NTP TECHNICAL REPORT

ON THE

TOXICOLOGY AND CARCINOGENESIS

STUDIES OF TRANSPLACENTAL AZT

(CAS NO. 30516-87-1)

IN SWISS (CD-1®) MICE

(*IN UTERO* STUDIES)

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

June 2006

NTP TR 522

NIH Publication No. 06-4458

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

FOREWORD

The National Toxicology Program (NTP) is an interagency program within the Public Health Service (PHS) of the Department of Health and Human Services (HHS) and is headquartered at the National Institute of Environmental Health Sciences of the National Institutes of Health (NIEHS/NIH). Three agencies contribute resources to the program: NIEHS/NIH, the National Institute for Occupational Safety and Health of the Centers for Disease Control and Prevention (NIOSH/CDC), and the National Center for Toxicological Research of the Food and Drug Administration (NCTR/FDA). Established in 1978, the NTP is charged with coordinating toxicological testing activities, strengthening the science base in toxicology, developing and validating improved testing methods, and providing information about potentially toxic substances to health regulatory and research agencies, scientific and medical communities, and the public.

The Technical Report series began in 1976 with carcinogenesis studies conducted by the National Cancer Institute. In 1981, this bioassay program was transferred to the NTP. The studies described in the Technical Report series are designed and conducted to characterize and evaluate the toxicologic potential, including carcinogenic activity, of selected substances in laboratory animals (usually two species, rats and mice). Substances selected for NTP toxicity and carcinogenicity studies are chosen primarily on the basis of human exposure, level of production, and chemical structure. The interpretive conclusions presented in NTP Technical Reports are based only on the results of these NTP studies. Extrapolation of these results to other species, including characterization of hazards and risks to humans, requires analyses beyond the intent of these reports. Selection *per se* is not an indicator of a substance's carcinogenic potential.

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CONTRIBUTORS

In Memoriam
The studies described in this report were initiated by the late G.N. Rao, D.V.M., Ph.D.

National Toxicology Program
Evaluated and interpreted results and reported findings

J.K. Dunnick, Ph.D., Study Scientist
R.A. Herbert, D.V.M., Ph.D., Study Pathologist
D.W. Bristol, Ph.D.
J.R. Bucher, Ph.D.
J.R. Hailey, D.V.M.
G.E. Kissling, Ph.D.
R.R. Maronpot, D.V.M.
S.D. Peddada, Ph.D.
J.H. Roycroft, Ph.D.
C.S. Smith, Ph.D.
G.S. Travlos, D.V.M.
K.L. Witt, M.S.

Southern Research Institute
Conducted studies and evaluated pathology findings

H.D. Giles, D.V.M., Ph.D., Principal Investigator
J.E. Heath, D.V.M.

Experimental Pathology Laboratories, Inc.
Provided pathology review

M.H. Hamlin, II, D.V.M., Principal Investigator
J.C. Peckham, D.V.M., M.S., Ph.D.
G. Willson, B.V.M.&S.

Dynamac Corporation
Prepared quality assurance audits

S. Brecher, Ph.D., Principal Investigator

NTP Pathology Working Group
Evaluated slides and prepared pathology report on mice (July 23, 2003)

W.G. Lieuallen, D.V.M., Ph.D., Chairperson
Pathology Associates, A Charles River Company
R.A. Herbert, D.V.M., Ph.D.
National Toxicology Program
G.D. Hill, D.V.M., Ph.D.
National Toxicology Program
E.E. McConnell, D.V.M., M.S.
ToxPath, Inc.
J.C. Peckham, D.V.M., M.S., Ph.D.
Experimental Pathology Laboratories, Inc.
G. Willson, B.V.M.&S.
Experimental Pathology Laboratories, Inc.
R.C. Sills, D.V.M., Ph.D.
National Toxicology Program
A. Nyska, D.V.M.
National Toxicology Program
Y. Tani, D.V.M., Ph.D.
National Toxicology Program

Constella Group, Inc.
Provided statistical analyses

P.W. Crockett, Ph.D., Principal Investigator
L.J. Betz, M.S.
K.P. McGowan, M.B.A.

Biotechnical Services, Inc.
Prepared Technical Report

S.R. Gunnels, M.A., Principal Investigator
L.M. Harper, B.S.
M.C. Joheim, M.S.
E.S. Rathman, M.S.
D.C. Serbus, Ph.D.

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SUMMARY

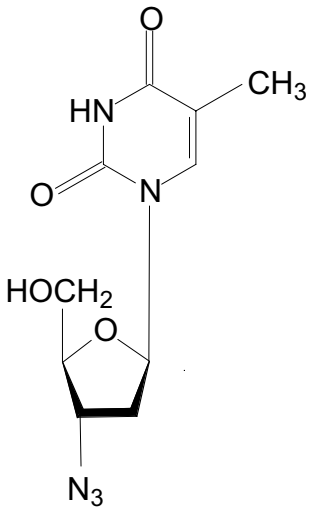
Background
3′-Azido-3′-deoxythymidine (AZT) is the most widely used agent for the treatment of people with acquired immune deficiency syndrome (AIDS) or seropositive for human immunodeficiency virus (HIV). AZT was known to cause cancer in mice born to mothers exposed to doses of 400 milligrams (mg) per kilogram (kg) of body weight or higher during pregnancy. In this study, we exposed female mice to lower concentrations of AZT (50 to 300 mg AZT/kg body weight) before and during pregnancy to determine if those doses also caused cancer in the offspring.

Methods
We gave groups of female mice doses ranging from 50 to 300 mg AZT/kg body weight by depositing the drug directly into each animal's stomach through a tube for a week, then allowing the females to mate with unexposed males. The females continued to be exposed throughout pregnancy until they delivered litters of pups. The offspring were maintained without drug administration for two years, after which tissues from more than 40 sites were examined for every animal.

Results
Female mice exposed to 200 or 300 mg AZT/kg body weight had lower body weights and fertility rates than females exposed to lower concentrations or unexposed controls. Male mice born to mothers exposed to 200 or 300 mg AZT/kg body weight had greater rates of lung cancer than did males born to unexposed animals. There were no differences in cancer rates at any sites in female mice born to AZT-treated mothers.

Conclusions
We conclude that exposure of pregnant female mice to AZT resulted in increased rates of lung cancer in their male offspring. There was no difference in cancer in female offspring of mothers exposed to 300 mg AZT/kg body weight or less during pregnancy.

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 study in this report was conducted to obtain information on AZT transplacental carcinogenicity at doses that were lower than those used in previous NCI studies and analogous to therapeutic doses. Male and female Swiss (CD-1®) mice were exposed to AZT (greater than 99% pure) during all of gestation. Genetic toxicology studies were conducted in mouse peripheral blood erythrocytes.

Groups of 22, 28, 34, or 46 female mice (F_0 generation) were administered AZT in 0.5% methylcellulose by gavage at doses of 50, 100, 200, or 300 mg AZT/kg body weight 7 days per week for 29 to 39 days (day of delivery). A vehicle control group of 22 female mice received methylcellulose alone. Each female group was divided into two groups with dosing started 1 week apart in order to facilitate cohabitation, mating, and delivery. Groups of six, six, seven, nine, or twelve undosed male mice were cohabited with the vehicle control and 50, 100, 200, and 300 mg/kg dosed females, respectively, on study days 9 to 13 and then discarded. Pups (F_1 generation) were culled (0, 50, and 100 mg/kg groups) to yield a maximum of five pups/sex per litter on postnatal day 4; no more than four pups/sex per litter were used in the study. On postnatal day 25, all surviving 200 and 300 mg/kg pups were placed on study. After culling and randomization to cage groups, the 0, 50, 100, 200, and 300 mg/kg groups consisted of 50, 50, 50, 37, and 32 male pups and 50, 50, 50, 40, and 42 female pups, respectively. Decreased litter size and fertility rates were observed in the 200 and 300 mg/kg F_0 dams.

Survival of all exposed groups of F_1 mice was similar to that of the vehicle controls. Mean body weights of 200 mg/kg males were generally less than those of the vehicle controls after week 29. Mean body weights of 300 mg/kg males were less during the first year of the study, but these mice recovered and body weights were generally similar to those of the vehicle controls at the end of the study.

The incidences of alveolar/bronchiolar carcinoma and of adenoma or carcinoma (combined) in 200 and 300 mg/kg males were significantly greater than those in the vehicle controls. The incidences of histiocytic cellular infiltration of the lung in 200 and 300 mg/kg males were significantly increased.

Genetic Toxicology

The NTP conducted a number of studies of the genetic toxicity of AZT, independent of this transplacental carcinogenicity study. In these genetic toxicity studies, AZT (50, 75, 100, or 150 mg/kg) administered to pregnant Swiss (CD-1®) dams, beginning prior to conception and continuing throughout gestation and lactation, induced high levels of micronucleated polychromatic erythrocytes (PCEs) in pups sampled on postnatal days 1 and 4. Direct gavage treatment of these transplacentally and lactationally exposed pups, beginning on postnatal day 4, resulted in further increases in the frequencies of micronucleated PCEs on postnatal days 8 and 21. The percentage of PCEs among erythrocytes in pups was significantly elevated over normal adult levels, indicating a high rate of erythropoiesis in neonatal mice. The percentage of PCEs was decreased in all pups exposed to AZT, consistent with treatment-related bone marrow toxicity.

Conclusions

Under the conditions of this study, there was *clear evidence of carcinogenic activity** in F_1 male mice exposed transplacentally to AZT based on increased incidences of alveolar/bronchiolar neoplasms. There was *no evidence of carcinogenic* activity in F_1 female mice exposed transplacentally to AZT at 50, 100, 200, or 300 mg/kg.

Reproductive toxicity in the form of decreased litter size and fertility rates was observed in dams in the 200 and 300 mg AZT/kg dose groups.

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

Summary of the Transplacental Study of AZT in Swiss (CD-1®) Mice

	Male	Female
Concentrations *in utero*	0, 50, 100, 200, or 300 mg/kg	0, 50, 100, 200, or 300 mg/kg
Body weights	200 mg/kg group less than the vehicle control group	Exposed groups similar to the vehicle control group
Survival rates	19/50, 20/50, 13/50, 7/37, 8/32	20/50, 18/50, 24/50, 21/40, 18/42
Nonneoplastic effects	None	None
Neoplastic effects	Lung: alveolar/bronchiolar carcinoma (5/50, 11/50, 6/50, 11/37, 8/32); alveolar/bronchiolar adenoma or carcinoma (14/50, 20/50, 13/50, 18/37, 18/32)	None
Equivocal findings	None	None
Level of evidence of carcinogenic activity	Clear evidence	No evidence
Genetic toxicology		
Micronucleated erythrocytes		
Mouse peripheral blood *in vivo*:	Positive when exposed transplacentally and lactationally and when administered by direct gavage	

Average Litter Size and Fertility Rates for Swiss (CD-1®) Mouse Dams in the Transplacental Study of AZT

	Vehicle Control	50 mg/kg	100 mg/kg	200 mg/kg	300 mg/kg
Number live[a]	10.9 ± 1.1	9.1 ± 0.7	8.2 ± 0.9	4.4 ± 0.7**	4.1 ± 0.7**
Percent of dams pregnant[b]	82	95	68	56*	39**

* Significantly different (P<0.05) from the vehicle control group by Dunnett's test (Dunnett, 1955) for number live or by Fisher's exact test (Gart *et al.*, 1979) for percent of dams pregnant

** P<0.01

[a] Data from Table C6

[b] Data from Table C4

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.

