ± 0.5	45.0 ± 0.2
Week 54	45.3 ± 0.3	45.2 ± 0.5	46.4 ± 0.5	45.1 ± 0.5
Week 66	47.6 ± 0.4	47.2 ± 0.6	46.0 ± 0.5	48.6 ± 0.5
Week 79	44.7 ± 0.5	46.4 ± 1.1	49.2 ± 2.5	45.8 ± 0.5
Hemoglobin (g/dL)				
Week 14	15.1 ± 0.1	15.1 ± 0.1	15.0 ± 0.2	14.9 ± 0.1
Week 27	15.3 ± 0.1	15.4 ± 0.1	15.4 ± 0.1	15.4 ± 0.1
Week 40	14.7 ± 0.2	14.6 ± 0.1	14.8 ± 0.2	15.0 ± 0.1
Week 54	15.1 ± 0.1	14.9 ± 0.2	15.4 ± 0.2	15.0 ± 0.1
Week 66	15.8 ± 0.2	15.7 ± 0.3	15.1 ± 0.2	16.1 ± 0.2
Week 79	14.9 ± 0.2	15.4 ± 0.3	16.2 ± 0.8	15.2 ± 0.2
Erythrocytes (10^6/μL)				
Week 14	9.43 ± 0.07	9.51 ± 0.02	9.46 ± 0.13	9.37 ± 0.10
Week 27	10.00 ± 0.05	9.99 ± 0.11	9.95 ± 0.06	9.93 ± 0.09
Week 40	9.48 ± 0.14	9.29 ± 0.06	9.43 ± 0.13	9.63 ± 0.07
Week 54	9.60 ± 0.06	9.60 ± 0.09	9.91 ± 0.12	9.67 ± 0.12
Week 66	9.77 ± 0.08	9.92 ± 0.13	9.62 ± 0.06	10.05 ± 0.11
Week 79	9.37 ± 0.14	9.84 ± 0.32	10.57 ± 0.63	9.60 ± 0.14
Reticulocytes (10^6/μL)				
Week 14	0.22 ± 0.02	0.23 ± 0.02	0.20 ± 0.02	0.20 ± 0.03
Week 27	0.17 ± 0.02	0.18 ± 0.01	0.16 ± 0.01	0.15 ± 0.02
Week 40	0.29 ± 0.03	0.22 ± 0.02	0.25 ± 0.03	0.28 ± 0.01
Week 54	0.31 ± 0.01	0.30 ± 0.02	0.31 ± 0.01	0.28 ± 0.01
Week 66	0.21 ± 0.02	0.21 ± 0.02	0.20 ± 0.01	0.25 ± 0.02
Week 79	0.13 ± 0.02	0.18 ± 0.04	0.15 ± 0.02	0.13 ± 0.01
Nucleated erythrocytes (10^3/μL)				
Week 14	0.00 ± 0.00	0.01 ± 0.01	0.01 ± 0.01	0.00 ± 0.00
Week 27	0.01 ± 0.01	0.01 ± 0.01	0.00 ± 0.00	0.00 ± 0.00
Week 40	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00
Week 54	0.00 ± 0.00	0.01 ± 0.01	0.00 ± 0.00	0.01 ± 0.01
Week 66	0.00 ± 0.00	0.00 ± 0.00[b]	0.01 ± 0.01	0.00 ± 0.00
Week 79	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00
Mean cell volume (fL)				
Week 14	48.7 ± 0.1	48.1 ± 0.3	48.0 ± 0.2*	48.3 ± 0.2
Week 27	45.7 ± 0.2	45.8 ± 0.3	45.7 ± 0.4	46.3 ± 0.2
Week 40	47.2 ± 0.3	47.2 ± 0.3	47.2 ± 0.2	46.7 ± 0.2
Week 54	47.2 ± 0.3	47.1 ± 0.3	46.8 ± 0.3	46.7 ± 0.3
Week 66	48.7 ± 0.3	47.6 ± 0.3	47.8 ± 0.4	48.3 ± 0.2
Week 79	47.7 ± 0.4	47.3 ± 0.5	46.7 ± 0.7	47.7 ± 0.6

TABLE K3
Hematology and Bone Marrow Data for Mice in the 2-Year Subcutaneous Study of α-Interferon A/D

	Vehicle Control	5,000 U α-IFN A	500 U α-IFN A/D	5,000 U α-IFN A/D
Female (continued)				
Hematology (continued)				
Clinical Pathology Groups (continued)				
n				
Week 14	10	9	10	9
Week 27	10	10	10	10
Week 40	9	10	10	9
Week 54	10	10	10	9
Week 66	10	10	9	10
Week 79	9	9	10	7
Mean cell hemoglobin (pg)				
Week 14	16.0 ± 0.1	15.9 ± 0.1	15.9 ± 0.1	16.0 ± 0.1
Week 27	15.3 ± 0.0	15.4 ± 0.1	15.5 ± 0.1**	15.5 ± 0.1
Week 40	15.6 ± 0.1	15.7 ± 0.0	15.7 ± 0.1	15.6 ± 0.0
Week 54	15.8 ± 0.1	15.6 ± 0.1	15.6 ± 0.1	15.5 ± 0.1
Week 66	16.2 ± 0.1	15.9 ± 0.2	15.7 ± 0.2	16.0 ± 0.0
Week 79	16.0 ± 0.1	15.7 ± 0.2	15.4 ± 0.3	15.9 ± 0.2
Mean cell hemoglobin concentration (g/dL)				
Week 14	32.8 ± 0.1	33.0 ± 0.2	33.2 ± 0.1	33.1 ± 0.1
Week 27	33.5 ± 0.2	33.7 ± 0.2	34.0 ± 0.3	33.5 ± 0.1
Week 40	33.0 ± 0.1	33.3 ± 0.1	33.3 ± 0.1	33.4 ± 0.2
Week 54	33.5 ± 0.1	33.1 ± 0.2	33.3 ± 0.1	33.2 ± 0.1
Week 66	33.3 ± 0.1	33.3 ± 0.2	32.9 ± 0.2	33.1 ± 0.1
Week 79	33.5 ± 0.2	33.1 ± 0.2	33.0 ± 0.2	33.2 ± 0.2
Platelets (10^3/μL)				
Week 14	1,244.9 ± 51.8	1,167.4 ± 51.0	1,185.7 ± 40.0	1,132.3 ± 45.6
Week 27	997.0 ± 55.2	996.6 ± 38.9	991.1 ± 33.6	1,021.8 ± 84.0
Week 40	1,115.7 ± 39.3	1,138.4 ± 43.5	1,129.4 ± 39.0	1,134.0 ± 58.1
Week 54	1,073.3 ± 76.6	1,096.6 ± 43.6	1,113.1 ± 56.5	1,053.3 ± 71.1
Week 66	1,043.5 ± 42.3	1,135.4 ± 63.0	1,210.6 ± 57.0	1,097.3 ± 39.9
Week 79	1,190.8 ± 27.2	1,392.9 ± 104.8	1,322.8 ± 79.8	1,269.0 ± 62.8
Leukocytes (10^3/μL)				
Week 14	5.26 ± 0.40	6.68 ± 0.47	5.43 ± 0.26	6.25 ± 0.49
Week 27	6.44 ± 0.44	6.70 ± 0.46	6.97 ± 0.35	6.59 ± 0.50
Week 40	5.98 ± 0.31	6.06 ± 0.48	6.15 ± 0.27	6.78 ± 0.33
Week 54	5.44 ± 0.45	5.13 ± 0.37	5.05 ± 0.51	5.10 ± 0.41
Week 66	5.41 ± 0.33	6.40 ± 0.50[b]	6.06 ± 0.34	5.26 ± 0.40
Week 79	5.70 ± 0.57	6.49 ± 0.61	5.76 ± 0.48	6.07 ± 0.46
Segmented neutrophils (10^3/μL)				
Week 14	0.70 ± 0.07	0.81 ± 0.09	0.90 ± 0.14	0.94 ± 0.14
Week 27	1.07 ± 0.14	0.97 ± 0.10	1.08 ± 0.08	0.95 ± 0.17
Week 40	1.03 ± 0.14	0.92 ± 0.13	1.23 ± 0.16	1.18 ± 0.05
Week 54	1.21 ± 0.14	1.19 ± 0.11	1.14 ± 0.15	1.01 ± 0.08
Week 66	1.05 ± 0.06	1.21 ± 0.15[b]	1.29 ± 0.10	1.04 ± 0.08
Week 79	1.35 ± 0.18	1.43 ± 0.16	1.10 ± 0.13	1.25 ± 0.18
Lymphocytes (10^3/μL)				
Week 14	4.41 ± 0.39	5.69 ± 0.44	4.37 ± 0.24	5.15 ± 0.44
Week 27	5.16 ± 0.37	5.52 ± 0.42	5.69 ± 0.36	5.42 ± 0.43
Week 40	4.77 ± 0.22	5.03 ± 0.43	4.80 ± 0.20	5.43 ± 0.36
Week 54	3.96 ± 0.38	3.65 ± 0.32	3.72 ± 0.44	3.78 ± 0.37
Week 66	4.06 ± 0.30	4.77 ± 0.38[b]	4.44 ± 0.33	3.91 ± 0.35
Week 79	4.25 ± 0.48	4.90 ± 0.58	4.55 ± 0.39	4.73 ± 0.41

TABLE K3
Hematology and Bone Marrow Data for Mice in the 2-Year Subcutaneous Study of α-Interferon A/D

	Vehicle Control	5,000 U α-IFN A	500 U α-IFN A/D	5,000 U α-IFN A/D
Female (continued)				
Hematology (continued)				
Clinical Pathology Groups (continued)				
n				
Week 14	10	9	10	9
Week 27	10	10	10	10
Week 40	9	10	10	9
Week 54	10	10	10	9
Week 66	10	10	9	10
Week 79	9	9	10	7
Atypical lymphocytes (10^3/μL)				
Week 14	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00
Week 27	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00
Week 40	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00
Week 54	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00
Week 66	0.00 ± 0.00	0.00 ± 0.00[b]	0.00 ± 0.00	0.00 ± 0.00
Week 79	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00
Monocytes (10^3/μL)				
Week 14	0.04 ± 0.02	0.02 ± 0.01	0.04 ± 0.02	0.04 ± 0.04
Week 27	0.02 ± 0.01	0.03 ± 0.02	0.04 ± 0.01	0.05 ± 0.02
Week 40	0.01 ± 0.01	0.00 ± 0.00	0.01 ± 0.01	0.05 ± 0.03
Week 54	0.14 ± 0.04	0.13 ± 0.03	0.09 ± 0.02	0.15 ± 0.03
Week 66	0.18 ± 0.02	0.28 ± 0.06[b]	0.21 ± 0.03	0.17 ± 0.03
Week 79	0.06 ± 0.03	0.12 ± 0.03	0.08 ± 0.03	0.05 ± 0.03
Eosinophils (10^3/μL)				
Week 14	0.10 ± 0.02	0.17 ± 0.03	0.12 ± 0.02	0.12 ± 0.02
Week 27	0.19 ± 0.05	0.18 ± 0.03	0.17 ± 0.05	0.17 ± 0.04
Week 40	0.17 ± 0.03	0.12 ± 0.02	0.11 ± 0.03	0.13 ± 0.04
Week 54	0.14 ± 0.02	0.16 ± 0.03	0.11 ± 0.03	0.16 ± 0.04
Week 66	0.12 ± 0.03	0.13 ± 0.02[b]	0.12 ± 0.03	0.15 ± 0.03
Week 79	0.04 ± 0.02	0.04 ± 0.02	0.03 ± 0.01	0.04 ± 0.03
Core Groups				
n	10	10	10	10
Hematocrit (%)	47.4 ± 3.4	43.2 ± 3.0	44.9 ± 2.9	45.3 ± 1.8
Hemoglobin (g/dL)	15.9 ± 1.1	14.6 ± 1.0	15.2 ± 0.9	15.4 ± 0.6
Erythrocytes (10^6/μL)	10.09 ± 0.93	9.08 ± 0.73	9.55 ± 0.72	9.61 ± 0.47
Reticulocytes (10^6/μL)	0.57 ± 0.06	0.50 ± 0.06	0.56 ± 0.08	0.49 ± 0.03
Nucleated erythrocytes (10^3/μL)	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00
Mean cell volume (fL)	47.9 ± 1.3	48.2 ± 0.9	47.3 ± 0.5	47.3 ± 0.6
Mean cell hemoglobin (pg)	16.1 ± 0.4	16.2 ± 0.3	16.0 ± 0.2	16.1 ± 0.2
Mean cell hemoglobin concentration (g/dL)	33.5 ± 0.2	33.6 ± 0.2	33.8 ± 0.2	34.1 ± 0.2
Platelets (10^3/μL)	1,071.7 ± 106.2	1,030.0 ± 129.4	1,065.3 ± 76.3	1,050.4 ± 67.8
Leukocytes (10^3/μL)	5.68 ± 1.03	5.25 ± 0.46	4.64 ± 0.60	4.64 ± 0.47
Segmented neutrophils (10^3/μL)	1.76 ± 0.25	1.48 ± 0.18	1.52 ± 0.22	1.29 ± 0.08
Lymphocytes (10^3/μL)	3.14 ± 0.92	2.88 ± 0.29	2.31 ± 0.34	2.49 ± 0.35
Atypical lymphocytes (10^3/μL)	0.38 ± 0.08	0.42 ± 0.06	0.42 ± 0.12	0.45 ± 0.07
Monocytes (10^3/μL)	0.35 ± 0.04	0.39 ± 0.06	0.32 ± 0.06	0.31 ± 0.05
Eosinophils (10^3/μL)	0.06 ± 0.02	0.08 ± 0.03	0.05 ± 0.02	0.10 ± 0.03

TABLE K3
Hematology and Bone Marrow Data for Mice in the 2-Year Subcutaneous Study of α-Interferon A/D

	Vehicle Control	5,000 U α-IFN A	500 U α-IFN A/D	5,000 U α-IFN A/D
Female (continued)				
Bone Marrow Analyses				
Clinical Pathology Groups				
n				
Week 54	10	9	10	9
Week 66	10	9	9	10
Week 79	9	9	10	7
Total femoral count (10^6/femur)				
Week 54	29.4 ± 1.3	25.3 ± 1.4	27.2 ± 1.0	25.6 ± 1.2
Week 66	30.0 ± 2.4	33.3 ± 1.9	32.5 ± 1.2	31.0 ± 1.2
Week 79	31.3 ± 2.4	30.7 ± 1.9	29.3 ± 2.2	28.4 ± 1.2
M:E ratio				
Week 54	1.84 ± 0.28	2.26 ± 0.21	2.12 ± 0.16	2.29 ± 0.20
Week 66	2.97 ± 0.21	3.13 ± 0.33	2.84 ± 0.32	2.78 ± 0.15
Week 79	1.53 ± 0.11	2.09 ± 0.13**	1.53 ± 0.15	2.36 ± 0.13**
Rubriblasts (10^6)				
Week 54	0.37 ± 0.06	0.30 ± 0.05	0.43 ± 0.05	0.43 ± 0.06
Week 66	0.15 ± 0.03	0.17 ± 0.04	0.17 ± 0.03	0.19 ± 0.03
Week 79	0.63 ± 0.09	0.60 ± 0.10	0.75 ± 0.08	0.44 ± 0.05
Prorubricytes (10^6)				
Week 54	0.34 ± 0.05	0.19 ± 0.02**	0.25 ± 0.04	0.16 ± 0.03**
Week 66	0.18 ± 0.02	0.16 ± 0.02	0.13 ± 0.03	0.18 ± 0.03
Week 79	1.00 ± 0.13	0.81 ± 0.12	0.83 ± 0.12	0.50 ± 0.08*
Rubricytes (10^6)				
Week 54	2.54 ± 0.34	3.16 ± 0.28	2.80 ± 0.30	3.00 ± 0.32
Week 66	3.41 ± 0.33	3.68 ± 0.39	4.13 ± 0.33	4.17 ± 0.22
Week 79	6.11 ± 0.64	4.16 ± 0.43**	5.54 ± 0.76	3.04 ± 0.11**
Metarubricytes (10^6)				
Week 54	4.12 ± 0.27	1.93 ± 0.21**	2.67 ± 0.17**	2.01 ± 0.19**
Week 66	1.32 ± 0.22	1.38 ± 0.14	1.46 ± 0.11	0.98 ± 0.10
Week 79	1.62 ± 0.27	1.61 ± 0.17	1.87 ± 0.18	1.69 ± 0.19
Myeloblasts (10^6)				
Week 54	0.50 ± 0.06	0.26 ± 0.05*	0.48 ± 0.07	0.49 ± 0.09
Week 66	0.34 ± 0.06	0.49 ± 0.05	0.45 ± 0.06	0.40 ± 0.05
Week 79	0.58 ± 0.07	0.70 ± 0.09	0.70 ± 0.07	0.60 ± 0.06
Promyelocytes (10^6)				
Week 54	0.46 ± 0.07	0.29 ± 0.06	0.39 ± 0.07	0.44 ± 0.08
Week 66	0.29 ± 0.05	0.26 ± 0.05	0.35 ± 0.04	0.41 ± 0.04
Week 79	0.94 ± 0.09	0.97 ± 0.10	0.83 ± 0.09	0.87 ± 0.06
Neutrophilic myelocytes (10^6)				
Week 54	0.69 ± 0.07	0.38 ± 0.05**	0.56 ± 0.05	0.64 ± 0.07
Week 66	0.58 ± 0.07	0.65 ± 0.17	0.70 ± 0.05	0.74 ± 0.07
Week 79	1.36 ± 0.23	1.09 ± 0.12	1.15 ± 0.14	0.67 ± 0.06*
Neutrophilic metamyelocytes (10^6)				
Week 54	1.59 ± 0.13	1.75 ± 0.14	2.25 ± 0.19	2.42 ± 0.29
Week 66	3.13 ± 0.24	3.25 ± 0.18	3.36 ± 0.21	2.89 ± 0.17
Week 79	1.94 ± 0.27	2.73 ± 0.35	1.92 ± 0.21	2.04 ± 0.25
Neutrophilic bands (10^6)				
Week 54	0.47 ± 0.10	0.42 ± 0.05	0.41 ± 0.08	0.65 ± 0.11
Week 66	0.38 ± 0.08	0.37 ± 0.07	0.37 ± 0.06	0.33 ± 0.05
Week 79	3.67 ± 0.54	1.74 ± 0.15**	2.03 ± 0.23*	1.78 ± 0.17*

TABLE K3
Hematology and Bone Marrow Data for Mice in the 2-Year Subcutaneous Study of α-Interferon A/D

	Vehicle Control	5,000 U α-IFN A	500 U α-IFN A/D	5,000 U α-IFN A/D
Female (continued)				
Bone Marrow Analyses (continued)				
Clinical Pathology Groups (continued)				
n				
Week 54	10	9	10	9
Week 66	10	9	9	10
Week 79	9	9	10	7
Neutrophilic segments (10^6)				
Week 54	8.18 ± 1.05	7.98 ± 0.81	7.72 ± 0.34	6.75 ± 0.54
Week 66	8.89 ± 0.94	9.59 ± 0.45	9.70 ± 0.59	9.10 ± 0.46
Week 79	4.43 ± 0.39	6.37 ± 0.68	5.75 ± 0.72	5.99 ± 0.42
Eosinophilic myelocytes (10^6)				
Week 54	0.039 ± 0.015	0.061 ± 0.019	0.031 ± 0.021	0.058 ± 0.027
Week 66	0.068 ± 0.026	0.108 ± 0.028	0.071 ± 0.017	0.140 ± 0.029
Week 79	0.130 ± 0.021	0.158 ± 0.057	0.066 ± 0.018	0.110 ± 0.030
Eosinophilic metamyelocytes (10^6)				
Week 54	0.06 ± 0.03	0.01 ± 0.01	0.05 ± 0.04	0.05 ± 0.02
Week 66	0.07 ± 0.02	0.12 ± 0.03	0.07 ± 0.02	0.15 ± 0.03
Week 79	0.26 ± 0.04	0.30 ± 0.07	0.12 ± 0.02*	0.34 ± 0.06
Eosinophilic bands (10^6)				
Week 54	0.06 ± 0.02	0.07 ± 0.02	0.08 ± 0.03	0.05 ± 0.02
Week 66	0.08 ± 0.02	0.09 ± 0.03	0.09 ± 0.02	0.12 ± 0.03
Week 79	0.30 ± 0.06	0.24 ± 0.05	0.19 ± 0.03	0.32 ± 0.07
Eosinophilic segments (10^6)				
Week 54	0.37 ± 0.07	0.73 ± 0.13	0.61 ± 0.08	0.74 ± 0.15
Week 66	0.52 ± 0.11	0.74 ± 0.08	0.60 ± 0.08	0.76 ± 0.06
Week 79	0.21 ± 0.03	0.47 ± 0.13	0.33 ± 0.05	0.51 ± 0.09*
Basophilic myelocytes (10^6)				
Week 54	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000
Week 66	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000
Week 79	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000
Basophilic metamyelocytes (10^6)				
Week 54	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000
Week 66	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000
Week 79	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000
Basophilic bands (10^6)				
Week 54	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000
Week 66	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000
Week 79	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000
Basophilic segments (10^6)				
Week 54	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000
Week 66	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000
Week 79	0.030 ± 0.012	0.020 ± 0.008	0.009 ± 0.009	0.011 ± 0.011
Bone marrow lymphocytes (10^6)				
Week 54	5.11 ± 0.43	3.26 ± 0.16**	4.18 ± 0.26	3.09 ± 0.37**
Week 66	5.61 ± 0.58	6.54 ± 1.11	5.65 ± 0.37	5.16 ± 0.29
Week 79	4.26 ± 0.40	5.02 ± 0.49	4.19 ± 0.40	6.13 ± 0.55
Bone marrow macrophages (10^6)				
Week 54	0.06 ± 0.02	0.07 ± 0.03	0.08 ± 0.02	0.07 ± 0.03
Week 66	0.11 ± 0.02	0.14 ± 0.02	0.14 ± 0.03	0.09 ± 0.03
Week 79	0.19 ± 0.04	0.16 ± 0.02	0.18 ± 0.04	0.12 ± 0.02

TABLE K3
Hematology and Bone Marrow Data for Mice in the 2-Year Subcutaneous Study of α-Interferon A/D

	Vehicle Control	5,000 U α-IFN A	500 U α-IFN A/D	5,000 U α-IFN A/D
Female (continued)				
Bone Marrow Analyses (continued)				
Clinical Pathology Groups (continued)				
n				
Week 54	10	9	10	9
Week 66	10	9	9	10
Week 79	9	9	10	7
Bone marrow monocytes (10^6)				
Week 54	0.07 ± 0.03	0.21 ± 0.05*	0.14 ± 0.04	0.18 ± 0.05
Week 66	0.04 ± 0.02	0.10 ± 0.03	0.06 ± 0.02	0.04 ± 0.01
Week 79	0.54 ± 0.06	0.47 ± 0.10	0.48 ± 0.07	0.34 ± 0.06
Megakaryo cells (10^6)				
Week 54	0.11 ± 0.03	0.05 ± 0.01	0.08 ± 0.02	0.08 ± 0.03
Week 66	0.13 ± 0.02	0.15 ± 0.03	0.09 ± 0.01	0.14 ± 0.03
Week 79	0.22 ± 0.03	0.10 ± 0.02**	0.13 ± 0.02	0.07 ± 0.01**
Plasma cells (10^6)				
Week 54	0.25 ± 0.05	0.21 ± 0.06	0.20 ± 0.04	0.22 ± 0.04
Week 66	0.36 ± 0.08	0.35 ± 0.07	0.33 ± 0.04	0.38 ± 0.06
Week 79	0.31 ± 0.05	0.31 ± 0.05	0.44 ± 0.06	0.48 ± 0.11
Mitotic figures (10^6)				
Week 54	0.46 ± 0.07	0.30 ± 0.04	0.50 ± 0.03	0.37 ± 0.06
Week 66	0.28 ± 0.07	0.31 ± 0.04	0.34 ± 0.07	0.35 ± 0.02
Week 79	0.07 ± 0.02	0.09 ± 0.05	0.10 ± 0.03	0.13 ± 0.03
Fat cells (10^6)				
Week 54	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000
Week 66	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000
Week 79	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000
Mast cells (10^6)				
Week 54	0.000 ± 0.000	0.000 ± 0.000	0.005 ± 0.005	0.004 ± 0.004
Week 66	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000
Week 79	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000
Smudge cells (10^6)				
Week 54	3.56 ± 0.38	3.63 ± 0.40	3.31 ± 0.25	3.67 ± 0.49
Week 66	3.53 ± 0.44	4.70 ± 0.37	4.25 ± 0.30	4.20 ± 0.41
Week 79	2.52 ± 0.22	2.54 ± 0.22	1.72 ± 0.24*	2.19 ± 0.14
Osteoblasts (10^6)				
Week 54	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000
Week 66	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000
Week 79	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000
Osteoclasts (10^6)				
Week 54	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000
Week 66	0.536 ± 0.536	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000
Week 79	0.008 ± 0.008	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000
Other bone marrow cells (10^6)				
Week 54	0.014 ± 0.010	0.000 ± 0.000	0.010 ± 0.007	0.000 ± 0.000
Week 66	0.011 ± 0.008	0.000 ± 0.000	0.006 ± 0.006	0.086 ± 0.017**
Week 79	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000
Neutrophilic hypersegments (10^6)				
Week 54	0.00 ± 0.00	0.06 ± 0.03**	0.00 ± 0.00	0.00 ± 0.00
Week 66	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00
Week 79	0.16 ± 0.03	0.20 ± 0.04	0.14 ± 0.03	0.20 ± 0.03

TABLE K3
Hematology and Bone Marrow Data for Mice in the 2-Year Subcutaneous Study of α-Interferon A/D

	Vehicle Control	5,000 U α-IFN A	500 U α-IFN A/D	5,000 U α-IFN A/D
Female (continued)				
Bone Marrow Analyses (continued)				
Core Groups				
n	10	10	9	10
Total femoral count (10^6/femur)	29.8 ± 1.0	31.9 ± 1.6	31.0 ± 2.9	26.3 ± 2.5
M:E ratio	1.57 ± 0.16	1.64 ± 0.19	1.97 ± 0.28[c]	1.53 ± 0.14
Rubriblasts (10^6)	0.45 ± 0.06	0.43 ± 0.05	0.37 ± 0.05	0.41 ± 0.05
Prorubricytes (10^6)	1.53 ± 0.14	1.61 ± 0.19	1.53 ± 0.39	1.34 ± 0.19
Rubricytes (10^6)	5.49 ± 0.34	6.23 ± 0.72	5.35 ± 0.90	4.91 ± 0.42
Metarubricytes (10^6)	2.03 ± 0.24	2.01 ± 0.33	2.02 ± 0.58	1.63 ± 0.28
Myeloblasts (10^6)	0.32 ± 0.05	0.32 ± 0.05	0.37 ± 0.04	0.23 ± 0.04
Promyelocytes (10^6)	0.41 ± 0.07	0.51 ± 0.10	0.46 ± 0.06	0.31 ± 0.07
Neutrophilic myelocytes (10^6)	0.97 ± 0.12	0.72 ± 0.14	0.96 ± 0.12	0.80 ± 0.14
Neutrophilic metamyelocytes (10^6)	1.44 ± 0.27	1.61 ± 0.24	1.52 ± 0.26	1.61 ± 0.28
Neutrophilic bands (10^6)	2.98 ± 0.52	2.56 ± 0.51	2.97 ± 0.52	1.86 ± 0.33
Neutrophilic segments (10^6)	7.74 ± 0.93	9.19 ± 0.67	8.85 ± 0.77	6.86 ± 1.14
Eosinophilic myelocytes (10^6)	0.015 ± 0.011	0.017 ± 0.017	0.037 ± 0.019	0.026 ± 0.018
Eosinophilic metamyelocytes (10^6)	0.04 ± 0.01	0.04 ± 0.02	0.02 ± 0.02	0.06 ± 0.03
Eosinophilic bands (10^6)	0.14 ± 0.04	0.23 ± 0.06	0.12 ± 0.03	0.27 ± 0.06
Eosinophilic segments (10^6)	0.27 ± 0.05	0.27 ± 0.04	0.26 ± 0.06	0.32 ± 0.07
Basophilic myelocytes (10^6)	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000
Basophilic metamyelocytes (10^6)	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000
Basophilic bands (10^6)	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000
Basophilic segments (10^6)	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000
Bone marrow lymphocytes (10^6)	2.44 ± 0.34	2.50 ± 0.37	2.64 ± 0.75	2.29 ± 0.42
Bone marrow macrophages (10^6)	0.20 ± 0.04	0.16 ± 0.03	0.20 ± 0.08	0.19 ± 0.05
Bone marrow monocytes (10^6)	0.31 ± 0.06	0.27 ± 0.04	0.32 ± 0.10	0.27 ± 0.06
Megakaryo cells (10^6)	0.14 ± 0.03	0.13 ± 0.02	0.15 ± 0.04	0.12 ± 0.04
Plasma cells (10^6)	0.40 ± 0.07	0.68 ± 0.13	0.71 ± 0.19	0.57 ± 0.15
Mitotic figures (10^6)	0.21 ± 0.05	0.32 ± 0.05	0.18 ± 0.04	0.19 ± 0.04
Fat cells (10^6)	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000
Mast cells (10^6)	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000
Smudge cells (10^6)	2.25 ± 0.34	2.11 ± 0.17	1.97 ± 0.41	1.99 ± 0.34
Osteoblasts (10^6)	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000
Osteoclasts (10^6)	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000
Other bone marrow cells (10^6)	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000
Neutrophilic hypersegments (10^6)	0.02 ± 0.01	0.05 ± 0.02	0.04 ± 0.02	0.02 ± 0.01

* Significantly different ($P \le 0.05$) from the control group by Dunn's or Shirley's test
** $P \le 0.01$
[a] Mean ± standard error. Statistical tests were performed on unrounded data.
[b] n = 9
[c] n = 10

TABLE K4
Hematology and Bone Marrow Data for Mice in the 2-Year Gavage Study of AZT/500 U α-Interferon A/D[a]

	Vehicle Control	30 mg AZT/kg + 500 U α-IFN A/D	60 mg AZT/kg + 500 U α-IFN A/D	120 mg AZT/kg + 500 U α-IFN A/D
Male				
Hematology				
Clinical Pathology Groups				
n				
Week 14	10	10	10	10
Week 27	10	10	10	10
Week 40	10	10	9	10
Week 54	9	8	8	7
Week 65	10	10	9	10
Week 79	10	10	7	8
Hematocrit (%)				
Week 14	46.0 ± 0.6	43.5 ± 0.3**	44.2 ± 0.3	43.7 ± 0.5*
Week 27	44.9 ± 0.7	44.0 ± 0.5	42.6 ± 1.3	42.7 ± 0.6
Week 40	44.9 ± 0.8	42.7 ± 1.0	44.3 ± 0.6	43.7 ± 0.8
Week 54	44.2 ± 0.5	42.3 ± 0.9	43.7 ± 0.6	40.8 ± 0.8*
Week 65	43.1 ± 0.8	42.2 ± 0.6	41.5 ± 0.5	38.8 ± 1.2**
Week 79	41.3 ± 2.1	35.8 ± 2.1	37.5 ± 1.4	38.1 ± 1.0
Hemoglobin (g/dL)				
Week 14	15.5 ± 0.2	14.7 ± 0.1**	14.9 ± 0.1**	14.7 ± 0.1**
Week 27	15.1 ± 0.3	14.7 ± 0.2	14.2 ± 0.4	14.2 ± 0.2
Week 40	14.7 ± 0.3	13.8 ± 0.4	14.5 ± 0.2	14.3 ± 0.3
Week 54	14.6 ± 0.2	13.8 ± 0.3	14.5 ± 0.3	13.4 ± 0.3*
Week 65	14.3 ± 0.3	13.8 ± 0.2	13.8 ± 0.2	12.6 ± 0.5**
Week 79	13.8 ± 0.7	12.0 ± 0.7	12.5 ± 0.6	12.6 ± 0.4
Erythrocytes (10^6/μL)				
Week 14	9.99 ± 0.10	9.22 ± 0.04**	9.20 ± 0.06**	8.92 ± 0.10**
Week 27	9.82 ± 0.17	9.25 ± 0.10**	8.96 ± 0.21**	8.84 ± 0.13**
Week 40	9.69 ± 0.13	9.09 ± 0.23*	8.90 ± 0.14**	8.71 ± 0.11**
Week 54	9.13 ± 0.13	8.70 ± 0.18	8.53 ± 0.10**	7.98 ± 0.17**
Week 65	9.01 ± 0.21	8.55 ± 0.15*	8.38 ± 0.09*	7.51 ± 0.36**
Week 79	9.18 ± 0.68	7.43 ± 0.53	7.42 ± 0.45	7.59 ± 0.20
Reticulocytes (10^6/μL)				
Week 14	0.23 ± 0.01	0.22 ± 0.02	0.25 ± 0.01	0.23 ± 0.01
Week 27	0.19 ± 0.02	0.19 ± 0.01	0.21 ± 0.02	0.20 ± 0.02
Week 40	0.26 ± 0.03	0.32 ± 0.05	0.25 ± 0.04	0.24 ± 0.02
Week 54	0.18 ± 0.02	0.18 ± 0.02	0.13 ± 0.01	0.17 ± 0.01
Week 65	0.43 ± 0.04	0.40 ± 0.03	0.41 ± 0.04	0.47 ± 0.06
Week 79	0.25 ± 0.03	0.31 ± 0.03	0.29 ± 0.11	0.25 ± 0.03
Nucleated erythrocytes (10^3/μL)				
Week 14	0.00 ± 0.00	0.01 ± 0.01	0.00 ± 0.00	0.00 ± 0.00
Week 27	0.00 ± 0.00	0.02 ± 0.02	0.02 ± 0.02	0.01 ± 0.01
Week 40	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00
Week 54	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00
Week 65	0.00 ± 0.00	0.00 ± 0.00[b]	0.00 ± 0.00	0.00 ± 0.00
Week 79	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00
Mean cell volume (fL)				
Week 14	46.0 ± 0.3	47.2 ± 0.2**	48.1 ± 0.2**	49.0 ± 0.3**
Week 27	45.8 ± 0.2	47.6 ± 0.3**	47.5 ± 0.5**	48.3 ± 0.4**
Week 40	46.3 ± 0.6	47.0 ± 0.5	49.8 ± 0.6**	50.2 ± 0.6**
Week 54	48.5 ± 0.8	48.6 ± 0.5	51.2 ± 0.4**	51.1 ± 0.5*
Week 65	47.9 ± 0.6	49.4 ± 0.4	49.4 ± 0.4	52.3 ± 1.5**
Week 79	45.6 ± 1.1	48.7 ± 1.4	51.1 ± 1.9**	50.1 ± 0.6**

TABLE K4
Hematology and Bone Marrow Data for Mice in the 2-Year Gavage Study of AZT/500 U α-Interferon A/D

	Vehicle Control	30 mg AZT/kg + 500 U α-IFN A/D	60 mg AZT/kg + 500 U α-IFN A/D	120 mg AZT/kg + 500 U α-IFN A/D
Male (continued)				
Hematology (continued)				
Clinical Pathology Groups (continued)				
n				
Week 14	10	10	10	10
Week 27	10	10	10	10
Week 40	10	10	9	10
Week 54	9	8	8	7
Week 65	10	10	9	10
Week 79	10	10	7	8
Mean cell hemoglobin (pg)				
Week 14	15.5 ± 0.0	16.0 ± 0.1**	16.2 ± 0.1**	16.5 ± 0.1**
Week 27	15.3 ± 0.1	15.9 ± 0.1**	15.9 ± 0.2*	16.0 ± 0.1**
Week 40	15.2 ± 0.2	15.2 ± 0.2	16.3 ± 0.3*	16.4 ± 0.2**
Week 54	16.0 ± 0.3	15.9 ± 0.2	17.0 ± 0.2*	16.7 ± 0.2
Week 65	15.9 ± 0.2	16.1 ± 0.2	16.5 ± 0.1*	16.9 ± 0.3**
Week 79	15.3 ± 0.4	16.3 ± 0.5	17.0 ± 0.4**	16.6 ± 0.3*
Mean cell hemoglobin concentration (g/dL)				
Week 14	33.7 ± 0.2	33.9 ± 0.1	33.6 ± 0.1	33.7 ± 0.1
Week 27	33.5 ± 0.2	33.5 ± 0.1	33.4 ± 0.1	33.2 ± 0.1
Week 40	32.8 ± 0.2	32.4 ± 0.4	32.7 ± 0.2	32.7 ± 0.2
Week 54	33.0 ± 0.1	32.7 ± 0.3	33.3 ± 0.2	32.7 ± 0.2
Week 65	33.2 ± 0.2	32.7 ± 0.2	33.4 ± 0.2	32.4 ± 0.3
Week 79	33.5 ± 0.3	33.5 ± 0.2	33.3 ± 0.5	33.2 ± 0.3
Platelets (10^3/μL)				
Week 14	1,239.1 ± 31.8	1,299.1 ± 41.8	1,364.0 ± 50.4	1,361.7 ± 28.0
Week 27	1,278.3 ± 57.6	1,288.6 ± 57.6	1,303.1 ± 113.9	1,419.9 ± 59.2
Week 40	1,374.1 ± 58.4	1,420.6 ± 78.2	1,481.4 ± 86.9	1,411.6 ± 78.1
Week 54	1,303.6 ± 109.2	1,444.6 ± 71.0	1,363.8 ± 45.7	1,548.4 ± 60.7
Week 65	1,689.4 ± 89.2	1,749.2 ± 93.6	1,843.7 ± 126.4	1,790.4 ± 172.3
Week 79	1,435.9 ± 111.9	1,403.8 ± 68.7	1,804.1 ± 69.8*	1,843.1 ± 79.0*
Leukocytes (10^3/μL)				
Week 14	7.77 ± 0.35	8.37 ± 0.36	7.64 ± 0.16	7.65 ± 0.54
Week 27	8.70 ± 0.56	8.17 ± 0.32	8.45 ± 0.53	9.99 ± 0.41
Week 40	9.67 ± 0.69	10.89 ± 0.74	9.08 ± 0.63	8.56 ± 0.63
Week 54	10.92 ± 1.16	12.26 ± 0.56	9.01 ± 1.23	12.37 ± 1.06
Week 65	10.86 ± 0.88	11.05 ± 0.59	10.36 ± 0.67	11.60 ± 0.97
Week 79	12.26 ± 0.94	14.72 ± 0.57	10.02 ± 0.86	11.36 ± 1.77
Segmented neutrophils (10^3/μL)				
Week 14	1.16 ± 0.08	1.38 ± 0.11	1.34 ± 0.11	1.06 ± 0.12
Week 27	2.10 ± 0.36	1.60 ± 0.13	1.65 ± 0.29	2.31 ± 0.16
Week 40	2.25 ± 0.20	2.77 ± 0.29	1.89 ± 0.19	1.93 ± 0.24
Week 54	3.14 ± 0.52	2.39 ± 0.33	2.60 ± 0.53	2.62 ± 0.27
Week 65	2.52 ± 0.26	2.54 ± 0.24[b]	2.47 ± 0.24	2.38 ± 0.25
Week 79	3.43 ± 0.44	3.82 ± 0.33	2.73 ± 0.26	2.83 ± 0.53
Lymphocytes (10^3/μL)				
Week 14	6.50 ± 0.30	6.84 ± 0.25	6.16 ± 0.14	6.48 ± 0.44
Week 27	6.32 ± 0.38	6.31 ± 0.33	6.50 ± 0.31	7.23 ± 0.31
Week 40	6.85 ± 0.50	7.31 ± 0.49	6.59 ± 0.40	6.26 ± 0.40
Week 54	7.37 ± 0.75	9.62 ± 0.57	6.22 ± 0.83	9.51 ± 0.93
Week 65	7.81 ± 0.65	8.18 ± 0.50[b]	7.38 ± 0.68	8.76 ± 0.78
Week 79	7.86 ± 0.59	9.67 ± 0.81	6.77 ± 0.67	7.92 ± 1.15

TABLE K4
Hematology and Bone Marrow Data for Mice in the 2-Year Gavage Study of AZT/500 U α-Interferon A/D

	Vehicle Control	30 mg AZT/kg + 500 U α-IFN A/D	60 mg AZT/kg + 500 U α-IFN A/D	120 mg AZT/kg + 500 U α-IFN A/D
Male (continued)				
Hematology (continued)				
Clinical Pathology Groups (continued)				
n				
Week 14	10	10	10	10
Week 27	10	10	10	10
Week 40	10	10	9	10
Week 54	9	8	8	7
Week 65	10	10	9	10
Week 79	10	10	7	8
Atypical lymphocytes (10^3/μL)				
Week 14	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00
Week 27	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00
Week 40	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00
Week 54	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00
Week 65	0.00 ± 0.00	0.00 ± 0.00[b]	0.00 ± 0.00	0.00 ± 0.00
Week 79	0.12 ± 0.04	0.12 ± 0.04	0.03 ± 0.02	0.04 ± 0.04
Monocytes (10^3/μL)				
Week 14	0.06 ± 0.02	0.06 ± 0.02	0.10 ± 0.02	0.07 ± 0.02
Week 27	0.08 ± 0.02	0.03 ± 0.02	0.07 ± 0.02	0.14 ± 0.03
Week 40	0.39 ± 0.11	0.58 ± 0.14	0.42 ± 0.14	0.21 ± 0.06
Week 54	0.33 ± 0.11	0.17 ± 0.06	0.16 ± 0.07	0.17 ± 0.10
Week 65	0.39 ± 0.07	0.42 ± 0.10[b]	0.38 ± 0.06	0.31 ± 0.05
Week 79	0.55 ± 0.16	0.69 ± 0.24	0.29 ± 0.05	0.37 ± 0.05
Eosinophils (10^3/μL)				
Week 14	0.05 ± 0.02	0.09 ± 0.03	0.05 ± 0.02	0.04 ± 0.02
Week 27	0.22 ± 0.06	0.23 ± 0.04	0.23 ± 0.04	0.31 ± 0.06
Week 40	0.17 ± 0.06	0.23 ± 0.04	0.19 ± 0.04	0.17 ± 0.07
Week 54	0.09 ± 0.04	0.08 ± 0.03	0.04 ± 0.02	0.07 ± 0.04
Week 65	0.15 ± 0.07	0.06 ± 0.03[b]	0.12 ± 0.05	0.16 ± 0.05
Week 79	0.20 ± 0.07	0.16 ± 0.04	0.14 ± 0.04	0.16 ± 0.07
Core Groups				
n	10	10	10	10
Hematocrit (%)	40.1 ± 1.4	39.2 ± 2.2	41.4 ± 2.9	37.5 ± 1.1
Hemoglobin (g/dL)	13.6 ± 0.5	13.0 ± 0.8	13.8 ± 1.0	12.5 ± 0.3
Erythrocytes (10^6/μL)	8.82 ± 0.35	7.97 ± 0.55	8.38 ± 0.59	7.35 ± 0.27*
Reticulocytes (10^6/μL)	0.31 ± 0.02	0.31 ± 0.04	0.36 ± 0.03	0.29 ± 0.02
Nucleated erythrocytes (10^3/μL)	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00[b]	0.00 ± 0.00
Mean cell volume (fL)	45.6 ± 0.6	49.6 ± 1.2**	49.7 ± 1.6**	51.2 ± 0.7**
Mean cell hemoglobin (pg)	15.5 ± 0.2	16.5 ± 0.4*	16.6 ± 0.5*	17.1 ± 0.3**
Mean cell hemoglobin concentration (g/dL)	33.9 ± 0.3	33.2 ± 0.3	33.5 ± 0.2	33.4 ± 0.2
Platelets (10^3/μL)	1,672.9 ± 89.3	1,881.4 ± 222.0	1,940.2 ± 146.2	2,138.9 ± 167.8
Leukocytes (10^3/μL)	14.65 ± 1.58	17.00 ± 1.20	10.84 ± 0.58[b]	13.10 ± 1.18
Segmented neutrophils (10^3/μL)	3.64 ± 0.39	4.44 ± 0.72	2.68 ± 0.18[b]	2.78 ± 0.17
Lymphocytes (10^3/μL)	6.44 ± 0.71	7.62 ± 1.17	4.88 ± 0.48[b]	6.49 ± 0.64
Atypical lymphocytes (10^3/μL)	3.61 ± 0.66	3.85 ± 0.40	2.60 ± 0.30[b]	3.20 ± 0.51
Monocytes (10^3/μL)	0.88 ± 0.19	0.92 ± 0.13	0.55 ± 0.09[b]	0.45 ± 0.10
Eosinophils (10^3/μL)	0.09 ± 0.02	0.18 ± 0.05	0.14 ± 0.03[b]	0.19 ± 0.05

TABLE K4
Hematology and Bone Marrow Data for Mice in the 2-Year Gavage Study of AZT/500 U α-Interferon A/D

	Vehicle Control	30 mg AZT/kg + 500 U α-IFN A/D	60 mg AZT/kg + 500 U α-IFN A/D	120 mg AZT/kg + 500 U α-IFN A/D
Male (continued)				
Bone Marrow Analyses				
Clinical Pathology Groups				
n				
Week 54	10	10	10	10
Week 65	10	10	9	10
Week 79	9	10	7	7
Total femoral count (10^6/femur)				
Week 54	30.9 ± 1.6	27.9 ± 1.0	27.9 ± 1.1	30.5 ± 0.8
Week 65	31.2 ± 2.4	34.8 ± 0.8	34.5 ± 1.2	34.8 ± 1.3
Week 79	27.8 ± 1.8	26.6 ± 1.9	30.1 ± 1.7	28.9 ± 1.0
M:E ratio				
Week 54	2.68 ± 0.37	2.12 ± 0.06	2.90 ± 0.17	3.37 ± 0.43
Week 65	3.00 ± 0.26	2.64 ± 0.25	3.20 ± 0.36	2.77 ± 0.23
Week 79	2.37 ± 0.34	3.92 ± 0.37**	2.89 ± 0.30	2.24 ± 0.27
Rubriblasts (10^6)				
Week 54	0.42 ± 0.06	0.36 ± 0.03	0.42 ± 0.05	0.42 ± 0.05
Week 65	0.31 ± 0.05	0.34 ± 0.04	0.33 ± 0.07	0.28 ± 0.05
Week 79	0.32 ± 0.03	0.32 ± 0.07	0.43 ± 0.10	0.30 ± 0.05
Prorubricytes (10^6)				
Week 54	0.79 ± 0.13	0.76 ± 0.05	0.73 ± 0.08	1.11 ± 0.17
Week 65	1.05 ± 0.16	1.41 ± 0.23	1.30 ± 0.24	1.56 ± 0.11
Week 79	1.19 ± 0.16	0.77 ± 0.11	1.10 ± 0.14	1.27 ± 0.13
Rubricytes (10^6)				
Week 54	3.95 ± 0.45	4.27 ± 0.20	3.14 ± 0.21	2.98 ± 0.28
Week 65	3.80 ± 0.35	4.58 ± 0.37	4.07 ± 0.40	4.49 ± 0.46
Week 79	3.74 ± 0.45	2.33 ± 0.12*	3.78 ± 0.46	4.16 ± 0.45
Metarubricytes (10^6)				
Week 54	1.37 ± 0.17	1.04 ± 0.12	0.90 ± 0.12*	0.52 ± 0.05**
Week 65	0.72 ± 0.16	1.03 ± 0.20	0.70 ± 0.12	0.69 ± 0.11
Week 79	1.11 ± 0.15	0.60 ± 0.12*	0.61 ± 0.06*	0.75 ± 0.19
Myeloblasts (10^6)				
Week 54	0.61 ± 0.09	0.47 ± 0.04	0.66 ± 0.10	0.82 ± 0.12
Week 65	0.63 ± 0.11	0.77 ± 0.10	0.76 ± 0.15	0.69 ± 0.06
Week 79	0.40 ± 0.06	0.53 ± 0.07	0.59 ± 0.07	0.38 ± 0.03
Promyelocytes (10^6)				
Week 54	0.84 ± 0.15	0.94 ± 0.07	0.77 ± 0.15	1.06 ± 0.14
Week 65	0.94 ± 0.14	1.13 ± 0.10	1.05 ± 0.11	1.20 ± 0.13
Week 79	0.59 ± 0.11	0.45 ± 0.03	0.77 ± 0.10	0.45 ± 0.08
Neutrophilic myelocytes (10^6)				
Week 54	1.02 ± 0.21	0.68 ± 0.06	1.35 ± 0.21	1.36 ± 0.12
Week 65	1.39 ± 0.19	1.88 ± 0.25	1.69 ± 0.16	2.04 ± 0.19
Week 79	1.47 ± 0.28	0.96 ± 0.13	1.43 ± 0.11	1.24 ± 0.13
Neutrophilic metamyelocytes (10^6)				
Week 54	1.45 ± 0.11	1.31 ± 0.09	1.23 ± 0.12	0.98 ± 0.10**
Week 65	2.30 ± 0.43	1.93 ± 0.12	2.01 ± 0.24	2.09 ± 0.23
Week 79	1.74 ± 0.46	1.03 ± 0.07	1.74 ± 0.14	1.48 ± 0.15
Neutrophilic bands (10^6)				
Week 54	2.04 ± 0.31	2.74 ± 0.26	1.71 ± 0.19	2.26 ± 0.15
Week 65	3.20 ± 0.34	3.25 ± 0.26	4.07 ± 0.38	4.03 ± 0.58
Week 79	3.54 ± 0.35	5.26 ± 0.63*	4.57 ± 0.38	4.01 ± 0.33

TABLE K4
Hematology and Bone Marrow Data for Mice in the 2-Year Gavage Study of AZT/500 U α-Interferon A/D

	Vehicle Control	30 mg AZT/kg + 500 U α-IFN A/D	60 mg AZT/kg + 500 U α-IFN A/D	120 mg AZT/kg + 500 U α-IFN A/D
Male (continued)				
Bone Marrow Analyses (continued)				
Clinical Pathology Groups (continued)				
n				
Week 54	10	10	10	10
Week 65	10	10	9	10
Week 79	9	10	7	7
Neutrophilic segments (10^6)				
Week 54	9.24 ± 0.61	6.87 ± 0.42*	8.68 ± 0.84	8.30 ± 0.76
Week 65	7.24 ± 0.47	8.58 ± 0.36	8.47 ± 0.81	7.73 ± 0.63
Week 79	5.81 ± 0.48	6.60 ± 0.64	6.46 ± 0.71	5.41 ± 0.40
Eosinophilic myelocytes (10^6)				
Week 54	0.046 ± 0.032	0.096 ± 0.037	0.036 ± 0.014	0.058 ± 0.019
Week 65	0.053 ± 0.020	0.045 ± 0.022	0.079 ± 0.028	0.079 ± 0.021
Week 79	0.024 ± 0.013	0.013 ± 0.009	0.021 ± 0.014	0.041 ± 0.016
Eosinophilic metamyelocytes (10^6)				
Week 54	0.05 ± 0.02	0.09 ± 0.03	0.07 ± 0.02	0.17 ± 0.04*
Week 65	0.17 ± 0.02	0.16 ± 0.03	0.12 ± 0.03	0.13 ± 0.04
Week 79	0.06 ± 0.02	0.07 ± 0.02	0.12 ± 0.03	0.13 ± 0.01
Eosinophilic bands (10^6)				
Week 54	0.20 ± 0.05	0.15 ± 0.03	0.09 ± 0.02	0.21 ± 0.03
Week 65	0.26 ± 0.04	0.30 ± 0.04	0.24 ± 0.05	0.29 ± 0.04
Week 79	0.26 ± 0.04	0.25 ± 0.05	0.24 ± 0.06	0.23 ± 0.03
Eosinophilic segments (10^6)				
Week 54	0.28 ± 0.04	0.20 ± 0.03	0.35 ± 0.05	0.26 ± 0.05
Week 65	0.26 ± 0.05	0.25 ± 0.05	0.26 ± 0.08	0.22 ± 0.05
Week 79	0.16 ± 0.03	0.31 ± 0.07	0.24 ± 0.04	0.23 ± 0.04
Basophilic myelocytes (10^6)				
Week 54	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000
Week 65	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000
Week 79	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000
Basophilic metamyelocytes (10^6)				
Week 54	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000
Week 65	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000
Week 79	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000
Basophilic bands (10^6)				
Week 54	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000
Week 65	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000
Week 79	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000
Basophilic segments (10^6)				
Week 54	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000
Week 65	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000
Week 79	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000
Bone marrow lymphocytes (10^6)				
Week 54	4.08 ± 0.58	2.94 ± 0.16	3.75 ± 0.35	5.29 ± 0.74
Week 65	4.33 ± 0.39	4.31 ± 0.38	4.02 ± 0.43	4.43 ± 0.58
Week 79	3.73 ± 0.42	3.25 ± 0.37	3.95 ± 0.46	4.25 ± 0.34
Bone marrow macrophages (10^6)				
Week 54	0.16 ± 0.04	0.13 ± 0.02	0.09 ± 0.02	0.15 ± 0.03
Week 65	0.13 ± 0.03	0.07 ± 0.03	0.13 ± 0.03	0.13 ± 0.02
Week 79	0.20 ± 0.03	0.11 ± 0.04*	0.13 ± 0.01	0.26 ± 0.04

TABLE K4
Hematology and Bone Marrow Data for Mice in the 2-Year Gavage Study of AZT/500 U α-Interferon A/D

	Vehicle Control	30 mg AZT/kg + 500 U α-IFN A/D	60 mg AZT/kg + 500 U α-IFN A/D	120 mg AZT/kg + 500 U α-IFN A/D
Male (continued)				
Bone Marrow Analyses (continued)				
Clinical Pathology Groups (continued)				
n				
Week 54	10	10	10	10
Week 65	10	10	9	10
Week 79	9	10	7	7
Bone marrow monocytes (10^6)				
Week 54	0.29 ± 0.05	0.25 ± 0.03	0.20 ± 0.04	0.27 ± 0.03
Week 65	0.27 ± 0.09	0.21 ± 0.03	0.23 ± 0.04	0.14 ± 0.04
Week 79	0.30 ± 0.05	0.22 ± 0.06	0.21 ± 0.04	0.33 ± 0.04
Megakaryo cells (10^6)				
Week 54	0.08 ± 0.03	0.14 ± 0.04	0.06 ± 0.01	0.12 ± 0.03
Week 65	0.03 ± 0.01	0.02 ± 0.01	0.04 ± 0.02	0.05 ± 0.01
Week 79	0.06 ± 0.02	0.06 ± 0.02	0.12 ± 0.01	0.06 ± 0.02
Plasma cells (10^6)				
Week 54	0.18 ± 0.04	0.25 ± 0.03	0.27 ± 0.02	0.28 ± 0.05
Week 65	0.18 ± 0.04	0.19 ± 0.06	0.36 ± 0.09	0.35 ± 0.10
Week 79	0.35 ± 0.07	0.54 ± 0.15	0.38 ± 0.07	0.24 ± 0.02
Mitotic figures (10^6)				
Week 54	0.25 ± 0.04	0.16 ± 0.02	0.24 ± 0.03	0.28 ± 0.05
Week 65	0.26 ± 0.04	0.32 ± 0.03	0.26 ± 0.07	0.29 ± 0.04
Week 79	0.35 ± 0.04	0.25 ± 0.03	0.41 ± 0.06	0.30 ± 0.03
Fat cells (10^6)				
Week 54	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000
Week 65	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000
Week 79	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000
Mast cells (10^6)				
Week 54	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000
Week 65	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000
Week 79	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000
Smudge cells (10^6)				
Week 54	3.60 ± 0.25	4.06 ± 0.15	3.13 ± 0.25	3.56 ± 0.23
Week 65	3.70 ± 0.32	4.02 ± 0.37	4.32 ± 0.27	3.94 ± 0.25
Week 79	2.44 ± 0.25	2.69 ± 0.23	2.82 ± 0.26	3.34 ± 0.26
Osteoblasts (10^6)				
Week 54	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000
Week 65	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000
Week 79	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000
Osteoclasts (10^6)				
Week 54	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000
Week 65	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000
Week 79	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000
Other bone marrow cells (10^6)				
Week 54	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000
Week 65	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000
Week 79	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000
Neutrophilic hypersegments (10^6)				
Week 54	0.08 ± 0.03	0.13 ± 0.02	0.19 ± 0.05	0.19 ± 0.04
Week 65	0.67 ± 0.18	1.09 ± 0.27	1.20 ± 0.22	0.78 ± 0.12
Week 79	0.32 ± 0.10	0.31 ± 0.06	0.39 ± 0.19	0.30 ± 0.08

TABLE K4
Hematology and Bone Marrow Data for Mice in the 2-Year Gavage Study of AZT/500 U α-Interferon A/D

	Vehicle Control	30 mg AZT/kg + 500 U α-IFN A/D	60 mg AZT/kg + 500 U α-IFN A/D	120 mg AZT/kg + 500 U α-IFN A/D
Male (continued)				
Bone Marrow Analyses (continued)				
Core Groups				
n	10	9	10	10
Total femoral count (10^6/femur)	33.5 ± 2.4	35.4 ± 2.3	33.9 ± 1.6	34.5 ± 1.7
M:E ratio	4.33 ± 0.75	4.99 ± 0.60	3.30 ± 0.39	4.36 ± 0.56
Rubriblasts (10^6)	0.31 ± 0.05	0.23 ± 0.06	0.30 ± 0.06	0.27 ± 0.05
Prorubricytes (10^6)	0.62 ± 0.13	0.57 ± 0.09	0.93 ± 0.16	0.80 ± 0.21
Rubricytes (10^6)	3.16 ± 0.40	2.98 ± 0.42	3.42 ± 0.31	3.34 ± 0.46
Metarubricytes (10^6)	0.48 ± 0.10	0.58 ± 0.24	0.67 ± 0.10	0.62 ± 0.14
Myeloblasts (10^6)	0.62 ± 0.08	0.61 ± 0.11	0.49 ± 0.10	0.51 ± 0.10
Promyelocytes (10^6)	0.70 ± 0.11	0.62 ± 0.10	0.66 ± 0.10	0.69 ± 0.10
Neutrophilic myelocytes (10^6)	1.49 ± 0.28	1.67 ± 0.17	1.53 ± 0.15	1.65 ± 0.15
Neutrophilic metamyelocytes (10^6)	1.82 ± 0.23	2.01 ± 0.23	1.20 ± 0.14*	1.44 ± 0.15
Neutrophilic bands (10^6)	2.93 ± 0.40	2.34 ± 0.40	2.76 ± 0.27	3.08 ± 0.37
Neutrophilic segments (10^6)	9.53 ± 0.87	11.30 ± 1.18	9.22 ± 1.18	11.23 ± 0.84
Eosinophilic myelocytes (10^6)	0.071 ± 0.025	0.024 ± 0.012	0.057 ± 0.021	0.070 ± 0.030
Eosinophilic metamyelocytes (10^6)	0.06 ± 0.02	0.04 ± 0.02	0.05 ± 0.02	0.09 ± 0.02
Eosinophilic bands (10^6)	0.14 ± 0.05	0.17 ± 0.03	0.17 ± 0.03	0.13 ± 0.03
Eosinophilic segments (10^6)	0.23 ± 0.05	0.25 ± 0.07	0.24 ± 0.05	0.23 ± 0.05
Basophilic myelocytes (10^6)	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000
Basophilic metamyelocytes (10^6)	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000
Basophilic bands (10^6)	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000
Basophilic segments (10^6)	0.006 ± 0.006	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000
Bone marrow lymphocytes (10^6)	5.08 ± 1.06	5.17 ± 1.08	5.80 ± 1.12	3.72 ± 0.38
Bone marrow macrophages (10^6)	0.19 ± 0.04	0.11 ± 0.04	0.19 ± 0.05	0.18 ± 0.04
Bone marrow monocytes (10^6)	0.33 ± 0.05	0.30 ± 0.07	0.30 ± 0.06	0.23 ± 0.04
Megakaryo cells (10^6)	0.07 ± 0.02	0.07 ± 0.03	0.05 ± 0.02	0.09 ± 0.04
Plasma cells (10^6)	0.52 ± 0.13	0.38 ± 0.05	0.46 ± 0.13	0.53 ± 0.08
Mitotic figures (10^6)	0.21 ± 0.04	0.22 ± 0.03	0.22 ± 0.04	0.31 ± 0.06
Fat cells (10^6)	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000
Mast cells (10^6)	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.036 ± 0.036
Smudge cells (10^6)	4.95 ± 0.42	5.76 ± 0.44	5.20 ± 0.49	5.26 ± 0.47
Osteoblasts (10^6)	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000
Osteoclasts (10^6)	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000
Other bone marrow cells (10^6)	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000
Neutrophilic hypersegments (10^6)	0.03 ± 0.02	0.27 ± 0.17	0.41 ± 0.14	0.15 ± 0.08

TABLE K4
Hematology and Bone Marrow Data for Mice in the 2-Year Gavage Study of AZT/500 U α-Interferon A/D

	Vehicle Control	30 mg AZT/kg + 500 U α-IFN A/D	60 mg AZT/kg + 500 U α-IFN A/D	120 mg AZT/kg + 500 U α-IFN A/D
Female				
Hematology				
Clinical Pathology Groups				
n				
Week 14	9	9	10	10
Week 27	9	10	10	10
Week 40	9	10	10	9
Week 54	8	9	10	10
Week 65	9	10	10	9
Week 79	10	10	9	9
Hematocrit (%)				
Week 14	44.3 ± 0.8	44.5 ± 0.4	44.1 ± 0.3	44.3 ± 0.4
Week 27	45.3 ± 0.4	44.2 ± 0.4	44.4 ± 0.4	44.5 ± 0.4
Week 40	46.5 ± 0.5	45.2 ± 0.4	45.4 ± 0.4	43.6 ± 0.4**
Week 54	48.8 ± 0.6	47.5 ± 0.3	46.6 ± 0.2**	47.0 ± 0.6*
Week 65	46.2 ± 0.4	46.0 ± 0.4	44.9 ± 0.6	43.6 ± 0.5**
Week 79	43.5 ± 0.6	42.9 ± 0.5	42.6 ± 0.6	41.2 ± 1.1
Hemoglobin (g/dL)				
Week 14	15.0 ± 0.2	15.1 ± 0.1	14.8 ± 0.1	14.9 ± 0.1
Week 27	15.1 ± 0.1	14.7 ± 0.1	14.6 ± 0.1	14.6 ± 0.1
Week 40	15.6 ± 0.2	15.2 ± 0.1*	15.2 ± 0.1	14.7 ± 0.1**
Week 54	16.4 ± 0.2	15.9 ± 0.1	15.5 ± 0.1**	15.5 ± 0.2**
Week 65	15.5 ± 0.2	15.4 ± 0.2	14.9 ± 0.2*	14.6 ± 0.2**
Week 79	14.7 ± 0.2	14.3 ± 0.2	14.3 ± 0.2	13.7 ± 0.4*
Erythrocytes (10^6/μL)				
Week 14	9.56 ± 0.17	9.31 ± 0.07*	9.00 ± 0.07**	8.92 ± 0.07**
Week 27	9.78 ± 0.09	9.18 ± 0.09**	8.96 ± 0.11**	8.88 ± 0.11**
Week 40	9.60 ± 0.12	8.98 ± 0.07**	8.87 ± 0.09**	8.40 ± 0.07**
Week 54	9.76 ± 0.15	9.07 ± 0.06**	8.78 ± 0.09**	8.70 ± 0.10**
Week 65	9.51 ± 0.09	8.86 ± 0.09**	8.60 ± 0.11**	8.17 ± 0.11**
Week 79	9.25 ± 0.11	8.89 ± 0.16	8.61 ± 0.09**	8.07 ± 0.21**
Reticulocytes (10^6/μL)				
Week 14	0.22 ± 0.03	0.28 ± 0.02	0.31 ± 0.02*	0.32 ± 0.02*
Week 27	0.29 ± 0.02	0.28 ± 0.02	0.30 ± 0.01	0.31 ± 0.01
Week 40	0.27 ± 0.02	0.17 ± 0.02*	0.14 ± 0.01**	0.15 ± 0.01**
Week 54	0.12 ± 0.01	0.13 ± 0.02	0.15 ± 0.02	0.11 ± 0.01
Week 65	0.18 ± 0.03	0.13 ± 0.02	0.13 ± 0.02	0.15 ± 0.03
Week 79	0.21 ± 0.02	0.18 ± 0.04[b]	0.26 ± 0.03	0.19 ± 0.03
Nucleated erythrocytes (10^3/μL)				
Week 14	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00
Week 27	0.00 ± 0.00	0.00 ± 0.00	0.01 ± 0.01	0.00 ± 0.00
Week 40	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00
Week 54	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00
Week 65	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00
Week 79	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00
Mean cell volume (fL)				
Week 14	46.4 ± 0.3	47.8 ± 0.2**	49.1 ± 0.2**	49.7 ± 0.1**
Week 27	46.4 ± 0.2	48.1 ± 0.2**	49.6 ± 0.3**	50.1 ± 0.3**
Week 40	48.4 ± 0.2	50.3 ± 0.2**	51.1 ± 0.2**	51.9 ± 0.4**
Week 54	50.0 ± 0.4	52.4 ± 0.2**	53.1 ± 0.3**	54.0 ± 0.3**
Week 65	48.6 ± 0.3	51.9 ± 0.4**	52.3 ± 0.8**	53.3 ± 0.4**
Week 79	47.0 ± 0.4	48.3 ± 0.7	49.5 ± 0.5**	51.1 ± 0.4**

TABLE K4
Hematology and Bone Marrow Data for Mice in the 2-Year Gavage Study of AZT/500 U α-Interferon A/D

	Vehicle Control	30 mg AZT/kg + 500 U α-IFN A/D	60 mg AZT/kg + 500 U α-IFN A/D	120 mg AZT/kg + 500 U α-IFN A/D
Female (continued)				
Hematology (continued)				
Clinical Pathology Groups (continued)				
n				
Week 14	9	9	10	10
Week 27	9	10	10	10
Week 40	9	10	10	9
Week 54	8	9	10	10
Week 65	9	10	10	9
Week 79	10	10	9	9
Mean cell hemoglobin (pg)				
Week 14	15.7 ± 0.1	16.2 ± 0.1**	16.4 ± 0.1**	16.8 ± 0.1**
Week 27	15.4 ± 0.1	16.0 ± 0.0**	16.3 ± 0.1**	16.4 ± 0.1**
Week 40	16.2 ± 0.1	16.9 ± 0.1**	17.2 ± 0.1**	17.5 ± 0.1**
Week 54	16.9 ± 0.1	17.5 ± 0.1**	17.7 ± 0.1**	17.8 ± 0.1**
Week 65	16.3 ± 0.1	17.4 ± 0.1**	17.4 ± 0.3**	17.9 ± 0.1**
Week 79	15.9 ± 0.1	16.1 ± 0.3	16.6 ± 0.2**	17.0 ± 0.1**
Mean cell hemoglobin concentration (g/dL)				
Week 14	33.8 ± 0.2	33.8 ± 0.1	33.5 ± 0.1	33.7 ± 0.1
Week 27	33.2 ± 0.1	33.2 ± 0.1	32.9 ± 0.2*	32.8 ± 0.1*
Week 40	33.5 ± 0.2	33.6 ± 0.1	33.5 ± 0.1	33.7 ± 0.2
Week 54	33.7 ± 0.2	33.4 ± 0.2	33.4 ± 0.1	33.0 ± 0.2*
Week 65	33.6 ± 0.2	33.5 ± 0.1	33.2 ± 0.2	33.6 ± 0.2
Week 79	33.7 ± 0.2	33.4 ± 0.2	33.6 ± 0.2	33.3 ± 0.2
Platelets (10^3/μL)				
Week 14	943.9 ± 40.6	978.8 ± 48.6	1,088.6 ± 43.3	1,082.3 ± 39.0
Week 27	1,015.4 ± 36.6	1,138.2 ± 57.8	1,116.7 ± 42.1	1,181.4 ± 34.5*
Week 40	1,035.7 ± 80.7	1,184.7 ± 72.0	1,196.3 ± 51.0	1,188.2 ± 70.9
Week 54	1,056.8 ± 64.1	1,114.8 ± 46.8	1,144.6 ± 47.4	1,119.6 ± 54.2
Week 65	1,202.1 ± 55.8	1,354.5 ± 48.9	1,208.3 ± 160.1	1,472.9 ± 60.9*
Week 79	1,177.8 ± 34.1	1,305.5 ± 68.9	1,281.3 ± 38.1	1,278.6 ± 66.4
Leukocytes (10^3/μL)				
Week 14	6.59 ± 0.29	6.96 ± 0.29	6.28 ± 0.29	6.78 ± 0.43
Week 27	6.30 ± 0.35	6.48 ± 0.28	5.97 ± 0.34	6.00 ± 0.58
Week 40	6.46 ± 0.50	6.79 ± 0.36	6.26 ± 0.36	6.97 ± 0.63
Week 54	5.66 ± 0.52	6.76 ± 0.27	5.13 ± 0.30	5.79 ± 0.37
Week 65	5.34 ± 0.36	5.17 ± 0.43	5.62 ± 0.43	4.94 ± 0.47
Week 79	4.76 ± 0.48	5.43 ± 0.45	4.83 ± 0.44	5.49 ± 0.46
Segmented neutrophils (10^3/μL)				
Week 14	0.97 ± 0.20	0.78 ± 0.08	0.81 ± 0.10	0.83 ± 0.11
Week 27	0.97 ± 0.07	1.03 ± 0.07	1.13 ± 0.11	0.94 ± 0.11
Week 40	1.38 ± 0.14	1.90 ± 0.44	1.12 ± 0.07	1.33 ± 0.09
Week 54	1.05 ± 0.15	1.27 ± 0.17	0.99 ± 0.13	0.97 ± 0.17
Week 65	1.05 ± 0.18	0.84 ± 0.13	1.06 ± 0.16	0.71 ± 0.11
Week 79	1.18 ± 0.11	1.35 ± 0.19	0.88 ± 0.17	1.33 ± 0.21
Lymphocytes (10^3/μL)				
Week 14	5.56 ± 0.26	6.12 ± 0.28	5.37 ± 0.28	5.79 ± 0.36
Week 27	5.15 ± 0.30	5.28 ± 0.26	4.70 ± 0.29	4.91 ± 0.52
Week 40	4.70 ± 0.41	4.51 ± 0.42	4.78 ± 0.42	5.25 ± 0.59
Week 54	4.42 ± 0.44	5.31 ± 0.30	3.95 ± 0.28	4.62 ± 0.25
Week 65	4.11 ± 0.26	4.21 ± 0.37	4.44 ± 0.36	4.14 ± 0.42
Week 79	3.31 ± 0.38	3.89 ± 0.34	3.76 ± 0.26	3.85 ± 0.44

TABLE K4
Hematology and Bone Marrow Data for Mice in the 2-Year Gavage Study of AZT/500 U α-Interferon A/D