For studies showing multiple chemical-related neoplastic effects that if considered individually would be assigned to different levels of evidence categories, the following convention has been adopted to convey completely the study results. In a study with clear evidence of carcinogenic activity at some tissue sites, other responses that alone might be deemed some evidence are indicated as “were also related” to chemical exposure. In studies with clear or some evidence of carcinogenic activity, other responses that alone might be termed equivocal evidence are indicated as “may have been” related to chemical exposure.

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 transplacental AZT on December 9, 2004, 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.

Mary Anna Thrall, D.V.M., M.S., Chairperson, Principal Reviewer
Department of Microbiology, Immunology and Pathology
Colorado State University
Fort Collins, CO

Diane F. Birt, Ph.D.
Department of Food Science & Human Nutrition
Iowa State University
Ames, IA

Kim Boekelheide, M.D., Ph.D., Principal Reviewer
Division of Biology and Medicine
Department of Pathology and Laboratory Medicine
Brown University
Providence, RI

Michael R. Elwell, D.V.M., Ph.D.
Pathology, Drug Safety Evaluation
Pfizer Global Research and Development
Groton, CT

Thomas A. Gasiewicz, Ph.D.
Department of Environmental Medicine
Environmental Health Sciences Center
University of Rochester School of Medicine
Rochester, NY

James E. Klaunig, Ph.D.
Division of Toxicology
Indiana University School of Medicine
Indianapolis, IN

Stephen M. Roberts, Ph.D.
Center for Environmental & Human Toxicology
University of Florida
Gainesville, FL

Richard D. Storer, M.P.H., Ph.D.
Department of Genetic and Cellular Toxicology
Merck Research Laboratories
West Point, PA

Mary Vore, Ph.D.
Graduate Center for Toxicology
University of Kentucky
Lexington, KY

Cheryl Lyn Walker, Ph.D., Principal Reviewer
Department of Carcinogenesis
M.D. Anderson Cancer Center
The University of Texas
Smithville, TX

SUMMARY OF TECHNICAL REPORTS REVIEW SUBCOMMITTEE COMMENTS

On December 9, 2004, the draft Technical Report on the toxicology and carcinogenesis studies of transplacental 3′-azido-3′-thymidine (AZT) 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. J.K. Dunnick, NIEHS, introduced the transplacental carcinogenicity studies of AZT by describing AZT's use as an antiviral drug to prevent transmission of human immunodeficiency virus (HIV), its metabolism and mutagenicity, and the design and results of the study in mice exposed to the drug transplacentally during pregnancy. The proposed conclusions were *some evidence of carcinogenic activity* in male Swiss CD-1® mice based on increased incidences of alveolar/bronchiolar neoplasms. There was *no evidence of carcinogenic activity* in female Swiss CD-1® mice exposed transplacentally to 50, 100, 200, or 300 mg/kg AZT. Reproductive toxicity in the form of decreased litter size and fertility rates was observed in dams in the 200 and 300 mg AZT/kg groups.

Dr. Walker, the first principal reviewer, inquired if there was more information about the extent of potential human exposure to AZT via this route. She disagreed with the conclusions in the male mice, thinking the lung neoplasms merited a conclusion of *clear evidence of carcinogenic activity*.

Dr. Boekelheide, the second principal reviewer, also thought the lung tumors in males merited a conclusion of *clear evidence of carcinogenic activity*.

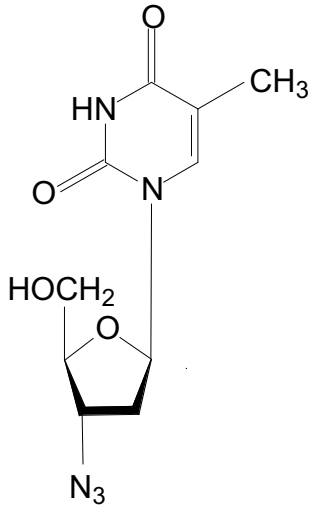
Dr. Thrall, the third principal reviewer, agreed with the conclusions as written.

Dr. Dunnick responded that new data from the World Health Organization indicated approximately 40 million adults now are infected with HIV worldwide, with about 60% in sub-Saharan Africa, and about 2 million give birth each year. The number receiving AZT treatment is much smaller, with approximately 6,000 children born per year in the United States having been exposed to AZT prenatally.

Dr. J.R. Hailey, NIEHS, said that the proposed conclusions were based on the program's judgement of the tumor response and not on mutational spectra data.

Dr. Walker moved, and Dr. Boekelheide seconded, that the conclusion for male mice be changed to *clear evidence of carcinogenic activity*, while the conclusion for female mice remain unchanged. The motion was passed with seven yes votes and two abstentions (Drs. Elwell and Storer).

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

3′-Azido-3′-deoxythymidine (AZT) is a dideoxynucleoside of thymine and a structural analogue of 2′-deoxythymidine, and it 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, 2004).

Production, Use, and Human Exposure

AZT was first synthesized in 1964 by Horowitz *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 was 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, 2004).

Guidelines for treating adults, adolescents, pregnant women, and children with AIDS have been established by the U.S. Department of Health and Human Services (2004). The most effective recommended therapies (referred to as Highly Active Antiretroviral Therapies, HAART) consist of combinations of drugs. AZT is supplied as a single drug for oral and intravenous administration (Retrovir®, zidovudine), as a combination drug of AZT and lamivudine (3TC Combivir®), and as a drug containing AZT, abacavir sulfate, and lamivudine (Trizivir®) (all from GlaxoSmithKline). AZT is usually included in the recommended therapy for adults, adolescents, and children (Gulick *et al.,* 1997; Hammer *et al.*, 1997; USDHHS, 2004). AZT is also included as part of a therapeutic regimen to prevent mother-to-child transmission of HIV (USDHHS, 2004). AZT has been shown to prevent the vertical transmission of HIV by nearly 70% (7.2% in treated patients versus 21.9% in a placebo control group; Connor *et al.*, 1994).

At the end of 2003, there were an estimated 35 to 42 million HIV infected people throughout the world. An estimated 950,000 people have been infected in the United States. About 2 million women with HIV give birth each year, and despite the availability of treatment, approximately 630,000 infants contract HIV infection each year (Steinbrook, 2004).

Pharmacology

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 deoxythymidine triphosphate. 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).

Absorption, Distribution, Metabolism, and Excretion

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 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).

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 uridine diphosphoglucuronosyl transferase, 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 P450 content and it is enhanced up to fivefold by the addition of nicotinamide-adenine dinucleotide phosphate, flavin adenine dinucleotide, and flavin mononucleotide. 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

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			0.76 ± 0.35 hrs	Patel *et al.*, 1989
		50 mg/kg			1.31 ± 1.05 hrs	
		100 mg/kg			2.03 ± 1.67 hrs	
		250 mg/kg			1.58 ± 0.81 hrs	
Mouse, $B6C3F_1$	oral	15 mg/kg	9.1 ± 1.5	18.3 ± 2.9 min	18.5 min	Trang *et al.*, 1993
		30 mg/kg	18.9 ± 0.5	21.7 ± 7.6 min	16.5 min	
		60 mg/kg	40.3 ± 7.2	15.0 ± 5.0 min	21.9 min	
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.

from rats, dogs, monkeys, and humans. In these systems, AZT is converted primarily to GAZT by hepatocytes from humans (63% to 73%) and monkeys (63% to 73%), whereas unchanged parent is predominant in rat (86% to 90%) and dog (95%) hepatocyte cultures. AMT is a minor metabolite in cultured hepatocytes from all species, and GAMT is not detected in cultured hepatocytes.

TOXICITY

Experimental Animals

In animals, AZT causes hematologic toxicities (Thompson *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 AZT/mL 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 gamma 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.

Heart toxicities associated with AZT treatment have been reported in rats, mice, and monkeys. Rats given approximately 29 to 102 mg AZT/kg per day in the drinking water for up to 49 days developed cardiac mitochondrial swelling with fractured and disrupted cristae (Lewis *et al.*, 1991). These ultrastructural defects did not reverse after a 14-day recovery period. Ultrastructural examination of cardiomyocytes of Sprague-Dawley rats given AZT in the drinking water at approximately 90 mg/kg per day showed disruption of cristae and increased size of mitochondria after 30 or 60 days of treatment; no alterations were seen in rats that received 120 days of treatment (Pindado *et al.*, 1994). Sprague-Dawley rats given intraperitoneal injections of approximately 17 to 51 mg AZT/kg for 3 months developed enlarged cardiomyocytic mitochondria with disorganized or absent cristae and increased serum concentrations of creatine kinase, lactate, and glucose (Lamperth *et al.*, 1991). In this study, mitochondria were isolated and functionally assayed; the authors concluded that AZT, a DNA chain terminator, was a mitochondrial toxin that affected oxidation-phosphorylation coupling and the activity of the mitochondrial respiratory chain.

AZT given to transgenic mice (that express replication-incompetent HIV) or FVB mice in drinking water at doses that delivered approximately 180 to 200 mg AZT/kg for 35 days developed cardiac toxicity characterized by mitochondrial destruction (Lewis *et al.*, 2000). Heart toxicities were also seen when AZT, lamivudine (3TC), and indinavir (IDV) combinations were given in the drinking water to transgenic mice or wild mice for 10 or 35 days (cumulative doses were approximately 141 mg AZT, 7 mg 3TC, and 32 mg IDV for 35 days of treatment) (Lewis *et al.*, 2001). Treatment-related histopathologic changes were described as numerous cardiomyocytes with granular cytoplasm in normal and transgenic mice. The lesions were generally more severe in transgenic mice. Neither interstitial inflammation nor fibrosis was found. The National Toxicology Program (1999) did not report cardiac toxicity in $B6C3F_1$ mice given AZT by oral gavage in corn oil at doses of 0, 50, 100, 200, 800, or 2,000 mg/kg for 14 days or at doses of 0, 30, 60, or 120 mg/kg for 2 years. However, in an NTP study where Swiss (CD-1®) mouse pups were exposed *in utero*, lactationally, and by direct gavage on postnatal days (PND) 4 through 28 with twice-daily doses of 75/37.5 mg/kg AZT/3TC or the vehicle control mixture of 0.1% polysorbate 80 and 0.2% methylcellulose, the hearts of PND 28 pups treated with AZT/3TC showed significant increases in the mean area and decreases in the mean number of cardiomyocytic mitochondria compared to vehicle controls (Bishop *et al.*, 2004a).

Studies in monkeys at the National Cancer Institute (NCI) showed that daily doses of AZT during the second half of gestation at approximately 86% of the recommended human daily dose caused mitochondrial abnormalities (Gerschenson *et al.*, 2000). In skeletal muscle, these abnormalities were characterized as abnormally shaped mitochondria with disrupted cristae. In heart muscle, small mitochondria in myocytes with myofibrillar loss and abnormal alignment of sarcomeres were observed.

Patients with HIV infection often have other associated diseases such as tuberculosis (CDC, 2002). A series of mouse studies conducted by The National Institute of Environmental Health Sciences (NIEHS) showed that AZT in combination with various drugs used in the treatment of tuberculosis yielded increased severity of AZT-associated toxicity and reproductive toxicity (Tables 3 and 4 and NIEHS, 1998; 1999a,b; 2000; 2001; 2002a,b). The tuberculosis drugs studied included pyrazinamide, trimethoprim/sulfamethoxazole and folic acid, isoniazid, rifabutin, and rifampicin.