	Vehicle Control	30 mg AZT/kg + 500 U α-IFN A/D	60 mg AZT/kg + 500 U α-IFN A/D	120 mg AZT/kg + 500 U α-IFN A/D
Female (continued)				
Hematology (continued)				
Clinical Pathology Groups (continued)				
n				
Week 14	9	9	10	10
Week 27	9	10	10	10
Week 40	9	10	10	9
Week 54	8	9	10	10
Week 65	9	10	10	9
Week 79	10	10	9	9
Atypical lymphocytes (10^3/μL)				
Week 14	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00
Week 27	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00
Week 40	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00
Week 54	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00
Week 65	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00
Week 79	0.01 ± 0.00	0.00 ± 0.00	0.01 ± 0.01	0.02 ± 0.01
Monocytes (10^3/μL)				
Week 14	0.00 ± 0.00	0.01 ± 0.01	0.01 ± 0.01	0.01 ± 0.01
Week 27	0.04 ± 0.02	0.03 ± 0.01	0.04 ± 0.02	0.05 ± 0.02
Week 40	0.22 ± 0.05	0.20 ± 0.04	0.17 ± 0.04	0.21 ± 0.06
Week 54	0.13 ± 0.02	0.06 ± 0.03	0.08 ± 0.02	0.09 ± 0.04
Week 65	0.07 ± 0.02	0.05 ± 0.01	0.06 ± 0.02	0.05 ± 0.02
Week 79	0.12 ± 0.03	0.10 ± 0.02	0.11 ± 0.02	0.14 ± 0.01
Eosinophils (10^3/μL)				
Week 14	0.07 ± 0.02	0.05 ± 0.02	0.09 ± 0.03	0.14 ± 0.02
Week 27	0.14 ± 0.02	0.13 ± 0.04	0.11 ± 0.02	0.10 ± 0.02
Week 40	0.16 ± 0.04	0.17 ± 0.03	0.19 ± 0.03	0.18 ± 0.04
Week 54	0.06 ± 0.03	0.11 ± 0.03	0.11 ± 0.04	0.12 ± 0.04
Week 65	0.12 ± 0.04	0.07 ± 0.02	0.06 ± 0.02	0.04 ± 0.02
Week 79	0.09 ± 0.02	0.07 ± 0.02	0.06 ± 0.01	0.10 ± 0.02
Core Groups				
n	10	10	10	10
Hematocrit (%)	47.4 ± 2.8	38.7 ± 2.0*	41.1 ± 2.2*	41.3 ± 1.3
Hemoglobin (g/dL)	15.8 ± 0.9	12.9 ± 0.7*	13.5 ± 0.7*	13.6 ± 0.4*
Erythrocytes (10^6/μL)	10.36 ± 0.67	8.01 ± 0.44**	7.96 ± 0.53**	7.80 ± 0.36**
Reticulocytes (10^6/μL)	0.68 ± 0.08	0.66 ± 0.08	0.79 ± 0.08	0.90 ± 0.14
Nucleated erythrocytes (10^3/μL)	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.01 ± 0.01
Mean cell volume (fL)	45.9 ± 0.7	48.4 ± 0.3**	52.3 ± 1.3**	53.4 ± 1.1**
Mean cell hemoglobin (pg)	15.3 ± 0.2	16.1 ± 0.1**	17.0 ± 0.3**	17.6 ± 0.3**
Mean cell hemoglobin concentration (g/dL)	33.4 ± 0.1	33.4 ± 0.2	32.7 ± 0.4	33.0 ± 0.2
Platelets (10^3/μL)	1,229.7 ± 68.8	1,534.7 ± 138.2	1,316.2 ± 91.5	1,203.3 ± 185.1
Leukocytes (10^3/μL)	7.00 ± 0.55	7.53 ± 0.70	8.39 ± 1.07	5.86 ± 0.84
Segmented neutrophils (10^3/μL)	1.88 ± 0.41	1.62 ± 0.13	2.32 ± 0.46	1.77 ± 0.48
Lymphocytes (10^3/μL)	4.47 ± 0.32	5.39 ± 0.65	5.47 ± 0.69	3.72 ± 0.50
Atypical lymphocytes (10^3/μL)	0.33 ± 0.07	0.26 ± 0.06	0.35 ± 0.09	0.18 ± 0.02
Monocytes (10^3/μL)	0.22 ± 0.05	0.19 ± 0.04	0.21 ± 0.03	0.13 ± 0.04
Eosinophils (10^3/μL)	0.09 ± 0.05	0.08 ± 0.02	0.04 ± 0.02	0.07 ± 0.02

TABLE K4
Hematology and Bone Marrow Data for Mice in the 2-Year Gavage Study of AZT/500 U α-Interferon A/D

	Vehicle Control	30 mg AZT/kg + 500 U α-IFN A/D	60 mg AZT/kg + 500 U α-IFN A/D	120 mg AZT/kg + 500 U α-IFN A/D
Female (continued)				
Bone Marrow Analyses				
Clinical Pathology Groups				
n				
Week 54	9	9	9	10
Week 65	9	10	8	9
Week 79	9	9	9	8
Total femoral count (10^6/femur)				
Week 54	27.0 ± 0.6	23.9 ± 1.0*	24.6 ± 0.7*	22.3 ± 0.9**
Week 65	28.0 ± 1.0	28.8 ± 1.3	27.2 ± 1.0	28.5 ± 1.1
Week 79	23.3 ± 1.7	24.1 ± 2.3	24.5 ± 1.9	26.1 ± 1.7
M:E ratio				
Week 54	1.78 ± 0.14	1.89 ± 0.09	1.96 ± 0.19	2.39 ± 0.10**
Week 65	1.91 ± 0.22	2.51 ± 0.19	1.83 ± 0.16	1.63 ± 0.18
Week 79	1.48 ± 0.17	1.73 ± 0.17	1.53 ± 0.18	1.99 ± 0.24
Rubriblasts (10^6)				
Week 54	0.50 ± 0.06	0.28 ± 0.02**	0.35 ± 0.07**	0.26 ± 0.03**
Week 65	0.32 ± 0.06	0.50 ± 0.07	0.35 ± 0.04	0.38 ± 0.06
Week 79	0.29 ± 0.06	0.46 ± 0.09	0.44 ± 0.07	0.43 ± 0.07
Prorubricytes (10^6)				
Week 54	1.27 ± 0.12	1.33 ± 0.11	1.12 ± 0.23	1.05 ± 0.08
Week 65	1.18 ± 0.22	1.15 ± 0.13	0.98 ± 0.15	1.61 ± 0.29
Week 79	1.06 ± 0.09	1.26 ± 0.20	1.39 ± 0.20	1.37 ± 0.21
Rubricytes (10^6)				
Week 54	4.22 ± 0.44	3.95 ± 0.13	4.01 ± 0.26	2.97 ± 0.20**
Week 65	4.40 ± 0.38	3.53 ± 0.44	4.64 ± 0.38	4.99 ± 0.45
Week 79	4.38 ± 0.52	4.35 ± 0.59	4.67 ± 0.54	4.36 ± 0.47
Metarubricytes (10^6)				
Week 54	1.53 ± 0.09	0.70 ± 0.09**	0.83 ± 0.14**	0.69 ± 0.13**
Week 65	0.87 ± 0.12	0.70 ± 0.10	0.92 ± 0.20	0.77 ± 0.12
Week 79	1.17 ± 0.20	0.89 ± 0.15	0.91 ± 0.18	0.75 ± 0.11
Myeloblasts (10^6)				
Week 54	0.36 ± 0.03	0.33 ± 0.04	0.47 ± 0.04	0.43 ± 0.09
Week 65	0.34 ± 0.03	0.35 ± 0.04	0.46 ± 0.08	0.46 ± 0.08
Week 79	0.26 ± 0.04	0.30 ± 0.03	0.35 ± 0.10	0.41 ± 0.10
Promyelocytes (10^6)				
Week 54	0.75 ± 0.11	0.57 ± 0.05	0.50 ± 0.03	0.76 ± 0.10
Week 65	0.60 ± 0.13	0.76 ± 0.10	0.60 ± 0.08	0.55 ± 0.13
Week 79	0.32 ± 0.06	0.41 ± 0.11	0.35 ± 0.05	0.36 ± 0.03
Neutrophilic myelocytes (10^6)				
Week 54	0.86 ± 0.09	0.83 ± 0.09	0.90 ± 0.11	0.90 ± 0.15
Week 65	0.84 ± 0.07	0.96 ± 0.12	1.05 ± 0.21	0.69 ± 0.12
Week 79	0.73 ± 0.09	1.12 ± 0.18	1.01 ± 0.17	1.02 ± 0.11
Neutrophilic metamyelocytes (10^6)				
Week 54	0.98 ± 0.11	0.74 ± 0.09	0.94 ± 0.08	0.89 ± 0.17
Week 65	1.54 ± 0.14	1.71 ± 0.17	2.15 ± 0.34	1.53 ± 0.19
Week 79	1.26 ± 0.15	1.04 ± 0.14	1.18 ± 0.16	1.11 ± 0.17
Neutrophilic bands (10^6)				
Week 54	2.07 ± 0.24	1.17 ± 0.28*	1.22 ± 0.13*	1.91 ± 0.23
Week 65	2.55 ± 0.28	3.11 ± 0.44	2.18 ± 0.19	2.37 ± 0.32
Week 79	2.32 ± 0.37	3.12 ± 0.48	2.38 ± 0.30	3.75 ± 0.56

TABLE K4
Hematology and Bone Marrow Data for Mice in the 2-Year Gavage Study of AZT/500 U α-Interferon A/D

	Vehicle Control	30 mg AZT/kg + 500 U α-IFN A/D	60 mg AZT/kg + 500 U α-IFN A/D	120 mg AZT/kg + 500 U α-IFN A/D
Female (continued)				
Bone Marrow Analyses (continued)				
Clinical Pathology Groups (continued)				
n				
Week 54	9	9	9	10
Week 65	9	10	8	9
Week 79	9	9	9	8
Neutrophilic segments (10^6)				
Week 54	7.38 ± 0.55	7.67 ± 0.60	6.71 ± 0.28	6.17 ± 0.65
Week 65	5.40 ± 0.47	6.46 ± 0.34	5.22 ± 0.70	5.53 ± 0.31
Week 79	4.14 ± 0.36	4.29 ± 0.66	4.82 ± 0.50	5.76 ± 0.81
Eosinophilic myelocytes (10^6)				
Week 54	0.068 ± 0.027	0.106 ± 0.025	0.120 ± 0.036	0.112 ± 0.019
Week 65	0.103 ± 0.034	0.077 ± 0.018	0.079 ± 0.024	0.056 ± 0.023
Week 79	0.007 ± 0.005	0.031 ± 0.012	0.016 ± 0.008	0.024 ± 0.009
Eosinophilic metamyelocytes (10^6)				
Week 54	0.11 ± 0.02	0.12 ± 0.03	0.17 ± 0.05	0.12 ± 0.03
Week 65	0.16 ± 0.05	0.14 ± 0.03	0.12 ± 0.03	0.18 ± 0.05
Week 79	0.07 ± 0.02	0.10 ± 0.02	0.09 ± 0.03	0.08 ± 0.03
Eosinophilic bands (10^6)				
Week 54	0.15 ± 0.02	0.12 ± 0.03	0.19 ± 0.04	0.19 ± 0.03
Week 65	0.28 ± 0.05	0.21 ± 0.03	0.17 ± 0.06	0.25 ± 0.05
Week 79	0.18 ± 0.03	0.35 ± 0.05*	0.20 ± 0.04	0.22 ± 0.04
Eosinophilic segments (10^6)				
Week 54	0.28 ± 0.03	0.21 ± 0.03	0.30 ± 0.06	0.34 ± 0.07
Week 65	0.27 ± 0.05	0.37 ± 0.04	0.16 ± 0.03	0.39 ± 0.07
Week 79	0.19 ± 0.02	0.27 ± 0.04	0.17 ± 0.03	0.18 ± 0.04
Basophilic myelocytes (10^6)				
Week 54	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000
Week 65	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000
Week 79	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000
Basophilic metamyelocytes (10^6)				
Week 54	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000
Week 65	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000
Week 79	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000
Basophilic bands (10^6)				
Week 54	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000
Week 65	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000
Week 79	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000
Basophilic segments (10^6)				
Week 54	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000
Week 65	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000
Week 79	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000
Bone marrow lymphocytes (10^6)				
Week 54	2.71 ± 0.17	2.02 ± 0.29	3.24 ± 0.26	2.52 ± 0.41
Week 65	4.63 ± 0.40	4.30 ± 0.40	3.87 ± 0.43	4.15 ± 0.38
Week 79	3.37 ± 0.35	2.83 ± 0.32	2.87 ± 0.25	2.46 ± 0.45
Bone marrow macrophages (10^6)				
Week 54	0.29 ± 0.04	0.18 ± 0.03	0.25 ± 0.04	0.13 ± 0.03**
Week 65	0.09 ± 0.01	0.11 ± 0.03	0.09 ± 0.02	0.09 ± 0.03
Week 79	0.15 ± 0.05	0.12 ± 0.02	0.12 ± 0.03	0.15 ± 0.04

TABLE K4
Hematology and Bone Marrow Data for Mice in the 2-Year Gavage Study of AZT/500 U α-Interferon A/D

	Vehicle Control	30 mg AZT/kg + 500 U α-IFN A/D	60 mg AZT/kg + 500 U α-IFN A/D	120 mg AZT/kg + 500 U α-IFN A/D
Female (continued)				
Bone Marrow Analyses (continued)				
Clinical Pathology Groups (continued)				
n				
Week 54	9	9	9	10
Week 65	9	10	8	9
Week 79	9	9	9	8
Bone marrow monocytes (10^6)				
Week 54	0.28 ± 0.03	0.18 ± 0.02	0.18 ± 0.04	0.18 ± 0.03
Week 65	0.17 ± 0.02	0.20 ± 0.05	0.13 ± 0.03	0.18 ± 0.03
Week 79	0.28 ± 0.06	0.27 ± 0.05	0.26 ± 0.06	0.34 ± 0.10
Megakaryo cells (10^6)				
Week 54	0.10 ± 0.03	0.09 ± 0.02	0.07 ± 0.02	0.07 ± 0.02
Week 65	0.06 ± 0.02	0.04 ± 0.02	0.03 ± 0.02	0.03 ± 0.02
Week 79	0.05 ± 0.01	0.10 ± 0.03	0.06 ± 0.02	0.06 ± 0.02
Plasma cells (10^6)				
Week 54	0.41 ± 0.03	0.30 ± 0.06	0.35 ± 0.04	0.24 ± 0.06*
Week 65	0.32 ± 0.11	0.22 ± 0.07	0.21 ± 0.06	0.22 ± 0.05
Week 79	0.21 ± 0.03	0.23 ± 0.05	0.45 ± 0.13	0.35 ± 0.12
Mitotic figures (10^6)				
Week 54	0.21 ± 0.03	0.17 ± 0.02	0.15 ± 0.03	0.20 ± 0.04
Week 65	0.31 ± 0.06	0.22 ± 0.02	0.19 ± 0.05	0.19 ± 0.03
Week 79	0.28 ± 0.04	0.24 ± 0.05	0.33 ± 0.07	0.38 ± 0.07
Fat cells (10^6)				
Week 54	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000
Week 65	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000
Week 79	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000
Mast cells (10^6)				
Week 54	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000
Week 65	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000
Week 79	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000
Smudge cells (10^6)				
Week 54	2.44 ± 0.11	2.86 ± 0.29	2.55 ± 0.14	2.11 ± 0.13
Week 65	3.55 ± 0.19	3.68 ± 0.37	3.55 ± 0.31	3.89 ± 0.37
Week 79	2.58 ± 0.21	2.33 ± 0.34	2.41 ± 0.25	2.55 ± 0.22
Osteoblasts (10^6)				
Week 54	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000
Week 65	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000
Week 79	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000
Osteoclasts (10^6)				
Week 54	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000
Week 65	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000
Week 79	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000
Other bone marrow cells (10^6)				
Week 54	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000
Week 65	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000
Week 79	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000
Neutrophilic hypersegments (10^6)				
Week 54	0.05 ± 0.03	0.05 ± 0.02	0.08 ± 0.03	0.04 ± 0.02
Week 65	0.15 ± 0.06	0.35 ± 0.10	0.44 ± 0.09*	0.37 ± 0.04
Week 79	0.26 ± 0.08	0.16 ± 0.04	0.36 ± 0.07	0.46 ± 0.15

TABLE K4
Hematology and Bone Marrow Data for Mice in the 2-Year Gavage Study of AZT/500 U α-Interferon A/D

	Vehicle Control	30 mg AZT/kg + 500 U α-IFN A/D	60 mg AZT/kg + 500 U α-IFN A/D	120 mg AZT/kg + 500 U α-IFN A/D
Female (continued)				
Bone Marrow Analyses (continued)				
Core Groups				
n	9	9	10	10
Total femoral count (10^6/femur)	33.8 ± 2.6	33.2 ± 1.2	30.7 ± 2.1	30.5 ± 2.9
M:E ratio	1.86 ± 0.15	2.38 ± 0.38	3.11 ± 0.47	4.76 ± 1.62
Rubriblasts (10^6)	0.44 ± 0.09	0.36 ± 0.08	0.43 ± 0.06	0.35 ± 0.05
Prorubricytes (10^6)	2.09 ± 0.42	1.50 ± 0.23	1.25 ± 0.23	0.79 ± 0.13**
Rubricytes (10^6)	4.16 ± 0.46	4.57 ± 0.66	3.40 ± 0.61	3.65 ± 0.65
Metarubricytes (10^6)	1.36 ± 0.26	0.74 ± 0.12	0.69 ± 0.16*	0.53 ± 0.14**
Myeloblasts (10^6)	0.40 ± 0.06	0.42 ± 0.06	0.35 ± 0.03	0.40 ± 0.07
Promyelocytes (10^6)	0.55 ± 0.11	0.61 ± 0.08	0.61 ± 0.06	0.60 ± 0.12
Neutrophilic myelocytes (10^6)	1.40 ± 0.31	1.03 ± 0.11	1.29 ± 0.22	1.32 ± 0.21
Neutrophilic metamyelocytes (10^6)	1.50 ± 0.21	1.34 ± 0.13	1.67 ± 0.32	1.62 ± 0.32
Neutrophilic bands (10^6)	3.25 ± 0.33	3.60 ± 0.41	3.67 ± 0.28	3.92 ± 0.63
Neutrophilic segments (10^6)	6.48 ± 0.58	7.39 ± 0.61	6.90 ± 0.65	8.10 ± 1.48
Eosinophilic myelocytes (10^6)	0.102 ± 0.029	0.144 ± 0.028	0.079 ± 0.022	0.089 ± 0.024
Eosinophilic metamyelocytes (10^6)	0.14 ± 0.04	0.17 ± 0.03	0.16 ± 0.04	0.15 ± 0.04
Eosinophilic bands (10^6)	0.27 ± 0.07	0.29 ± 0.07	0.19 ± 0.05	0.29 ± 0.06
Eosinophilic segments (10^6)	0.19 ± 0.06	0.15 ± 0.04	0.16 ± 0.04	0.17 ± 0.03
Basophilic myelocytes (10^6)	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000
Basophilic metamyelocytes (10^6)	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000
Basophilic bands (10^6)	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000
Basophilic segments (10^6)	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000
Bone marrow lymphocytes (10^6)	5.33 ± 0.64	4.76 ± 0.54	4.07 ± 0.45	3.27 ± 0.66*
Bone marrow macrophages (10^6)	0.18 ± 0.05	0.14 ± 0.02	0.10 ± 0.01	0.15 ± 0.03
Bone marrow monocytes (10^6)	0.24 ± 0.04	0.23 ± 0.04	0.29 ± 0.11	0.28 ± 0.08
Megakaryo cells (10^6)	0.14 ± 0.03	0.13 ± 0.05	0.08 ± 0.02	0.07 ± 0.01
Plasma cells (10^6)	0.35 ± 0.08	0.60 ± 0.13	0.56 ± 0.09	0.62 ± 0.19
Mitotic figures (10^6)	0.34 ± 0.07	0.33 ± 0.05	0.28 ± 0.05	0.31 ± 0.07
Fat cells (10^6)	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000
Mast cells (10^6)	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000
Smudge cells (10^6)	4.84 ± 0.47	4.67 ± 0.44	4.44 ± 0.25	3.87 ± 0.39
Osteoblasts (10^6)	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000
Osteoclasts (10^6)	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000
Other bone marrow cells (10^6)	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000
Neutrophilic hypersegments (10^6)	0.08 ± 0.05	0.20 ± 0.08	0.37 ± 0.07	0.41 ± 0.14

* Significantly different ($P \leq 0.05$) from the control group by Dunn's or Shirley's test
** $P \leq 0.01$
[a] Mean ± standard error. Statistical tests were performed on unrounded data.
[b] n = 9

TABLE K5
Hematology and Bone Marrow Data for Mice in the 2-Year Gavage Study of AZT/5,000 U α-Interferon A/D[a]

	Vehicle Control	30 mg AZT/kg + 5,000 U α-IFN A/D	60 mg AZT/kg + 5,000 U α-IFN A/D	120 mg AZT/kg + 5,000 U α-IFN A/D
Male				
Hematology				
Clinical Pathology Groups				
n				
Week 14	10	10	10	10
Week 27	10	10	10	10
Week 40	10	9	10	10
Week 54	10	10	10	10
Week 66	10	10	9	9
Week 79	10	9	10	10
Hematocrit (%)				
Week 14	48.9 ± 0.4	48.7 ± 0.5	47.4 ± 0.5	47.5 ± 0.8
Week 27	46.3 ± 0.5	45.4 ± 0.5	45.7 ± 0.5	43.8 ± 0.3**
Week 40	44.7 ± 0.8	43.5 ± 0.8	44.2 ± 0.4	41.2 ± 1.1
Week 54	44.5 ± 0.9	45.7 ± 0.4	44.0 ± 0.5	42.4 ± 0.7
Week 66	44.9 ± 0.8	42.7 ± 0.7	43.9 ± 0.5	45.1 ± 2.0
Week 79	43.0 ± 1.0	42.5 ± 1.0	40.3 ± 1.4	41.2 ± 1.1
Hemoglobin (g/dL)				
Week 14	16.4 ± 0.1	16.1 ± 0.2	15.8 ± 0.1**	15.8 ± 0.2*
Week 27	15.3 ± 0.2	15.0 ± 0.2	15.2 ± 0.2	14.6 ± 0.1**
Week 40	15.0 ± 0.3	14.6 ± 0.3	14.8 ± 0.1	13.8 ± 0.4*
Week 54	14.6 ± 0.3	15.1 ± 0.2	14.5 ± 0.2	13.9 ± 0.3
Week 66	15.1 ± 0.3	14.1 ± 0.2*	14.6 ± 0.2	14.9 ± 0.7
Week 79	14.3 ± 0.3	13.9 ± 0.4	13.3 ± 0.5	13.5 ± 0.4
Erythrocytes (10^6/μL)				
Week 14	10.59 ± 0.10	10.21 ± 0.12*	9.78 ± 0.08**	9.58 ± 0.13**
Week 27	10.19 ± 0.10	9.56 ± 0.12**	9.62 ± 0.12**	8.98 ± 0.07**
Week 40	9.94 ± 0.11	9.38 ± 0.13**	9.32 ± 0.09**	8.50 ± 0.22**
Week 54	9.53 ± 0.20	9.19 ± 0.15	8.90 ± 0.11*	8.24 ± 0.14**
Week 66	9.48 ± 0.15	8.65 ± 0.13**	8.79 ± 0.11	8.98 ± 0.44*
Week 79	8.96 ± 0.27	8.64 ± 0.34	7.83 ± 0.37*	7.95 ± 0.33*
Reticulocytes (10^6/μL)				
Week 14	0.24 ± 0.02[b]	0.26 ± 0.04[b]	0.25 ± 0.02[c]	0.27 ± 0.02[b]
Week 27	0.21 ± 0.01	0.15 ± 0.01*	0.17 ± 0.01	0.19 ± 0.01
Week 40	0.31 ± 0.02	0.22 ± 0.02	0.22 ± 0.02	0.24 ± 0.03
Week 54	0.28 ± 0.02	0.22 ± 0.02	0.26 ± 0.02	0.27 ± 0.02
Week 66	0.22 ± 0.02	0.22 ± 0.02	0.17 ± 0.01	0.20 ± 0.02
Week 79	0.18 ± 0.03	0.18 ± 0.02	0.20 ± 0.03	0.20 ± 0.02
Nucleated erythrocytes (10^3/μL)				
Week 14	0.04 ± 0.01	0.01 ± 0.01	0.02 ± 0.01	0.02 ± 0.02
Week 27	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.01 ± 0.01
Week 40	0.01 ± 0.01	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00
Week 54	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00
Week 66	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00
Week 79	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00
Mean cell volume (fL)				
Week 14	46.2 ± 0.2	47.7 ± 0.4**	48.5 ± 0.3**	49.6 ± 0.3**
Week 27	45.4 ± 0.2	47.5 ± 0.5**	47.5 ± 0.2**	48.8 ± 0.3**
Week 40	45.0 ± 0.4	46.3 ± 0.6*	47.4 ± 0.7**	48.5 ± 0.6**
Week 54	46.7 ± 0.6	49.8 ± 0.5**	49.5 ± 0.7**	51.5 ± 0.4**
Week 66	47.4 ± 0.4	49.4 ± 0.5**	49.9 ± 0.6**	50.4 ± 0.5**
Week 79	48.1 ± 0.6	49.4 ± 0.9	51.9 ± 1.1**	52.3 ± 1.3**

TABLE K5
Hematology and Bone Marrow Data for Mice in the 2-Year Gavage Study of AZT/5,000 U α-Interferon A/D

	Vehicle Control	30 mg AZT/kg + 5,000 U α-IFN A/D	60 mg AZT/kg + 5,000 U α-IFN A/D	120 mg AZT/kg + 5,000 U α-IFN A/D
Male (continued)				
Hematology (continued)				
Clinical Pathology Groups (continued)				
n				
Week 14	10	10	10	10
Week 27	10	10	10	10
Week 40	10	9	10	10
Week 54	10	10	10	10
Week 66	10	10	9	9
Week 79	10	9	10	10
Mean cell hemoglobin (pg)				
Week 14	15.5 ± 0.1	15.7 ± 0.1	16.2 ± 0.1**	16.5 ± 0.1**
Week 27	15.0 ± 0.1	15.7 ± 0.1**	15.9 ± 0.1**	16.3 ± 0.1**
Week 40	15.1 ± 0.1	15.5 ± 0.2*	15.9 ± 0.2*	16.3 ± 0.2**
Week 54	15.3 ± 0.2	16.5 ± 0.2**	16.3 ± 0.3**	16.9 ± 0.2**
Week 66	16.0 ± 0.2	16.3 ± 0.1	16.6 ± 0.2	16.6 ± 0.2
Week 79	16.0 ± 0.3	16.2 ± 0.2	17.1 ± 0.3*	17.1 ± 0.3*
Mean cell hemoglobin concentration (g/dL)				
Week 14	33.6 ± 0.2	33.0 ± 0.2	33.4 ± 0.3	33.3 ± 0.2
Week 27	33.1 ± 0.1	33.0 ± 0.2	33.4 ± 0.1	33.3 ± 0.1
Week 40	33.6 ± 0.1	33.5 ± 0.2	33.5 ± 0.1	33.5 ± 0.1
Week 54	32.8 ± 0.2	33.1 ± 0.1	32.9 ± 0.1	32.7 ± 0.2
Week 66	33.7 ± 0.1	33.0 ± 0.2*	33.3 ± 0.1	33.1 ± 0.1
Week 79	33.2 ± 0.2	32.8 ± 0.2	33.0 ± 0.2	32.7 ± 0.3
Platelets (10^3/μL)				
Week 14	1,005.2 ± 60.8	1,003.4 ± 36.4	1,008.1 ± 59.0	961.0 ± 24.5
Week 27	1,096.0 ± 29.9	1,191.1 ± 33.5	1,195.8 ± 55.9	1,261.6 ± 45.7*
Week 40	1,181.2 ± 37.3	1,448.6 ± 94.0*	1,229.2 ± 52.1	1,354.8 ± 63.3
Week 54	1,274.7 ± 54.5	1,213.5 ± 57.1	1,503.1 ± 109.5	1,299.4 ± 57.7
Week 66	1,207.5 ± 68.3	1,403.0 ± 53.8	1,416.6 ± 74.2	1,504.4 ± 60.7**
Week 79	1,524.9 ± 88.5	1,963.0 ± 129.4*	1,729.2 ± 75.3	1,785.5 ± 125.3
Leukocytes (10^3/μL)				
Week 14	7.57 ± 0.34	7.53 ± 0.64	7.53 ± 0.32	6.99 ± 0.22
Week 27	7.04 ± 0.44	7.24 ± 0.44	7.71 ± 0.25	7.34 ± 0.30
Week 40	8.87 ± 0.71	8.87 ± 1.06	9.27 ± 0.61	8.47 ± 0.68
Week 54	8.19 ± 0.63	7.51 ± 0.53	7.23 ± 0.42	7.54 ± 0.55
Week 66	9.07 ± 0.72	9.46 ± 0.64	8.67 ± 1.04	8.88 ± 0.69
Week 79	11.80 ± 1.12	11.30 ± 0.91	11.03 ± 1.23	10.78 ± 1.08
Segmented neutrophils (10^3/μL)				
Week 14	1.03 ± 0.16	1.09 ± 0.18	1.01 ± 0.12	0.82 ± 0.13
Week 27	1.32 ± 0.15	1.47 ± 0.21	1.49 ± 0.17	1.37 ± 0.16
Week 40	2.00 ± 0.23	2.07 ± 0.34	2.08 ± 0.34	1.95 ± 0.30
Week 54	1.68 ± 0.16	1.51 ± 0.14	1.49 ± 0.11	1.66 ± 0.17
Week 66	2.01 ± 0.23	2.12 ± 0.14	1.91 ± 0.25	1.78 ± 0.17
Week 79	2.82 ± 0.30	2.79 ± 0.30	2.90 ± 0.47	2.92 ± 0.42
Lymphocytes (10^3/μL)				
Week 14	6.42 ± 0.26	6.23 ± 0.51	6.38 ± 0.25	5.98 ± 0.23
Week 27	5.47 ± 0.37	5.54 ± 0.33	5.89 ± 0.28	5.66 ± 0.25
Week 40	6.55 ± 0.56	6.56 ± 0.80	6.91 ± 0.34	6.21 ± 0.49
Week 54	6.03 ± 0.50	5.61 ± 0.38	5.36 ± 0.32	5.45 ± 0.40
Week 66	6.64 ± 0.51	6.80 ± 0.49	6.23 ± 0.75	6.65 ± 0.55
Week 79	8.55 ± 0.86	8.02 ± 0.90	7.53 ± 1.04	7.53 ± 1.00

TABLE K5
Hematology and Bone Marrow Data for Mice in the 2-Year Gavage Study of AZT/5,000 U α-Interferon A/D

	Vehicle Control	30 mg AZT/kg + 5,000 U α-IFN A/D	60 mg AZT/kg + 5,000 U α-IFN A/D	120 mg AZT/kg + 5,000 U α-IFN A/D
Male (continued)				
Hematology (continued)				
Clinical Pathology Groups (continued)				
n				
Week 14	10	10	10	10
Week 27	10	10	10	10
Week 40	10	9	10	10
Week 54	10	10	10	10
Week 66	10	10	9	9
Week 79	10	9	10	10
Atypical lymphocytes (10^3/μL)				
Week 14	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00
Week 27	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00
Week 40	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00
Week 54	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00
Week 66	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00
Week 79	0.00 ± 0.00	0.00 ± 0.00	0.21 ± 0.21	0.00 ± 0.00
Monocytes (10^3/μL)				
Week 14	0.02 ± 0.01	0.03 ± 0.01	0.03 ± 0.01	0.01 ± 0.01
Week 27	0.08 ± 0.03	0.05 ± 0.02	0.09 ± 0.04	0.09 ± 0.03
Week 40	0.15 ± 0.04	0.11 ± 0.05	0.09 ± 0.04	0.06 ± 0.04
Week 54	0.28 ± 0.03	0.19 ± 0.05	0.21 ± 0.03	0.26 ± 0.03
Week 66	0.23 ± 0.05	0.33 ± 0.05	0.32 ± 0.07	0.34 ± 0.06
Week 79	0.28 ± 0.07	0.31 ± 0.06	0.25 ± 0.05	0.26 ± 0.05
Eosinophils (10^3/μL)				
Week 14	0.10 ± 0.02	0.18 ± 0.03	0.10 ± 0.03	0.19 ± 0.03
Week 27	0.17 ± 0.03	0.18 ± 0.04	0.23 ± 0.04	0.22 ± 0.04
Week 40	0.18 ± 0.05	0.12 ± 0.04	0.19 ± 0.05	0.26 ± 0.06
Week 54	0.19 ± 0.03	0.20 ± 0.03	0.17 ± 0.03	0.17 ± 0.02
Week 66	0.20 ± 0.03	0.22 ± 0.03	0.21 ± 0.03	0.12 ± 0.02
Week 79	0.13 ± 0.05	0.14 ± 0.05	0.13 ± 0.03	0.06 ± 0.03
Core Groups				
n	10	10	10	10
Hematocrit (%)	37.0 ± 3.6	36.8 ± 2.7	35.5 ± 2.1	33.0 ± 1.4
Hemoglobin (g/dL)	12.4 ± 1.2	12.3 ± 0.8	11.7 ± 0.8	10.5 ± 0.5
Erythrocytes (10^6/μL)	9.11 ± 1.02	8.64 ± 0.64	7.98 ± 0.56	7.00 ± 0.38
Reticulocytes (10^6/μL)	0.36 ± 0.03	0.33 ± 0.03	0.34 ± 0.03	0.34 ± 0.02
Nucleated erythrocytes (10^3/μL)	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00
Mean cell volume (fL)	41.4 ± 1.0	42.7 ± 0.5	44.9 ± 1.1*	47.9 ± 2.2**
Mean cell hemoglobin (pg)	13.8 ± 0.3	14.4 ± 0.2	14.7 ± 0.4	15.1 ± 0.3**
Mean cell hemoglobin concentration (g/dL)	33.4 ± 0.3	33.6 ± 0.3	32.8 ± 0.7	31.9 ± 0.9
Platelets (10^3/μL)	1,507.0 ± 164.0	1,783.1 ± 222.4	2,312.5 ± 134.3**	2,476.3 ± 157.4**
Leukocytes (10^3/μL)	18.21 ± 1.57	16.44 ± 2.28	15.12 ± 1.52	16.70 ± 1.36
Segmented neutrophils (10^3/μL)	5.52 ± 0.89	4.92 ± 0.51	4.27 ± 0.39	4.56 ± 0.37
Lymphocytes (10^3/μL)	10.34 ± 0.92	9.58 ± 1.76	8.77 ± 1.24	10.11 ± 1.14
Atypical lymphocytes (10^3/μL)	1.78 ± 0.26	1.28 ± 0.17	1.49 ± 0.28	1.56 ± 0.22
Monocytes (10^3/μL)	0.39 ± 0.08	0.48 ± 0.13	0.43 ± 0.07	0.38 ± 0.04
Eosinophils (10^3/μL)	0.18 ± 0.06	0.19 ± 0.07	0.16 ± 0.06	0.10 ± 0.04

TABLE K5
Hematology and Bone Marrow Data for Mice in the 2-Year Gavage Study of AZT/5,000 U α-Interferon A/D

	Vehicle Control	30 mg AZT/kg + 5,000 U α-IFN A/D	60 mg AZT/kg + 5,000 U α-IFN A/D	120 mg AZT/kg + 5,000 U α-IFN A/D
Male (continued)				
Bone Marrow Analyses				
Clinical Pathology Groups				
n				
Week 54	9	10	10	10
Week 66	10	10	10	9
Week 79	10	9	10	9
Total femoral count (10^6/femur)				
Week 54	28.3 ± 2.2	32.6 ± 1.6	30.3 ± 1.2	30.9 ± 0.9
Week 66	31.1 ± 0.8	33.1 ± 1.3	29.7 ± 1.3	31.0 ± 0.9
Week 79	38.1 ± 1.2	38.0 ± 1.5	36.4 ± 1.2	34.6 ± 1.1
M:E ratio				
Week 54	1.92 ± 0.12	2.76 ± 0.24*	2.45 ± 0.15	2.72 ± 0.20*
Week 66	2.82 ± 0.29	3.14 ± 0.39	3.83 ± 0.53	3.58 ± 0.69
Week 79	2.88 ± 0.27	3.57 ± 0.55	4.60 ± 0.78	3.52 ± 0.37
Rubriblasts (10^6)				
Week 54	0.60 ± 0.10	0.57 ± 0.09	0.54 ± 0.06	0.48 ± 0.05
Week 66	0.32 ± 0.04	0.37 ± 0.07	0.26 ± 0.04	0.25 ± 0.04
Week 79	0.26 ± 0.03	0.28 ± 0.04	0.31 ± 0.04	0.29 ± 0.06
Prorubricytes (10^6)				
Week 54	0.41 ± 0.05	0.78 ± 0.09**	0.55 ± 0.08	0.50 ± 0.06
Week 66	0.51 ± 0.10	0.71 ± 0.10	0.58 ± 0.09	0.59 ± 0.07
Week 79	0.67 ± 0.09	0.94 ± 0.20	0.68 ± 0.11	0.68 ± 0.13
Rubricytes (10^6)				
Week 54	3.61 ± 0.28	3.54 ± 0.37	3.44 ± 0.18	3.47 ± 0.26
Week 66	4.08 ± 0.42	3.90 ± 0.40	2.96 ± 0.46	3.70 ± 0.65
Week 79	4.81 ± 0.32	4.09 ± 0.43	3.63 ± 0.64*	3.85 ± 0.34
Metarubricytes (10^6)				
Week 54	2.16 ± 0.17	1.45 ± 0.11*	1.76 ± 0.22	1.54 ± 0.12*
Week 66	1.30 ± 0.17	1.12 ± 0.18	1.22 ± 0.28	0.98 ± 0.21
Week 79	1.20 ± 0.18	0.52 ± 0.11**	0.72 ± 0.10	0.62 ± 0.12*
Myeloblasts (10^6)				
Week 54	0.39 ± 0.09	0.34 ± 0.06	0.33 ± 0.08	0.23 ± 0.05
Week 66	0.42 ± 0.06	0.23 ± 0.04	0.36 ± 0.05	0.31 ± 0.04
Week 79	0.49 ± 0.10	0.54 ± 0.08	0.58 ± 0.09	0.53 ± 0.06
Promyelocytes (10^6)				
Week 54	0.19 ± 0.05	0.26 ± 0.04	0.30 ± 0.04	0.21 ± 0.06
Week 66	0.45 ± 0.06	0.41 ± 0.06	0.42 ± 0.05	0.46 ± 0.05
Week 79	0.50 ± 0.07	0.60 ± 0.06	0.62 ± 0.12	0.68 ± 0.09
Neutrophilic myelocytes (10^6)				
Week 54	1.02 ± 0.13	1.28 ± 0.09	0.89 ± 0.07	0.63 ± 0.07*
Week 66	0.86 ± 0.11	1.18 ± 0.19	0.87 ± 0.15	0.98 ± 0.11
Week 79	1.33 ± 0.13	1.21 ± 0.09	1.57 ± 0.24	1.36 ± 0.17
Neutrophilic metamyelocytes (10^6)				
Week 54	2.97 ± 0.28	3.77 ± 0.39	3.14 ± 0.14	3.66 ± 0.28
Week 66	1.72 ± 0.20	1.36 ± 0.22	1.65 ± 0.29	1.67 ± 0.19
Week 79	2.55 ± 0.36	1.81 ± 0.21	1.75 ± 0.36	1.48 ± 0.19
Neutrophilic bands (10^6)				
Week 54	0.27 ± 0.04	0.34 ± 0.05	0.33 ± 0.06	0.35 ± 0.03
Week 66	1.58 ± 0.13	1.89 ± 0.33	1.52 ± 0.27	1.98 ± 0.24
Week 79	2.43 ± 0.32	2.17 ± 0.52	3.18 ± 0.53	1.82 ± 0.28

TABLE K5
Hematology and Bone Marrow Data for Mice in the 2-Year Gavage Study of AZT/5,000 U α-Interferon A/D

	Vehicle Control	30 mg AZT/kg + 5,000 U α-IFN A/D	60 mg AZT/kg + 5,000 U α-IFN A/D	120 mg AZT/kg + 5,000 U α-IFN A/D
Male (continued)				
Bone Marrow Analyses (continued)				
Clinical Pathology Groups (continued)				
n				
Week 54	9	10	10	10
Week 66	10	10	10	9
Week 79	10	9	10	9
Neutrophilic segments (10^6)				
Week 54	7.71 ± 0.60	10.19 ± 0.68*	9.37 ± 0.43	10.33 ± 0.76*
Week 66	10.90 ± 0.59	11.94 ± 1.00	11.02 ± 0.71	10.42 ± 0.73
Week 79	11.42 ± 0.93	12.18 ± 1.52	12.18 ± 1.25	11.57 ± 0.82
Eosinophilic myelocytes (10^6)				
Week 54	0.020 ± 0.014	0.000 ± 0.000	0.022 ± 0.017	0.000 ± 0.000
Week 66	0.025 ± 0.013	0.072 ± 0.020	0.029 ± 0.015	0.020 ± 0.015
Week 79	0.028 ± 0.019	0.018 ± 0.018	0.031 ± 0.020	0.020 ± 0.014
Eosinophilic metamyelocytes (10^6)				
Week 54	0.15 ± 0.04	0.09 ± 0.03	0.14 ± 0.03	0.12 ± 0.03
Week 66	0.03 ± 0.02	0.10 ± 0.03	0.06 ± 0.02	0.05 ± 0.02
Week 79	0.08 ± 0.03	0.07 ± 0.04	0.07 ± 0.02	0.05 ± 0.03
Eosinophilic bands (10^6)				
Week 54	0.11 ± 0.04	0.10 ± 0.03	0.07 ± 0.02	0.12 ± 0.03
Week 66	0.12 ± 0.02	0.11 ± 0.03	0.18 ± 0.03	0.22 ± 0.04
Week 79	0.22 ± 0.08	0.17 ± 0.02	0.18 ± 0.02	0.25 ± 0.06
Eosinophilic segments (10^6)				
Week 54	0.20 ± 0.02	0.21 ± 0.05	0.30 ± 0.04	0.27 ± 0.04
Week 66	0.33 ± 0.06	0.28 ± 0.07	0.29 ± 0.07	0.28 ± 0.07
Week 79	0.27 ± 0.06	0.28 ± 0.05	0.35 ± 0.08	0.45 ± 0.07
Basophilic myelocytes (10^6)				
Week 54	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000
Week 66	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000
Week 79	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000
Basophilic metamyelocytes (10^6)				
Week 54	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000
Week 66	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000
Week 79	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000
Basophilic bands (10^6)				
Week 54	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000
Week 66	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000
Week 79	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000
Basophilic segments (10^6)				
Week 54	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000
Week 66	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000
Week 79	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000
Bone marrow lymphocytes (10^6)				
Week 54	3.71 ± 0.51	4.10 ± 0.32	4.10 ± 0.35	4.00 ± 0.16
Week 66	3.04 ± 0.21	3.71 ± 0.33	3.13 ± 0.35	3.81 ± 0.44
Week 79	5.52 ± 0.50	6.45 ± 0.87	4.71 ± 0.63	5.69 ± 0.69
Bone marrow macrophages (10^6)				
Week 54	0.24 ± 0.04	0.36 ± 0.05	0.34 ± 0.05	0.34 ± 0.04
Week 66	0.08 ± 0.03	0.11 ± 0.03	0.18 ± 0.04	0.09 ± 0.02
Week 79	0.11 ± 0.03	0.23 ± 0.07	0.15 ± 0.03	0.21 ± 0.05

TABLE K5
Hematology and Bone Marrow Data for Mice in the 2-Year Gavage Study of AZT/5,000 U α-Interferon A/D

	Vehicle Control	30 mg AZT/kg + 5,000 U α-IFN A/D	60 mg AZT/kg + 5,000 U α-IFN A/D	120 mg AZT/kg + 5,000 U α-IFN A/D
Male (continued)				
Bone Marrow Analyses (continued)				
Clinical Pathology Groups (continued)				
n				
Week 54	9	10	10	10
Week 66	10	10	10	9
Week 79	10	9	10	9
Bone marrow monocytes (10^6)				
Week 54	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00
Week 66	0.22 ± 0.04	0.19 ± 0.02	0.33 ± 0.07	0.19 ± 0.05
Week 79	0.28 ± 0.06	0.24 ± 0.04	0.33 ± 0.07	0.34 ± 0.07
Megakaryo cells (10^6)				
Week 54	0.10 ± 0.02	0.13 ± 0.02	0.08 ± 0.01	0.16 ± 0.04
Week 66	0.05 ± 0.03	0.07 ± 0.02	0.09 ± 0.02	0.10 ± 0.03
Week 79	0.12 ± 0.03	0.09 ± 0.02	0.11 ± 0.02	0.19 ± 0.08
Plasma cells (10^6)				
Week 54	0.14 ± 0.04	0.13 ± 0.03	0.10 ± 0.02	0.16 ± 0.05
Week 66	0.16 ± 0.05	0.12 ± 0.02	0.22 ± 0.03*	0.30 ± 0.05*
Week 79	0.38 ± 0.07	0.42 ± 0.11	0.31 ± 0.08	0.27 ± 0.10
Mitotic figures (10^6)				
Week 54	0.24 ± 0.04	0.27 ± 0.06	0.24 ± 0.04	0.26 ± 0.06
Week 66	0.13 ± 0.03	0.12 ± 0.03	0.15 ± 0.03	0.16 ± 0.03
Week 79	0.27 ± 0.04	0.16 ± 0.04	0.12 ± 0.04	0.19 ± 0.04
Fat cells (10^6)				
Week 54	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000
Week 66	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000
Week 79	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000
Mast cells (10^6)				
Week 54	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000
Week 66	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000
Week 79	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000
Smudge cells (10^6)				
Week 54	4.09 ± 0.61	4.64 ± 0.37	4.24 ± 0.25	4.03 ± 0.29
Week 66	4.80 ± 0.25	5.14 ± 0.15	4.22 ± 0.50	4.43 ± 0.25
Week 79	5.13 ± 0.42	5.47 ± 0.27	4.85 ± 0.29	4.15 ± 0.45
Osteoblasts (10^6)				
Week 54	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000
Week 66	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000
Week 79	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000
Osteoclasts (10^6)				
Week 54	0.021 ± 0.015	0.037 ± 0.014	0.010 ± 0.007	0.044 ± 0.014
Week 66	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000
Week 79	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000
Other bone marrow cells (10^6)				
Week 54	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000
Week 66	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000
Week 79	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000
Neutrophilic hypersegments (10^6)				
Week 54	0.09 ± 0.03	0.05 ± 0.02	0.17 ± 0.04	0.21 ± 0.04
Week 66	0.02 ± 0.02	0.01 ± 0.01	0.02 ± 0.01	0.02 ± 0.01
Week 79	0.13 ± 0.07	0.10 ± 0.04	0.07 ± 0.03	0.22 ± 0.11

TABLE K5
Hematology and Bone Marrow Data for Mice in the 2-Year Gavage Study of AZT/5,000 U α-Interferon A/D

	Vehicle Control	30 mg AZT/kg + 5,000 U α-IFN A/D	60 mg AZT/kg + 5,000 U α-IFN A/D	120 mg AZT/kg + 5,000 U α-IFN A/D
Male (continued)				
Bone Marrow Analyses (continued)				
Core Groups				
n	10	10	10	10
Total femoral count (10^6/femur)	31.2 ± 1.3	31.5 ± 2.1	28.7 ± 3.0	28.1 ± 1.6
M:E ratio	3.70 ± 0.47	4.55 ± 0.67	4.53 ± 0.77	4.37 ± 0.91
Rubriblasts (10^6)	0.17 ± 0.05	0.20 ± 0.05	0.13 ± 0.03	0.14 ± 0.03
Prorubricytes (10^6)	0.75 ± 0.12	0.66 ± 0.14	0.66 ± 0.12	0.67 ± 0.14
Rubricytes (10^6)	3.24 ± 0.31	3.01 ± 0.44	2.46 ± 0.41	2.88 ± 0.49
Metarubricytes (10^6)	0.87 ± 0.18	0.58 ± 0.11	0.41 ± 0.10	0.50 ± 0.07
Myeloblasts (10^6)	0.35 ± 0.06	0.46 ± 0.08	0.26 ± 0.03	0.28 ± 0.04
Promyelocytes (10^6)	0.83 ± 0.11	1.05 ± 0.16	0.56 ± 0.05	0.74 ± 0.10
Neutrophilic myelocytes (10^6)	1.45 ± 0.21	1.46 ± 0.22	1.21 ± 0.18	1.19 ± 0.18
Neutrophilic metamyelocytes (10^6)	1.57 ± 0.16	1.73 ± 0.23	1.42 ± 0.29	1.46 ± 0.16
Neutrophilic bands (10^6)	3.97 ± 0.45	3.62 ± 0.56	4.22 ± 0.81	4.17 ± 0.51
Neutrophilic segments (10^6)	7.81 ± 0.66	8.45 ± 0.86	6.85 ± 0.81	6.63 ± 0.68
Eosinophilic myelocytes (10^6)	0.005 ± 0.005	0.022 ± 0.012	0.025 ± 0.019	0.060 ± 0.029
Eosinophilic metamyelocytes (10^6)	0.10 ± 0.03	0.05 ± 0.02	0.06 ± 0.02	0.09 ± 0.02
Eosinophilic bands (10^6)	0.20 ± 0.04	0.21 ± 0.04	0.18 ± 0.03	0.17 ± 0.05
Eosinophilic segments (10^6)	0.23 ± 0.03	0.25 ± 0.03	0.19 ± 0.03	0.15 ± 0.04
Basophilic myelocytes (10^6)	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000
Basophilic metamyelocytes (10^6)	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000
Basophilic bands (10^6)	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000
Basophilic segments (10^6)	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000
Bone marrow lymphocytes (10^6)	3.89 ± 0.51	4.68 ± 0.80	5.06 ± 0.58	3.82 ± 0.45
Bone marrow macrophages (10^6)	0.12 ± 0.03	0.12 ± 0.03	0.11 ± 0.02	0.08 ± 0.02
Bone marrow monocytes (10^6)	0.20 ± 0.05	0.15 ± 0.04	0.23 ± 0.06	0.19 ± 0.03
Megakaryo cells (10^6)	0.04 ± 0.02	0.09 ± 0.04	0.03 ± 0.02	0.07 ± 0.02
Plasma cells (10^6)	0.58 ± 0.23	0.43 ± 0.12	0.50 ± 0.10	0.62 ± 0.18
Mitotic figures (10^6)	0.23 ± 0.06	0.22 ± 0.06	0.20 ± 0.04	0.25 ± 0.07
Fat cells (10^6)	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000
Mast cells (10^6)	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000
Smudge cells (10^6)	4.56 ± 0.39	4.08 ± 0.37	3.92 ± 0.50	3.87 ± 0.30
Osteoblasts (10^6)	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000
Osteoclasts (10^6)	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000
Other bone marrow cells (10^6)	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000
Neutrophilic hypersegments (10^6)	1.93 ± 0.27	1.67 ± 0.27	1.61 ± 0.44	1.56 ± 0.33

TABLE K5
Hematology and Bone Marrow Data for Mice in the 2-Year Gavage Study of AZT/5,000 U α-Interferon A/D

	Vehicle Control	30 mg AZT/kg + 5,000 U α-IFN A/D	60 mg AZT/kg + 5,000 U α-IFN A/D	120 mg AZT/kg + 5,000 U α-IFN A/D
Female				
Hematology				
Clinical Pathology Groups				
n				
Week 14	10	9	9	9
Week 27	9	10	9	10
Week 40	9	9	10	10
Week 54	9	9	9	9
Week 66	8	10	9	10
Week 79	8	7	8	8
Hematocrit (%)				
Week 14	46.0 ± 0.6	45.9 ± 0.5	45.2 ± 0.8	44.6 ± 0.5
Week 27	45.6 ± 0.5	43.9 ± 0.4	43.9 ± 0.5	44.1 ± 0.5
Week 40	45.8 ± 0.4	45.4 ± 0.5	44.8 ± 0.5	44.7 ± 0.4
Week 54	46.7 ± 0.4	45.3 ± 0.4	45.1 ± 0.7**	44.9 ± 0.3**
Week 66	46.2 ± 0.3	46.0 ± 0.3	45.1 ± 0.5	46.2 ± 0.6
Week 79	49.3 ± 4.1	44.7 ± 0.5	43.4 ± 0.7	44.7 ± 0.6
Hemoglobin (g/dL)				
Week 14	15.3 ± 0.2	15.3 ± 0.2	15.2 ± 0.2	14.8 ± 0.2
Week 27	15.2 ± 0.2	14.7 ± 0.2	14.6 ± 0.1	14.7 ± 0.1
Week 40	15.5 ± 0.1	15.3 ± 0.2	15.1 ± 0.1	15.0 ± 0.2
Week 54	15.5 ± 0.1	15.0 ± 0.1*	14.7 ± 0.2**	14.8 ± 0.1**
Week 66	15.6 ± 0.1	15.6 ± 0.1	15.0 ± 0.1	15.4 ± 0.2
Week 79	16.7 ± 1.4	15.1 ± 0.2	14.6 ± 0.3	14.9 ± 0.3
Erythrocytes (10^6/μL)				
Week 14	10.27 ± 0.20	9.90 ± 0.14	9.64 ± 0.17*	9.29 ± 0.13**
Week 27	9.72 ± 0.09	9.03 ± 0.08**	8.83 ± 0.09**	8.79 ± 0.06**
Week 40	9.91 ± 0.09	9.40 ± 0.11**	9.09 ± 0.08**	8.86 ± 0.08**
Week 54	9.75 ± 0.12	8.92 ± 0.06**	8.63 ± 0.12**	8.54 ± 0.07**
Week 66	9.80 ± 0.09	9.19 ± 0.06**	8.83 ± 0.13**	8.99 ± 0.16**
Week 79	10.15 ± 0.83	8.71 ± 0.08**	8.34 ± 0.14**	8.33 ± 0.11**
Reticulocytes (10^6/μL)				
Week 14	0.15 ± 0.03[c]	0.16 ± 0.02	0.17 ± 0.02[d]	0.14 ± 0.02[d]
Week 27	0.25 ± 0.02	0.20 ± 0.02	0.20 ± 0.02	0.15 ± 0.02**
Week 40	0.24 ± 0.02	0.15 ± 0.02*	0.16 ± 0.02*	0.10 ± 0.02**
Week 54	0.32 ± 0.02	0.36 ± 0.02	0.32 ± 0.03	0.42 ± 0.03*
Week 66	0.27 ± 0.04	0.22 ± 0.02	0.22 ± 0.03	0.24 ± 0.02
Week 79	0.23 ± 0.03	0.18 ± 0.01	0.19 ± 0.02	0.19 ± 0.02
Nucleated erythrocytes (10^3/μL)				
Week 14	0.01 ± 0.01	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00
Week 27	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00
Week 40	0.00 ± 0.00	0.01 ± 0.01	0.01 ± 0.01	0.01 ± 0.01
Week 54	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00
Week 66	0.01 ± 0.01	0.00 ± 0.00[c]	0.00 ± 0.00	0.00 ± 0.00
Week 79	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00
Mean cell volume (fL)				
Week 14	44.9 ± 0.5	46.4 ± 0.4*	46.9 ± 0.4**	48.0 ± 0.3**
Week 27	46.9 ± 0.3	48.6 ± 0.2**	49.7 ± 0.1**	50.1 ± 0.3**
Week 40	46.2 ± 0.3	48.3 ± 0.2**	49.2 ± 0.3**	50.4 ± 0.2**
Week 54	47.9 ± 0.5	50.8 ± 0.2**	52.2 ± 0.2**	52.6 ± 0.2**
Week 66	47.2 ± 0.5	50.1 ± 0.3**	51.1 ± 0.4**	51.5 ± 0.4**
Week 79	48.6 ± 0.3	51.3 ± 0.3**	52.2 ± 0.7**	53.6 ± 0.5**

TABLE K5
Hematology and Bone Marrow Data for Mice in the 2-Year Gavage Study of AZT/5,000 U α-Interferon A/D

	Vehicle Control	30 mg AZT/kg + 5,000 U α-IFN A/D	60 mg AZT/kg + 5,000 U α-IFN A/D	120 mg AZT/kg + 5,000 U α-IFN A/D
Female (continued)				
Hematology (continued)				
Clinical Pathology Groups (continued)				
n				
Week 14	10	9	9	9
Week 27	9	10	9	10
Week 40	9	9	10	10
Week 54	9	9	9	9
Week 66	8	10	9	10
Week 79	8	7	8	8
Mean cell hemoglobin (pg)				
Week 14	15.0 ± 0.1	15.5 ± 0.1**	15.8 ± 0.1**	16.0 ± 0.2**
Week 27	15.6 ± 0.1	16.3 ± 0.1**	16.6 ± 0.1**	16.7 ± 0.1**
Week 40	15.6 ± 0.1	16.3 ± 0.0**	16.6 ± 0.1**	16.9 ± 0.1**
Week 54	15.9 ± 0.1	16.8 ± 0.1**	17.1 ± 0.1**	17.4 ± 0.1**
Week 66	15.9 ± 0.2	17.0 ± 0.1**	17.0 ± 0.1**	17.1 ± 0.2**
Week 79	16.4 ± 0.1	17.3 ± 0.2**	17.5 ± 0.3**	17.8 ± 0.2**
Mean cell hemoglobin concentration (g/dL)				
Week 14	33.3 ± 0.2	33.4 ± 0.2	33.6 ± 0.2	33.4 ± 0.3
Week 27	33.4 ± 0.1	33.5 ± 0.2	33.3 ± 0.2	33.3 ± 0.1
Week 40	33.9 ± 0.2	33.8 ± 0.2	33.8 ± 0.2	33.6 ± 0.2
Week 54	33.1 ± 0.3	33.2 ± 0.2	32.7 ± 0.2	33.0 ± 0.2
Week 66	33.8 ± 0.2	33.9 ± 0.1	33.3 ± 0.1	33.2 ± 0.2
Week 79	33.7 ± 0.2	33.8 ± 0.2	33.5 ± 0.2	33.2 ± 0.2
Platelets (10^3/μL)				
Week 14	979.9 ± 57.4	810.9 ± 61.3	915.1 ± 75.4	956.3 ± 47.7
Week 27	953.6 ± 37.9	1,080.5 ± 52.7	1,060.4 ± 48.1	1,094.0 ± 60.8
Week 40	1,074.8 ± 51.0	1,153.4 ± 33.4	1,146.4 ± 43.7	1,158.9 ± 62.7
Week 54	1,053.0 ± 41.0	1,039.8 ± 55.5	1,180.9 ± 71.1	1,211.4 ± 65.5
Week 66	1,016.3 ± 50.5	945.6 ± 45.3	1,180.0 ± 39.8	1,122.0 ± 56.6
Week 79	1,115.0 ± 92.0	1,357.4 ± 75.1	1,352.3 ± 108.3	1,342.6 ± 74.7
Leukocytes (10^3/μL)				
Week 14	6.78 ± 0.34	5.89 ± 0.35	5.70 ± 0.25	6.50 ± 0.66
Week 27	6.79 ± 0.47	6.35 ± 0.35	5.78 ± 0.23	6.18 ± 0.32
Week 40	6.15 ± 0.34	6.24 ± 0.44	6.52 ± 0.33	5.08 ± 0.37
Week 54	4.87 ± 0.32	4.62 ± 0.26	4.38 ± 0.21	5.18 ± 0.25
Week 66	4.69 ± 0.33	4.87 ± 0.35[c]	4.44 ± 0.39	4.41 ± 0.20
Week 79	4.02 ± 0.18	5.45 ± 0.31*	4.83 ± 0.45	4.81 ± 0.31
Segmented neutrophils (10^3/μL)				
Week 14	1.12 ± 0.10	0.85 ± 0.13	0.88 ± 0.11	1.22 ± 0.35
Week 27	0.96 ± 0.10	0.97 ± 0.06	1.02 ± 0.10	0.91 ± 0.10
Week 40	1.05 ± 0.12	1.28 ± 0.15	1.11 ± 0.12	0.86 ± 0.09
Week 54	0.91 ± 0.08	0.99 ± 0.11	0.98 ± 0.13	0.86 ± 0.07
Week 66	1.25 ± 0.27	1.06 ± 0.09[c]	0.96 ± 0.13	0.95 ± 0.08
Week 79	1.22 ± 0.19	1.10 ± 0.05	1.16 ± 0.13	0.99 ± 0.10
Lymphocytes (10^3/μL)				
Week 14	5.38 ± 0.30	4.80 ± 0.31	4.59 ± 0.26	5.00 ± 0.56
Week 27	5.70 ± 0.44	5.13 ± 0.31	4.56 ± 0.17*	5.08 ± 0.27
Week 40	4.95 ± 0.30	4.75 ± 0.28	5.26 ± 0.28	4.04 ± 0.32
Week 54	3.68 ± 0.29	3.16 ± 0.17	3.08 ± 0.19	3.96 ± 0.22
Week 66	3.10 ± 0.45	3.48 ± 0.28[c]	3.11 ± 0.31	3.19 ± 0.15
Week 79	2.62 ± 0.20	3.85 ± 0.46*	3.40 ± 0.38	3.59 ± 0.20*

TABLE K5
Hematology and Bone Marrow Data for Mice in the 2-Year Gavage Study of AZT/5,000 U α-Interferon A/D

	Vehicle Control	30 mg AZT/kg + 5,000 U α-IFN A/D	60 mg AZT/kg + 5,000 U α-IFN A/D	120 mg AZT/kg + 5,000 U α-IFN A/D
Female (continued)				
Hematology (continued)				
Clinical Pathology Groups (continued)				
n				
Week 14	10	9	9	9
Week 27	9	10	9	10
Week 40	9	9	10	10
Week 54	9	9	9	9
Week 66	8	10	9	10
Week 79	8	7	8	8
Atypical lymphocytes (10^3/μL)				
Week 14	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00
Week 27	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00
Week 40	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00
Week 54	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00
Week 66	0.00 ± 0.00	0.00 ± 0.00[c]	0.00 ± 0.00	0.00 ± 0.00
Week 79	0.00 ± 0.00	0.19 ± 0.19	0.00 ± 0.00	0.00 ± 0.00
Monocytes (10^3/μL)				
Week 14	0.10 ± 0.04	0.08 ± 0.03	0.06 ± 0.02	0.07 ± 0.04
Week 27	0.00 ± 0.00	0.02 ± 0.02	0.01 ± 0.01	0.01 ± 0.01
Week 40	0.03 ± 0.02	0.00 ± 0.00	0.04 ± 0.02	0.01 ± 0.01
Week 54	0.19 ± 0.05	0.20 ± 0.06	0.14 ± 0.03	0.20 ± 0.05
Week 66	0.19 ± 0.03	0.17 ± 0.01[c]	0.17 ± 0.03	0.13 ± 0.01
Week 79	0.11 ± 0.01	0.09 ± 0.03	0.14 ± 0.02	0.11 ± 0.03
Eosinophils (10^3/μL)				
Week 14	0.18 ± 0.04	0.16 ± 0.04	0.16 ± 0.04	0.21 ± 0.04
Week 27	0.13 ± 0.03	0.22 ± 0.05	0.18 ± 0.05	0.18 ± 0.04
Week 40	0.13 ± 0.03	0.20 ± 0.06	0.12 ± 0.03	0.17 ± 0.05
Week 54	0.09 ± 0.03	0.27 ± 0.06*	0.18 ± 0.04	0.16 ± 0.03
Week 66	0.14 ± 0.03	0.16 ± 0.04[c]	0.20 ± 0.03	0.13 ± 0.02
Week 79	0.07 ± 0.02	0.21 ± 0.05*	0.13 ± 0.02	0.12 ± 0.01
Core Groups				
n	10	9	10	10
Hematocrit (%)	42.6 ± 3.2	46.8 ± 3.4	40.6 ± 0.6	40.1 ± 0.4
Hemoglobin (g/dL)	13.0 ± 0.9	14.6 ± 0.9	12.5 ± 0.2	12.2 ± 0.2
Erythrocytes (10^6/μL)	9.42 ± 0.83	9.85 ± 0.67	8.19 ± 0.17	7.95 ± 0.10*
Reticulocytes (10^6/μL)	0.22 ± 0.02	0.25 ± 0.02	0.13 ± 0.02*	0.12 ± 0.02*
Nucleated erythrocytes (10^3/μL)	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00
Mean cell volume (fL)	45.7 ± 1.3	47.5 ± 0.6	49.7 ± 0.7**	50.5 ± 0.6**
Mean cell hemoglobin (pg)	14.0 ± 0.3	14.9 ± 0.3*	15.3 ± 0.2**	15.3 ± 0.2**
Mean cell hemoglobin concentration (g/dL)	30.7 ± 0.3	31.4 ± 0.8	30.8 ± 0.2	30.3 ± 0.2
Platelets (10^3/μL)	1,130.0 ± 130.3	1,220.2 ± 149.6	1,645.9 ± 67.1**	1,599.9 ± 72.9**
Leukocytes (10^3/μL)	8.48 ± 0.97	8.12 ± 0.94	8.38 ± 1.14	7.02 ± 0.65
Segmented neutrophils (10^3/μL)	2.60 ± 0.37	3.04 ± 0.50	3.20 ± 0.91	2.22 ± 0.28
Lymphocytes (10^3/μL)	5.48 ± 0.78	4.71 ± 0.63	4.70 ± 0.71	4.41 ± 0.50
Atypical lymphocytes (10^3/μL)	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00
Monocytes (10^3/μL)	0.29 ± 0.05	0.23 ± 0.04	0.29 ± 0.05	0.24 ± 0.03
Eosinophils (10^3/μL)	0.11 ± 0.04	0.15 ± 0.05	0.20 ± 0.04	0.15 ± 0.04

TABLE K5
Hematology and Bone Marrow Data for Mice in the 2-Year Gavage Study of AZT/5,000 U α-Interferon A/D

	Vehicle Control	30 mg AZT/kg + 5,000 U α-IFN A/D	60 mg AZT/kg + 5,000 U α-IFN A/D	120 mg AZT/kg + 5,000 U α-IFN A/D
Female (continued)				
Bone Marrow Analyses				
Clinical Pathology Groups				
n				
Week 54	9	9	9	9
Week 66	8	10	8	9
Week 79	9	7	9	9
Total femoral count (10^6/femur)				
Week 54	26.7 ± 1.5	27.2 ± 2.2	26.6 ± 1.4	27.5 ± 2.2
Week 66	28.9 ± 1.6	28.2 ± 0.7	28.6 ± 0.8	26.8 ± 1.0
Week 79	33.3 ± 2.1	30.8 ± 1.5	30.1 ± 0.9	30.1 ± 0.9
M:E ratio				
Week 54	1.86 ± 0.09	2.04 ± 0.08	1.81 ± 0.11	2.08 ± 0.15
Week 66	1.95 ± 0.16	1.94 ± 0.14	2.45 ± 0.35	2.43 ± 0.12*
Week 79	2.24 ± 0.30	2.31 ± 0.23	2.57 ± 0.23	3.04 ± 0.24
Rubriblasts (10^6)				
Week 54	0.78 ± 0.12	0.69 ± 0.09	0.80 ± 0.06	0.51 ± 0.07
Week 66	0.34 ± 0.06	0.37 ± 0.05	0.47 ± 0.05	0.28 ± 0.03
Week 79	0.31 ± 0.03	0.31 ± 0.04	0.32 ± 0.04	0.39 ± 0.06
Prorubricytes (10^6)				
Week 54	0.57 ± 0.10	0.55 ± 0.09	0.65 ± 0.08	0.49 ± 0.08
Week 66	0.26 ± 0.05	0.47 ± 0.07	0.42 ± 0.07	0.41 ± 0.06
Week 79	1.13 ± 0.19	1.07 ± 0.17	0.89 ± 0.12	0.91 ± 0.16
Rubricytes (10^6)				
Week 54	3.61 ± 0.19	3.63 ± 0.39	3.81 ± 0.27	3.59 ± 0.34
Week 66	4.21 ± 0.50	4.30 ± 0.21	4.28 ± 0.42	3.58 ± 0.29
Week 79	4.75 ± 0.47	4.27 ± 0.25	3.85 ± 0.34	3.21 ± 0.23**
Metarubricytes (10^6)				
Week 54	1.80 ± 0.18	1.60 ± 0.13	1.72 ± 0.12	1.92 ± 0.16
Week 66	1.59 ± 0.15	1.34 ± 0.12	0.92 ± 0.13**	0.96 ± 0.09**
Week 79	0.97 ± 0.15	0.85 ± 0.16	0.91 ± 0.27	0.58 ± 0.09
Myeloblasts (10^6)				
Week 54	0.34 ± 0.03	0.37 ± 0.04	0.30 ± 0.04	0.33 ± 0.11
Week 66	0.44 ± 0.09	0.40 ± 0.05	0.33 ± 0.04	0.40 ± 0.06
Week 79	0.46 ± 0.08	0.46 ± 0.07	0.50 ± 0.06	0.53 ± 0.09
Promyelocytes (10^6)				
Week 54	0.28 ± 0.04	0.18 ± 0.05	0.20 ± 0.06	0.24 ± 0.06
Week 66	0.30 ± 0.05	0.26 ± 0.07	0.32 ± 0.07	0.53 ± 0.19
Week 79	0.50 ± 0.09	0.58 ± 0.09	0.61 ± 0.09	0.68 ± 0.23
Neutrophilic myelocytes (10^6)				
Week 54	0.94 ± 0.07	0.99 ± 0.14	0.60 ± 0.09	0.92 ± 0.12
Week 66	1.00 ± 0.09	0.69 ± 0.09	0.75 ± 0.06	1.68 ± 0.42
Week 79	1.37 ± 0.26	1.38 ± 0.17	1.16 ± 0.18	1.64 ± 0.29
Neutrophilic metamyelocytes (10^6)				
Week 54	3.22 ± 0.19	3.39 ± 0.45	2.61 ± 0.12	3.36 ± 0.42
Week 66	2.78 ± 0.21	2.58 ± 0.15	3.17 ± 0.26	1.62 ± 0.33
Week 79	1.66 ± 0.40	1.01 ± 0.17	0.99 ± 0.08	1.26 ± 0.16
Neutrophilic bands (10^6)				
Week 54	0.25 ± 0.04	0.29 ± 0.10	0.20 ± 0.03	0.24 ± 0.04
Week 66	0.18 ± 0.04	0.28 ± 0.03	0.39 ± 0.09*	0.57 ± 0.11**
Week 79	2.20 ± 0.23	2.58 ± 0.43	2.44 ± 0.30	2.29 ± 0.27

TABLE K5
Hematology and Bone Marrow Data for Mice in the 2-Year Gavage Study of AZT/5,000 U α-Interferon A/D