Humans

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 and Carlisle, 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.

A few patients receiving long-term AZT therapy have been reported to have 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).

The U.S. Department of Health and Human Services updates information on current treatment regimens for HIV and observed toxicities on an ongoing basis (USDHHS, 2004). Common adverse effects noted from AZT use in humans include bone marrow suppression, anemia and/or neutropenia, and subjective complaints including gastrointestinal intolerance, headache, insomnia, and asthenia. In addition, lactic acidosis with hepatic steatosis has been reported as a rare side effect from nucleoside/nucleotide analogue reverse transcriptase inhibitors (NRTIs), including AZT combinations.

In humans and in animals, NRTIs such as AZT inhibit DNA polymerase gamma, an enzyme responsible for mitochondrial DNA. This has been reported to lead to mitochondrial dysfunction (Dalakas *et al.*, 1990; Arnaudo *et al.*, 1991; Lamperth *et al.*, 1991; Brinkman *et al.*, 1999; USDHHS, 2004). Mitochondrial DNA dysfunction may result in pancreatitis, peripheral neuropathy, myopathy, and cardiomyopathy (Kakuda, 2000; USDHHS, 2004). It is thought that combinations of NRTIs will act synergistically to induce mitochondrial dysfunction. Protease inhibitors may aggravate this mechanism (USDHHS, 2004).

Lipodystrophy (fat redistribution syndrome) may be seen in patients receiving NRTIs, and is related to mitochondrial toxicities (Brinkman *et al.*, 1999; Kakuda *et al.*, 1999; Mallal *et al.*, 2000; USDHHS, 2004). Metabolic complications of HAART therapies include vascular necrosis, decreased bone density, and skin rashes (USDHHS, 2004)

A French group reported that eight cases of uninfected infants with *in utero* and/or neonatal exposure to either ZDV/3TC (four infants) or ZDV alone (four infants) developed mitochondrial dysfunction after the first few months of treatment (Blanche *et al.*, 1999; Mofenson, 2000). A study in the United States did not associate cardiac toxicity with perinatal exposure to ZDV in infants (Lipshultz *et al.*, 2000). A recent study suggests that mitochondrial damage in children of mothers taking AZT may persist for up to 2 years after birth (Poirier *et al.*, 2003). *In vitro* studies suggest that the HIV virus infection by itself may lead to cardiac toxicity (Raidel *et al.*, 2002).

Table 3
Subchronic Toxicity Studies of AZT with Pyrazinamide, Rifampicin, and Isoniazid in Male and Female B6C3F$_1$ Mice[a]

NIEHS AIDS Therapeutic Toxicity Reports	Drug Combination	Histopathologic Findings from Drug Combination	Hematologic Findings from Drug Combination	Severity of Drug Combination Toxicity in Comparison to Each Drug Alone
5 (NIEHS, 1999b)	AZT (0, 200, or 400 mg/kg per day) + pyrazinamide (0, 1,000, or 1,500 mg/kg per day)	Male and/or female mice: bone marrow atrophy	Macrocytic anemia, thrombocytosis, reticulocytopenia, reticulocytosis	Combination drug toxicity exceeded individual drug toxicity
6 (NIEHS, 2001)	AZT (0, 100, 200, or 400 mg/kg per day) + rifampicin (0, 100, 200, or 400 mg/kg per day)	Male and/or female mice: bone marrow atrophy, cytoplasmic vacuolization of hepatocytes, thymic atrophy, cellular depletion in the spleen	Anemia	Combination drug toxicity exceeded individual drug toxicity
8 (NIEHS, 2002b)	AZT (0, 200, or 400 mg/kg per day + isoniazid (0, 50, 100, or 150 mg/kg per day)	Male and/or female mice: bone marrow cell depletion, splenic hematopoiesis, hepatocellular hypertrophy	Anemia, increased mean cell volume and mean cell hemoglobin, reticulo-cytopenia, reticulocytosis, thrombocytosis, leukopenia, neutropenia, lymphopenia	Combination drug toxicity exceeded individual drug toxicity

[a] 13-week studies

Table 4
Selected Findings from the Reproductive, Developmental, and General Toxicity Studies of AZT in Combination with Other Drugs in Male and Female Swiss (CD-1®) Mice[a]

NIEHS AIDS Therapeutic Toxicity Reports	Study Drug Combination	Histopathologic Findings in F_0 Dams/Sires	Hematologic Findings in F_0 Dams/Sires	Mean Live Litter Size–Female Mice Group A	Mean Live Litter Size–Female Mice Group B	Severity of Drug Combination Toxicity in Comparison to Each Drug Alone
2 (NIEHS, 1998)	AZT (0, 200, or 400 mg/kg per day) + trimethoprim/ sulfamethoxazole, (0, 1,000, 2,000, or 3,000 mg/kg per day) + folinic acid (0 or 10 mg/kg per day)	Male and/or female A and/or B mice: Decline in hematopoiesis-thymic atrophy; thyroid hyperplasia; bone marrow depletion; hepatocyte hypertrophy	Anemia; leukopenia; reticulocytopenia; thrombocytosis	Mean litter size for 0, 200, or 400 mg/kg AZT: 11, 4.8**, 0.8*	Mean litter size for 0, 200, or 400 mg/kg AZT: 11.3, 9.7, 7.8	Combination drug toxicity exceeded individual drug toxicity Folinic acid did not ameliorate toxic effects from AZT alone or from the AZT + trimethoprim/ sulfamethoxazole combination
3 (NIEHS, 1999a)	AZT (0, 100, 200, or 400 mg/kg per day) + isoniazid (0, 50, 100, or 150 mg/kg per day)	Female A mice: splenic enlargement	Female A mice: anemia; leukopenia; thrombocytosis Male mice: moderate anemia	Mean litter size for 0, 100, 200, or 400 mg/kg AZT: 12.5, 9.3, 8.6, 1.4**	Mean litter size for 0, 100, 200, or 400 mg/kg AZT: 12.4, 12.5, 11.6, 12.7	Combination drug toxicity exceeded individual drug toxicity
4 (NIEHS, 2000)	AZT (0, 200, or 400 mg/kg per day) + rifabutin (0, 80, 320, or 400 mg/kg per day)	Male and/or female A mice: hepatocellular cytoplasmic alteration; hyperplasia, ulceration, and inflammation of the forestomach; cystic degeneration and chronic inflammation of the glandular stomach; cellular depletion of the bone marrow; atrophy of the spleen; mixed cell infiltration in the lung Female B mice: no significant alteration	Anemia; thrombocytosis; decreased neutrophil count; thrombocytosis; increase in alanine aminotransferase activity and bile acid concentration	Mean litter size for 0, 200, or 400 mg/kg AZT: 11.1, 6.2**, 4.6**	Mean litter size for 0, 200, or 400 mg/kg AZT: 11.2, 12, 10.7	Combination drug toxicity exceeded individual drug toxicity

Table 4
Selected Findings from the Reproductive, Developmental, and General Toxicity Studies of AZT in Combination with Other Drugs in Male and Female Swiss (CD-1®) Mice

NIEHS AIDS Therapeutic Toxicity Reports	Study Drug Combination	Histopathologic Findings in F_0 Dams/Sires	Hematologic Findings in F_0 Dams/Sires	Mean Live Litter Size–Female Mice Group A	Mean Live Litter Size–Female Mice Group B	Severity of Drug Combination Toxicity in Comparison to Each Drug Alone
7 (NIEHS, 2002a)	AZT (0, 200, or 400 mg/kg per day) + pyrazinamide (0, 300, 1,500, or 3,000 mg/kg per day)	Male and/or female A mice: hepatocellular glycogen depletion; bone marrow depletion; hematopoietic cell proliferatioin; atrophy of splenic red pulp; hepato-cellular glycogen depletion Female B mice: not evaluated	Anemia; increased mean cell volume; increased mean cell hemoglobin; reticulocytopenia; reticulocytosis; thrombocytosis; leukopenia; neutropenia; lymphopenia	Mean litter size for 0, 200, or 400 mg/kg AZT: 10.9, 8.3, 3.9**	Mean litter size for 0, 200, or 400 mg/kg AZT: 12.5, 12.8, 10.5	Combination drug toxicity exceeded individual drug toxicity Reproductive toxicity exceeded individual drug toxicity

* Significantly different (P<0.05) from the vehicle control group by the Cochran-Armitage and Fisher exact tests
** P<0.01
[a] Male mice dosed from study day 5 to study day 25 or 26, female A mice dosed throughout pregnancy and mated to treated males (results from dosing with AZT alone), female B mice dosed on study day 6 through 15 of gestation and mated to untreated males (results from dosing with AZT alone)

Reproductive Toxicity and Teratogenicity

Experimental Animals

In a series of studies in rats, mice, and rabbits, AZT has been shown to cause adverse reproductive effects but no teratogenic effects.

Zidovudine was evaluated for adverse effects on reproductive and fetal development in CD (Sprague-Dawley) rats and New Zealand White rabbits (Greene *et al.*, 1996). Male and female CD rats were given twice-daily oral AZT doses of 0, 25, 75, or 225 mg/kg, approximately six hours apart. Males were dosed for 85 days prior to mating, and continued on dosing throughout two mating cycles for a total of 175 dosing days. Treated males were mated to females (F_0) dosed for 26 days prior to mating and throughout gestation and lactation. Early resorptions and decreased litter size were noted following parental dosing with 75 or 225 mg/kg. In a second mating, treated males were mated to untreated females and the pups were monitored for growth, survival, and developmental characteristics. All reproductive parameters were normal. The authors concluded that the embryotoxicity of AZT noted with the first mating (treated males with treated females) was not mediated by a genotoxic effect in the males. The liveborn offspring showed no developmental abnormalities or teratogenic effects. Also in these studies, pregnant New Zealand White rabbits given an oral dose of 250 mg AZT/kg body weight per day during gestation days 6 to 18 had reduced weight gain, anemia, and increased late fetal deaths. The liveborn offspring showed no developmental abnormalities or teratogenic effects.

When pregnant CD-1® mice were given daily intragastric doses of 25 mg AZT/kg body weight per day during days 12 to 18 of gestation, no developmental toxicity was seen in the F_1 generation (Diwan *et al.*, 2000). When these treated offspring were mated to untreated offspring, the liveborn F_2 pups showed no adverse effects on reproductive parameters.

Other studies have shown that AZT can cause cytotoxic effects in preimplantation mouse embryos by inhibition of blastocyst and postblastocyst development at doses similar to human therapeutic doses (Toltzis *et al.*, 1991; (USDHHS, 2004).

Humans

There have been no reported increases in congenital abnormalities in infants born to women with antepartum AZT exposure (Connor *et al.*, 1994; Sperling *et al.*, 1998). The NIH panel cautions that definitive conclusions regarding teratogenic risk cannot be thoroughly evaluated because of limited numbers of children evaluated (Reggy *et al.*, 1997; NIAID, 1999; USDHHS, 2004).

The Antiretroviral Pregnancy Registry (2003) has been established to collect data on the effects of *in utero* exposure to AZT and/or other antivirals. Coadministration of lamivudine with AZT did not appear to alter the pharmacokinetics of AZT in adults (Wang *et al.*, 1999). In this study, when abacavir was coadministered with AZT, the C_{max} of AZT decreased by approximately 20%, the T_{max} for AZT was delayed by 0.5 hours, and the mean area under the plasma concentration versus time curve for the 5′-glucuronide metabolite of AZT was increased by up to 40%.

AZT crosses the human placenta, achieving umbilical cord:maternal blood ratios of about 0.8:1.0 (Olivero *et al.*, 1999a). AZT is excreted in human breast milk (USDHHS, 2004). When AZT crosses the human placenta, it is incorporated into the DNA of cord blood leukocytes (Olivero *et al.*, 1999a). AZT has also been shown to cross the placenta of mice (Olivero *et al.*, 1997) and of monkeys (Ewings *et al.*, 2000).

Carcinogenicity

Experimental Animals

Preclinical studies in rodents have been conducted by GlaxoSmithKline to determine the potential for toxicity and/or cancer from exposure to AZT. AZT was administered to CD rats by oral gavage once a day at 0, 80, 220, or 600 mg AZT/kg body weight per day for up to 2 years (Ayers *et al.*, 1996a). Because of anemia, the high dose was reduced to 450 mg/kg per day at day 91; on day 278, the high dose was again reduced to 300 mg/kg per day. Squamous cell carcinomas of the vagina occurred in two females receiving 300 mg/kg; no vaginal tumors/hyperplasia occurred in any other group of female rats. These investigators also administered AZT to CD-1® mice by oral gavage at 0, 30, 60, or 120 mg/kg per day. Because of anemia, the doses were

reduced to 0, 20, 30, or 40 mg/kg per day at day 90, where they remained for the rest 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 in one female receiving 40 mg/kg, and one squamous polyp of the vagina in one female receiving 40 mg/kg. Although the incidences of hyperplasia of the vaginal epithelium were not increased above that in the controls, the severity of this lesion increased with increasing doses of AZT.

In order to clarify the role of AZT in producing vaginal tumors, AZT was administered intravaginally to CD-1® mice for 22 months (Ayers *et al.*, 1996b). Higher incidences of vaginal neoplasms occurred than were seen in the AZT oral gavage study in CD-1® mice. There was a retrograde flow of urine from the discharge point at the base of the vulva into the region of the vagina where the vaginal tumors occurred. In mice, 90% of AZT is eliminated in the 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 in mice (4 to 5 days), the investigators concluded that prolonged exposure of the vaginal epithelium to the relatively high concentrations of AZT in the urine could explain the observed vaginal neoplasms. In humans, the concentration of free AZT in the urine is low, and the authors concluded that the vaginal tumors seen in mice would not necessarily be predictive of vaginal tumors in humans (Ayers *et al.*, 1996b).

The NTP's 2-year studies of AZT and AZT/interferon were conducted in $B6C3F_1$ mice (NTP, 1999). AZT was administered to male and female mice by oral gavage at doses of 0, 30, 60, or 120 mg/kg per day in two equal doses, at least 6 hours apart, 5 days per week for 105 weeks. In the AZT/interferon studies, male and female mice received AZT by oral 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; the 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 (all without AZT), three times per week for 105 weeks. There was *equivocal evidence of carcinogenic activity* of AZT in male mice based on marginally 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.

AZT is genotoxic in fetal mice and monkeys and is a moderately strong transplacental carcinogen in mice (Olivero *et al.*, 1997; Diwan *et al.*, 1999). In these NCI studies, AZT was given to CD-1® mice at doses of 12.5 or 25 mg (equivalent to up to 1,000 mg AZT/kg nonpregnant body weight or 450 mg AZT/kg of terminal body weight) orally on days 12 to 18 of gestation. AZT incorporated into nuclear and mitochondrial DNA of the fetuses. A dose-dependent increase in tumor multiplicity in the lung, liver, and female reproductive organs occurred. In another transplacental carcinogenicity study, CD-1® mice were given 20 or 40 mg AZT/kg body weight per day in the drinking water from gestation day 10 through lactation day 21 (Ayers *et al.*, 1997). Some of the pups from these litters were then continued on AZT treatment by daily gavage at 20 or 40 mg/kg per day for 24 months. AZT tumor findings were limited to the vagina. Transplacental carcinogenicity studies have not been performed for AZT in combination with other antiviral drugs.

Humans

There have been no studies reported in the literature on any association between AZT and/or HAART and cancer. Cancer often takes many years to develop, and follow-up of patients is continuing (Antiretroviral Pregnancy Registry, 2003). An NIH panel has recommended long-term follow-up in children receiving *in utero* exposure to AZT and other antiretroviral drugs (Reggy *et al.*, 1997).

Genetic Toxicity

AZT is a DNA-reactive chemical that is positive in the *Salmonella* mutation assay (strain TA102, with and without hamster liver S9) (NTP, 1999) and has been shown to increase mutation frequencies and induce chromosomal damage in mammalian cells *in vivo* and *in vitro*. Its genetic effects have been assessed both in laboratory

animals and in humans. A brief summary of the extensive genetic toxicity literature follows.

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, as well as 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 cultured Chinese hamster ovary cells (effective concentrations were lower in experiments with human lymphocytes). In cytogenetic studies in Chinese hamster ovary cells conducted by the NTP, sister chromatid exchanges were remarkably elevated by AZT, particularly in the absence of S9 activation, but no induction of chromosomal aberrations was observed (NTP, 1999).

In vivo, AZT has been shown to be an effective inducer of micronucleated erythrocytes (markers of chromosomal damage) in rats and mice exposed through various combinations of routes and exposure durations (Oleson and Getman, 1990; Phillips *et al.*, 1991). Significantly increased micronucleus frequencies (6 to 27 times the frequency in concurrent controls), were noted in peripheral blood and bone marrow erythrocytes of mice after multiple treatments with 100 to 2,000 mg AZT/kg 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 (Phillips *et al.*, 1991). In apparent contrast to these results, no induction of micronuclei was reported in an acute *in vivo* bone marrow test with male mice (Motimaya *et al.*, 1994); in this test, AZT was administered as a single intraperitoneal injection at doses ranging from approximately 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 only a single treatment was used rather than the more chronic administration characteristic of human dosing regimens. The experiments of Dertinger *et al.* (1996) helped to clarify the apparent lack of genetic damage from low doses of AZT in laboratory mice. These investigators treated BALB/c mice with 17 mg AZT/kg per day, 5 days a week for 2 weeks and analyzed peripheral blood for frequency of micronucleated polychromatic erythrocytes using highly sensitive flow cytometric procedures. They observed a significant increase in micronucleated erythrocytes in AZT-treated mice compared to the background frequencies established from these same mice 2 weeks prior to the initiation of AZT exposure. They further reported an apparent differential sensitivity to induction of micronucleated erythrocytes between male and female mice, with females demonstrating almost twice the increase over background (31%) compared to that seen in males (17%). This may have implications for data interpretation of standard micronucleus assays, particularly at low doses, as most investigators use male rodents in laboratory assays. A recent report supplied further evidence of the ability of AZT to induce genetic damage in treated animals. Von Tungeln *et al.* (2002) exposed newborn $B6C3F_1$ mice to AZT or 3TC alone (200 mg/kg per day for each chemical), or to AZT/3TC (200/200 mg/kg per day), on postnatal days 1 to 8; 24 and 48 hours after the final treatment, the frequency of micronucleated erythrocytes in bone marrow was measured, and 3 weeks after final treatment, gene mutations at the thymidine kinase (*Tk*) locus in spleen lymphocytes were measured. Both endpoints were significantly increased by AZT and the combination AZT/3TC, but not by 3TC alone. Further analyses indicated that the increased mutation frequencies noted at the *Tk* locus resulted from loss of heterozygosity.

Incorporation of AZT into the DNA of leukocytes and multiple organs of cynomolgus monkeys was demonstrated following a 30-day treatment period (40 mg/day, by nasogastric intubation) (Olivero *et al.*, 2001). Organ-specific differences in the amount of AZT incorporation were noted, and the average levels of incorporation were similar to what had been reported for human leukocytes (Olivero *et al.*, 1999b).

The relevance of the positive results from animal mutation studies to humans is not yet clear, but numerous investigations have yielded data supporting a potential for genetic damage in humans exposed to AZT and other nucleoside analogs. Several studies have demonstrated increased mutation frequencies in cultured human lymphoblastoid cells following AZT exposure. For example, there are a number of studies showing incorporation of AZT into DNA of human lymphoblastoid cells, followed by loss of heterozygosity at loci for the *Tk* (Meng *et al.*, 2000a), hypoxanthine phosphoribosyltransferase

(*Hprt*) (Sussman *et al.*, 1999), and adenine phosphoribosyltransferase (Meng *et al.*, 2000b) genes, resulting in significant increases in mutant frequencies. Meng *et al.* (2000c) reported that exposure of TK6 human lymphoblastoid cells to a combination of AZT and didanosine (ddI) yielded enhanced incorporation of AZT into DNA and elevated mutation frequencies at the *Hprt* and *Tk* loci over the incorporation and mutation rates seen with AZT alone. Analysis of the AZT-induced mutational spectra in these TK6 cells showed an increase in complete gene deletions, a result consistent with DNA chain termination and loss of heterozygosity (Meng *et al.*, 2002). *In vivo*, anti-AZT radioimmunoassays were used to demonstrate that AZT is incorporated into lymphocyte DNA of HIV-infected adults taking AZT (Olivero *et al.*, 1999b).

As for an assessment of induced chromosomal damage in humans treated with AZT, there is little information available at this time. An early paper by Shafik *et al.* (1991) reported significantly increased chromosomal aberration frequencies in lymphocytes of AIDS patients treated with AZT alone, compared to a healthy control group. However, studies reported by Robbins *et al.* (2001) showed no increases over a 4-month treatment period in lymphocyte or sperm chromosomal aberration frequencies in HIV-infected men receiving a variety of AZT-containing combination antiretroviral therapies. In these studies, each subject served as his own control, with baseline aberration frequencies determined before the initiation of treatment and then used as the basis of comparison to lymphocyte and sperm chromosomal aberration frequencies determined at various timepoints during treatment.

Because AZT is a critical component of antiretroviral therapy administered to pregnant HIV-infected women in an effort to reduce maternal-infant transmission of the virus, a number of studies in animals and humans have looked at the potential for AZT-induced DNA damage following *in utero* exposure. Pregnant CD-1® mice and *Erythrocebus patas* monkeys were treated with AZT (mice, 12.5 or 25 mg/day; monkeys, 10 mg/day) during critical periods of gestation, and AZT incorporation into both nuclear and mitochondrial DNA, along with telomere length of chromosomes, as measured in the newborns (Olivero *et al.*, 1997). The transplacentally exposed animals showed significant AZT incorporation into nuclear as well as mitochondrial DNA of several organs, and decreased telomere lengths were seen in chromosomes from liver and brain cells of mice, but not monkeys. Similarly, a human-equivalent dose of AZT (8 mg/kg) administered continuously over 4 hours to pregnant *rhesus* macaques just prior to hysterotomy at the end of gestation (one of the therapeutic protocols used in humans to reduce maternal-infant transmission of HIV) resulted in AZT incorporation into DNA extracted from cells of numerous fetal organs (Poirier *et al.*, 1999). Transplacental exposure of fetal *E. patas* monkeys to AZT/3TC (approximately 6/3.6 mg/kg per day administered to the pregnant female) resulted in higher levels of AZT incorporation into DNA and shortening of telomeres in the fetuses at term, compared to treatment with AZT alone (Olivero *et al.*, 2002). As part of a reproductive toxicity assessment of AZT in laboratory mice, Bishop *et al.* (2004b) treated pregnant CD-1® mice with combinations of AZT/ddI throughout gestation and lactation, and directly dosed the pups via gavage beginning on PND 4. AZT/ddI doses for both the dams and the pups were 50/250, 75/375, or 150/750 mg/kg per day. The lowest treatment level used in this study compared well with the human equivalent therapeutic doses of AZT and ddI. Peripheral blood micronucleus frequencies were assessed in mouse pups at PNDs 1, 4, 8, and 21; dams were assessed after 4 months of treatment. Highly significantly increased frequencies of micronucleated erythrocytes were seen in all groups of animals at all timepoints for each dose level. The highest frequencies of micronucleated polychromatic erythrocytes were observed in pups on PNDs 8 and 21, after the initiation of direct gavage on PND 4 (Bishop *et al.*, 2004b). A follow-up experiment using AZT and ddI as separate treatments in a similar protocol revealed that the observed genetic damage in pups and dams was directly attributable to AZT alone (Tables E1 and E3; Witt *et al.*, 2004); no significant increase in micronucleated polychromatic erythrocytes in ddI-exposed pups was observed (Witt *et al.*, 2004). Thus, genetic effects can be induced and measured in newborn humans, mice, and monkeys following exposure to AZT alone or in combination with other antiretroviral drugs *in utero*.