	Vehicle Control	30 mg AZT/kg + 5,000 U α-IFN A/D	60 mg AZT/kg + 5,000 U α-IFN A/D	120 mg AZT/kg + 5,000 U α-IFN A/D
Female (continued)				
Bone Marrow Analyses (continued)				
Clinical Pathology Groups (continued)				
n				
Week 54	9	9	9	9
Week 66	8	10	8	9
Week 79	9	7	9	9
Neutrophilic segments (10^6)				
Week 54	6.63 ± 0.41	7.01 ± 0.56	7.77 ± 0.61	7.53 ± 0.97
Week 66	6.59 ± 0.59	7.67 ± 0.48	8.11 ± 0.24	7.04 ± 0.50
Week 79	8.00 ± 0.66	7.84 ± 0.61	7.84 ± 0.26	8.09 ± 0.48
Eosinophilic myelocytes (10^6)				
Week 54	0.054 ± 0.021	0.051 ± 0.017	0.033 ± 0.012	0.039 ± 0.021
Week 66	0.015 ± 0.010	0.028 ± 0.013	0.050 ± 0.016	0.080 ± 0.037
Week 79	0.026 ± 0.013	0.196 ± 0.050*	0.143 ± 0.046	0.081 ± 0.034
Eosinophilic metamyelocytes (10^6)				
Week 54	0.22 ± 0.04	0.36 ± 0.06	0.33 ± 0.06	0.34 ± 0.05
Week 66	0.20 ± 0.05	0.12 ± 0.03	0.23 ± 0.04	0.10 ± 0.03
Week 79	0.12 ± 0.02	0.20 ± 0.05	0.10 ± 0.03	0.11 ± 0.03
Eosinophilic bands (10^6)				
Week 54	0.14 ± 0.07	0.16 ± 0.06	0.12 ± 0.04	0.17 ± 0.03
Week 66	0.11 ± 0.04	0.12 ± 0.04	0.18 ± 0.03	0.18 ± 0.05
Week 79	0.17 ± 0.04	0.14 ± 0.04	0.26 ± 0.04	0.24 ± 0.04
Eosinophilic segments (10^6)				
Week 54	0.25 ± 0.06	0.33 ± 0.04	0.35 ± 0.05	0.34 ± 0.06
Week 66	0.32 ± 0.08	0.22 ± 0.07	0.34 ± 0.01	0.37 ± 0.05
Week 79	0.27 ± 0.05	0.29 ± 0.08	0.35 ± 0.08	0.23 ± 0.06
Basophilic myelocytes (10^6)				
Week 54	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000
Week 66	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000
Week 79	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000
Basophilic metamyelocytes (10^6)				
Week 54	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000
Week 66	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000
Week 79	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000
Basophilic bands (10^6)				
Week 54	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000
Week 66	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000
Week 79	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000
Basophilic segments (10^6)				
Week 54	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000
Week 66	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000
Week 79	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000
Bone marrow lymphocytes (10^6)				
Week 54	3.78 ± 0.34	3.55 ± 0.23	3.27 ± 0.33	4.05 ± 0.42
Week 66	4.63 ± 0.55	4.57 ± 0.77	4.04 ± 0.38	4.63 ± 0.63
Week 79	5.10 ± 1.08	4.37 ± 0.77	4.40 ± 0.33	4.62 ± 0.54
Bone marrow macrophages (10^6)				
Week 54	0.16 ± 0.02	0.23 ± 0.08	0.18 ± 0.04	0.21 ± 0.04
Week 66	0.16 ± 0.01	0.14 ± 0.03	0.07 ± 0.02	0.13 ± 0.04
Week 79	0.14 ± 0.02	0.19 ± 0.06	0.13 ± 0.02	0.14 ± 0.05

TABLE K5
Hematology and Bone Marrow Data for Mice in the 2-Year Gavage Study of AZT/5,000 U α-Interferon A/D

	Vehicle Control	30 mg AZT/kg + 5,000 U α-IFN A/D	60 mg AZT/kg + 5,000 U α-IFN A/D	120 mg AZT/kg + 5,000 U α-IFN A/D
Female (continued)				
Bone Marrow Analyses (continued)				
Clinical Pathology Groups (continued)				
n				
Week 54	9	9	9	9
Week 66	8	10	8	9
Week 79	9	7	9	9
Bone marrow monocytes (10^6)				
Week 54	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00
Week 66	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00
Week 79	0.37 ± 0.12	0.16 ± 0.06	0.25 ± 0.04	0.22 ± 0.05
Megakaryo cells (10^6)				
Week 54	0.09 ± 0.02	0.13 ± 0.02	0.12 ± 0.03	0.06 ± 0.02
Week 66	0.07 ± 0.02	0.11 ± 0.02	0.15 ± 0.03	0.10 ± 0.02
Week 79	0.07 ± 0.02	0.08 ± 0.04	0.08 ± 0.02	0.09 ± 0.02
Plasma cells (10^6)				
Week 54	0.20 ± 0.03	0.21 ± 0.06	0.18 ± 0.04	0.24 ± 0.06
Week 66	0.24 ± 0.04	0.22 ± 0.04	0.21 ± 0.02	0.17 ± 0.04
Week 79	0.22 ± 0.05	0.31 ± 0.06	0.30 ± 0.04	0.26 ± 0.06
Mitotic figures (10^6)				
Week 54	0.23 ± 0.06	0.23 ± 0.04	0.27 ± 0.04	0.29 ± 0.03
Week 66	0.21 ± 0.04	0.13 ± 0.03	0.28 ± 0.05	0.17 ± 0.04
Week 79	0.31 ± 0.06	0.26 ± 0.05	0.22 ± 0.04	0.23 ± 0.03
Fat cells (10^6)				
Week 54	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000
Week 66	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000
Week 79	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000
Mast cells (10^6)				
Week 54	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000
Week 66	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000
Week 79	0.000 ± 0.000	0.046 ± 0.046	0.000 ± 0.000	0.000 ± 0.000
Smudge cells (10^6)				
Week 54	3.21 ± 0.55	3.28 ± 0.52	3.03 ± 0.43	2.66 ± 0.31
Week 66	5.25 ± 0.37	4.15 ± 0.26*	3.82 ± 0.25**	3.71 ± 0.33**
Week 79	5.16 ± 0.32	4.18 ± 0.47	4.38 ± 0.30	4.29 ± 0.22
Osteoblasts (10^6)				
Week 54	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000
Week 66	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000
Week 79	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000
Osteoclasts (10^6)				
Week 54	0.008 ± 0.008	0.012 ± 0.008	0.006 ± 0.006	0.006 ± 0.006
Week 66	0.038 ± 0.015	0.033 ± 0.013	0.035 ± 0.020	0.017 ± 0.008
Week 79	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000
Other bone marrow cells (10^6)				
Week 54	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000
Week 66	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000
Week 79	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000
Neutrophilic hypersegments (10^6)				
Week 54	0.19 ± 0.04	0.28 ± 0.05	0.21 ± 0.08	0.31 ± 0.08
Week 66	0.06 ± 0.03	0.06 ± 0.03	0.08 ± 0.04	0.02 ± 0.02
Week 79	0.08 ± 0.06	0.14 ± 0.04	0.10 ± 0.05	0.08 ± 0.04

TABLE K5
Hematology and Bone Marrow Data for Mice in the 2-Year Gavage Study of AZT/5,000 U α-Interferon A/D

	Vehicle Control	30 mg AZT/kg + 5,000 U α-IFN A/D	60 mg AZT/kg + 5,000 U α-IFN A/D	120 mg AZT/kg + 5,000 U α-IFN A/D
Female (continued)				
Bone Marrow Analyses (continued)				
Core Groups				
n	10	10	9	10
Total femoral count (10^6/femur)	29.6 ± 2.4	29.9 ± 2.4	22.9 ± 1.7	24.4 ± 1.7
M:E ratio	2.78 ± 0.39	2.76 ± 0.22	5.06 ± 0.57**	6.26 ± 0.73**
Rubriblasts (10^6)	0.23 ± 0.06	0.17 ± 0.04	0.12 ± 0.03	0.14 ± 0.02
Prorubricytes (10^6)	0.94 ± 0.16	0.96 ± 0.21	0.41 ± 0.08*	0.49 ± 0.05
Rubricytes (10^6)	3.59 ± 0.41	3.32 ± 0.37	1.59 ± 0.18**	1.59 ± 0.25**
Metarubricytes (10^6)	1.07 ± 0.20	0.86 ± 0.10	0.47 ± 0.09*	0.38 ± 0.05**
Myeloblasts (10^6)	0.45 ± 0.09	0.58 ± 0.12	0.30 ± 0.03	0.45 ± 0.06
Promyelocytes (10^6)	0.65 ± 0.08	0.78 ± 0.10	0.51 ± 0.09	0.60 ± 0.08
Neutrophilic myelocytes (10^6)	1.53 ± 0.22	1.69 ± 0.14	1.24 ± 0.12	1.61 ± 0.21
Neutrophilic metamyelocytes (10^6)	1.67 ± 0.17	1.93 ± 0.25	1.42 ± 0.13	1.47 ± 0.13
Neutrophilic bands (10^6)	3.24 ± 0.38	2.61 ± 0.25	2.30 ± 0.23	3.06 ± 0.29
Neutrophilic segments (10^6)	6.45 ± 0.52	6.01 ± 0.88	5.54 ± 0.53	6.97 ± 0.90
Eosinophilic myelocytes (10^6)	0.055 ± 0.025	0.028 ± 0.013	0.062 ± 0.019	0.021 ± 0.009
Eosinophilic metamyelocytes (10^6)	0.10 ± 0.04	0.12 ± 0.03	0.14 ± 0.03	0.14 ± 0.03
Eosinophilic bands (10^6)	0.21 ± 0.04	0.26 ± 0.04	0.26 ± 0.04	0.22 ± 0.04
Eosinophilic segments (10^6)	0.08 ± 0.03	0.15 ± 0.03	0.10 ± 0.02	0.12 ± 0.02
Basophilic myelocytes (10^6)	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000
Basophilic metamyelocytes (10^6)	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000
Basophilic bands (10^6)	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000
Basophilic segments (10^6)	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000
Bone marrow lymphocytes (10^6)	4.14 ± 0.82	5.28 ± 0.83	4.22 ± 0.71	3.15 ± 0.40
Bone marrow macrophages (10^6)	0.08 ± 0.02	0.12 ± 0.02	0.08 ± 0.02	0.09 ± 0.03
Bone marrow monocytes (10^6)	0.17 ± 0.05	0.25 ± 0.05	0.16 ± 0.04	0.18 ± 0.04
Megakaryo cells (10^6)	0.06 ± 0.02	0.07 ± 0.02	0.02 ± 0.01	0.06 ± 0.02
Plasma cells (10^6)	0.30 ± 0.06	0.50 ± 0.10	0.41 ± 0.06	0.43 ± 0.07
Mitotic figures (10^6)	0.31 ± 0.06	0.26 ± 0.05	0.19 ± 0.03	0.19 ± 0.06
Fat cells (10^6)	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000
Mast cells (10^6)	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000
Smudge cells (10^6)	4.33 ± 0.73	3.95 ± 0.40	3.34 ± 0.33	3.03 ± 0.40
Osteoblasts (10^6)	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000
Osteoclasts (10^6)	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000
Other bone marrow cells (10^6)	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000
Neutrophilic hypersegments (10^6)	1.25 ± 0.19	1.30 ± 0.21	1.27 ± 0.38	1.87 ± 0.43

* Significantly different ($P \le 0.05$) from the control group by Dunn's or Shirley's test
** $P \le 0.01$
[a] Mean ± standard error. Statistical tests were performed on unrounded data.
[b] n = 8
[c] n = 9
[d] n = 6

APPENDIX L
REPRODUCTIVE TISSUE EVALUATIONS AND ESTROUS CYCLE CHARACTERIZATION

TABLE L1
Summary of Reproductive Tissue Evaluations and Estrous Cycle Characterization for Mice in the 14-Week Gavage Study of AZT[a]

	Vehicle Control	100 mg/kg	800 mg/kg	2,000 mg/kg
Male				
n	10	10	10	10
Core Study				
Weights (g)				
Necropsy body wt	32.4 ± 0.6	35.1 ± 1.1	33.8 ± 0.7	32.0 ± 0.6
L. cauda epididymis	0.0195 ± 0.0010	0.0215 ± 0.0015	0.0217 ± 0.0007	0.0194 ± 0.0009
L. epididymis	0.0470 ± 0.0014	0.0526 ± 0.0019*	0.0512 ± 0.0016[b]	0.0443 ± 0.0013
L. testis	0.1152 ± 0.0026	0.1196 ± 0.0027	0.1119 ± 0.0046	0.0996 ± 0.0020**
Spermatid measurements				
Spermatid heads (10^7/g testis)	20.34 ± 1.32	19.32 ± 0.76	19.84 ± 1.03	19.71 ± 0.81
Spermatid heads (10^7/testis)	2.32 ± 0.12	2.32 ± 0.11	2.22 ± 0.15	1.97 ± 0.10
Spermatid count (mean/10^{-4} mL suspension)	72.58 ± 3.90	72.35 ± 3.56	69.20 ± 4.63	61.45 ± 3.07
Epididymal spermatozoal measurements				
Motility (%)	33.36 ± 6.69	37.96 ± 5.58	24.77 ± 4.64	23.15 ± 3.37
Concentration (10^6/g cauda epididymal tissue)	987 ± 87	857 ± 61	835 ± 60	896 ± 93
Recovery Study				
Weights (g)				
Necropsy body wt	37.1 ± 1.0	39.7 ± 0.6	40.0 ± 1.2	37.1 ± 0.9
L. cauda epididymis	0.0174 ± 0.0007[b]	0.0181 ± 0.0008	0.0178 ± 0.0005	0.0182 ± 0.0007
L. epididymis	0.0471 ± 0.0009	0.0493 ± 0.0012	0.0493 ± 0.0010	0.0461 ± 0.0011
L. testis	0.1175 ± 0.0021	0.1180 ± 0.0028	0.1177 ± 0.0026	0.1122 ± 0.0014
Spermatid measurements				
Spermatid heads (10^7/g testis)	21.23 ± 1.17	23.29 ± 1.25	23.14 ± 0.94	23.09 ± 0.90
Spermatid heads (10^7/testis)	2.50 ± 0.15	2.73 ± 0.10	2.71 ± 0.10	2.59 ± 0.10
Spermatid count (mean/10^{-4} mL suspension)	78.20 ± 4.79	85.23 ± 3.25	84.75 ± 3.03	80.83 ± 2.99
Epididymal spermatozoal measurements				
Motility (%)	92.49 ± 0.62	91.23 ± 0.82	91.89 ± 0.96	91.80 ± 0.81
Concentration (10^6/g cauda epididymal tissue)	1,582 ± 105[b]	1,319 ± 59*	1,466 ± 89	1,023 ± 70**

TABLE L1
Summary of Reproductive Tissue Evaluations and Estrous Cycle Characterization for Mice in the 14-Week Gavage Study of AZT

	Vehicle Control	100 mg/kg	800 mg/kg	2,000 mg/kg
Female				
n	10	10	10	9
Initial smear (end of dosing)				
Estrous cycle length (days)	4.55 ± 0.16	4.28 ± 0.12[c]	4.55 ± 0.22	4.56 ± 0.18
Estrous stages (% of cycle)				
Diestrus	25.0	33.3	24.2	28.7
Proestrus	15.8	15.8	19.2	23.1
Estrus	40.0	31.7	37.5	25.9
Metestrus	18.3	17.5	19.2	19.4
Uncertain diagnoses	0.8	1.7	0.0	2.8
Final smear (end of recovery)				
Necropsy body wt	30.8 ± 1.5	32.2 ± 0.7	33.3 ± 1.1	29.8 ± 1.1
Estrous cycle length (days)	4.25 ± 0.13	4.10 ± 0.07	4.25 ± 0.13	4.06 ± 0.06
Estrous stages (% of cycle)				
Diestrus	27.5	36.7	27.5	31.5
Proestrus	17.5	18.3	13.3	16.7
Estrus	34.2	31.7	36.7	32.4
Metestrus	20.8	23.3	22.5	19.4

* Significantly different ($P \leq 0.05$) from the vehicle control group by Dunnett's test (core study, left epididymal weight) or Shirley's test (recovery study, epididymal spermatozoal concentration)

** Significantly different ($P \leq 0.01$) from the vehicle control group by Williams' test (core study, left testis weight) or Shirley's test (recovery study, epididymal spermatozoal concentration)

[a] Weights, spermatid and epididymal spermatozoal measurements, and estrous cycle lengths are presented as mean ± standard error. Differences from the vehicle control group for necropsy body weight, left cauda epididymal weight (core study), and organ weights (recovery study) are not significant by Dunnett's test; differences from the vehicle control group for spermatid measurements, epididymal spermatozoal measurements (core study), epididymal spermatozoal motility (recovery study), and estrous cycle length are not significant by Dunn's test. By multivariate analysis of variance, dosed females do not differ significantly from the vehicle control females in the relative length of time spent in the estrous stages.

[b] n = 9

[c] Estrous cycle was longer than 12 days or was unclear in 1 of 10 animals.

APPENDIX M
NEUROBEHAVIORAL DATA

TABLE M1
Neurobehavioral Data for Mice in the 14-Week Gavage Study of AZT[a]

	Vehicle Control	100 mg/kg	800 mg/kg	2,000 mg/kg
Male				
Core Study				
n	10	10	10	10
Body weight (g)				
Day −3	19.6 ± 1.0	19.7 ± 0.7	21.4 ± 0.5	21.6 ± 0.6
Day 44	28.5 ± 0.4	28.8 ± 0.5	27.9 ± 0.4	28.0 ± 0.5
Day 88	32.2 ± 0.6	34.5 ± 1.0	33.0 ± 0.7	31.6 ± 0.6
Body temperature (° C)				
Day −3	36.5 ± 0.2	37.0 ± 0.2	37.3 ± 0.2**	38.0 ± 0.3**
Day 44	37.2 ± 0.2	37.3 ± 0.2	36.9 ± 0.2	36.7 ± 0.1
Day 88	37.1 ± 0.2	36.7 ± 0.2	36.9 ± 0.1	37.5 ± 0.3
Landing footsplay (Trial 1)				
Day −3	47.4 ± 2.6	50.8 ± 2.4	43.7 ± 3.3	51.0 ± 3.2
Day 44	42.1 ± 2.2	40.9 ± 2.9	37.5 ± 2.6	42.3 ± 1.2
Day 88	39.7 ± 2.4	44.8 ± 2.6	44.8 ± 2.9	45.2 ± 1.9
Landing footsplay (Trial 2)				
Day −3	44.5 ± 1.7	50.2 ± 1.6	48.2 ± 2.4	47.0 ± 1.6
Day 44	37.6 ± 1.1	41.6 ± 1.8	38.8 ± 2.2	42.0 ± 2.0
Day 88	41.4 ± 2.7	43.7 ± 2.3	41.2 ± 2.4	42.4 ± 2.1
Landing footsplay (avg)				
Day −3	46.0 ± 1.9	50.5 ± 1.5	46.0 ± 2.6	49.0 ± 2.0
Day 44	39.9 ± 1.0	41.3 ± 1.7	38.2 ± 2.0	42.2 ± 1.1
Day 88	40.6 ± 2.5	44.3 ± 2.1	43.0 ± 2.2	43.8 ± 1.4
Forelimb grip strength (Trial 1)				
Day −3	99.0 ± 5.4	115.0 ± 11.6	103.5 ± 8.2	113.5 ± 7.2
Day 44	140.0 ± 6.2	141.0 ± 8.3	136.0 ± 5.0	131.0 ± 9.0
Day 88	130.5 ± 5.4	126.0 ± 4.0	124.0 ± 3.6	130.0 ± 4.0
Forelimb grip strength (Trial 2)				
Day −3	111.0 ± 6.3	100.0 ± 8.8	109.0 ± 6.0	111.5 ± 4.8
Day 44	140.0 ± 6.8	143.0 ± 6.2	134.5 ± 8.2	136.5 ± 8.3
Day 88	128.0 ± 6.2	132.5 ± 3.7	122.0 ± 3.6	128.5 ± 5.9
Forelimb grip strength (avg)				
Day −3	105.0 ± 4.0	107.5 ± 9.4	106.3 ± 6.5	112.5 ± 4.2
Day 44	140.0 ± 6.2	142.0 ± 6.5	135.3 ± 4.9	133.8 ± 7.7
Day 88	129.3 ± 5.4	129.3 ± 3.8	123.0 ± 3.4	129.3 ± 4.8
Hindlimb grip strength (Trial 1)				
Day −3	65.0 ± 6.2	46.0 ± 7.4	60.0 ± 8.9	60.5 ± 6.6
Day 44	48.0 ± 5.0	60.5 ± 7.2	41.5 ± 3.9	60.5 ± 6.2
Day 88	52.5 ± 3.4	56.5 ± 2.4	54.0 ± 2.4	55.5 ± 3.2
Hindlimb grip strength (Trial 2)				
Day −3	57.5 ± 4.0	51.0 ± 6.3	63.0 ± 7.3	54.0 ± 7.1
Day 44	62.5 ± 8.1	58.0 ± 5.8	56.5 ± 7.2	62.0 ± 6.2
Day 88	52.0 ± 3.7	55.0 ± 2.8	54.5 ± 3.3	55.0 ± 3.6
Hindlimb grip strength (avg)				
Day −3	62.3 ± 4.7	48.5 ± 6.3	61.5 ± 7.6	60.3 ± 4.3
Day 44	55.3 ± 6.2	59.3 ± 5.4	49.0 ± 4.9	61.3 ± 5.8
Day 88	52.3 ± 3.4	55.8 ± 2.4	53.8 ± 2.7	55.3 ± 3.3
Total motor activity				
Day −3	837.8 ± 74.2	658.0 ± 97.2	745.9 ± 84.7	734.2 ± 109.6
Day 44	1,534.6 ± 86.7	1,593.5 ± 128.4	1,287.9 ± 74.7	1,377.7 ± 114.9
Day 88	1,593.0 ± 79.0	1,611.3 ± 319.2	1,183.2 ± 118.6	1,397.1 ± 175.1
Ambulatory motor activity				
Day −3	550.9 ± 54.0	443.1 ± 71.6	427.8 ± 67.2	540.2 ± 62.1
Day 44	1,090.3 ± 72.3	1,168.3 ± 99.0	884.8 ± 61.3	983.2 ± 84.2
Day 88	1,141.7 ± 70.1	1,180.5 ± 245.6	838.7 ± 90.1	982.5 ± 132.9

TABLE M1
Neurobehavioral Data for Mice in the 14-Week Gavage Study of AZT

	Vehicle Control	100 mg/kg	800 mg/kg	2,000 mg/kg
Male (continued)				
Core Study (continued)				
n	10	10	10	10
Total nonambulatory motor activity				
Day −3	286.9 ± 24.1	214.9 ± 30.6	318.1 ± 34.3	286.5 ± 19.7
Day 44	444.3 ± 22.0	425.2 ± 33.5	403.1 ± 27.0	394.5 ± 36.8
Day 88	451.3 ± 21.1	430.8 ± 74.9	344.5 ± 30.8	414.6 ± 48.4
Thermal latency (seconds)				
Day −3	0.91 ± 0.09	0.96 ± 0.17	1.25 ± 0.18	0.92 ± 0.10
Day 44	1.29 ± 0.26	0.85 ± 0.08	1.16 ± 0.21	1.11 ± 0.16
Day 88	1.08 ± 0.12	1.16 ± 0.18	0.92 ± 0.07	0.92 ± 0.08
Threshold crossing - acoustic (milliseconds)				
Day −3	23.5 ± 2.9[b]	23.0 ± 1.0[c]	93.0 ± 33.8[d]	25.9 ± 8.2[e]
Day 44	80.4 ± 37.4[f]	46.7 ± 29.7[g]	46.0 ± 8.0[c]	19.0 ± 3.0[c]
Day 88	38.0 ± 6.9[h]	28.3 ± 5.4[h]	51.7 ± 29.6[e]	62.0 ± 19.8[i]
Threshold crossing - air puff (latency)				
Day −3	64.0 ± 10.2	52.0 ± 11.1[i]	54.2 ± 10.5	44.4 ± 9.2
Day 44	40.9 ± 6.8[e]	41.4 ± 7.1[e]	65.3 ± 26.9[h]	29.5 ± 4.6[h]
Day 88	31.4 ± 3.8	28.0 ± 1.4	22.0 ± 4.1	22.2 ± 1.9
Peak amplitude - acoustic (g)				
Day −3	6.90 ± 0.65[b]	10.70 ± 3.30[c]	7.40 ± 1.02[d]	7.47 ± 1.16[e]
Day 44	8.80 ± 2.64[f]	6.47 ± 0.18[g]	5.95 ± 0.35[c]	7.05 ± 0.95[c]
Day 88	8.46 ± 0.94[h]	10.83 ± 1.80[h]	11.17 ± 2.71[e]	7.79 ± 1.40[i]
Peak amplitude - air puff (magnitude)				
Day −3	14.6 ± 2.8	11.1 ± 3.0[i]	17.8 ± 4.3	17.1 ± 5.7
Day 44	13.9 ± 3.8[e]	14.6 ± 5.1[e]	22.7 ± 11.5[h]	14.5 ± 3.3[h]
Day 88	26.2 ± 4.8	24.1 ± 7.0	18.0 ± 4.8	31.2 ± 7.2
Time of peak - acoustic (milliseconds)				
Day −3	31.0 ± 2.6[b]	32.0 ± 4.0[c]	98.0 ± 33.4[d]	29.4 ± 7.6[e]
Day 44	84.4 ± 36.5[f]	49.3 ± 30.3[g]	55.0 ± 13.0[c]	22.0 ± 4.0[c]
Day 88	42.0 ± 6.5[h]	34.0 ± 4.9[h]	56.9 ± 29.1[e]	65.3 ± 19.6[i]
Time of peak - air puff (latency)				
Day −3	73.0 ± 10.1	57.3 ± 11.2[i]	64.2 ± 12.0	54.6 ± 9.5
Day 44	47.4 ± 7.0[e]	49.1 ± 7.2[e]	83.3 ± 34.6[h]	40.5 ± 2.7[h]
Day 88	38.4 ± 3.8	35.0 ± 1.8	31.4 ± 4.2	31.0 ± 3.0
Recovery Study				
n	10	10	10	10
Body weight (g)				
Day −3	21.8 ± 0.3	22.6 ± 0.4	22.5 ± 0.4	22.1 ± 0.4
Day 44	28.8 ± 0.5	29.2 ± 0.3	29.4 ± 0.6	27.9 ± 0.3
Day 88	32.6 ± 0.8	34.1 ± 0.6	33.9 ± 0.9	32.0 ± 0.7
Day 116	37.0 ± 0.9	38.9 ± 0.7	38.4 ± 1.2	37.0 ± 0.9
Body temperature (° C)				
Day −3	37.1 ± 0.1	37.4 ± 0.1	38.1 ± 0.1**	37.4 ± 0.2
Day 44	38.1 ± 0.2	37.4 ± 0.2	38.1 ± 0.2	37.9 ± 0.1
Day 88	36.7 ± 0.2	36.3 ± 0.2	36.0 ± 0.2*	35.8 ± 0.2**
Day 116	38.1 ± 0.2	37.5 ± 0.2	37.7 ± 0.2	37.4 ± 0.5
Landing footsplay (Trial 1)				
Day −3	49.3 ± 2.2	48.7 ± 1.4	47.5 ± 2.5	44.5 ± 1.8
Day 44	45.5 ± 3.1	40.7 ± 1.8	44.7 ± 3.0	39.9 ± 2.9
Day 88	41.2 ± 2.4	45.8 ± 3.4	40.9 ± 1.8	42.5 ± 2.8
Day 117	41.6 ± 2.4	44.8 ± 1.9	44.8 ± 2.4	41.7 ± 2.3

TABLE M1
Neurobehavioral Data for Mice in the 14-Week Gavage Study of AZT

	Vehicle Control	100 mg/kg	800 mg/kg	2,000 mg/kg
Male (continued)				
Recovery Study (continued)				
n	10	10	10	10
Landing footsplay (Trial 2)				
Day −3	46.2 ± 1.9	47.7 ± 2.3	47.8 ± 2.6	45.0 ± 2.3
Day 44	46.0 ± 2.5	43.1 ± 2.4	42.2 ± 2.2	39.6 ± 2.8
Day 88	38.6 ± 1.9	42.9 ± 2.1	40.4 ± 3.1	43.6 ± 2.3
Day 117	38.8 ± 1.7	46.0 ± 2.8*	43.4 ± 2.3	43.9 ± 1.9
Landing footsplay (avg)				
Day −3	47.8 ± 1.6	48.2 ± 1.6	47.7 ± 1.4	44.8 ± 1.6
Day 44	45.8 ± 1.9	41.9 ± 1.1	43.5 ± 2.1	39.8 ± 2.4
Day 88	39.9 ± 2.0	44.4 ± 2.0	40.7 ± 2.2	43.1 ± 2.1
Day 117	40.2 ± 2.0	45.4 ± 2.1	44.1 ± 2.1	42.8 ± 1.7
Forelimb grip strength (Trial 1)				
Day −3	98.5 ± 5.5	101.5 ± 6.9	100.0 ± 7.8	105.0 ± 6.0
Day 44	150.0 ± 7.0	140.5 ± 5.6	140.0 ± 10.4	144.5 ± 9.4
Day 88	139.0 ± 8.3	124.5 ± 4.7	136.5 ± 7.8	126.5 ± 6.3
Day 117	145.0 ± 8.5	147.5 ± 8.9	147.5 ± 9.1	153.5 ± 4.3
Forelimb grip strength (Trial 2)				
Day −3	89.0 ± 6.3	107.5 ± 6.9	102.5 ± 6.9	109.5 ± 9.0
Day 44	156.0 ± 7.8	152.0 ± 4.8	151.0 ± 10.3	135.5 ± 4.8
Day 88	132.5 ± 8.1	133.0 ± 7.9	132.5 ± 7.6	133.0 ± 7.3
Day 117	162.5 ± 4.8	145.0 ± 7.4	155.5 ± 7.2	152.0 ± 3.3
Forelimb grip strength (avg)				
Day −3	93.8 ± 2.8	104.5 ± 5.8	101.3 ± 6.5	107.3 ± 5.5
Day 44	153.0 ± 5.1	146.3 ± 4.3	145.5 ± 8.1	140.0 ± 5.3
Day 88	135.8 ± 7.5	128.8 ± 6.0	134.5 ± 7.6	129.8 ± 6.6
Day 117	153.8 ± 5.9	146.3 ± 7.4	151.5 ± 7.8	152.8 ± 2.9
Hindlimb grip strength (Trial 1)				
Day −3	46.5 ± 10.2	48.5 ± 9.0	52.0 ± 4.8	42.5 ± 4.5
Day 44	50.5 ± 8.1	56.0 ± 3.4	57.0 ± 5.3	54.5 ± 6.5
Day 88	57.0 ± 5.6	60.5 ± 5.9	56.5 ± 4.6	58.5 ± 4.5
Day 117	89.5 ± 6.2	81.0 ± 5.7	86.5 ± 4.9	81.5 ± 9.6
Hindlimb grip strength (Trial 2)				
Day −3	36.5 ± 2.2	45.5 ± 7.9	53.0 ± 7.2	40.0 ± 5.8
Day 44	55.5 ± 8.3	63.0 ± 6.4	63.0 ± 8.2	41.0 ± 5.4
Day 88	58.5 ± 3.7	62.5 ± 5.6	63.0 ± 4.2	61.5 ± 7.5
Day 117	89.0 ± 7.5	77.5 ± 4.8	77.5 ± 4.5	81.0 ± 8.6
Hindlimb grip strength (avg)				
Day −3	41.5 ± 5.7	47.0 ± 8.0	52.5 ± 4.0	41.3 ± 3.6
Day 44	53.0 ± 5.7	59.5 ± 4.1	60.0 ± 6.3	47.8 ± 5.5
Day 88	57.8 ± 4.5	61.5 ± 5.7	59.8 ± 3.9	60.0 ± 5.9
Day 117	89.3 ± 5.0	79.3 ± 3.8	82.0 ± 4.0	81.3 ± 7.6
Total motor activity				
Day −3	643.3 ± 87.4	857.4 ± 81.2	767.2 ± 112.6	749.8 ± 94.3
Day 44	1,227.7 ± 80.5	1,257.0 ± 101.1	1,207.0 ± 146.8	1,189.7 ± 69.5
Day 88	1,549.4 ± 369.5	1,390.8 ± 218.3	1,360.8 ± 232.0	1,129.7 ± 82.8
Day 117	1,184.4 ± 74.7	1,232.4 ± 73.8	1,231.2 ± 84.5	1,210.5 ± 71.9
Ambulatory motor activity				
Day −3	376.1 ± 55.2	538.2 ± 72.2	513.9 ± 88.1	468.9 ± 60.8
Day 44	786.8 ± 65.6	882.9 ± 81.1	848.8 ± 117.1	799.1 ± 47.6
Day 88	1,090.1 ± 318.1	966.2 ± 182.0	966.1 ± 193.7	718.9 ± 56.4
Day 117	802.4 ± 54.7	848.3 ± 71.7	830.3 ± 70.0	829.3 ± 62.0

TABLE M1
Neurobehavioral Data for Mice in the 14-Week Gavage Study of AZT

	Vehicle Control	100 mg/kg	800 mg/kg	2,000 mg/kg
Male (continued)				
Recovery Study (continued)				
n	10	10	10	10
Total nonambulatory motor activity				
Day −3	267.2 ± 37.9	319.2 ± 36.9	253.3 ± 29.1	280.9 ± 39.5
Day 44	440.9 ± 32.5	374.1 ± 29.8	358.2 ± 38.4	390.6 ± 28.0
Day 88	459.3 ± 56.8	424.6 ± 39.2	394.7 ± 42.4	410.8 ± 35.1
Day 117	382.0 ± 30.7	384.1 ± 12.9	400.9 ± 26.5	381.2 ± 25.2
Thermal latency (seconds)				
Day −3	0.99 ± 0.10	0.81 ± 0.05	1.09 ± 0.17	1.11 ± 0.10
Day 44	1.36 ± 0.17	0.96 ± 0.10	1.39 ± 0.19	1.11 ± 0.11
Day 88	0.94 ± 0.13	1.24 ± 0.16	1.33 ± 0.14	1.03 ± 0.11
Day 117	1.62 ± 0.15	1.51 ± 0.11	1.31 ± 0.10	1.51 ± 0.11
Threshold crossing - acoustic (milliseconds)				
Day −3	38.0 ± 7.3[d]	86.7 ± 47.7[d]	37.1 ± 5.2[e]	98.9 ± 33.9[e]
Day 44	48.9 ± 21.7[i]	49.7 ± 20.7[e]	32.4 ± 8.3[f]	56.9 ± 26.9[e]
Day 88	30.4 ± 6.5	27.4 ± 3.2	47.6 ± 12.7	27.6 ± 4.6[i]
Day 117	62.7 ± 27.2[i]	52.0 ± 15.7[i]	34.4 ± 9.8[i]	56.5 ± 15.7[h]
Threshold crossing - air puff (latency)				
Day −3	37.6 ± 5.5	35.6 ± 8.3	38.2 ± 9.1	35.4 ± 6.2
Day 44	33.8 ± 5.5	25.4 ± 3.8	29.8 ± 3.6	33.2 ± 4.2
Day 88	23.8 ± 0.8	23.0 ± 3.8	28.2 ± 2.2	21.1 ± 3.0[i]
Day 117	27.6 ± 1.3	27.2 ± 0.8	28.2 ± 2.4	27.4 ± 1.1
Peak amplitude - acoustic (g)				
Day −3	7.45 ± 1.13[d]	5.60 ± 1.01[e]	7.61 ± 0.57[e]	7.33 ± 0.87[e]
Day 44	8.57 ± 0.75[i]	10.76 ± 2.43[e]	10.62 ± 3.72[f]	14.30 ± 7.96[e]
Day 88	11.85 ± 3.55	10.38 ± 1.55	6.60 ± 0.65	9.01 ± 0.78[i]
Day 117	6.32 ± 0.38[i]	7.61 ± 0.51[i]	9.90 ± 1.37*[i]	6.99 ± 0.64[h]
Peak amplitude - air puff (magnitude)				
Day −3	43.7 ± 19.3	24.3 ± 10.2	18.5 ± 5.8	33.6 ± 10.3
Day 44	19.7 ± 3.0	15.4 ± 4.2	26.0 ± 11.6	15.4 ± 4.5
Day 88	18.7 ± 4.3	23.4 ± 5.4	18.0 ± 4.2	18.1 ± 4.8[i]
Day 117	15.5 ± 2.7	17.2 ± 2.5	16.4 ± 2.4	12.6 ± 2.5
Time of peak - acoustic (milliseconds)				
Day −3	41.3 ± 6.7[d]	91.0 ± 47.3[d]	42.3 ± 4.8[e]	104.0 ± 32.7[e]
Day 44	55.6 ± 21.5[i]	58.6 ± 20.1[e]	38.0 ± 7.0[f]	60.0 ± 26.9[e]
Day 88	35.2 ± 6.8	34.6 ± 4.0	36.4 ± 5.6	32.4 ± 4.6[i]
Day 117	64.7 ± 27.0[i]	58.2 ± 16.0[i]	38.2 ± 9.9[i]	59.5 ± 16.8[h]
Time of peak - air puff (latency)				
Day −3	44.5 ± 8.0	47.6 ± 9.9	49.4 ± 9.4	53.6 ± 11.7
Day 44	43.0 ± 6.2	31.6 ± 4.8	37.6 ± 5.1	43.2 ± 7.5
Day 88	32.2 ± 2.6	33.2 ± 5.8	35.0 ± 2.2	28.9 ± 3.9[i]
Day 117	33.6 ± 2.3	35.8 ± 3.4	33.4 ± 2.3	30.2 ± 3.8