STUDY RATIONALE

A meeting was held at the NIH to review the results of two AZT transplacental carcinogenicity studies (National Institute of Allergy and Infectious Diseases, 1999; Reggy *et al.*, 1997). The panel unanimously concluded that the known benefits of AZT in preventing perinatal HIV transmission outweighed any concern of transplacental carcinogenesis.

The one positive AZT transplacental study was designed to maximize the occurrence of transplacental carcinogenesis by giving large AZT doses (approximately 400 to 800 mg/kg) (Olivero *et al.*, 1997; Diwan *et al.*, 1999), while the other negative study (Ayers *et al.*, 1997) was designed to examine effects of AZT administered at lower doses (20 and 40 mg/kg) more closely related to those used in the clinic.

This NIEHS AZT transplacental carcinogenicity study was designated to bridge the gap between these two previous studies using AZT doses of 0, 50, 100, 200, and 300 mg/kg.

MATERIALS AND METHODS

Procurement and Characterization AZT

A single lot of AZT (A980427A) was obtained from Raylo Chemicals (Edmonton, Alberta, Canada) by the analytical chemistry laboratory, Research Triangle Institute (Research Triangle Park, NC), and used during the gestational exposure phase of the study. Identity and purity analyses were conducted by the analytical chemistry laboratory. Stability analyses were conducted by Midwest Research Institute (Kansas City, MO) on a separate lot of AZT (809796) obtained from Burroughs Wellcome Company (Research Triangle Park, NC). Reports on analyses performed in support of the AZT studies are on file at the National Institute of Environmental Health Sciences. The study was conducted by Southern Research Institute (Birmingham, AL).

Lot A980427A of the chemical, a white crystalline powder, was identified as AZT by infrared and nuclear magnetic resonance spectroscopy. All spectra were consistent with the literature spectra (Horowitz, 1964; *Aldrich,* 1993) and with the structure of AZT. The infrared and nuclear magnetic resonance spectra are presented in Figures F1 and F2.

The purity of Lot A980427A was determined by high-performance liquid chromatography (HPLC). The purity of lot A980427A was determined to be greater than 99%.

Stability studies of lot 809796 were conducted by Midwest Research Institute using HPLC. AZT stored in amber septum vials was stable for at least 2 weeks at temperatures up to 60° C. To ensure stability, the bulk chemical was stored protected from light at approximately 5° C.

Methylcellulose

A lot of methylcellulose (986713) was obtained from Fisher Scientific (Pittsburgh, PA) for use as the vehicle.

Preparation and Analysis of Dose Formulations

The dose formulations were prepared twice during the gestational phase of the study by mixing AZT with 0.5% methylcellulose (Table F1). Formulations were stored refrigerated and protected from light for up to 35 days.

Homogeneity studies of the 2.5 and 15.0 mg/mL dose formulations were performed by the analytical chemistry laboratory using HPLC. Stability studies of a solution of 2 mg AZT/0.5% methylcellulose were performed by Midwest Research Institute for lot 809796 using HPLC. Homogeneity was confirmed and stability was confirmed for at least 3 weeks for dose formulations stored protected from light at room temperature, and for up to 3 hours when stored exposed to light and air at room temperatures. Stability was checked during the course of the study. Formulations of 15 mg AZT/mL 0.5% methylcellulose were found to be stable for 85 days when stored refrigerated and protected from light.

Periodic analyses of the dose formulations of AZT were conducted by the analytical chemistry laboratory using HPLC. The dose formulations were analyzed prospectively and during use; the highest dose formulation was also analyzed after use (Table F2). All dose formulations were within 10% of the target concentration at each analysis point.

2-Year Study

Study Design

Total daily doses (20 mL/kg) of AZT were divided into two equal doses (10 mL/kg per dose) that were administered to female mice by gavage approximately 6 hours apart from study day 0 to the day of delivery (29 to 39 days). Male mice were not dosed. Males were

cohabited with females on study days 9 through 13. During cohabitation periods, the females were examined daily for the presence of a vaginal plug as an indicator of pregnancy. When a vaginal plug was evident, the female was removed from the cohabitation cage and housed individually; for each female, the day of plugging was designated as day 0 of gestation.

Total daily doses administered to F_0 female mice were 50, 100, 200, or 300 mg AZT/kg body weight in a 0.5% methylcellulose vehicle. A control group was administered only the methlycellulose vehicle.

The 0, 50, 100, 200, and 300 mg/kg F_0 groups consisted of 22, 22, 28, 34, and 46 females respectively (equally divided into two groups to facilitate cohabitation, mating, and delivery) and six, six, seven, nine, and 12 untreated males used in mating. Details on the matings are presented in Appendix D.

F_0 females were weighed on days -1, 0, 4, 12, 16, 20, 23 or 25, and 26 and at necropsy. Sperm-negative females not delivering were discarded after gestation day 34, and dams given 50 mg/kg were discarded after postnatal day 21. Partial necropsies were performed on sperm-positive females that did not deliver by presumed gestation day 25 and on 0, 100, 200, and 300 mg/kg dams after postnatal day 21. The uterus for all F_0 females was removed and press-plated between glass slides. The number of implantation sites was recorded, and the number of pups delivered was subtracted to calculate the number of *in utero* losses. Survival, body weight, and reproductive performance data for female F_0 mice are presented in Appendix C.

Pups (F_1 generation) were culled (0, 50, and 100 mg/kg groups) to yield four or five pups/sex per litter on postnatal day 4; no more than four pups/sex per litter were used in the study. On postnatal day 25, all surviving pups for the 200 and 300 mg/kg groups were placed on study; some litters had more than four males or more than four females. After culling and randomization to cage groups, the 0, 50, 100, 200, and 300 mg/kg groups consisted of 50, 50, 50, 37, and 32 male pups and 50, 50, 50, 40, and 42 female pups, respectively. F_1 mice were continued on study until postnatal week 101 without further dosing. Further information on the litters is presented in Appendix C.

Source and Specification of Animals

Male and female Swiss (CD-1®) mice (F_0 generation) were obtained from Charles River Laboratories (Raleigh, NC) for use in the transplacental study. Mice were quarantined for 10 days before the beginning of the studies. Mice were approximately 13 weeks old at the beginning of the study. The health of the animals was monitored during the studies according to the protocols of the NTP Sentinel Animal Program (Appendix H).

Animal Maintenance

F_0 male mice were housed individually and F_0 female mice were housed five per cage until cohabitation. During cohabitation, one male was housed with one or two females; females were then housed individually. F_1 mice were housed with their dams until postnatal day 21; for the remainder of the study, males were housed individually and females were housed five per cage. Litter mates were not housed together. In order to provide equal cage loading for groups with less than 50 mice (200 and 300 mg/kg), unused mice from the lower dose groups were used as filler animals. Feed and water were available *ad libitum*. Further details of animal maintenance are given in Table 5. Information on feed composition and contaminants is provided in Appendix G.

Clinical Examinations and Pathology

All animals were observed twice daily for mortality and moribundity. For F_1 mice, clinical findings and body weights were recorded once every 4 weeks beginning at postnatal week 5.

Complete necropsies and microscopic examinations were performed on all F_1 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, trimmed and processed, embedded in paraffin, sectioned to a thickness of 5 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 5.

Microscopic evaluations were completed by the study laboratory pathologist, and the pathology data were entered into the Toxicology Data Management System. The slides, paraffin blocks, and residual wet tissues were

sent to the NTP Archives for inventory, slide/block match, and wet tissue audit. The slides, individual animal data records, and pathology tables were evaluated by an independent quality assessment laboratory. The individual animal records and tables were compared for accuracy, the slide and tissue counts were verified, and the histotechnique was evaluated. A quality assessment pathologist evaluated slides from all tumors and all potential target organs, which included the heart and lung. In addition, the quality assessment pathologist reviewed all lesions in the bone marrow, forestomach, harderian gland, kidney, liver, lymph nodes, pancreas, spleen, and reproductive tissues of vehicle control and 300 mg/kg mice. In male mice, the thymus and salivary glands were reviewed for lymphoid hyperplasia and the glandular stomach for proliferative lesions. Female mice were reviewed for edema in the cecum and colon and fibrous osteodystrophy, hyperostosis, and osteopetrosis in the bone.

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 5
Experimental Design and Materials and Methods in the Transplacental Carcinogenicity Study of AZT in Swiss CD-1® Mice

Study Laboratory
Southern Research Institute, Birmingham, AL

Strain and Species
Swiss (CD-1®) mice

Animal Source
Charles River Laboratories, Raleigh, NC

Time Held Before Study
10 days

Average Age When Study Began
13 weeks (F_0 mice)

Date of First Dose
F_0 females: May 21, 1999, for Group 1 mice and May 28, 1999, for Group 2 mice

Duration of Dosing
Study day 0 through day of delivery (or day prior to sacrifice if no pups delivered); minimum of 29 days, maximum of 39 days

Date of Last Dose
June 19 to 27, 1999, for group 1 mice (depending on date of delivery)
June 26 to July 5, 1999, for group 2 mice (depending on date of delivery)

Necropsy Dates
F_1 mice: April 23 through 27, 2001

Size of Study Groups
F_0 mice: 0, 50, 100, 200, and 300 mg/kg groups had 6, 6, 7, 9, or 12 males and 22, 22, 28, 34, or 46 females, respectively (equally divided into groups 1 and 2)
F_1 mice: 0, 50, 100, 200, and 300 mg/kg groups had 50, 50, 50, 37, or 32 males and 50, 50, 50, 40, or 42 females, respectively

Method of Distribution
F_0 mice: Animals were assigned to groups using a stratified weight method and then assigned to study groups in random order
F_1 mice: Pups were culled as appropriate on days 4 and 25 or 26 and were assigned to cages in random order, except litter mates were not housed together whenever possible.

Animals per Cage
F_0 mice: Females were housed five per cage prior to mating, and males were individually housed except during mating. During cohabitation, one male and one or two females were housed together. After cohabitation, each female was housed alone.
F_1 mice: Pups were housed with their respective dams until weaning at postnatal day 25 or 26. After weaning, F_1 males were individually housed and females were housed five per cage; "filler" animals (extra animals from lower dose groups that were not selected for study) were caged with mice from the 200 and 300 mg/kg groups to equalize cage occupancy across the groups.

Method of Animal Identification
F_0 dams and sires by tail tattoo; F_1 pups individually by foot tattoo and correlated with dam and dose group at weaning by tail tattoo

Diet
NIH-07 pelleted feed (Zeigler Brothers, Inc., Gardners, PA), available *ad libitum*

Water
Tap water (Birmingham municipal supply) via automated watering system, available *ad libitum*

TABLE 5
Experimental Design and Materials and Methods in the Transplacental Carcinogenicity Study of AZT in Swiss CD-1® Mice

Cages
Polycarbonate with solid bottoms and sides (Lab Products, Inc., Maywood, NJ)

Bedding
ALPHA-dri™ bedding (Shepherd Specialty Papers, Inc., Kalamazoo, MI) during cohabitation, gestation, and lactation periods, not changed after gestation day 16; heat-treated hardwood Sani-Chip® bedding (P.J. Murphy Forest Products Corp., Montville, NJ) after weaning

Cage Filters
Reemay® spun-bonded polyester (Dupont; Wilmington, DE)

Racks
Stainless steel (Lab Products, Inc., Maywood, NJ)

Animals Room Environment
Temperature: 72° ± 3°F
Relative humidity: 50% ± 15%
Room fluorescent light: 12 hours/day
Room air changes: 10/hour

Doses
F_0 females received 0, 50, 100, 200, or 300 mg AZT per kg body weight per day in an aqueous solution of 0.5% methylcellulose by gavage, divided into two equal volumes (10 mL/kg body weight) administered twice daily.

Type and Frequency of Observation
All mice were observed twice daily; clinical findings and body weights were recorded once every 4 weeks beginning postnatal week 5

Method of Sacrifice
Carbon dioxide asphyxiation

Necropsy
After pups were weaned, partial necropsies were performed on all dams from the 0, 100, 200, and 300 mg/kg groups that delivered and all sperm-positive females that did not deliver; the uterus of each of these females was removed and press-plated to assess the number of implantation sites. Complete necropsies were performed on all F_1 mice.

Histopathology
Complete histopathology was performed on F_1 mice. In addition to gross lesions and tissue masses, the following tissues were examined: adrenal gland, bone, brain, clitoral gland, esophagus, gallbladder, harderian gland, heart and aorta, large intestine (cecum, colon, rectum), small intestine (duodenum, jejunum, ileum), kidney, liver, lung and bronchi, lymph nodes (mandibular and mesenteric), mammary gland, nose, ovary, pancreas, parathyroid gland, pituitary gland, preputial gland, prostate gland, salivary gland, seminal vesicle, skin, spleen, spinal cord, stomach (forestomach and glandular), testis with epididymus, thymus, thyroid gland, trachea, urinary bladder, uterus and vagina. The sciatic nerve and skeletal muscle were examined when clinical findings indicated possible neuromuscular involvement.

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 (F_1 mice only). Animals found dead of other than natural causes 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, and B4 as the numbers of animals bearing such lesions at a specific anatomic site and the numbers of animals with that site examined microscopically. For calculation of statistical significance, the incidences of most neoplasms (Tables A3 and B3) and all nonneoplastic lesions are given as the numbers of animals affected at each site examined microscopically. However, when macroscopic examination was required to detect neoplasms in certain tissues (e.g., harderian gland, intestine, mammary gland, and skin) before microscopic evaluation, or when neoplasms had multiple potential sites of occurrence (e.g., leukemia or lymphoma), the denominators consist of the number of animals on which a necropsy was performed. Tables A3 and B3 also give the survival-adjusted neoplasm rate for each group and each site-specific neoplasm. This survival-adjusted rate (based on the Poly-3 method described below) accounts for differential mortality by assigning a reduced risk of neoplasm, proportional to the third power of the fraction of time on study, only to site-specific, lesion-free animals that do not reach terminal sacrifice.

Litter effects on lung tumors, liver tumors, and skin lesions were tested using a mixed effects logistic regression model (McCullagh and Nelder, 1989). Survival time, dose and sex of the pup were included in the model as fixed effects. Litter effects were included as random effects and were assumed to be normally distributed with unknown variance. Because multiple litters had the same sire, a sire effect was also tested using mixed effects logistic regression models, where sire was the random effect rather than litter. To investigate sex-specific effects, analyses were also performed on male and female pups separately; the sex of the pup was not included as a predictor in these models.

Analysis of Neoplasm and Nonneoplastic Lesion Incidences

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

This method yields a lesion prevalence rate that depends only upon the choice of a shape parameter for a Weibull hazard function describing cumulative lesion incidence over time (Bailer and Portier, 1988). Unless otherwise specified, a value of k=3 was used in the analysis of site-specific lesions. This value was recommended by Bailer and Portier (1988) following an evaluation of neoplasm onset time distributions for a variety of site-specific neoplasms in control F344 rats and $B6C3F_1$ mice (Portier *et al.,* 1986). Bailer and Portier (1988) showed that the Poly-3 test gave valid results if the true value of k was anywhere in the range from 1 to 5. A further advantage of the Poly-3 method is that it does not require lesion lethality assumptions. Variation introduced by the use of risk weights, which reflect differential mortality, was accommodated by adjusting the variance of the Poly-3 statistic as recommended by Bieler and Williams (1993).

Tests of significance included pairwise comparisons of each exposed group with controls and a test for an overall exposure-related trend. Continuity-corrected Poly-3 tests were used in the analysis of lesion incidence, and reported P values are one sided. The significance of lower incidences or decreasing trends in lesions is represented as 1–P with the letter N added (e.g., P=0.99 is presented as P=0.01N).

Analysis of Continuous Variables

Dams' body weights at necropsy were analyzed in three groups, according to the number of days that the dam was in the study (< 30 days, 30 to 44 days, >45 days). Dams that died before 30 days died of gavage accidents; dams that were sacrificed between 30 and 44 days had no pups and dams that were sacrificed on or after day 45 had pups. Dams' body weights were tested for equality across dose groups using parametric analysis of variance. Significant differences were followed by Dunnett's test (1955) to determine which dosed groups significantly differed from the vehicle control group. Parametric analysis of variance and Dunnett's test were also used for other normally distributed variables, such as numbers of implantations, numbers of live births, numbers of live males, and numbers of live females. Numbers of *in utero* losses, and numbers of male and female pups found dead were not normally distributed, therefore, nonparametric analysis of variance and a related multiple comparisons procedure were used (Dunn's test, 1964). Numbers of males and females per litter were compared using paired t-tests within each exposure group. Analyses were conducted on numbers of live and dead pups per litter on postnatal day 0 and 4, the day that culling occurred.

Analysis of Dichotomous Events

Incidences of dichotomous events, such as pregnant versus not pregnant, were compared across dose or exposure groups using the Cochran-Armitage trend test (Armitage, 1971). Significant trends were followed by pairwise comparisons of each dosed or exposed group with the vehicle control group using Fisher's exact test (Gart *et al.*, 1979).

Quality Assurance Methods

The transplacental study was conducted in compliance with Food and Drug Administration Good Laboratory Practice Regulations (21 CFR, Part 58). In addition, as records from the transplacental study were submitted to the NTP Archives, this study was 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

In an independent reproductive toxicity study conducted by NTP, the genetic toxicity of AZT was assessed by measuring the frequency of micronucleated (MN) erythrocytes in Swiss (CD-1®) mouse pups and their dams following transplacental, lactational, and/or gavage exposure. The percentage of polychromatic erythrocytes (PCEs) was also measured as a rough indicator of chemical-induced hematopoietic toxicity. Micronuclei (literally "small nuclei" or Howell-Jolly bodies) are biomarkers of induced structural or numerical chromosomal alterations and are formed when acentric fragments or whole chromosomes fail to incorporate into either of two daughter nuclei during cell division (Schmid, 1975; Heddle *et al.*, 1983).

The genetic toxicity studies have evolved from an earlier effort by the NTP to develop a comprehensive database permitting a critical anticipation of a chemical's carcinogenicity in experimental animals based on numerous considerations, including the molecular structure of the chemical and its observed effects in short-term *in vitro* and *in vivo* genetic toxicity tests (structure-activity relationships). The short-term tests were originally developed to clarify proposed mechanisms of chemical-induced DNA damage based on the relationship between electrophilicity and mutagenicity (Miller and Miller, 1977) and the somatic mutation theory of cancer (Straus, 1981; Crawford, 1985). However, it should be noted that not all cancers arise through genotoxic mechanisms.

DNA reactivity combined with *Salmonella* mutagenicity is highly correlated with induction of carcinogenicity in multiple species/sexes of rodents and at multiple tissue sites (Ashby and Tennant, 1991). A positive response in the *Salmonella* test was shown to be the most predictive *in vitro* indicator for rodent carcinogenicity (89% of the *Salmonella* mutagens are rodent carcinogens) (Tennant *et al.,* 1987; Zeiger *et al.,* 1990). Additionally, no battery of tests that included the *Salmonella* test improved the predictivity of the *Salmonella* test alone. However, these other tests can provide useful information on the types of DNA and chromosomal damage induced by the chemical under investigation.

The predictivity for carcinogenicity of a positive response in acute *in vivo* bone marrow chromosome aberration or micronucleus tests appears to be less than that in the *Salmonella* test (Shelby *et al.,* 1993; Shelby and Witt, 1995). However, clearly positive results in long-term peripheral blood micronucleus tests have high

predictivity for rodent carcinogenicity (Witt *et al.,* 2000); negative results in this assay do not correlate well with either negative or positive results in rodent carcinogenicity studies. 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. Most organic chemicals that are identified by the International Agency for Research on Cancer as human carcinogens, other than hormones, are genotoxic. The vast majority of these are detected by both the *Salmonella* assay and rodent bone marrow cytogenetics tests (Shelby, 1988; Shelby and Zeiger, 1990).

RESULTS

REPRODUCTIVE PERFORMANCE

Survival, body weight, and reproductive data for female F_0 mice are presented in Appendix C. As presented in Appendix C, there were no significant differences between numbers of male and female pups: live at day 0, dead at day 0, born on day 0, dead by day 4, culled, or remaining after day 4 (by paired t-tests) (Tables C6 and C7). Decreased litter size and fertility rates were observed in dams at 200 and 300 mg/kg (Tables C4 and C6).

2-YEAR STUDY

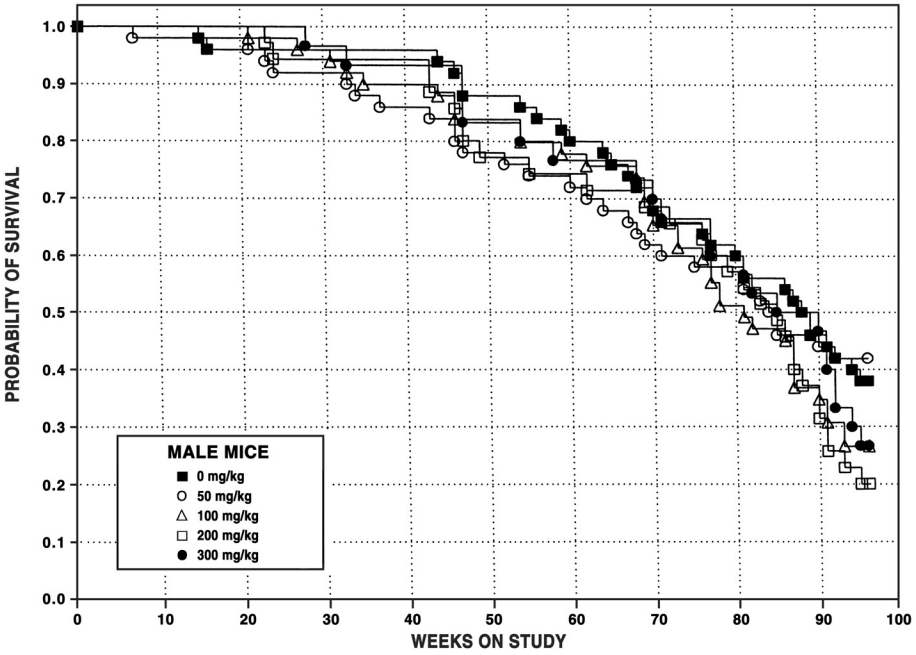
Survival

Estimates of 2-year survival probabilities for F_1 male and female mice are shown in Table 6 and in the Kaplan-Meier survival curves (Figure 1). Treatment with AZT had no significant effect on the survival of exposed groups of male or female mice.