TABLE M1
Neurobehavioral Data for Mice in the 14-Week Gavage Study of AZT

	Vehicle Control	100 mg/kg	800 mg/kg	2,000 mg/kg
Female				
Core Study				
n				
Day −3	10	10	10	10
Day 44	10	9	10	10
Day 88	10	9	10	9
Body weight (g)				
Day −3	15.5 ± 0.6	15.3 ± 0.5	17.2 ± 0.5	17.0 ± 0.5
Day 44	23.9 ± 0.7	23.9 ± 0.2	23.3 ± 0.4	23.3 ± 0.5
Day 88	29.1 ± 1.3	28.1 ± 0.4	27.5 ± 0.7	27.0 ± 1.0
Body temperature (° C)				
Day −3	37.0 ± 0.3	36.8 ± 0.2	37.3 ± 0.2	37.5 ± 0.2
Day 44	37.8 ± 0.1	37.8 ± 0.1	37.9 ± 0.2	37.7 ± 0.1
Day 88	37.2 ± 0.1	37.0 ± 0.1	36.6 ± 0.1*	36.8 ± 0.1
Landing footsplay (Trial 1)				
Day −3	43.1 ± 2.8	40.3 ± 1.9	43.9 ± 2.4	41.6 ± 2.7
Day 44	44.5 ± 2.3	45.7 ± 2.9	41.2 ± 2.4	48.2 ± 2.2
Day 88	45.1 ± 2.6	41.9 ± 2.3	45.5 ± 2.5	41.9 ± 1.3
Landing footsplay (Trial 2)				
Day −3	44.0 ± 1.7	43.0 ± 2.8	41.8 ± 1.5	48.0 ± 2.4
Day 44	39.2 ± 1.3	43.0 ± 2.2	40.9 ± 1.3	41.8 ± 2.3
Day 88	44.1 ± 2.4	40.6 ± 1.6	42.4 ± 2.5	40.2 ± 1.6
Landing footsplay (avg)				
Day −3	43.6 ± 1.4	41.7 ± 2.0	42.9 ± 1.4	44.8 ± 1.4
Day 44	41.9 ± 1.5	44.3 ± 2.0	41.1 ± 1.5	45.0 ± 1.5
Day 88	44.6 ± 2.0	41.2 ± 1.7	44.0 ± 1.9	41.1 ± 1.0
Forelimb grip strength (Trial 1)				
Day −3	106.0 ± 8.8	107.5 ± 6.7	96.5 ± 4.1	86.5 ± 8.2
Day 44	106.5 ± 2.4	104.4 ± 2.4	103.5 ± 3.9	108.0 ± 2.5
Day 88	105.0 ± 2.7	110.0 ± 7.6	107.5 ± 5.9	114.4 ± 4.1
Forelimb grip strength (Trial 2)				
Day −3	107.0 ± 7.2	111.5 ± 9.9	97.5 ± 5.7	108.0 ± 6.1
Day 44	106.0 ± 1.5	99.4 ± 3.4	102.5 ± 4.0	108.0 ± 2.0
Day 88	105.5 ± 4.8	105.0 ± 5.7	108.0 ± 7.2	116.7 ± 6.2
Forelimb grip strength (avg)				
Day −3	106.5 ± 6.4	109.5 ± 6.8	97.0 ± 4.2	97.3 ± 5.5
Day 44	106.3 ± 1.5	101.9 ± 1.9	103.0 ± 3.7	108.0 ± 1.7
Day 88	105.3 ± 3.3	107.5 ± 6.4	107.8 ± 5.9	115.6 ± 4.1
Hindlimb grip strength (Trial 1)				
Day −3	38.0 ± 6.1	39.5 ± 3.8	47.0 ± 10.1	43.5 ± 5.2
Day 44	50.0 ± 2.5	43.9 ± 2.2	51.0 ± 3.1	46.0 ± 2.3
Day 88	53.5 ± 3.4	50.0 ± 3.2	52.5 ± 4.8	50.6 ± 4.4
Hindlimb grip strength (Trial 2)				
Day −3	33.5 ± 6.0	41.0 ± 6.0	43.0 ± 5.4	34.0 ± 4.6
Day 44	49.5 ± 1.7	44.4 ± 2.3	52.0 ± 2.5	47.5 ± 2.6
Day 88	51.5 ± 3.0	52.8 ± 5.1	53.0 ± 3.4	50.6 ± 5.3
Hindlimb grip strength (avg)				
Day −3	35.8 ± 3.9	40.3 ± 4.4	45.0 ± 7.1	38.8 ± 4.6
Day 44	49.8 ± 1.9	44.2 ± 2.2	51.5 ± 2.7	46.8 ± 2.4
Day 88	52.5 ± 3.1	51.4 ± 3.6	52.8 ± 4.0	50.6 ± 4.5
Total motor activity				
Day −3	718.0 ± 95.6	566.4 ± 56.3	655.8 ± 94.7	786.7 ± 61.8
Day 44	1,020.8 ± 71.4	972.3 ± 96.8	1,001.7 ± 101.3	817.1 ± 102.8
Day 88	934.3 ± 51.4	1,016.8 ± 48.2	999.4 ± 46.7	851.6 ± 96.1
Ambulatory motor activity				
Day −3	474.9 ± 70.5	351.9 ± 32.6	414.4 ± 70.9	464.7 ± 50.9
Day 44	689.2 ± 56.0	675.0 ± 68.6	682.6 ± 81.8	520.5 ± 65.9
Day 88	619.9 ± 47.4	660.9 ± 40.3	659.3 ± 42.5	571.3 ± 68.4

TABLE M1
Neurobehavioral Data for Mice in the 14-Week Gavage Study of AZT

	Vehicle Control	100 mg/kg	800 mg/kg	2,000 mg/kg
Female (continued)				
Core Study (continued)				
n				
Day −3	10	10	10	10
Day 44	10	9	10	10
Day 88	10	9	10	9
Total nonambulatory motor activity				
Day −3	243.1 ± 28.1	214.5 ± 28.1	241.4 ± 30.1	322.0 ± 29.1
Day 44	331.6 ± 22.5	297.3 ± 35.2	329.1 ± 29.7	296.6 ± 43.3
Day 88	314.4 ± 15.2	355.9 ± 14.3	340.1 ± 16.8	280.2 ± 30.2
Thermal latency (seconds)				
Day −3	1.22 ± 0.20	1.25 ± 0.20	1.15 ± 0.13	1.11 ± 0.16
Day 44	0.70 ± 0.04	0.78 ± 0.09	0.76 ± 0.03	0.84 ± 0.09
Day 88	0.80 ± 0.10	0.72 ± 0.04	0.83 ± 0.08	0.76 ± 0.06
Threshold crossing - acoustic (milliseconds)				
Day −3	—[j]	148.0[k]	—	—
Day 44	32.0[k]	44.0 ± 14.7[g]	310.0[k]	34.0 ± 12.0[c]
Day 88	26.0 ± 6.6[h]	68.5 ± 27.3[h]	96.5 ± 37.3[h]	40.9 ± 8.9[e]
Threshold crossing - air puff (latency)				
Day −3	49.6 ± 7.4	50.6 ± 5.0	58.4 ± 10.7	48.0 ± 5.6
Day 44	80.9 ± 40.5[e]	54.7 ± 14.5[d]	56.4 ± 13.9[i]	72.0 ± 31.5[h]
Day 88	31.2 ± 1.8	28.0 ± 1.2	23.6 ± 1.2**	32.9 ± 4.9
Peak amplitude - acoustic (g)				
Day −3	—	5.90[k]	—	—
Day 44	8.10[k]	6.30 ± 0.92[g]	6.30[k]	7.40 ± 1.70[c]
Day 88	13.56 ± 5.64[h]	6.73 ± 0.89[h]	6.73 ± 0.81[h]	8.09 ± 1.76[e]
Peak amplitude - air puff (magnitude)				
Day −3	14.0 ± 3.1	17.9 ± 3.6	10.0 ± 1.4	15.5 ± 2.5
Day 44	14.6 ± 2.9[e]	12.4 ± 2.8[d]	8.1 ± 1.3[i]	14.3 ± 3.7[h]
Day 88	20.8 ± 6.8	18.8 ± 3.6	25.5 ± 6.9	27.4 ± 6.5
Time of peak - acoustic (milliseconds)				
Day −3	—	154.0[k]	—	—
Day 44	36.0[k]	46.0 ± 13.6[g]	314.0[k]	38.0 ± 12.0[c]
Day 88	28.5 ± 6.1[h]	70.0 ± 27.0[h]	98.8 ± 36.9[h]	43.1 ± 8.6[e]
Time of peak - air puff (latency)				
Day −3	59.0 ± 5.4	67.4 ± 7.7	71.6 ± 10.2	62.4 ± 5.5
Day 44	99.1 ± 49.6[e]	59.3 ± 13.8[d]	58.9 ± 13.8[i]	79.5 ± 30.4[h]
Day 88	40.2 ± 3.3	34.4 ± 2.1	31.0 ± 2.6	44.7 ± 6.3
Recovery Study				
n				
Day −3	10	10	10	10
Day 44	10	10	10	9
Day 88	10	10	10	9
Day 116	10	10	10	9
Body weight (g)				
Day −3	17.3 ± 0.6	18.6 ± 0.2	17.3 ± 0.7	18.2 ± 0.4
Day 44	23.6 ± 0.7	23.5 ± 0.6	24.1 ± 0.4	23.5 ± 0.3
Day 88	27.5 ± 0.9	28.1 ± 0.5	28.3 ± 0.7	26.6 ± 0.6
Day 116	31.3 ± 1.4	32.1 ± 0.6	33.3 ± 1.0	30.4 ± 1.0
Body temperature (° C)				
Day −3	37.8 ± 0.1	37.7 ± 0.1	37.8 ± 0.1	37.5 ± 0.1
Day 44	38.0 ± 0.1	38.1 ± 0.1	37.9 ± 0.1	37.9 ± 0.1
Day 88	37.5 ± 0.1	37.1 ± 0.2	37.0 ± 0.2*	37.1 ± 0.1
Day 116	37.2 ± 0.1	37.5 ± 0.2	37.1 ± 0.2	37.6 ± 0.1

TABLE M1
Neurobehavioral Data for Mice in the 14-Week Gavage Study of AZT

	Vehicle Control	100 mg/kg	800 mg/kg	2,000 mg/kg
Female (continued)				
Recovery Study (continued)				
n				
Day −3	10	10	10	10
Day 44	10	10	10	9
Day 88	10	10	10	9
Day 116	10	10	10	9
Landing footsplay (Trial 1)				
Day −3	46.4 ± 1.7	46.6 ± 1.9	44.2 ± 2.3	44.3 ± 2.6
Day 44	41.9 ± 3.2	42.8 ± 2.7	40.6 ± 3.3	45.9 ± 3.2
Day 88	40.5 ± 3.6	45.2 ± 1.7	44.8 ± 2.0	37.9 ± 1.2
Day 116	43.9 ± 3.2	45.7 ± 4.3	50.9 ± 1.4	49.4 ± 3.7
Landing footsplay (Trial 2)				
Day −3	44.3 ± 2.9	42.7 ± 2.1	46.2 ± 2.0	45.3 ± 2.7
Day 44	44.8 ± 3.0	43.4 ± 3.2	36.2 ± 1.6	45.2 ± 3.4
Day 88	44.6 ± 2.2	39.8 ± 2.1	42.3 ± 3.3	40.0 ± 1.8
Day 116	45.6 ± 2.3	47.3 ± 1.8	48.6 ± 1.8	48.1 ± 4.0
Landing footsplay (avg)				
Day −3	45.4 ± 2.1	44.7 ± 1.3	45.2 ± 1.9	44.8 ± 1.7
Day 44	43.4 ± 2.5	43.1 ± 2.5	38.4 ± 2.0	45.6 ± 2.9
Day 88	42.6 ± 2.8	42.5 ± 1.6	43.6 ± 2.4	38.9 ± 1.3
Day 116	44.8 ± 2.6	46.2 ± 2.9	50.3 ± 1.3	48.8 ± 3.4
Forelimb grip strength (Trial 1)				
Day −3	101.5 ± 6.1	104.0 ± 8.6	95.5 ± 12.1	121.5 ± 7.1
Day 44	123.0 ± 8.1	124.0 ± 7.6	113.0 ± 7.1	117.8 ± 8.6
Day 88	119.5 ± 6.7	129.0 ± 8.5	128.5 ± 9.0	125.0 ± 8.1
Day 116	99.0 ± 6.7	103.0 ± 5.2	99.5 ± 8.0	103.3 ± 9.1
Forelimb grip strength (Trial 2)				
Day −3	108.0 ± 8.4	97.5 ± 3.8	93.0 ± 5.6	115.5 ± 8.9
Day 44	122.5 ± 7.4	115.5 ± 7.0	113.0 ± 7.2	116.1 ± 6.5
Day 88	130.0 ± 9.9	115.5 ± 5.7	120.5 ± 7.9	123.9 ± 8.2
Day 116	101.0 ± 6.7	101.5 ± 5.0	96.0 ± 7.2	95.0 ± 7.5
Forelimb grip strength (avg)				
Day −3	104.8 ± 6.4	100.8 ± 4.5	94.3 ± 7.2	118.5 ± 4.4
Day 44	122.8 ± 6.6	119.8 ± 6.1	113.0 ± 6.6	116.9 ± 7.4
Day 88	124.8 ± 7.2	122.3 ± 6.2	124.5 ± 6.5	124.4 ± 7.2
Day 116	100.0 ± 6.4	102.3 ± 4.6	97.8 ± 7.5	99.2 ± 7.5
Hindlimb grip strength (Trial 1)				
Day −3	60.5 ± 9.0	48.0 ± 11.5	69.0 ± 10.7	58.0 ± 7.6
Day 44	51.5 ± 3.1	56.5 ± 6.4	54.0 ± 6.0	43.3 ± 4.9
Day 88	57.0 ± 5.0	52.5 ± 2.8	66.3 ± 8.1	55.6 ± 5.7
Day 116	54.0 ± 3.3	55.5 ± 3.8	51.0 ± 3.7	45.6 ± 3.5
Hindlimb grip strength (Trial 2)				
Day −3	58.5 ± 11.2	67.0 ± 10.7	66.5 ± 11.2	70.5 ± 10.8
Day 44	58.0 ± 3.9	49.5 ± 4.0	58.5 ± 4.0	44.4 ± 3.2
Day 88	61.0 ± 3.5	55.5 ± 5.5	62.5 ± 4.6	50.6 ± 7.8
Day 116	51.5 ± 4.1	54.5 ± 4.0	49.5 ± 2.0	53.3 ± 4.2
Hindlimb grip strength (avg)				
Day −3	59.5 ± 9.6	47.5 ± 7.1	67.8 ± 9.4	64.3 ± 8.9
Day 44	54.8 ± 2.3	53.0 ± 4.8	56.3 ± 4.0	43.9 ± 3.3*
Day 88	59.0 ± 4.1	54.0 ± 3.4	64.4 ± 5.6	53.1 ± 6.1
Day 116	52.8 ± 3.4	55.0 ± 3.8	50.3 ± 2.5	49.4 ± 3.4
Total motor activity				
Day −3	557.5 ± 81.5	618.7 ± 57.7	641.4 ± 86.1	612.0 ± 77.4
Day 44	956.0 ± 54.6	847.8 ± 67.9	898.4 ± 64.3	853.1 ± 75.4
Day 88	886.1 ± 54.2	906.4 ± 57.0	940.8 ± 68.2	867.1 ± 75.7
Day 116	1,199.1 ± 154.6	1,081.6 ± 168.8	1,142.2 ± 191.3	1,093.3 ± 91.7

TABLE M1
Neurobehavioral Data for Mice in the 14-Week Gavage Study of AZT

	Vehicle Control	100 mg/kg	800 mg/kg	2,000 mg/kg
Female (continued)				
Recovery Study (continued)				
n				
Day −3	10	10	10	10
Day 44	10	10	10	9
Day 88	10	10	10	9
Day 116	10	10	10	9
Ambulatory motor activity				
Day −3	349.0 ± 62.6	395.1 ± 38.4	414.1 ± 57.1	373.2 ± 51.6
Day 44	586.6 ± 28.3	549.7 ± 49.0	600.1 ± 45.5	550.3 ± 49.9
Day 88	552.2 ± 38.8	590.0 ± 47.2	615.9 ± 51.1	570.7 ± 57.4
Day 116	779.6 ± 110.9	662.4 ± 118.1	688.9 ± 126.2	671.2 ± 74.4
Total nonambulatory motor activity				
Day −3	208.5 ± 30.4	223.6 ± 30.2	227.3 ± 33.8	238.8 ± 32.8
Day 44	369.4 ± 34.6	298.1 ± 21.9	298.3 ± 26.7	302.8 ± 30.5
Day 88	333.9 ± 23.7	316.4 ± 20.5	324.9 ± 27.3	296.4 ± 26.4
Day 116	419.5 ± 50.5	419.2 ± 56.0	453.2 ± 74.8	422.1 ± 36.3
Thermal latency (seconds)				
Day −3	1.31 ± 0.14	1.29 ± 0.14	1.21 ± 0.15	1.16 ± 0.29
Day 44	0.92 ± 0.14	0.71 ± 0.04	0.85 ± 0.04	0.89 ± 0.15
Day 88	0.80 ± 0.07	0.74 ± 0.06	0.74 ± 0.04	0.76 ± 0.05
Day 116	1.10 ± 0.15	1.13 ± 0.10	1.21 ± 0.16	1.70 ± 0.84
Threshold crossing - acoustic (milliseconds)				
Day −3	40.0 ± 18.0[c]	36.0 ± 14.0[c]	35.0 ± 13.0[c]	—
Day 44	30.7 ± 7.7[g]	160.5 ± 28.8[b]	72.5 ± 51.2[b]	121.3 ± 27.3[g]
Day 88	35.4 ± 9.2[e]	35.8 ± 5.3[i]	104.0 ± 30.1[d]	63.4 ± 28.1[e]
Day 116	38.9 ± 6.7[e]	92.5 ± 30.8[h]	33.8 ± 6.1[h]	63.7 ± 28.6[e]
Threshold crossing - air puff (latency)				
Day −3	46.1 ± 6.5	42.4 ± 4.8	47.8 ± 5.2	44.2 ± 3.7[i]
Day 44	43.4 ± 6.0	44.0 ± 4.7	38.4 ± 7.7	42.2 ± 3.8
Day 88	29.2 ± 7.2	30.8 ± 4.6	32.6 ± 5.7	32.9 ± 5.2
Day 116	27.6 ± 1.0	28.4 ± 3.7	31.6 ± 2.1[i]	27.3 ± 1.2
Peak amplitude - acoustic (g)				
Day −3	21.37 ± 14.82[g]	5.65 ± 0.25[c]	6.25 ± 0.15[c]	—
Day 44	6.90 ± 0.55[g]	6.58 ± 0.46[b]	6.48 ± 0.80[b]	6.20 ± 0.53[g]
Day 88	7.49 ± 1.09[e]	7.31 ± 0.51[i]	5.52 ± 0.20[d]	7.69 ± 1.31[e]
Day 116	6.71 ± 0.43[e]	8.25 ± 1.44[h]	8.89 ± 2.32[h]	5.94 ± 0.29[e]
Peak amplitude - air puff (magnitude)				
Day −3	18.8 ± 5.6	26.8 ± 10.3	13.2 ± 2.8	13.2 ± 3.6[i]
Day 44	13.2 ± 2.5	9.6 ± 2.4	13.6 ± 3.7	14.2 ± 3.5
Day 88	14.3 ± 3.2	11.1 ± 1.7	19.4 ± 3.9	13.2 ± 2.7
Day 116	46.8 ± 16.9	19.3 ± 3.8	20.5 ± 8.2[i]	22.4 ± 6.1
Time of peak - acoustic (milliseconds)				
Day −3	29.3 ± 15.7[g]	38.0 ± 14.0[c]	39.0 ± 17.0[c]	—
Day 44	33.3 ± 8.4[g]	165.0 ± 27.7[b]	74.0 ± 50.7[b]	126.0 ± 26.4[g]
Day 88	37.4 ± 8.7[e]	38.9 ± 5.4[i]	106.3 ± 30.6[d]	66.6 ± 28.3[e]
Day 116	42.0 ± 6.9[e]	99.0 ± 31.4[h]	37.5 ± 6.0[h]	66.3 ± 28.2[e]
Time of peak - air puff (latency)				
Day −3	66.4 ± 8.4	50.6 ± 3.2	57.6 ± 6.5	50.9 ± 5.3[i]
Day 44	52.2 ± 4.7	47.0 ± 4.5	45.0 ± 7.1	52.4 ± 4.4
Day 88	34.4 ± 7.6	34.2 ± 4.9	42.2 ± 6.6	37.6 ± 5.5
Day 116	37.6 ± 2.8	35.2 ± 4.7	42.4 ± 6.2[i]	33.1 ± 1.9

* Significantly different ($P \leq 0.05$) from the control group by Dunn's or Shirley's test
** $P \leq 0.01$
[a] Mean ± standard error. Statistical tests were performed on unrounded data. Body weights of dosed animals were not significantly different from those of the control group by Williams' or Dunnett's test.
[b] n = 4 [c] n = 2 [d] n = 6 [e] n = 7 [f] n = 5 [g] n = 3 [h] n = 8 [i] n = 9 [j] n = 0 [k] n = 1

APPENDIX N
DETERMINATIONS OF
AZT CONCENTRATIONS IN PLASMA

TABLE N1
Plasma Concentrations of AZT in Mice in the 2-Year Gavage Study of AZT[a]

	Vehicle Control	30 mg/kg	60 mg/kg	120 mg/kg
Male				
Clinical Pathology Groups				
n	3	3	3	3
Time After Dosing (minutes)				
15	—[b]	5.50 ± 0.69	12.4 ± 2.5	20.9 ± 9.2
30	—	3.38 ± 0.91	6.56 ± 1.5	11.3 ± 0.67
60	—	0.862 ± 0.41	1.69 ± 0.46	6.43 ± 2.4
90	—	0.389 ± 0.30	0.599 ± 0.43	2.10 ± 0.25
120	—	0.198 ± 0.053	0.505 ± 0.14	0.633 ± 0.46
Core Groups				
n	—[c]	3	3	3
Time After Dosing (minutes)				
0[d]		—	—	—
5		10.4 ± 3.8	20.1 ± 6.6	47.8 ± 4.6
15		12.7 ± 1.4	24.2 ± 5.1	60.4 ± 30
30		7.62 ± 3.6	16.9 ± 4.6	67.0 ± 14
60		4.64 ± 1.2	8.58 ± 4.2	24.8 ± 16
90		1.55 ± 0.58	2.36 ± 1.1	23.9 ± 23
120		1.81 ± 2.4	1.92 ± 1.8	10.3 ± 0.59
Female				
Clinical Pathology Groups				
n	3	3	3	3
Time After Dosing (minutes)				
15	—	11.8 ± 1.5	24.8 ± 4.5	53.1 ± 5.1
30	—	7.60 ± 1.1	17.7 ± 4.9	58.0 ± 23
60	—	2.42 ± 0.78	6.08 ± 4.7	11.3 ± 1.3
90	—	0.483 ± 0.22	1.64 ± 0.70	3.31 ± 1.9
120	—	0.224 ± 0.11	0.501[e]	1.29[e]
Core Groups				
n	—[c]	3	3	3
Time After Dosing (minutes)				
0[d]		—	—	—
5		14.3 ± 3.3	29.0 ± 6.6	46.6 ± 13
15		18.3 ± 1.2	18.9 ± 1.5	88.2 ± 28
30		8.21 ± 2.5	27.4 ± 6.1	65.3 ± 12
60		5.68 ± 0.35	12.2 ± 4.7	20.5 ± 9.1
90		2.47 ± 1.3	6.26 ± 5.8	18.7 ± 9.1
120		0.971 ± 0.57	3.08 ± 1.8	11.1 ± 9.0

[a] Data are given in µg/mL as mean ± standard deviation.
[b] Values were below the experimental limit of quantitation (0.103 µg/mL).
[c] Plasma analyses were not performed on core study vehicle control animals.
[d] n = 5; these animals were not dosed on the day of blood collection.
[e] n = 2; no statistical analyses performed

APPENDIX O
CHEMICAL CHARACTERIZATION AND DOSE FORMULATION STUDIES

CHEMICAL CHARACTERIZATION AND DOSE FORMULATION STUDIES

PROCUREMENT AND CHARACTERIZATION

AZT

3′-Azido-3′-deoxythymidine (AZT) was obtained from the Burroughs Wellcome Company (Research Triangle Park, NC) in three lots (809796, 80/0557-130-B, and 86/5082-184). Lot 809796 was used during the 14-week study and 2-year AZT and AZT/α-interferon A/D studies, and lots 80/0557-130-B and 86/5082-184 were used during the 2-year AZT and AZT/α-interferon A/D 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 AZT and AZT/α-interferon A/D studies are on file at the National Institute of Environmental Health Sciences (NIEHS).

All lots of the chemical, a white to slightly off-white fine powder, were identified as AZT by infrared spectroscopy. Lots 809796 and 80/0557-130-B were also identified by ultraviolet/visible and nuclear magnetic resonance spectroscopy. All spectra were consistent with the literature spectra (Horwitz *et al.*, 1964; SRI, 1987) of AZT. The infrared and nuclear magnetic spectra are presented in Figures O1 and O2. The melting point ranges of lots 809796 and 80/0557-130-B were 123.5° to 124.5° C and 121.5° to 123.5° C, respectively, and were consistent with a literature reference (Horwitz *et al.*, 1964). For lot 809796, the optical rotation value was $[\alpha]_D^{21} = +46.6° \pm 0.2°$, which was not consistent with information from the manufacturer or a literature reference (Horwitz *et al.*, 1964) but was consistent with values determined by the study laboratory (SRI, 1987). An additional determination of the optical rotation value for lot 809796 under conditions described by the supplier indicated a value of $[\alpha]_D^{25} = +60.9° \pm 0.3°$, which was consistent with the value reported by the supplier. For lot 80/0557-130-B, the optical rotation value of $[\alpha]_D^{25} = +61.5° \pm 0.4°$ was consistent with the results from the second determination for lot 809796. For lot 80/0557-130-B, the partition coefficient between octanol and pH 7.4 phosphate buffer was determined to be 0.05 at room temperature, and the maximum solubility in water at 25° C was determined to be 22.8 mg/mL.

The purities of lots 809796 and 80/0557-130-B were determined using elemental analyses, Karl Fischer water analysis, functional group titration, thin-layer chromatography (TLC), and high-performance liquid chromatography (HPLC). For functional group titration, the samples were dissolved in pyridine and then titrated with 0.1 N tetrabutylammonium hydroxide in isopropanol to a potentiometric endpoint. The titration was monitored with a glass indicating electrode and a calomel reference electrode filled with 1 M methanolic (lot 809796) tetrabutylammonium chloride. TLC was performed on Silica Gel 60A K6F plates (lot 809796) or Whatman Silica Gel 60A F-254 plates (lot 80/0557-130-B) with two solvent systems: 1) methanol:ethyl acetate (50:50) and 2) toluene:ethanol (90:10). The plates were examined under ultraviolet light (254 nm) with a spray prepared by dissolving 0.5 g potassium permanganate in 100 mL of 1 N sodium hydroxide. After spraying, the plates were heated at 100° C for 2 to 3 minutes (lot 809796) or at 110° C for 1 minute (lot 80/0557-130-B). *p*-Acetophenetidide was used as a reference standard. For lot 809796, HPLC was performed with a Phenomenex Spherex ODS column with ultraviolet detection (254 nm) and a solvent system of water:methanol (82:18). For lot 80/0557-130-B, HPLC was performed with a Regis Val-U-Pak HP column with ultraviolet detection (254 nm) and a solvent system of water:methanol (80:20). For each lot, the flow rate was 1.0 mL/minute.

For lot 809796, elemental analyses for carbon, hydrogen, and nitrogen were in agreement with the theoretical values for AZT. Karl Fischer water analysis indicated 0.10% ± 0.03% water. Functional group titration indicated a purity of 101.4% ± 0.5%. TLC by system 1 indicated a major spot and a trace impurity; TLC by system 2 indicated a major spot and a minor impurity. HPLC indicated one major peak

and two impurities with a combined area of 1.8% relative to the major peak area. One of these impurities was identified as thymine from an ultraviolet spectrum (190 nm to 350 nm range) obtained with a diode array detector, and the thymine content was estimated to be 0.80% ± 0.01% with the same HPLC system as used for the purity analysis of lot 809796 but with a Burdick and Jackson OD5 C_{18} column, a solvent ratio of 90:10, and uracil as the internal standard. The overall purity of lot 809796 was determined to be approximately 98%.

For lot 80/0557-130-B, elemental analyses for carbon, hydrogen, and nitrogen were in agreement with the theoretical values for AZT. Karl Fischer water analysis indicated 0.04% ± 0.01% water. Functional group titration indicated a purity of 102.1% ± 0.5%. TLC by each system indicated a major spot and a trace impurity. HPLC indicated one major peak and two impurities with a combined area of 1.6% relative to the major peak area. A concomitant analysis of lot 80/0557-130-B with lot 809786 was performed using the HPLC system used for the purity analysis of lot 80/0557-130-B but with a Burdick and Jackson OD5 C_{18} column, a solvent ratio of 75:25, and an internal standard of (-)-6-methylaminopurine riboside. Major peak comparisons of lot 80/0557-130-B with lot 809796 indicated a purity of 100.3% ± 0.9% for lot 80/0557-130-B relative to lot 809796. The overall purity of lot 80/0557-130-B was determined to be approximately 98%.

The purity of lot 86/5082-184 relative to that of lot 80/0557-130-B was determined by the study laboratory using HPLC. HPLC was performed with a Burdick and Jackson OD5 C_{18} column with ultraviolet detection (254 nm) and a solvent system of 0.005 M triethanolamine in water:methanol (70:30) adjusted to pH 7 with phosphoric acid. The flow rate was 1.0 mL/minute, and (-)-6-methylaminopurine riboside was the internal standard. The purity of lot 86/5082-184 relative to lot 80/0557-130-B was determined to be approximately 102%.

Accelerated stability studies of lot 809796 of the bulk chemical were performed by the analytical chemistry laboratory. HPLC was performed with the same system used for the major peak comparisons of lot 80/0557-130-B with lot 809796. These studies indicated that AZT 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 in the original container (double plastic bags inside a metal can) in the dark at room temperature (approximately 22° C) for 2 months after receipt before the 14-week study began and at approximately –20° C thereafter. Stability was monitored during the 14-week and 2-year studies using HPLC. No degradation of the bulk chemical was detected.

Methylcellulose

Methylcellulose was obtained from Fisher Scientific Company (Pittsburgh, PA) in one lot (876672), which was used during the 14-week study, the 2-year AZT study, and the 2-year AZT/α-interferon A/D studies. Identity, purity, and stability analyses were conducted by the analytical chemistry laboratory.

The chemical, a white powder, was identified as methylcellulose by infrared, ultraviolet/visible, and nuclear magnetic resonance spectroscopy. All spectra were consistent with those expected for the structure of methylcellulose. The infrared spectrum was consistent with the literature spectrum (*Sadtler Standard Spectra*) of methylcellulose. No melting point was observed up to 300° C; the sample decomposed at 250° to 300° C.

The purity of lot 876672 was determined by elemental analyses, Karl Fischer water analysis, functional group titration, and HPLC. The methoxy group content was estimated from the nuclear magnetic resonance spectrum. United States Pharmacopeia (USP) XXI analyses for the identification, apparent viscosity, weight loss on drying, residue on ignition, arsenic content, heavy metal content, and percent methoxy content were also performed. For functional group titration, a methoxy group determination was performed by Galbraith Laboratories, Inc. (Knoxville, TN). HPLC was performed with a Toyo Soda TSK G4000 SW column with

refractive index detection and a solvent system of 0.005 M sodium dodecyl sulfate in water. The flow rate was 1.0 mL/minute.

Elemental analyses for carbon and hydrogen were in agreement with the theoretical values for methylcellulose based on 1.8 degrees of substitution and corrected for 1.94% water. In addition, elemental analyses indicated 0.058% sodium. Karl Fischer water analysis indicated 1.94% ± 0.03% water. Functional group titration indicated 30.62% ± 0.08% methoxy group content; this value is consistent with the theoretical value, assuming 1.8 degrees of substitution (30.4%), and with the estimate of the methoxy group content from the nuclear magnetic spectrum (31.7%). The complete battery of USP tests for methylcellulose indicated the following results: the chemical was identified as methylcellulose; the apparent viscosity was 3,749 to 4,060 cP; the weight loss on drying was 1.9% ± 0.3%; the residue on ignition was less than 0.3%; the tests for arsenic and heavy metals were passed; and the methoxy group content was 30.3% ± 0.2% for lot 876672 and 28.3% ± 0.0% for the USP reference material. The chemical met the USP specifications for methylcellulose for all analyses. HPLC indicated one major peak and no impurities with areas greater than or equal to 0.1% relative to the major peak area. Cumulative analytical data indicated that lot 876672 of methylcellulose was suitable for use as a dosing vehicle.

Accelerated stability studies of the bulk chemical were performed by the analytical chemistry laboratory. Gas chromatography (USP XXI method) was performed to determine the methoxy group content using thermal conductivity detection with a helium carrier gas at a flow rate of 20 mL/minute, a 10% SP-2100 on 100/120 Chromosorb WHP glass column, an isothermal oven temperature of 100° C, and toluene as the internal standard. These studies indicated that methylcellulose was stable as a bulk chemical for 3 weeks when stored protected from light at temperatures up to 60° C. To ensure stability, the bulk chemical was stored in the original containers in the dark at room temperature. Stability was monitored by Galbraith Laboratories, Inc., during the 14-week and 2-year studies using gas chromatography to determine methoxy group content. Results of duplicate analyses were all within the required range of 27.5% to 31.5% methoxy group content. No degradation of the bulk chemical was detected.

α-Interferon A/D and α-Interferon A

α-Interferon A/D and α-interferon A were obtained from Hoffman-La Roche (Nutley, NJ). α-Interferon A/D was obtained in one lot (1084), which was used during the 2-year α-interferon A/D and AZT/α-interferon A/D studies. α-Interferon A was obtained in one lot (019116), which was used during the 2-year α-interferon A/D study. Antiviral activity assays were conducted by the study laboratory.

Information from the manufacturer indicated a protein concentration of 2.8 mg/mL and a bulk activity of 1.5×10^8 U/mL for lot 1084 of α-interferon A/D and a protein concentration of 5.47 mg/mL and a bulk activity of 1.095×10^9 U/mL for lot 019116 of α-interferon A. The bulk chemical was stored in the original containers (plastic bottles) at approximately −20° C from receipt until 2 weeks before the 2-year studies began and at −140° or −180° C in the vapor phase of a liquid nitrogen cryopreservation vat thereafter.