TABLE 6
Survival of Swiss (CD-1®) Mice in the Transplacental Study of AZT

	Vehicle Control	50 mg/kg	100 mg/kg	200 mg/kg	300 mg/kg
Male					
Animals initially in study	50	50	50	37	32
Accidental deaths[a]	0	0	1	0	2
Other[a]	0	0	0	1	0
Moribund	23	21	25	23	12
Natural deaths	8	9	11	6	10
Animals surviving to study termination	19	20[e]	13	7	8[e]
Percent probability of survival at end of study[b]	38	42	27	20	27
Mean survival (days)[c]	550	515	521	513	511
Survival analysis[d]	P=0.249	P=1.000	P=0.288	P=0.161	P=0.553
Female					
Animals initially in study	50	50	50	40	42
Accidental death	0	1	0	0	0
Moribund	16	18	11	10	15
Natural deaths	14	13	15	9	9
Animals surviving to study termination	20[e]	18[e]	24	21[f]	18[e]
Percent probability of survival at end of study	40	37	48	50	45
Mean survival (days)	562	542	574	610	553
Survival analysis	P=0.398N	P=0.549	P=0.521N	P=0.336N	P=0.942N

[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 exposed group columns. A negative trend or a lower mortality in an exposed group is indicated by **N**.
[e] Includes one animal that died or was sacrificed moribund the last week of study
[f] Includes two animals that died the last week of study



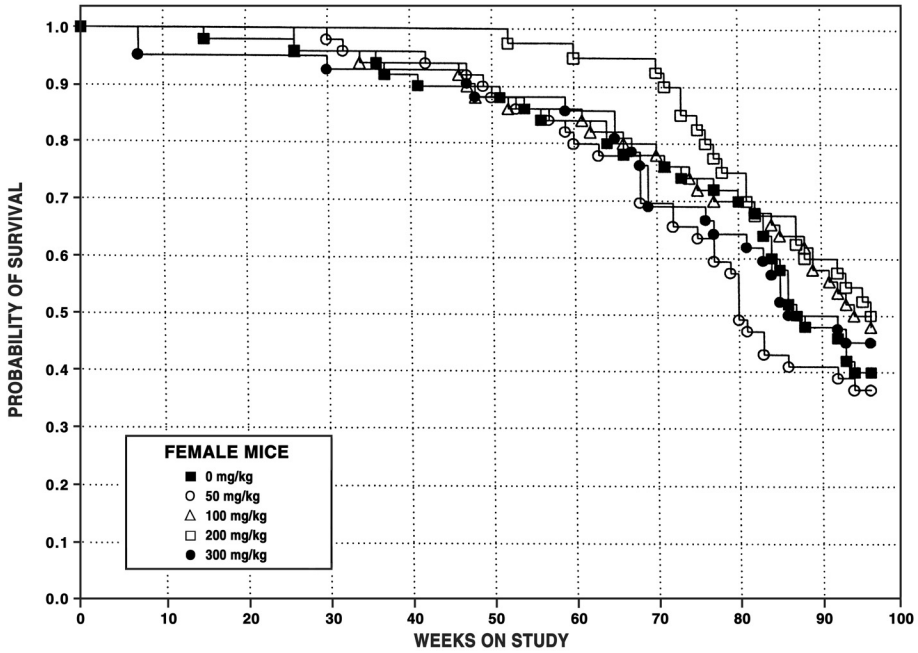


FIGURE 1
Kaplan-Meier Survival Curves for Swiss (CD-1®) Mice in the Transplacental Study of AZT

Body Weights and Clinical Findings

Mean body weights of 50 and 100 mg/kg males and all exposed groups of females were generally similar to those of the vehicle controls throughout the study (Tables 7 and 8; Figure 2). Mean body weights of 200 mg/kg males were generally less than those of the vehicle controls after week 29. Those of 300 mg/kg males were less during the first year of the study, but these mice recovered and body weights were generally similar to those of the vehicle controls at the end of the study.

Skin lesions believed to be compatible with a previously reported condition in Swiss (CD-1®) mice and recognized as "progressive necrotizing dermatitis" (Slattum *et al.*, 1998; Smith *et al.*, 2000) occurred in all groups of male and female (except 100 mg/kg) mice including vehicle controls but were more prevalent in male mice (42 males and 21 females; Table 9). The skin lesion was responsible for moribund sacrifices, but because of the random distribution within groups, was not considered to be related to AZT exposure. Grossly, the lesions appeared as focal ulcers/abscesses about the ears, neck, and shoulders that histologically were diagnosed as ulcers and associated chronic inflammation and epidermal hyperplasia. Slattum *et al.* (1998) suggested that genetic factors could play a role in the etiology of skin lesions, and that physiologic and anatomic defects in the auditory system that are observed in CD-1® mice could result in self-inflicted trauma to the pinna (Shone *et al.*, 1991; Le Calvez *et al.*, 1998).

TABLE 7
Mean Body Weights and Survival of Male Swiss (CD-1®) Mice in the Transplacental Study of AZT

Weeks on Study	Vehicle Control		50 mg/kg			100 mg/kg			200 mg/kg			300 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	Av. Wt. (g)	Wt. (% of controls)	No. of Survivors
5	28.1	50	26.3	94	50	26.4	94	50	26.9	96	37	25.6	91	32
9	40.3	50	37.6	93	49	38.1	95	50	38.7	96	37	36.9	92	30
13	44.6	50	42.6	96	49	42.9	96	50	43.7	98	37	41.4	93	30
17	48.8	48	46.4	95	49	46.6	96	50	45.8	94	37	44.7	92	30
21	49.6	48	48.4	98	49	48.2	97	50	47.5	96	37	46.1	93	30
25	52.6	48	50.1	95	46	50.6	96	49	50.6	96	34	47.6	91	30
29	53.3	48	51.3	96	46	50.7	95	48	50.9	96	34	48.9	92	29
33	54.8	48	51.7	94	46	51.2	93	47	52.0	95	34	48.8	89	29
37	54.1	48	51.3	95	44	51.1	95	45	51.6	95	34	49.5	92	28
41	55.4	48	53.1	96	43	52.6	95	45	52.3	94	34	50.7	92	28
45	56.1	47	53.3	95	42	53.4	95	44	52.2	93	32	51.5	92	28
49	56.0	44	53.5	96	39	52.5	94	41	52.7	94	29	52.5	94	25
53	56.3	44	55.1	98	38	53.3	95	41	53.9	96	28	52.0	92	25
57	56.0	42	54.9	98	37	54.6	98	39	53.3	95	27	53.3	95	24
61	56.3	40	55.0	98	36	54.2	96	38	52.2	93	26	53.4	95	23
65	56.5	39	54.7	97	34	53.7	95	37	52.6	93	25	53.6	95	23
69	55.4	36	54.8	99	32	54.2	98	35	52.0	94	25	52.4	95	22
73	55.7	33	55.3	99	30	55.0	99	31	51.1	92	23	53.8	97	20
77	53.6	32	55.2	103	29	54.0	101	29	52.4	98	22	51.8	97	20
81	54.8	30	52.2	95	28	55.4	101	25	49.5	90	19	53.5	98	17
85	54.2	28	55.0	102	24	54.1	100	23	49.0	90	17	51.6	95	16
89	55.4	24	53.1	96	23	53.3	96	18	48.6	88	13	50.5	91	15
93	54.5	21	52.2	96	21	52.8	97	14	50.2	92	8	51.9	95	10
Mean for weeks														
1-93	52.3		50.6	97		50.4	96		49.1	94		48.8	93	

TABLE 8
Mean Body Weights and Survival of Female Swiss (CD-1®) Mice in the Transplacental Study of AZT

Weeks on Study	Vehicle Control		50 mg/kg			100 mg/kg			200 mg/kg			300 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	Av. Wt. (g)	Wt. (% of controls)	No. of Survivors
5	21.4	50	20.2	94	50	20.4	95	50	22.3	104	40	19.4	91	42
9	30.2	50	28.5	94	50	28.7	95	50	30.6	101	40	28.4	94	40
13	35.2	50	33.2	94	50	33.5	95	50	35.5	101	40	34.1	97	40
17	39.9	49	36.9	93	50	37.4	94	50	39.9	100	40	39.9	100	40
21	41.9	49	38.8	93	50	39.7	95	50	41.9	100	40	41.8	100	40
25	45.3	49	42.3	93	50	42.8	95	50	45.4	100	40	45.3	100	40
29	46.7	48	44.1	94	50	44.4	95	48	46.3	99	40	46.3	99	40
33	48.7	48	46.6	96	48	42.1	86	48	48.6	100	40	45.4	93	39
37	48.2	46	46.9	97	48	48.2	100	47	49.5	103	40	50.0	104	39
41	51.3	46	49.7	97	48	49.9	97	47	51.2	100	40	51.2	100	39
45	52.7	45	52.7	100	47	49.4	94	47	54.4	103	40	49.1	93	39
49	51.1	45	50.5	99	46	51.9	102	44	52.1	102	40	51.8	101	37
53	53.1	44	51.9	98	43	53.2	100	43	52.9	100	39	52.6	99	37
57	55.3	42	55.2	100	43	53.0	96	43	55.8	101	39	49.7	90	37
61	54.7	42	53.6	98	39	58.4	107	43	53.5	98	38	62.9	115	36
65	54.8	40	55.2	101	38	56.2	103	41	53.1	97	38	52.8	96	36
69	55.6	39	54.5	98	34	55.9	101	40	52.1	94	38	54.0	97	31
73	56.7	38	54.4	96	32	57.3	101	38	52.6	93	36	55.3	98	29
77	55.9	37	52.8	95	31	57.1	102	36	52.6	94	32	46.5	83	28
80									50.4	NA	30			
81	56.3	35	55.3	98	24	57.8	103	35	55.4	98	30	56.7	101	26
85	56.2	30	55.4	99	21	57.7	103	32	53.5	95	27	55.8	99	24
89	56.2	24	55.6	99	20	57.8	103	29	51.9	92	24	56.5	101	21
93	54.4	22	56.6	104	19	57.2	105	27	50.2	92	22	58.3	107	19
Mean for weeks														
1-93	48.8		47.4	97		48.3	99		48.0	98		48.0	98	