Each lot of the α-interferon A/D and α-interferon A bulk chemicals was measured for vesicular stomatitis virus (VSV) antiviral activity (Table O1). The antiviral activities (titers) of α-interferon A/D and α-interferon A were determined with the viral cytopathic effect assay as follows: Alex Chang Hypernephroma cells in RPMI 1640 medium, supplemented with 10% fetal bovine serum and 2 mM glutamine, were seeded into the wells of a 96-well microtiter plate at a density of 1×10^5 cells/well. Samples of interferon were then added in dilution series, and the plate was incubated at 37° ± 1° C under 5% carbon dioxide for 24 hours. A predetermined quantity of VSV was then added to each well, and the incubation was continued for an additional 24 hours or until a cytopathic effect, as evidenced by cell lysis, was clearly evident in the virus control wells (cells + virus, no added interferon). Neutral red dye was then added to each well, and the plate was incubated another hour during which cells that survived the viral

challenge took up dye, while dead or lysed cells did not. The dye solution along with the nonadherent and dead cells and cell debris were removed by careful washing with 0.85% sodium chloride, and the neutral red taken up by surviving cells was extracted by adding 100 µL of 50% ethanol in 0.1 M phosphate buffer to each well. The absorbance at 550 nm was recorded for each well and entered into a computer, which transformed the data into a titration curve (percent control absorption at 550 nm versus interferon dilution) and calculated the dilution of interferon that conferred 50% protection (50% of the control value) against viral challenge. The reciprocal of this dilution was multiplied by any previous dilutions to yield the actual titer of the interferon in laboratory units, which were converted to international units using a correction factor determined by calibrating the α-interferon A/D and α-interferon A laboratory standards with an international standard of interferon of known titer. In these studies, an international standard preparation of α_2-interferon obtained from the National Institute of Allergy and Infectious Diseases was used to calibrate the reference standards of α-interferon A/D and α-interferon A used for preparation of dose formulations and routine analysis. Complete details of the procedures used and the results are on file at NIEHS.

PREPARATION AND ANALYSIS OF DOSE FORMULATIONS

AZT

The dosing vehicle was prepared by mixing methylcellulose with heated deionized water and then diluting with water to form a 0.5% solution, which was allowed to cool. AZT was then mixed with the dosing vehicle until a homogeneous suspension was obtained to give the required concentrations (Table O2). The dose formulations were stored at room temperature (at the beginning of the 14-week study) or refrigerated at approximately 5° C in amber glass bottles in the dark for up to 20 days.

Homogeneity studies of a 200 mg/g solution of lot 809796 were performed by the analytical chemistry laboratory using HPLC with the same system used for the purity analysis of lot 86/5082-184 but with a solvent system of 0.005 M triethanolamine in water:methanol (80:20). Stability studies of a 2 mg/g solution were also performed using the same HPLC system. Homogeneity was confirmed, and the stability of the solution was confirmed for 3 weeks at room temperature when stored in the dark and for 3 hours when open to air and light.

Periodic analyses of the dose formulations of AZT were conducted at the study laboratory using HPLC. For the 14-week study, the formulations were analyzed every 4 to 8 weeks (Table O3). During the 2-year studies, the formulations were analyzed every 4 to 8 weeks (Table O4). All of the dose formulations analyzed and used during the 14-week study were within 10% of the target concentrations. All of the dose formulations analyzed and used during the 2-year AZT and AZT/α-interferon A/D studies were within 10% of the target concentrations. All of the animal room samples were also within 10% of the target concentrations.

α-Interferon A/D and α-Interferon A

The dosing vehicle was prepared by aseptically mixing sterile C57Bl/6 mouse serum (Harlan Sprague-Dawley, Inc., Indianapolis, IN) in Earle's Balanced Salt Solution (Grand Island Biologicals Co.) to achieve a 10% solution. The vehicle was adjusted to a pH of approximately 7.2. Based on titers determined for the bulk chemicals, dose formulations were prepared by dilution of the stock solution. Therefore, the same amount (quantity of pure recombinant protein) of α-interferon A/D or α-interferon A was administered to the animals throughout the 2-year studies. α-Interferon A/D and α-interferon A were thawed at room temperature, and serial dilutions were prepared in the vehicle under sterile conditions using sterile pipettes and a calibrated Matrix Electropette (Table O2). The dose formulations were stored in sterile, Teflon®-capped, brown glass dosing vials at 4° C. Samples for antiviral activity assays were stored at −140° C or cryopreserved in liquid nitrogen.

Sterility of the dose preparations was monitored with a 2-week incubation in both Sabouraud's broth and thioglycollate broth at 37° C followed by a visual examination for microbial growth. Stability of α-interferon A/D and α-interferon A dose formulations had been previously established for 42 days.

Periodic analyses of the antiviral activity of the dose formulations of α-interferon A/D and α-interferon A were conducted at the study laboratory using the same methods as for the bulk chemicals. These analyses demonstrated that interferon dose formulations used in the studies retained antiviral activity under normal dosing conditions. However, the differences between the titers of dose formulations determined by the cytopathic effect assay (observed) and the titers expected from making known dilutions of the calibrated laboratory standards (theoretical) were consistently greater than 10%. Because of this variability and the demonstrated stability of antiviral activity under dosing conditions, routine analysis of interferon dose formulations by the cytopathic effect assay was discontinued in October 1991. The long-term stability of laboratory standards from which dose formulations were prepared was confirmed with the cytopathic effect assay in March 1993.

FIGURE O1
Infrared Absorption Spectrum of AZT

FIGURE O2
Nuclear Magnetic Resonance Spectrum of AZT

TABLE O1
Results of Analyses for Vesicular Stomatitis Virus Activities of α-Interferon A/D and α-Interferon A Bulk Chemicals in the 2-Year Gavage Studies of AZT and α-Interferon A/D

TABLE O1
Results of Analyses for Vesicular Stomatitis Virus Activities of α-Interferon A/D and α-Interferon A Bulk Chemicals in the 2-Year Gavage Studies of AZT and α-Interferon A/D

TABLE O1
Results of Analyses for Vesicular Stomatitis Virus Activities of α-Interferon A/D and α-Interferon A Bulk Chemicals in the 2-Year Gavage Studies of AZT and α-Interferon A/D

TABLE O1
Results of Analyses for Vesicular Stomatitis Virus Activities of α-Interferon A/D and α-Interferon A Bulk Chemicals in the 2-Year Gavage Studies of AZT and α-Interferon A/D

TABLE O1
Results of Analyses for Vesicular Stomatitis Virus Activities of α-Interferon A/D and α-Interferon A Bulk Chemicals in the 2-Year Gavage Studies of AZT and α-Interferon A/D

TABLE O2
Preparation and Storage of Dose Formulations in the Gavage Studies of AZT and α-Interferon A/D

	14-Week Study	2-Year Studies
Preparation	The dosing vehicle was prepared by mixing methylcellulose with heated deionized water and then diluting with water to form a 0.5% solution, which was allowed to cool. AZT was added to the required amount of vehicle and stirred with a magnetic stirrer until a homogeneous preparation was obtained. Doses were prepared every 2 weeks.	AZT: Same as 14-week study α-Interferon A/D and α-interferon A: Interferon was diluted with the dosing vehicle (Earle's Balanced Salt Solution, pH 7.2, with 10% mouse serum) to the desired concentrations.
Chemical Lot Number	AZT: 809796 Methylcellulose: 876672	AZT: 809796, 80/0557-130-B, 86/5082-184 Methylcellulose: 876672 α-Interferon A/D: 1084 α-Interferon A: 019116
Maximum Storage Time	20 days	AZT: 20 days α-Interferon A/D and α-interferon A: 42 days
Storage Conditions	Stored in amber glass bottles in the dark at room temperature or refrigerated at approximately 5° C	AZT: Stored in amber glass bottles in the dark and refrigerated at approximately 5° C α-Interferon A/D and α-interferon A: Stored in Teflon®-capped brown glass vials at approximately 4° C
Study Laboratory	Southern Research Institute (Birmingham, AL)	Southern Research Institute (Birmingham, AL)

TABLE O3
Results of Analyses of Dose Formulations Administered to Mice in the 14-Week Gavage Study of AZT

Date Prepared	Date Analyzed	Target Concentration (mg/g)	Determined Concentration[a] (mg/g)	Difference from Target (%)
27 March 1989	28 March 1989	1.25[b]	1.26	+1
		1.25[b]	1.24	−1
		1.25[b]	1.24	−1
		1.25	1.24	−1
		2.50	2.54	+2
		5.00	5.05	+1
		20.0	19.2	−4
		50.0	48.8	−2
22 May 1989	23-24 May 1989	1.25	1.28	+2
		2.50	2.41	−4
		5.00	5.08	+2
		20.0	20.2	+1
		50.0	52.8	+6
3 July 1989	5 July 1989	1.25	1.12	−10
		2.50	2.42	−3
		5.00	4.99	0
		20.0	20.0	0
		50.0	50.4	+1

[a] Results of duplicate analyses. Dosing volume = 20 mL/kg; 1.25 mg/g = 25 mg/kg, 2.50 mg/g = 50 mg/kg, 5.00 mg/g = 100 mg/kg, 20.0 mg/g = 400 mg/kg, 50.0 mg/g = 1,000 mg/kg.
[b] Homogeneity analyses; not used for dosing

TABLE O4
Results of Analyses of AZT Dose Formulations Administered to Mice in the 2-Year Gavage Studies of AZT and AZT/α-Interferon A/D

Date Prepared	Date Analyzed	Target Concentration (mg/g)	Determined Concentration[a] (mg/g)	Difference from Target (%)
29 June 1990	2 July 1990	1.50	1.44	−4
		3.00	2.90	−3
		6.00	5.87	−2
	20 July 1990[b]	1.50	1.49	−1
		3.00	3.06	+2
		6.00	6.09	+2
24 August 1990	24 August 1990	1.50	1.47	−2
		3.00	3.03	+1
		6.00	6.01	0
21 September 1990	10-11 October 1990	1.50	1.50	0
		3.00	3.03	+1
		6.00	5.87	−2
	10-11 October 1990[b]	1.50	1.50	0
		3.00	3.03	+1
		6.00	6.16	+3
30 November 1990	3 December 1990	1.50	1.46	−3
		3.00	3.12	+4
		6.00	5.96	−1
28 December 1990	4 January 1991	1.50	1.51	+1
		3.00	2.98	−1
		6.00	6.06	+1
	21-22 January 1991[b]	1.50	1.53	+2
		3.00	3.02	+1
		6.00	6.01	0
22 February 1991	25 February 1991	1.50	1.55	+3
		1.50	1.55	+3
		3.00	3.07	+2
		3.00	3.04	+1
		6.00	6.05	+1
		6.00	6.00	0
8 March 1991	28 March 1991	1.50	1.48	−1
		3.00	3.04	+1
		6.00	6.15	+3
19 April 1991	22 April 1991	1.50	1.39	−7
		1.50	1.42	−5
		3.00	2.95	−2
		3.00	3.10	+3
		6.00	6.02	0
		6.00	6.31	+5

TABLE O4
Results of Analyses of AZT Dose Formulations Administered to Mice in the 2-Year Gavage Studies of AZT and AZT/α-Interferon A/D

Date Prepared	Date Analyzed	Target Concentration (mg/g)	Determined Concentration (mg/g)	Difference from Target (%)
14 June 1991	17 June 1991	1.50	1.45	−3
		1.50	1.44	−4
		3.00	2.96	−1
		3.00	2.99	0
		6.00	5.93	−1
		6.00	6.04	+1
	8 July 1991[b]	1.50	1.51	+1
		1.50	1.51	+1
		3.00	2.90	−3
		3.00	3.02	+1
		6.00	5.80	−3
		6.00	6.03	+1
9 August 1991	13 August 1991	1.50	1.49	−1
		1.50	1.49	−1
		3.00	3.01	0
		3.00	3.02	+1
		6.00	6.04	+1
		6.00	6.00	0
4 October 1991	7-8 October 1991	1.50	1.47	−2
		1.50	1.48	−1
		3.00	2.97	−1
		3.00	2.97	−1
		6.00	5.92	−1
		6.00	5.97	−1
2 December 1991	2-3 December 1991	1.50	1.55	+3
		1.50	1.55	+3
		3.00	3.02	+1
		3.00	3.03	+1
		6.00	6.05	+1
		6.00	6.03	+1
	20 December 1991[b]	1.50	1.51	+1
		1.50	1.51	+1
		3.00	3.05	+2
		3.00	3.05	+2
		6.00	6.08	+1
		6.00	6.00	0
24 January 1992	27 January 1992	1.50	1.47	−2
		1.50	1.48	−1
		3.00	3.01	0
		3.00	3.02	+1
		6.00	6.10	+2
		6.00	6.05	+1
20 March 1992	23-24 March 1992	1.50	1.50	0
		1.50	1.48	−1
		3.00	2.91	−3
		3.00	2.96	−1
		6.00	5.86	−2
		6.00	5.89	−2

TABLE O4
Results of Analyses of AZT Dose Formulations Administered to Mice in the 2-Year Gavage Studies of AZT and AZT/α-Interferon A/D

Date Prepared	Date Analyzed	Target Concentration (mg/g)	Determined Concentration (mg/g)	Difference from Target (%)
18 May 1992	18-19 May 1992	1.50	1.55	+3
		1.50	1.47	−2
		3.00	2.97	−1
		3.00	3.00	0
		6.00	5.98	0
		6.00	6.01	0
	5 June 1992[b]	1.50	1.49	−1
		1.50	1.50	0
		3.00	2.99	0
		3.00	3.01	0
		6.00	5.96	−1
		6.00	5.94	−1
26 June 1992	29 June 1992	1.50	1.53	+2
		3.00	2.96	−1
		6.00	5.95	−1
	17 & 21 July 1992[b]	1.50	1.49	−1
		3.00	3.03	+1
		6.00	6.06	+1
21 August 1992	24 August 1992	1.50	1.47	−2
		3.00	2.98	−1
		6.00	5.89	−2
18 September 1992	21 September 1992	1.50	1.53	+2
		3.00	3.01	0
		6.00	5.94	−1
	9 October 1992[b]	1.50	1.50	0
		3.00	3.02	+1
		6.00	6.08	+1
13 November 1992	16 November 1992	1.50	1.49	−1
		3.00	3.00	0
		6.00	6.01	0

[a] Results of duplicate analyses. Dosing volume = 10 mL/kg; 1.50 mg/g = 15 mg/kg, 3.00 mg/g = 30 mg/kg, 6.00 mg/g = 60 mg/kg.
[b] Animal room samples

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

TABLE P1
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 P2
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 P3
Nutrient Composition of NIH-07 Rat and Mouse Ration

Nutrient	Mean ± Standard Deviation	Range	Number of Samples
Protein (% by weight)	23.45 ± 0.52	22.2 – 24.3	31
Crude fat (% by weight)	5.33 ± 0.19	5.00 – 5.90	31
Crude fiber (% by weight)	3.40 ± 0.34	2.60 – 4.30	31
Ash (% by weight)	6.41 ± 0.19	6.11 – 6.81	31
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)	6,641 ± 1,207	5,510 – 11,450	31
Vitamin D (IU/kg)	4,450 ± 1,382	3,000 – 6,300	4
α-Tocopherol (ppm)	35.43 ± 8.98	22.5 – 48.9	11
Thiamine (ppm)	17.71 ± 2.07	14.0 – 22.0	31
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 (%)	1.16 ± 0.09	1.00 – 1.49	31
Phosphorus (%)	0.92 ± 0.04	0.76 – 1.00	31
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 P4
Contaminant Levels in NIH-07 Rat and Mouse Ration[a]

	Mean ± Standard Deviation[b]	Range	Number of Samples
Contaminants			
Arsenic (ppm)	0.43 ± 0.20	0.10 – 0.70	31
Cadmium (ppm)	0.11 ± 0.07	0.04 – 0.20	31
Lead (ppm)	0.34 ± 0.22	0.10 – 1.00	31
Mercury (ppm)[c]	0.02	0.02 – 0.03	31
Selenium (ppm)	0.34 ± 0.11	0.05 – 0.60	31
Aflatoxins (ppb)	< 5.0		31
Nitrate nitrogen (ppm)[d]	9.22 ± 5.09	2.90 – 21.0	31
Nitrite nitrogen (ppm)[d]	0.18 ± 0.12	0.10 – 0.70	31
BHA (ppm)[e]	2.35 ± 3.72	1.00 – 20.0	31
BHT (ppm)[e]	1.52 ± 1.43	1.0 – 8.00	31
Aerobic plate count (CFU/g)	84,481 ± 147,567	4,100 – 710,000	31
Coliform (MPN/g)	3 ± 0.2	3 – 4	31
Escherichia coli (MPN/g)	< 3		31
Salmonella (MPN/g)	Negative		31
Total nitrosoamines (ppb)[f]	7.51 ± 1.86	4.70 – 11.40	31
N-Nitrosodimethylamine (ppb)[f]	5.42 ± 1.14	2.90 – 8.20	31
N-Nitrosopyrrolidine (ppb)[f]	2.08 ± 1.24	1.00 – 6.00	31
Pesticides (ppm)			
α-BHC	< 0.01		31
-BHC	< 0.02		31
-BHC	< 0.01		31
-BHC	< 0.01		31
Heptachlor	< 0.01		31
Aldrin	< 0.01		31
Heptachlor epoxide	< 0.01		31
DDE	< 0.01		31
DDD	< 0.01		31
DDT	< 0.01		31
HCB	< 0.01		31
Mirex	< 0.01		31
Methoxychlor	< 0.05		31
Dieldrin	< 0.01		31
Endrin	< 0.01		31
Telodrin	< 0.01		31
Chlordane	< 0.05		31
Toxaphene	< 0.10		31
Estimated PCBs	< 0.20		31
Ronnel	< 0.01		31
Ethion	< 0.02		31
Trithion	< 0.05		31
Diazinon	< 0.10		31
Methyl parathion	< 0.02		31
Ethyl parathion	< 0.02		31
Malathion	0.20 ± 0.21	0.05 – 0.97	31
Endosulfan I	< 0.01		31
Endosulfan II	< 0.01		31
Endosulfan sulfate	< 0.03		31

[a] CFU = colony forming units; MPN = most probable number; BHC = hexachlorocyclohexane or benzene hexachloride
[b] For values less than the limit of detection, the detection limit is given as the mean.
[c] All values except for the September, November, and December 1991 milling dates were less than the detection limit. The detection limit is given as the mean.
[d] Sources of contamination: alfalfa, grains, and fish meal
[e] Sources of contamination: soy oil and fish meal
[f] All values were corrected for percent recovery.

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

Method and Test	Time of Analysis
14-Week Study	
ELISA	
Ectromelia virus	Study termination
GDVII (mouse encephalomyelitis virus)	Study termination
LCM (lymphocytic choriomeningitis virus)	Study termination
MVM (minute virus of mice)	Study termination
Mouse adenoma virus	Study termination
MHV (mouse hepatitis virus)	Study termination
Mycoplasma arthritidis	Study termination
Mycoplasma pulmonis	Study termination
PVM (pneumonia virus of mice)	Study termination
Reovirus 3	Study termination
Sendai	Study termination
Immunofluorescence Assay	
EDIM (epizootic diarrhea of infant mice)	Study termination
Reovirus 3	Study termination (males only)
Hemagglutination Inhibition	
K (papovavirus)	Study termination
Polyoma virus	Study termination

2-Year AZT Study

ELISA	
Ectromelia virus	7, 12, and 19 months, study termination
EDIM	7, 12, and 19 months, study termination
GDVII	7, 12, and 19 months, study termination
LCM	7, 12, and 19 months, study termination
Mouse adenoma virus-FL	7, 12, and 19 months, study termination
MHV	5, 7, 10, 12, and 19 months, study termination
M. arthritidis	19 months and study termination
M. pulmonis	19 months and study termination
PVM	7, 12, and 19 months, study termination
Reovirus 3	5, 7, 12, and 19 months, study termination
Sendai	5, 7, 10, 12, and 19 months, study termination
Immunofluorescence Assay	
Ectromelia virus	19 months
EDIM	7, 12, and 19 months
GDVII	19 months
MHV	10 months
Reovirus 3	5, 7, and 19 months
Hemagglutination Inhibition	
K	7, 12, and 19 months, study termination
MVM	7, 12, and 19 months, study termination
Polyoma virus	7, 12, and 19 months, study termination

2-Year α-Interferon A/D Study

ELISA	
Ectromelia virus	7, 13, and 19 months, study termination
EDIM	13 and 19 months, study termination
GDVII	7, 13, and 19 months, study termination
LCM	7, 13, and 19 months, study termination
Mouse adenoma virus-FL	7, 13, and 19 months, study termination
MHV	3, 7, 13, and 19 months, study termination
M. arthritidis	Study termination
M. pulmonis	Study termination
PVM	7, 13, and 19 months, study termination
Reovirus 3	3, 7, 13, and 19 months, study termination
Sendai	3, 7, 13, and 19 months, study termination
Immunofluorescence Assay	
EDIM	7 and 19 months
GDVII	19 months
Mouse adenoma virus-FL	13 months
Reovirus 3	13 months and study termination
Hemagglutination Inhibition	
K	7, 13, and 19 months, study termination
MVM	7, 13, and 19 months, study termination
Polyoma virus	7, 13, and 19 months, study termination

2-Year AZT/500 U α-Interferon A/D Study

ELISA

Ectromelia virus	7, 8, 12, and 18 months, study termination
EDIM	12 and 18 months, study termination
GDVII	7, 8, 12, and 18 months, study termination
LCM	7, 8, 12, and 18 months, study termination
Mouse adenoma virus-FL	7, 8, 12, and 18 months, study termination
MHV	2, 7, 8, 12, and 18 months, study termination
M. arthritidis	18 months and study termination
M. pulmonis	18 months and study termination
PVM	7, 8, 12, and 18 months, study termination
Reovirus 3	2, 7, 8, 12, and 18 months, study termination
Sendai	2, 7, 8, 12, and 18 months, study termination

Immunofluorescence Assay

EDIM	7, 8, and 18 months, study termination
GDVII	12 months
LCM	7 and 18 months
Mouse adenoma virus-FL	7, 12, and 18 months
MHV	7 months
Reovirus 3	2 and 7 months

Hemagglutination Inhibition

K	7, 8, 12, and 18 months, study termination
MVM	7, 8, 12, and 18 months, study termination
Polyoma virus	7, 8, 12, and 18 months, study termination

2-Year AZT/5,000 U α-Interferon A/D Study

ELISA

Ectromelia virus	6, 12, and 18 months, study termination
EDIM	6, 12, and 18 months, study termination
GDVII	6, 12, and 18 months, study termination
LCM	6, 12, and 18 months, study termination
Mouse adenoma virus-FL	6, 12, and 18 months, study termination
MHV	6, 12, and 18 months, study termination
M. arthritidis	18 months and study termination
M. pulmonis	18 months and study termination
PVM	6, 12, and 18 months, study termination
Reovirus 3	6, 12, and 18 months, study termination
Sendai	6, 12, and 18 months, study termination

Immunofluorescence Assay

EDIM	6 and 12 months, study termination
GDVII	12 months
LCM	Study termination
MVM	6 months
Mouse adenoma virus-FL	Study termination
Reovirus 3	6, 12, and 18 months

2-Year AZT/5,000 U α-Interferon A/D Study (continued)

Hemagglutination Inhibition

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

Results of serology tests are presented in Table Q1.

TABLE Q1
Murine Virus Antibody Determinations for Mice in the 14-Week and 2-Year Studies of AZT and AZT/α-Interferon A/D

Interval	Incidence of Antibody in Sentinel Animals	Positive Serologic Reaction for
14-Week Study		
Study termination	1/8	Reovirus 3[a]
2-Year Studies		
AZT		
Core Groups		
5 Months	7/10	MHV
	1/10	Reovirus 3
7 Months	6/9	MHV
10 Months	1/1	MHV
12 Months	7/10	MHV
19 Months	5/9	MHV
Study termination	10/10	MHV
Clinical Pathology Groups		
5 Months	10/10	MHV
7 Months	9/9	MHV
12 Months	3/10	MHV
19 Months	6/10	MHV
α-Interferon A/D		
Core Groups		
3 Months	6/10	MHV
7 Months	5/7	MHV
13 Months	6/8	MHV
19 Months	7/9	MHV
Study termination	10/10	MHV
	2/10	*M. arthritidis*[b]
	1/10	Reovirus 3[a]
Clinical Pathology Groups		
3 Months	8/10	MHV
7 Months	8/9	MHV
13 Months	9/10	MHV
19 Months	8/9	MHV

TABLE Q1
Murine Virus Antibody Determinations for Mice in the 14-Week and 2-Year Studies of AZT and AZT/α-Interferon A/D

Interval	Incidence of Antibody in Sentinel Animals	Positive Serologic Reaction for
2-Year Studies (continued)		
AZT/500 U α-Interferon A/D		
Core Groups		
2 Months	4/10	MHV
7 Months	5/10	MHV
12 Months	5/9	MHV
18 Months	7/10	MHV
Study termination	10/10	MHV
Clinical Pathology Groups		
6 Months	1/9	MVM[c]
12 Months	1/10	EDIM
	1/10	MHV
	5/10	Reovirus 3[a]
18 Months	5/10	*M. arthritidis*[b]
AZT/5,000 U α-Interferon A/D		
Core Groups		
12 Months	1/8	Reovirus 3[a]
18 Months	1/8	Reovirus 3[a]
Study termination	2/10	*M. arthritidis*[b]
Clinical Pathology Groups		
2 Months	9/10	MHV
7 Months	8/10	MHV
8 Months	1/1	MHV
12 Months	5/10	MHV
18 Months	5/9	MHV

[a] The positive response for Reovirus 3 could not be confirmed by Western blot or colony epidemiology procedures; therefore, the titer is considered a false positive.

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

[c] The sample positive for MVM was also evaluated for parvovirus antibodies by immunofluorescence assay; the result was negative.

APPENDIX R
IMPACT OF *HELICOBACTER HEPATICUS* INFECTION IN B6C3F$_1$ MICE FROM 12 NTP 2-YEAR CARCINOGENESIS STUDIES

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IMPACT OF *HELICOBACTER HEPATICUS* INFECTION IN B6C3F$_1$ MICE FROM 12 NTP 2-YEAR CARCINOGENESIS STUDIES

ABSTRACT

Male and female B6C3F$_1$ mice from 12 NTP 2-year carcinogenesis studies were found to be infected with *Helicobacter hepaticus*. Many of the male mice from nine of these studies ("affected" studies) had an associated hepatitis. The current evaluations were performed in an attempt to determine if the data from the *H. hepaticus*-affected NTP B6C3F$_1$ mouse studies were compromised and unsuitable for cancer hazard identification. The incidences of neoplasms of the liver (both hepatocellular neoplasms and hemangiosarcoma), but not of other organs in control male B6C3F$_1$ mice, were found to be increased in affected studies compared to control males from unaffected studies. The increased incidence of hepatocellular neoplasms was observed in those males exhibiting *H. hepaticus*-associated hepatitis. Other observations further differentiated control male mice from affected and unaffected studies. H-*ras* codon 61 CAA-to-AAA mutations were less common in liver neoplasms in males from affected studies compared to historical and unaffected study controls. In addition, increases in cell proliferation rates and apoptosis were observed in the livers of male mice with *H. hepaticus*-associated hepatitis. These data support the hypothesis that the increased incidence of liver neoplasms is associated with *H. hepaticus* and that hepatitis may be important in the pathogenesis. Therefore, interpretation of carcinogenic effects in the liver of B6C3F$_1$ mice may be confounded if there is *H. hepaticus*-associated hepatitis.

INTRODUCTION

Helicobacter-Induced Diseases

Since the bacterium *H. pylori* was isolated from humans in 1983, numerous *Helicobacter* species have been identified in several laboratory and domestic animal species. Their pathogenicity varies, with some species inducing significant disease while others appear merely to colonize the gastrointestinal tract. *H. pylori* is known to cause chronic gastritis and peptic ulcers in humans (Marshall and Warren, 1984; Graham, 1989; Lee *et al.*, 1993) and, more recently, has been linked to adenocarcinoma and mucosa-associated lymphoma of the stomach (Fox *et al.*, 1989; Nomura *et al.*, 1991; Parsonnet *et al.*, 1991; Wotherspoon *et al.*, 1993). Based on epidemiological and pathology findings, the International Agency for Research on Cancer (1994) has classified *H. pylori* as a group 1 carcinogen in humans. *H. hepaticus* is associated with an increase in liver neoplasm incidences in A/JCr mice (Ward *et al.*, 1994a; Fox *et al.*, 1996).

H. hepaticus commonly colonizes the gastrointestinal tract of many strains of mice from many sources (Fox *et al.*, 1994; Ward *et al.*, 1994b; Shames *et al.*, 1995). It has been shown to be pathogenic, with hepatitis highly prevalent in some strains of mice (A/JCr, BALB/cAnNCr, C3H/HeNCr, SJL/NCr, and SCID/NCr) (Ward *et al.*, 1994b). Intestinal colonization does not necessarily result in subsequent hepatitis, and the conditions that lead to migration of the organism from the intestine to the liver have not been determined. *H. hepaticus* appears to reside primarily within the bile canaliculi. Male mice were reported to have a greater incidence and severity of hepatitis than female mice, and this finding occurred in NTP studies as well. The recently identified *H. bilis*, like *H. hepaticus*, colonizes the biliary tract, liver, and intestine of mice. While *H. bilis* has been identified in animals with chronic hepatitis, whether it caused the hepatitis is not known (Fox *et al.*, 1995).

The pathogenesis of *H. hepaticus*-induced disease has not been fully characterized. In susceptible strains of mice, *H. hepaticus* can cause acute, focal, nonsuppurative, necrotizing hepatitis, which progresses to chronic, active hepatitis characterized by minimal necrosis, hepatocytomegaly, oval cell hyperplasia, and

cholangitis. *H. hepaticus* has been found to possess high levels of urease (Fox *et al.*, 1994). *H. hepaticus* is often isolated from the cecum and colon but is not necessarily isolated from the liver of A/JCr mice, even though these animals develop severe hepatitis. Culture supernatants from several strains of *H. hepaticus* and several other *Helicobacter* species were shown to cause cytopathic effects in a rodent hepatocyte cell line (Taylor *et al.*, 1995). Ward *et al.* (1996) suggested that autoimmunity may play a role in the progressive hepatitis and carcinogenesis in livers infected with *H. hepaticus*.

NTP Infectious Disease Surveillance

In 1993, during the histological evaluation of an NTP 2-year study, pathologists identified a constellation of liver lesions (hepatitis) in control and treated male mice that was consistent with what would later be described in mice infected with *H. hepaticus* (Ward *et al.*, 1993, 1994a; Fox *et al.*, 1994). Subsequently, pathology results from all mouse studies begun since 1984 (67 two-year studies) were reviewed for diagnoses of the characteristic hepatitis; the lesions were identified in nine studies (NTP, 1998a,b,c,d, 1999a,b). Silver stains revealed helical bacteria consistent with *Helicobacter* present in the liver of male mice in the nine studies.

Every reasonable measure is taken to prevent the occurrence of infectious diseases during NTP 2-year carcinogenicity studies. When infections occasionally occur, care is taken to identify the causal agent and its source, measures are taken to ensure that animals in later studies will not be infected, and the potential impact on biological parameters (primarily neoplastic endpoints) important in interpretation of the study is determined. To date, animals (control and treated) from a few studies have had a mild pulmonary inflammatory response presumed to be caused by an infectious agent. In other studies, there have been utero-ovarian infections with *Klebsiella* sp. (Rao *et al.*, 1987) and fungal infections of the nasal cavity. For scientifically valid reasons, interpretation of chemical-related effects was not considered significantly compromised in any of these studies. Unlike the previous infections, *H. hepaticus* involves the liver, the major metabolic organ, and has been associated with an increase in incidences of liver neoplasms in the A/JCr mouse (Ward *et al.*, 1994a). Therefore, when the contemporary epizootic of *H. hepaticus* infection in the United States affected several NTP studies, use of the data for hazard identification was questioned. The first step was to determine the extent of the infection within NTP studies and then evaluate the impact the infection had on biological parameters important in interpretation of the carcinogenic potential of test chemicals.

MATERIALS AND METHODS

Histologic Examination

Studies in which mice were potentially infected with *H. hepaticus* were identified by reviewing the summary pathology tables for characteristic diagnoses: oval and/or biliary epithelial hyperplasia, hepatocyte enlargement (often diagnosed as karyomegaly), chronic inflammation, and regenerative hyperplasia. All 13-week and 2-year studies begun by the NTP since 1984 and for which complete pathology data were available (67 two-year studies) were examined. Eight contemporary studies in which the characteristic lesions were not identified from pathology tables were randomly selected for histologic reevaluation. Slides containing sections of hematoxylin- and eosin-stained livers from 20 to 25 control and 20 to 25 high-dose male mice from each of seven 2-year studies and one 13-week study (10 animals from each group) were reexamined microscopically for the presence of hepatitis potentially related to *H. hepaticus* infection. Hepatitis consistent with that observed with *H. hepaticus* infection was not observed in any of these studies.

Liver sections from five or more animals from each of nine 2-year studies in which hepatitis was observed were prepared using the Warthin-Starry silver stain or Steiner's modification to identify silver-positive helical bacteria.

PCR-RFLP Detection of *Helicobacter* DNA

Assays based on polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) were conducted at the NIEHS (Malarkey *et al.*, 1997) and the University of Missouri Research Animal Diagnostic and Investigative Laboratory (MU-RADIL) (Riley *et al.*, 1996) on liver tissue from approximately 20 animals from each of 32 NTP 2-year studies (including the nine affected studies) and three NTP 13-week studies. The majority of these studies were selected because they were begun at approximately the same time (1988-1990) as the nine affected studies. Also, two earlier studies (1984-1985; mouse life-span and *p*-nitroaniline studies) and one later study (1993; methyleugenol) were selected. The mouse life-span study was designed to evaluate the incidences of spontaneous changes associated with age; therefore, there is no NTP Technical Report. Frozen tissue was available from 22 of these studies, while only formalin-fixed tissue was available for the remaining ten 2-year studies and the three 13-week studies. Most of the assays were conducted by MU-RADIL, which used *Helicobacter* genus-specific primers; MU-RADIL used restriction endonucleases on a subset of positives to determine if the species was *H. hepaticus*. DNA was isolated from frozen liver samples with a QIAamp Tissue Kit (Qiagen Inc., Chatsworth, CA) according to the manufacturer's recommendations or routine phenol/chloroform extraction (Malarkey *et al.*, 1997). DNA content and purity were determined spectrophotometrically by measuring the A_{260}/A_{280} optical density ratio. To isolate DNA from paraffin-embedded samples, five 10-µm sections were washed twice with 1 mL xylene and twice with 500 µL ethanol. Tissues were then dried within a vacuum centrifuge prior to DNA isolation as described above. Routine measures were taken to avoid contamination at every step from tissue collection to PCR amplification, and concurrently run controls without DNA were consistently negative.

Statistical Analyses

Multiple regression procedures were used to compare control neoplasm rates in the nine affected studies with the 26 unaffected contemporary studies which had no histologic evidence of *H. hepaticus*-associated liver disease. While frozen liver tissue was unavailable from 13 of these 26 studies, none showed the hepatitis indicative of *H. hepaticus* and thus were assumed to be unaffected. Potential confounding factors such as body weight, date study was begun, route of administration, and animal supplier were included as covariables in the statistical analysis.

Analysis for H-*ras* Codon 61 CAA-to-AAA Mutations

For analyses of formalin-fixed tissue, three to five unstained serial sections (10 µm thick) were cut from paraffin blocks containing hepatocellular adenomas or carcinomas. Paraffin-embedded tissues were deparaffinized and rehydrated prior to being digested with proteinase k overnight at 55° C to isolate DNA. Frozen tissues were digested with 10 mg/mL pronase in 1% sodium dodecyl sulfate in TNE buffer (10 mM TRIS, 150 mM NaCl, and 2 mM EDTA; pH 7.5) overnight at 37° C; DNA was isolated by phenol chloroform extraction and precipitated with ethanol (Marmur, 1961; Sills *et al.*, 1995).

Nested primers were used for amplification of exon 2 of H-*ras* by PCR. The outer primers were 5'-CCA CTA AGC CTG TTG TGT TTT GCA G-3' (forward primer) and 5'-CTG TAC TGA TGG ATG TCC TCG AAG GA-3' (reverse primer). The inner primers (second round of amplification) were 5'-GAC ATC TTA GAC ACA GCA GTT-3' (forward primer) and 5'-GGT GTT GTT GAT GGC AAA TAC-3' (reverse primer). Although the normal sequence of codon 60 is GCT, the forward PCR primer is made with a T at the penultimate 3' base to create the restriction site for Mse1.

A nonradioactive RFLP method was employed to identify CAA-to-AAA mutations in the H-*ras* gene at codon 61 in liver neoplasms (Lee and Drinkwater, 1995). This was based on Mse1 enzyme restriction cutting only the sequence 5'-TTAA-3'. Thus, Mse1 will detect C→A conversion mutation at the first position of codon 61.

Analysis of PCNA and Apoptosis

Detailed methods are included in a report by Nyska *et al*. (1997). Cell proliferation was assessed in nonneoplastic areas of the liver, kidney, and lung by determining a PCNA S-phase labeling index (the percentage of cells in S phase). The identification of apoptotic cells was based on morphologic criteria (Garewal *et al.*, 1996; Goldsworthy *et al.*, 1996) and confirmed immunohistochemically by the terminal deoxynucleotidyl transferase-mediated dUTP-biotin nick end labeling (TUNEL) procedure (Gavrieli *et al.*, 1992).

RESULTS AND DISCUSSION

Identification of *H. hepaticus* Infection in NTP Studies

Determining the extent of *H. hepaticus* infection involved a three-pronged approach of histologic evaluation, silver stains, and PCR-RFLP based assays; all were necessary because of the limitations identified for each. In NTP studies, and as reported in other studies (Ward *et al.*, 1994b), there were no obvious clinical signs of infection, and the only significant histologic lesion (hepatitis) was observed in the liver, primarily in males. Therefore, summary pathology tables were reviewed to identify studies that may have been affected by *H. hepaticus*-associated hepatitis. Male mice from nine studies were identified (Table R1) as having the hepatitis. Eight of the nine studies were begun during a time span of about 6 months (July 1990 to January 1991), while the other study was begun much earlier (October 1988). The hepatitis was not observed in any 13-week studies. Use of histologic evaluation for identification of infected animals has limitations, however. It is somewhat insensitive, as *H. hepaticus* has been cultured and identified by PCR-RFLP methods within livers of animals with no histological evidence of infection (Fox *et al.*, 1999). This may be explained in part by the limited sampling (two liver sections) and the sometimes focal nature of *H. hepaticus*-associated hepatitis. Also, while in the more severely affected animals the hepatitis appears somewhat characteristic, component lesions of the hepatitis are not pathognomonic, and, when the hepatitis is subtle in 2-year old animals, it is more difficult to recognize or attribute to *H. hepaticus*.

Within affected studies, the incidences of the hepatitis in male mice varied from 16% to 78% (Table R1). While generally mild to moderate, the hepatitis varied in severity from barely detectable in some animals to extensive liver involvement and regeneration in others. Only a few females were identified as having the characteristic hepatitis (Table R1). In general, the incidences and severities of *H. hepaticus*-associated hepatitis were similar between control and treated groups. This constellation of nonneoplastic liver lesions, while not pathognomonic, was certainly suggestive of an *H. hepaticus* infection, particularly when observed in control animals. Characteristic lesions included proliferation of oval and/or biliary epithelial cells, hepatocyte enlargement (diagnosed as karyomegaly), and chronic inflammation. In many instances, areas of regenerative hyperplasia were identified within diseased liver.

Helicobacter spp. are not usually observed on routine histologic examination of hematoxylin and eosin-stained sections of liver. The methods for confirmation of infection with *Helicobacter* include Warthin-Starry silver stain or Steiner's modification (Garvey *et al.*, 1985) of this stain for direct microscopic observation of the organisms in tissue; however, this can be a relatively insensitive technique when few organisms are present. In most instances, histologic differentiation between *Helicobacter* species is not possible. Speciation can usually be accomplished with electron microscopy, but this technique is both time consuming and labor intensive. Microbiologic culture of feces, cecal smears, and fresh or frozen liver is also possible. Currently, assays involving amplification of the DNA of the organism using PCR are the most rapid and perhaps the most sensitive methods of detection, and the use of restriction endonucleases has allowed a determination of the species present. PCR-based methods also can be used on feces, cecal contents, or liver homogenates and are most sensitive when using fresh or frozen tissue (Riley *et al.*, 1996; Malarkey *et al.*, 1997).

Using Warthin-Starry silver stains or Steiner's modification on the livers of five or more animals per study, helical bacteria (*Helicobacter*) were identified in animals from the nine affected studies. In some animals, helical bacteria were numerous, suggesting a heavy bacterial burden in these infected animals. However, even in these animals with abundant organisms, few to none were observed in proliferative hepatic lesions such as foci and neoplasms. Helical bacteria were not identified in approximately 25% of males with moderate hepatitis and were rarely identified in males without hepatitis or in females. The absence of identification of helical organisms by silver stains does not preclude infection, nor does the presence of organisms confirm *H. hepaticus*. Based upon current knowledge, however, the characteristic liver lesions in $B6C3F_1$ mice, coupled with the presence of silver-positive helical organisms, are highly suggestive of *H. hepaticus* infection.

As the NTP evaluation evolved, PCR-based assays were developed that appeared more sensitive than histologic evaluation and silver stains for identification and speciation of *Helicobacter*. Therefore, PCR-RFLP-based assays were used to confirm the presence of pathogenic *Helicobacter* (primarily *H. hepaticus*) within the nine affected studies and to determine whether there was *H. hepaticus* infection in other NTP studies. Unfortunately, none of the PCR-based assays had been specifically developed for, or proven reliable for use with, formalin-fixed tissue. Frozen tissue was available from a limited number of animals from a limited number of NTP studies, including only three of the nine affected studies. Furthermore, available frozen liver was almost always limited to tissue from a neoplasm, and, based upon results obtained with silver stains, organisms are generally not readily observed within proliferative hepatic lesions, even when organisms are abundant in adjacent liver tissue. Because the availability of frozen tissue was limited, a PCR-RFLP-based assay was developed and evaluated (Malarkey *et al.*, 1997) for use with frozen or formalin-fixed tissue.

The NIEHS and MU-RADIL laboratories conducted PCR-RFLP-based assays on 32 NTP 2-year studies and three NTP 13-week studies (data not shown); frozen tissues from 22 of the 2-year studies were available. All three bioassays in which hepatitis was identified and for which frozen tissue was available were positive for *H. hepaticus* by the PCR-RFLP-based assays (Table R2). At a third laboratory, *H. hepaticus* was also cultured from the liver tissue of animals in one of these studies (Fox *et al.*, 1999). Formalin-fixed tissues from two of the three studies were evaluated and were also positive; these tissues had been fixed in formalin for less than 48 hours. In the other six affected studies, for which only formalin-fixed tissue was available, *H. hepaticus* was identified in only 1 of 120 animals (Table R2). This decreased sensitivity was considered to be related to the prolonged formalin fixation (Malarkey *et al.*, 1997) rather than proof of an absence of *H. hepaticus*. The presence or absence of *H. hepaticus* apparently cannot be confirmed with current PCR-RFLP-based assays in liver that has been fixed in formalin for long periods (weeks or months). In the three 13-week studies with formalin-fixed tissue, only 1 of 30 animals was positive for *H. hepaticus*.

Within the three affected, PCR-RFLP-positive 2-year studies, *H. hepaticus* was often identified by PCR in frozen livers of mice that had no overt hepatitis. In fact, based upon the combined data from two studies (including PCR results from three laboratories), of 57 animals without characteristic liver lesions, 13 of 24 male mice (54%) and 17 of 33 female mice (52%) were positive for *H. hepaticus*. Furthermore, *H. hepaticus* was identified by PCR in frozen liver of several animals from three "unaffected" studies in which hepatitis typical of that associated with *H. hepaticus* was not observed (Table R2). Apparent variability occurs between various strains of mice and between individual mice from affected studies in developing hepatitis in response to *H. hepaticus* infection. One would assume that, within affected studies, most or all animals have been exposed to the organism, and even animals resistant to developing hepatitis may have organisms within the liver. This assumption is supported by the fact that animals without hepatitis are often positive with PCR-RFLP-based assays. Therefore, although alternative explanations are possible, the three PCR-RFLP-positive studies in which liver lesions are absent are assumed to be true positives. In fact, helical organisms were identified with a silver stain in one animal from one of these studies (Malarkey

et al., 1997). Therefore, in addition to assessing the affect of *H. hepaticus* in the nine affected 2-year studies, the significance of a positive PCR-RFLP assay for *H. hepaticus* in the absence of liver lesions is also an important question.

Inconsistent Results with PCR-Based Methods

As with any technique, the PCR-RFLP-based assays have limitations even when used to assay fresh and frozen tissue. One assessment of the variability in results of PCR and serologic analyses for *Helicobacter* among three commercial laboratories revealed significant inconsistencies (Dew *et al.*, 1997). Others (J.M. Ward and J. Thigpen, personal communications) have obtained similarly inconsistent results when sending replicate samples to different laboratories. Though the number of samples evaluated by both the NIEHS and MU-RADIL laboratories was limited, there was good, but not complete, correlation of PCR-RFLP results. Also, within the affected studies, the PCR assays were not positive in some animals with liver disease. This result may be explained, in part, by the fact that the only frozen tissues available were neoplasms; as described above, neoplasms are expected to have fewer organisms.

Analysis of *H. hepaticus*-Affected and Unaffected Studies for Incidence of Common Neoplasms

To determine whether the incidences of various neoplasms were different between control groups from affected and unaffected studies, the nine affected studies were compared to 26 unaffected studies begun at relatively similar times (Table R3). There were no statistically significant differences in body weight or survival among the affected and unaffected studies. The neoplasms evaluated represent those that occurred at high enough incidences in various organs for statistically significant differences to be detected. Using multiple regression procedures, male mice in the nine affected studies were demonstrated to have a significantly ($P < 0.05$) increased incidence of only two neoplasm types, both of which were in the liver (hepatocellular neoplasms and hemangiosarcoma), when compared to the unaffected studies. Because of these differences, there was also a corresponding significant difference in the overall incidence of malignant neoplasms (all sites) as well as in the overall proportion of neoplasm-bearing animals. No other tissue site showed a significant difference in the incidence of neoplasms. For female mice, the slightly increased incidence of hepatocellular neoplasms observed in the affected studies was not statistically significant.

This seemingly simple analysis is complicated by several potential confounding variables. There have been coordinate, time-related increases in body weight and in the incidence of liver neoplasms in mice in NTP studies (Haseman, 1992). Table R4 presents the liver neoplasm incidences in relation to the dates the studies began and clearly shows the increases in liver neoplasm incidences and body weights (Seilkop, 1995). In assessing differences in neoplasm incidences between *H. hepaticus*-affected and unaffected studies, the most relevant comparison would be between studies begun at approximately the same time. The starts of 20 of the 26 unaffected studies were clustered near the early part of the time frame (April 1988 to June 1990), while the starts of the affected studies were clustered toward the later end, with eight of the nine studies begun between July 1990 and January 1991; incidences of liver neoplasms in these later studies are expected to be higher based on trends in body weight alone. While the slightly increased incidences of liver neoplasms observed in female control mice in the nine affected studies is likely due to clustering in time, clearly, this alone cannot account for the increased liver neoplasm incidences observed in control male mice in the affected studies (Table R3).

Ideally, unaffected studies used in the above comparison should not only be free of histologic evidence of infection with *H. hepaticus* but should be confirmed as negative by PCR assays. Thirteen of these 26 studies could not be confirmed as negative by PCR because frozen tissue was not available; however, *H. hepaticus*-associated hepatitis was not present in any of the 26 studies. Because these and other data reported to date suggest that hepatitis is associated with neoplasm development in the liver, it seems reasonable to include those 13 studies, unconfirmed by PCR, in this analysis. The majority of the 13 studies confirmed as negative by PCR were begun much earlier than the clearly affected studies, and,

therefore, comparing them alone to the nine affected studies is not reasonable. Although not presented here, a number of comparisons were made with various groupings of studies based on the degree of confidence in their infection status. Although the outcomes of the various comparisons varied somewhat, incidences of hepatocellular neoplasms and hemangiosarcomas of the liver were consistently increased in control male mice from affected studies compared to control males from unaffected studies. Significantly increased liver neoplasm incidences generally were not observed in females. Importantly, the following data corroborate the findings and association with *H. hepaticus* identified in these analyses.

Analysis of Hepatitis-Positive and Hepatitis-Negative Mice for Liver Neoplasm Incidence

Several infectious agents known to be associated with increased incidences of neoplasms cause chronic inflammation in the target tissue or organ. It is commonly hypothesized that this inflammatory process may cause or contribute to the development of neoplasms. One approach to address this was to stratify the mice from the affected studies according to the severity of hepatitis and examine liver neoplasm incidences in relation to these groupings. Thus, animals within the nine affected studies were placed into three groups: 1) animals with mild to moderate hepatitis considered related to *H. hepaticus* infection (+), 2) animals with minimal to mild hepatitis that may have been associated with *H. hepaticus* (±), and 3) animals with no hepatitis that was considered to be associated with *H. hepaticus* (–). Within these groupings, the incidence of liver neoplasms was significantly increased ($P < 0.05$) in males with mild to moderate *H. hepaticus*-associated hepatitis (+) when compared to animals without such hepatitis (Table R5). The neoplasm incidence in animals with minimal lesions (±) was also increased. The liver neoplasm incidence in males without hepatitis (58%) was similar to the incidence (54.8%) in males from the 26 unaffected studies (Table R3). This analysis clearly suggests an association of *H. hepaticus*-associated hepatitis with increased liver neoplasm incidences. Females showed a similar trend, albeit not significant; however, these comparisons are weak because of the low numbers of females with hepatitis.

Analysis of H-*ras* Oncogene Mutations in Liver Neoplasms in Mice from Affected and Unaffected Studies

Liver neoplasms commonly occur in control $B6C3F_1$ mice in 2-year studies. In the historical database of 333 male and female mice with liver neoplasms, 106 (32%) had H-*ras* codon 61 CAA-to-AAA mutations (Maronpot *et al.*, 1995). This historical control database is composed primarily of male data; however, adequate numbers of females have been assayed, and there was no significant difference in the incidences of CAA-to-AAA mutations between males and females.

In an attempt to examine further whether *H. hepaticus* infection had an effect on the development of hepatocellular neoplasms, neoplasms from control male mice from selected affected (NTP, 1998a,b, 1999a) and unaffected (NTP, 1993, 1999c) studies were evaluated for H-*ras* codon 61 CAA-to-AAA mutations (Table R6). Only 6% (2/33) of the hepatocellular neoplasms from control males with hepatitis from three affected studies had this mutation. This percentage is significantly ($P < 0.01$) less than the 32% (11/34) observed in males from the two unaffected studies and less than the 32% (106/333) that occurred in historical control animals. In addition, neoplasms from males without hepatitis from the affected, PCR-positive triethanolamine study (NTP, 1999a) and the unaffected, PCR-positive methyleugenol study (NTP, 1999d) were evaluated; the incidences of mutations in those groups were 3/14 (21%) and 2/17 (12%), respectively.

Neoplasms from control female mice (none had hepatitis) from affected and unaffected studies were evaluated for the CAA-to-AAA mutation (Table R6). The mutation rate was low in both the affected studies (1/25; 4%) and the unaffected study (1/11; 9%) when compared to the 32% observed in the historical control groups.

The finding of a different H-*ras* mutation profile in neoplasms of male mice from affected studies tends to support the association of increased neoplasm incidences with *H. hepaticus*, although there is no mechanistic understanding behind this observation. In a study of *H. hepaticus*-infected A/JCr mice, *ras* mutations were not detected in the 25 hepatocellular neoplasms analyzed using a PCR/single-strand conformation polymorphism assay (Sipowicz *et al.*, 1997). Because of the low spontaneous rate of liver neoplasms in the A/JCr mouse, there are few or no conclusive data on *ras* mutations in uninfected animals, however. Point mutations at codons 12, 13, and 61 of the Ki-, Ha- and N-*ras* genes were not identified in 45 early gastric carcinomas in humans, whether or not *H. pylori* was present (Craanen *et al.*, 1995). If the increased incidence of hepatocellular neoplasms is associated with hepatitis, as many suspect, then one would expect the neoplasms from animals without hepatitis to have a similar mutational profile as that of the historical controls. The data do not provide a clear answer, because the hepatitis-free males from the affected triethanolamine study (NTP, 1999a) and the males from the methyleugenol study (NTP, 1999d), which were positive by PCR but lacked hepatitis, had mutation frequencies between those of the unaffected controls and the hepatitis-positive mice. Furthermore, mutations in neoplasms from females, none of which had hepatitis, from two affected and one unaffected study were very low compared to the historical controls. These findings were unexpected, and their significance is not understood.

H. hepaticus-Associated Alterations in Cell Kinetics

Studies evaluating cell kinetics were completed to explore further the link between hepatitis and the increased incidence of liver neoplasms (Table R7; Nyska *et al.*, 1997). One of the major objectives was to determine whether there were differences between PCNA labeling indices in the livers of animals with hepatitis from three affected studies, triethanolamine, cobalt sulfate heptahydrate, and chloroprene (NTP, 1998a,b, 1999a), compared to animals without hepatitis, whether from the same three affected studies or from an unaffected study, 1-trans-delta^9-tetrahydrocannabinol (NTP, 1996). Male mice with hepatitis from the three affected studies had a significantly increased ($P < 0.001$) labeling index, with a 24-fold increase over males from the unaffected study and a sixfold increase over males without hepatitis from the same three affected studies (Table R7). The labeling index increase in these mice was substantial and was considered biologically significant. Male mice without hepatitis from the three affected studies had a significantly greater labeling index (increased fourfold) than male mice from the unaffected study (Table R7). The significance of this finding is uncertain, as differences of a similar magnitude were observed in other comparisons. For example, the labeling index of females from the unaffected 1-trans-delta^9-tetrahydrocannabinol study (Table R7; NTP, 1996) was increased fivefold over females from the PCR-positive, hepatitis-negative scopolamine hydrobromide trihydrate study (NTP, 1997). Such differences may be within the limits of normal variability for 2-year-old animals.

A second objective of the cell proliferation studies of the liver was to determine if labeling indices were increased in animals from the PCR-positive, hepatitis-negative methyleugenol (NTP, 1999d), scopolamine hydrobromide trihydrate (NTP, 1997), and mouse life-span studies compared to an unaffected PCR-negative and hepatitis-negative 1-trans-delta^9-tetrahydrocannabinol study (NTP, 1996). The scopolamine hydrobromide trihydrate study was evaluated and included in the study by Nyska *et al.* (1997), while the methyleugenol and mouse life-span studies were completed later and are included in Table R7. The labeling indices of males from two of these three studies were almost identical to those of males from the unaffected study. However, the labeling index of males from the mouse life-span study is increased approximately fivefold over that of males from the unaffected study as well as fivefold over the labeling indices of males from the two like studies of scopolamine hydrobromide trihydrate and methyleugenol. This finding suggests that the increase observed in the mouse life-span study is not attributable to the presence of *H. hepaticus*, as two other studies also positive for *H. hepaticus* did not show a similar increase.

The cell proliferation data for the liver from NTP studies are consistent with data from a study by Fox *et al.* (1996) in which cell proliferation indices were evaluated at 8, 10, and 13 months in the A/JCr mouse, which is generally believed to be more susceptible to *H. hepaticus*-associated hepatitis than the B6C3F$_1$

mouse. In the study by Fox *et al*. (1996), cell proliferation rates were significantly increased at all time points in males. Some increases were observed in females in that study but did not reach statistical significance. An increased incidence of hepatocellular neoplasms was observed only in the males. Though liver lesions were observed in females in that study, they were less severe than those in males.

In addition to the liver, cell proliferation indices (PCNA) were evaluated in the kidneys and lungs of male and female mice in affected studies versus those in unaffected studies (Nyska *et al.*, 1997). No apparent effect of *H. hepaticus* infection or the presence of hepatitis on PCNA indices was observed for the kidneys or lungs.

Apoptosis (programmed cell death) is another important parameter in evaluations of cell kinetics. The apoptotic index in the liver of male mice with hepatitis from an affected study, cobalt sulfate heptahydrate (NTP, 1998b), was significantly ($P < 0.01$) greater than that observed in males from the unaffected 1-trans-delta^9-tetrahydrocannabinol study and the PCR-positive, hepatitis-negative scopolamine hydrobromide trihydrate study (Nyska *et al.*, 1997). For females, there were no significant differences among the three studies.

Two 13-week studies which were begun during the same time as the nine affected studies were randomly selected for evaluation of PCNA indices. *H. hepaticus* was not identified in either of the studies by PCR-RFLP; however, as with all NTP 13-week studies, only tissue fixed in formalin for an unspecified period was available. Because of this, no true negative control group was available; therefore, the labeling index of these 19- to 20-week-old animals was compared to values cited in the literature (Eldridge and Goldsworthy, 1996) for 20-week-old B6C3F$_1$ mice. The labeling index in the NTP studies clearly was not increased (data not shown).

The Impact of *H. hepaticus* on the Interpretation of 2-Year Carcinogenesis Studies

Increases in the incidences of neoplasms are associated with a number of infectious agents. The chronic inflammation caused by these agents has been hypothesized to be important in the pathogenesis of the increased neoplasm incidences (e.g., gastric cancer associated with *H. pylori*). The increased incidences of liver neoplasms in male mice from the nine affected NTP studies were observed in the animals with *H. hepaticus*-associated hepatitis. Neoplasms from males with hepatitis tended to have an H-*ras* mutation profile different from that of animals from unaffected studies. Further, cell replication rates at 2 years were significantly higher in males with hepatitis compared to those in males without hepatitis. The data suggest that *H. hepaticus*-associated hepatitis is associated with the increased incidences of liver neoplasms in the male B6C3F$_1$ mouse. Therefore, the most important consideration in evaluating the impact of *H. hepaticus* infection on the interpretation of study results appears to be the presence or absence of significant hepatitis.

For any carcinogenicity study, data within and specific to the individual study provide the greatest basis for an accurate interpretation. However, it is prudent to consider and evaluate all data or information which may affect the interpretation. Based upon the data presented in this and other reports, general guidelines emerge that may be useful in interpreting potential chemical-associated carcinogenic effects in *H. hepaticus*-infected B6C3F$_1$ mice. In a study with sufficient evidence of *H. hepaticus*-associated hepatitis (> 10% of the animals having the characteristic hepatitis may be a reasonable guideline), interpretation of increased incidences of liver neoplasms (hepatocellular neoplasms and hemangiosarcoma) of male mice is considered to be potentially confounded.

Altered chemical uptake and metabolism, due to the intestinal load of *H. hepaticus* and to *H. hepaticus*-associated liver disease, respectively, are possible reasons for considering that the male mouse response to chemical administration at sites other than the liver should also be considered confounded. Data do not currently exist that definitively answer this question. In this group of nine studies, however, there is no evidence to suggest that affected mice responded to chemical treatment in organs other than the liver in a

manner different from mice in nonaffected studies. Within each study, there was excellent concordance in chemical-associated neoplasms between the male mice and the females, which had little or no hepatitis (Table R8). Furthermore, analyses indicate that *H. hepaticus* is not associated with neoplastic responses outside the liver; incidences of neoplasms at sites other than the liver were not different between control groups from affected and unaffected studies (Table R3). Cell replication rates in two major organs (lung and kidney) also were not increased in control groups from affected studies compared to those from unaffected studies.

One of the more difficult issues to address is whether interpretation of a treatment-related increase in liver neoplasm incidences in the female mouse is confounded when *H. hepaticus*-associated hepatitis is present within the male mice in the study. Most evidence to date links hepatitis with the increased liver neoplasm incidences observed in males, and female $B6C3F_1$ mice in affected studies do not have significant hepatitis at 2 years. The lack of hepatitis in females, however, is based on an analysis in which only late time points were evaluated histologically. Therefore, it is conceivable that hepatitis along with increased cell proliferation could have occurred earlier and resolved by 18 months to 2 years. Data collected to date, however, suggest that *H. hepaticus*-associated hepatitis is a late-developing and persistent disease in the $B6C3F_1$ mouse. *H. hepaticus*-associated hepatitis has never been observed in any NTP 13-week studies, including five begun during the same 6-month time span as eight of the nine affected 2-year studies. Also, within affected 2-year studies, more males (51%) that were 18 to 24 months of age had hepatitis than those (34%) that were 12 to 18 months of age. This is consistent with a report by Ward *et al*. (1994b) that *H. hepaticus*-associated liver lesions are not observed at early time points in the $B6C3F_1$ mouse.

Nonetheless, within affected studies, female control mice did have a slightly elevated incidence of liver neoplasms when compared to control mice from unaffected studies, and the data derived from the H-*ras* mutation frequency analysis were inconclusive. The possibility that *H. hepaticus*-infected female mice from affected studies may respond differently to a liver carcinogen than mice from unaffected studies cannot be eliminated at this time. However, because within an affected study hepatitis is observed only rarely in females, until definitive data suggest otherwise, it is concluded that the interpretation of an apparent chemical-induced neoplastic effect in the liver of female mice is not confounded. To censor the few females with *H. hepaticus*-associated hepatitis from any statistical analyses of hepatocellular neoplasms would be prudent. Studies in the ostensibly more sensitive A/JCr mouse (Fox *et al.*, 1996) also showed significant increases in neoplasm incidences and cell proliferation rates in the liver of *H. hepaticus*-infected males, but not females.

Another concern is how to interpret possible chemical-related effects in a study in which the status of *H. hepaticus* infection cannot be determined by PCR-RFLP because only tissues fixed in formalin for more than 48 hours are available. While histologic evaluation is inadequate to identify infection, it appears adequate for identifying hepatitis severe enough to alter the outcome of the study. Therefore, in the absence of significant histologic evidence of *H. hepaticus*-associated hepatitis, the outcome of a 2-year study should not be considered potentially compromised.

The causality between *H. hepaticus* infection and neoplasia has not been proven in the $B6C3F_1$ mouse in these studies, nor has the mechanism of this association been determined; further studies are needed. However, sufficient information exists to make reasonable scientific judgments relative to the interpretation of data from the nine 2-year carcinogenicity studies in the $B6C3F_1$ mouse. Refinements to the above interpretive positions may occur if warranted by future information.

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TABLE R1
Incidence of *Helicobacter hepaticus*-Associated Hepatitis in Control B6C3F$_1$ Mice from Nine NTP 2-Year Studies[a]

Study	Incidence of Hepatitis (%)	
	Males	Females
Sodium xylenesulfonate	78	4
AZT/5,000 U α-interferon A/D	76	4
Cobalt sulfate heptahydrate	72	8
AZT/500 U α-interferon A/D	66	0
Chloroprene	54	0
Theophylline	32	0
α-Interferon A/D	22	4
Triethanolamine	20	0
AZT	16	2
Average	48	2

[a] Includes regeneration and mild to marked (excludes minimal) chronic inflammation, karyomegaly, oval cell hyperplasia, and bile duct hyperplasia. AZT = 3′-azido-3′-deoxythymidine

TABLE R2
Identification of *Helicobacter hepaticus* with PCR-RFLP-Based Assays in Control B6C3F$_1$ Mice from 32 NTP 2-Year Studies and Three NTP 13-Week Studies[a]

Type of Sample	Total Studies	*H. hepaticus*-Positive Studies[b]	
		Affected Studies	Unaffected Studies
13-Week Studies			
Formalin-fixed liver	3	—	1/3[c]
2-Year Studies			
Frozen liver	22	3/3	3/19
Formalin-fixed liver	10	1/6[c]	0/4

[a] PCR-RFLP = polymerase chain reaction-restriction fragment length polymorphism
[b] Number of *H. hepaticus*-positive studies/number of affected or unaffected studies. Affected studies are those in which hepatitis typical of that associated with *H. hepaticus* infection occurred in many male mice.
[c] Only one animal in the positive study was positive for *H. hepaticus*.

TABLE R3
Comparison of Neoplasm Incidences in Control B6C3F$_1$ Mice from *Helicobacter hepaticus*-Affected and Unaffected NTP 2-Year Studies

	Males		Females	
	Affected Studies[a]	Unaffected Studies	Affected Studies	Unaffected Studies
Number of studies	9	26	9	26
Survival (%)	64	71	68	68
12-Month body wt (g)	48.0	48.3	48.1	47.0
Neoplasm incidence (%)				
Liver	71.3*	54.8	50.3	40.5
Lung	26.6	23.2	7.6	10.3
Pituitary gland	0.4	0.8	14.7	14.3
Harderian gland	5.6	6.1	6.0	4.9
Lymphoma	6.9	6.3	16.2	15.5
Circulatory system	9.8	6.0	5.3	4.7
liver only	7.1*	2.5	—	—
All benign	61.8	57.2	59.1	54.6
All malignant	61.3*	40.9	50.0	44.2
All neoplasms	88.0*	77.4	82.7	75.4

* Significantly different ($P \leq 0.05$) from the unaffected studies
[a] Affected studies are those in which hepatitis typical of that associated with *H. hepaticus* infection occurred in many male mice.

TABLE R4
Liver Neoplasm Incidences and Body Weights of Control B6C3F$_1$ Mice in Relation to Study Start Dates of *Helicobacter hepaticus*-Affected and Unaffected NTP 2-Year Studies[a]

Study Start Date	Liver Neoplasm Incidence (%)		Mean Body Weight (g)	
	Affected Studies[a]	Unaffected Studies	Affected Studies	Unaffected Studies
Male				
April to September 1988	—	43.8 (8)[b]	—	46.2 (8)
October 1988	62.0 (1)	—	48.3 (1)	—
November 1988 to September 1989	—	52.6 (7)	—	48.7 (7)
October 1989 to June 1990	—	61.2 (5)	—	48.9 (5)
July 1990 to January 1991	72.5 (8)	66.2 (4)	48.0 (8)	49.0 (4)
February 1991 to April 1992	—	68.0 (2)	—	52.8 (2)
Average	71.3	54.8	48.0	48.3
Female				
April to September 1988	—	31.1 (8)	—	44.8 (8)
October 1988	46.0 (1)	—	46.4 (1)	—
November 1988 to September 1989	—	39.9 (7)	—	47.2 (7)
October 1989 to June 1990	—	38.6 (5)	—	45.9 (5)
July 1990 to January 1991	50.9 (8)	54.2 (4)	48.3 (8)	48.0 (4)
February 1991 to April 1992	—	58.0 (2)	—	55.6 (2)
Average	50.3	40.5	48.1	47.0

[a] Includes nine affected studies (those in which hepatitis typical of that associated with *H. hepaticus* infection occurred in many male mice) and 26 unaffected studies
[b] Number of studies is given in parentheses.

TABLE R5
Association of Liver Neoplasm Incidence and Severity of *Helicobacter hepaticus*-Associated Hepatitis in Control B6C3F$_1$ Mice from Nine Affected NTP 2-Year Studies[a]

Severity of Hepatitis	Liver Neoplasm Incidence	
	Males	Females
Absent	101/175 (58%)	196/396 (49%)
Minimal	44/57 (77%)	23/42 (55%)
Mild/moderate	176/218 (81%)	7/11 (64%)
Significance of association	P < 0.05	NS[b]

[a] Affected studies are those in which hepatitis typical of that associated with *H. hepaticus* infection occurred in many male mice.
[b] NS = not significant

TABLE R6
H-*ras* Codon 61 AAA Mutations in Spontaneous Liver Neoplasms in Control B6C3F$_1$ Mice from *Helicobacter hepaticus*-Affected and Unaffected NTP 2-Year Studies

Study	Affected[a]	H-*ras* AAA Mutations
Male		
Cobalt sulfate heptahydrate	+	0/10 (0%)
Chloroprene	+	1/13 (8%)
Triethanolamine	+	1/10 (10%)
Oxazepam	—	7/18 (39%)
Diethanolamine	—	4/16 (25%)
Historical control database		106/333 (32%)
Female		
Chloroprene	+	0/10 (0%)
Triethanolamine	+	1/15 (7%)
Diethanolamine	—	1/11 (9%)
Historical control database		106/333 (32%)

[a] + = affected; — = not affected. Affected studies are those in which hepatitis typical of that associated with *H. hepaticus* infection occurred in many male mice.

TABLE R7
Proliferating Cell Nuclear Antigen Labeling Indices in the Liver of Control B6C3F$_1$ Mice[a]

	Hepatitis	No. of Animals	PCNA Labeling Index[b]	Average PCNA Labeling Index[c]
Male				
Cobalt sulfate heptahydrate[d]	+	15	0.535 ± 0.129	
Chloroprene[d]	+	12	1.452 ± 0.386	
Triethanolamine[d]	+	9	1.215 ± 0.374	1.011
Cobalt sulfate heptahydrate	—	7	0.175 ± 0.117	
Chloroprene	—	10	0.296 ± 0.124	
Triethanolamine	—	12	0.100 ± 0.042	0.186
1-Trans-delta^9-tetrahydrocannabinol[e]	—	15	0.042 ± 0.011	
Scopolamine hydrobromide trihydrate[f]	—	14	0.043 ± 0.012	
Methyleugenol[f]	—	14	0.077 ± 0.020	
Mouse life-span study[f]	—	15	0.217 ± 0.880	
Female				
Cobalt sulfate heptahydrate	+	5	0.161 ± 0.062	
Cobalt sulfate heptahydrate	—	17	0.055 ± 0.015	
Chloroprene	—	12	0.154 ± 0.050	
Triethanolamine	—	12	0.138 ± 0.053	0.108
1-Trans-delta^9-tetrahydrocannabinol	—	13	0.156 ± 0.047	
Scopolamine hydrobromide trihydrate	—	15	0.032 ± 0.009	

[a] A portion of these data are presented in Nyska *et al*. (1997). + = hepatitis present; — = no hepatitis present
[b] Mean ± standard error; PCNA = proliferating cell nuclear antigen
[c] Average of the mean labeling indices for animals from all three studies
[d] Affected study (one in which hepatitis typical of that associated with *H. hepaticus* occurred in many male mice)
[e] Unaffected study (one in which the typical hepatitis did not occur in mice)
[f] Unaffected study with no typical hepatitis, but positive for *H. hepaticus* by polymerase chain reaction-restriction fragment length polymorphism-based assay

TABLE R8
Summary of Target Sites of Carcinogenicity in B6C3F$_1$ Mice from NTP 2-Year Studies with *Helicobacter hepaticus*-Associated Hepatitis

	Males	Females
Chloroprene	Lung Circulatory system[a] Harderian gland Forestomach Kidney	Lung Circulatory system Harderian gland Forestomach Liver Skin Mesentery Zymbal's gland Mammary gland
Cobalt sulfate heptahydrate[b]	Lung	Lung
Triethanolamine	Liver	Liver
AZT[c]	None	Vagina
Sodium xylenesulfonate	None	None
Theophylline	None	None

[a] Hemangioma and hemangiosarcoma of the liver were excluded from the analysis in males.
[b] An apparent treatment-related increase in the incidence of hemangiosarcoma of the liver was discounted in male mice because of the presence of *H. hepaticus*.
[c] AZT = 3′-azido-3′-deoxythymidine. Includes four studies: AZT; α-interferon A/D; AZT/500 U α-interferon A/D; and AZT/5,000 U α-interferon A/D