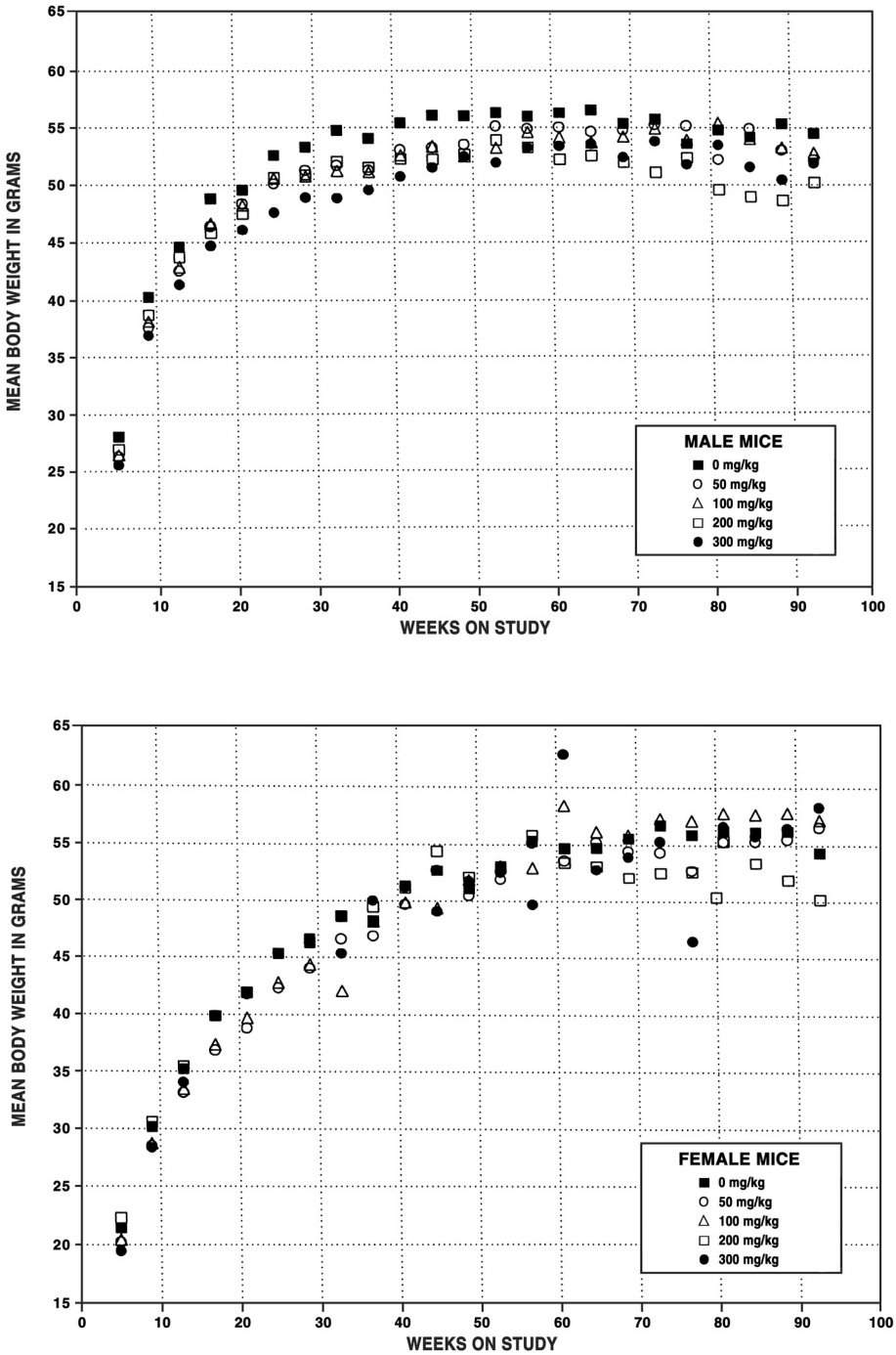


FIGURE 2
Growth Curves for Swiss (CD-1®) Mice in the Transplacental Study of AZT

TABLE 9
Number of Animals per Group Sacrificed Moribund and Also Presenting with Skin Ulceration at Gross Necropsy[a]

	Vehicle Control	50 mg/kg	100 mg/kg	200 mg/kg	300 mg/kg
Male					
Number of animals with skin ulcer	11/50	6/50	13/50	7/37	5/32
Day of first moribund sacrifice	111	147	229	167	192
Mixed model test	0.206	0.854	0.818	0.335	0.324
Female					
Number of animals with skin ulcer	9/50	5/50	0/50	3/40	4/42
Day of first moribund sacrifice	255	207	NA	488	453
Mixed model test	0.647	0.357	0.069	0.816	0.331

[a] Mixed effects logistic models, adjusting for survival, were used to test dose and litter effects. P values for litter effects for males = 0.102, for females = 0.081, for males and females combined = 0.042. Beneath the vehicle control column is the P value associated with the trend test after adjusting for survival. Beneath the exposed group columns are the P values corresponding to pairwise comparisons between the vehicle controls and that exposed group after adjusting for survival.

Pathology and Statistical Analyses

This section describes the statistically significant or biologically noteworthy changes in the incidences of neoplasms and nonneoplastic lesions of the lung and miscellaneous organs and tissues. Summaries of the incidences of neoplasms and nonneoplastic lesions, individual animal tumor diagnoses, and statistical analyses of primary neoplasms that occurred with an incidence of at least 5% in at least one animal group are presented in Appendix A for male mice and Appendix B for female mice.

Lung: There were increased incidences of alveolar/bronchiolar carcinoma and alveolar/bronchiolar adenoma or carcinoma (combined) in male mice exposed to 50, 200, or 300 mg/kg; the incidences in the 200 and 300 mg/kg groups were significantly greater than those in the vehicle controls (Tables 10 and A3). Alveolar/bronchiolar adenoma or carcinoma (combined) occurred significantly earlier in males exposed to 200 mg/kg (P=0.015) or 300 mg/kg (P=0.042) than in vehicle controls. Alveolar/bronchiolar carcinomas occurred significantly earlier in males exposed to 200 mg/kg (P=0.014) than in vehicle controls, but this was not true in 300 mg/kg males (P=0.096). The mean survival times, in days, for males with carcinoma were: vehicle control, 646; 50 mg/kg, 589; 100 mg/kg, 620; 200 mg/kg, 573; and 300 mg/kg, 613; (P=0.043). For males with adenoma or carcinoma (combined), mean survival days were 641, 567, 599, 552, and 564 (P=0.021). There were no significant differences in survival times for the females.

The incidences of histiocytic cellular infiltration in 200 and 300 mg/kg male mice and alveolar epithelial hyperplasia in 100 mg/kg female mice were significantly greater than those in the vehicle controls (Tables 10, A4, and B4).

Microscopically, alveolar/bronchiolar adenomas were well-demarcated hypercellular masses that distorted the normal septal architecture and caused slight compression of the surrounding parenchyma. They consisted of well-differentiated cuboidal to round cells that formed papillary structures that projected into the alveolar spaces or bronchiolar lumen. Alveolar/bronchiolar carcinomas were more irregular hypercellular masses that effaced the normal septal architecture and had variable peripheral compression and invasion of the adjacent parenchyma. Growth patterns were heterogeneous with pleomorphic, polygonal to columnar cells arranged as solid sheets or papillary structures.

Alveolar epithelial hyperplasia consisted of focal thickening of the alveolar septa caused by increased numbers of prominent, cuboidal cells (presumably type II pneumocytes) with maintenance of normal alveolar septal architecture. Histiocytic cellular infiltration consisted of variable numbers of activated macrophages within the

TABLE 10
Incidences of Neoplasms and Nonneoplastic Lesions of the Lung in Swiss (CD-1®) Mice in the Transplacental Study of AZT[a]

	Vehicle Control	50 mg/kg	100 mg/kg	200 mg/kg	300 mg/kg
Male					
Number Examined Microscopically	50	50	50	37	32
Infiltration Cellular, Histiocyte[b]	12 (2.3)[c]	16 (2.9)	13 (2.8)	16* (3.2)	14* (3.0)
Alveolar Epithelium Hyperplasia	6 (1.5)	3 (2.3)	0	1 (1.0)	4 (2.8)
Alveolar/bronchiolar Adenoma, Multiple	3	0	0	1	1
Alveolar/bronchiolar Adenoma (includes multiple)	10	13	8	9	11
Alveolar/bronchiolar Carcinoma, Multiple	1	5	1	6*	3
Alveolar/bronchiolar Carcinoma (includes multiple)					
Overall rate[d]	5/50 (10%)	11/50 (22%)	6/50 (12%)	11/37 (30%)	8/32 (25%)
Adjusted rate[e]	14.9%	33.0%	19.9%	45.1%	38.7%
Terminal rate[f]	2/19 (11%)	5/21 (24%)	4/13 (31%)	3/7 (43%)	3/8 (38%)
First incidence (days)	619	363	482	341	376
Poly-3 test[g]	P=0.014	P=0.068	P=0.422	P=0.009	P=0.043
Alveolar/bronchiolar Adenoma or Carcinoma					
Overall rate	14/50 (28%)	20/50 (40%)	13/50 (26%)	18/37 (49%)	18/32 (56%)
Adjusted rate	40.2%	54.5%	40.5%	66.3%	72.9%
Terminal rate	7/19 (37%)	9/21 (43%)	7/13 (54%)	5/7 (71%)	6/8 (75%)
First incidence (days)	560	229	322	167	229
Poly-3 test	P=0.002	P=0.156	P=0.592	P=0.027	P=0.007
Female					
Number Examined Microscopically	50	49	50	40	42
Infiltration Cellular, Histiocyte	12 (2.3)	11 (3.0)	21 (2.9)	12 (3.4)	10 (2.8)
Alveolar Epithelium, Hyperplasia	2 (1.5)	2 (2.0)	10* (2.0)	3 (2.7)	2 (2.0)
Alveolar/bronchiolar Adenoma, Multiple	0	3	1	0	0
Alveolar/bronchiolar Adenoma (includes multiple)	7	6	8	4	7
Alveolar/bronchiolar Carcinoma, Multiple	1	0	2	4	2
Alveolar/bronchiolar Carcinoma (includes multiple)	5	6	8	8	5
Alveolar/bronchiolar Adenoma or Carcinoma					
Overall rate	10/50 (20%)	11/49 (22%)	14/50 (28%)	12/40 (30%)	11/42 (26%)
Adjusted rate	27.7%	34.1%	36.4%	35.1%	36.1%
Terminal rate	5/20 (25%)	6/18 (33%)	9/24 (38%)	7/20 (35%)	8/19 (42%)
First incidence (days)	573	560	432	359	453
Poly-3 test	P=0.296	P=0.377	P=0.286	P=0.338	P=0.315

* Significantly different ($P \leq 0.05$) from the vehicle control group by the Poly-3 test
[a] No NTP historical tumor database for Swiss (CD-1®) mice is available
[b] Number of animals with lesion
[c] Average severity grade of lesions in affected animals: 1=minimal, 2=mild, 3=moderate, 4=marked
[d] Number of animals with neoplasm per number of animals with lung examined microscopically
[e] Poly-3 estimated neoplasm incidence after adjustment for intercurrent mortality
[f] Observed incidence at terminal kill
[g] Beneath the vehicle control incidence is the P value associated with the trend test. Beneath the exposed group incidence are the P values corresponding to pairwise comparisons between the vehicle controls and that exposed group. The Poly-3 test accounts for differential mortality in animals that do not reach terminal sacrifice.

alveolar spaces. Infiltrates were often most prevalent in alveoli adjacent to the lung neoplasms and are considered secondary to the presence of neoplasms in the lung.

Miscellaneous Changes: There were increases in the incidences of a number of nonneoplastic lesions in exposed mice, but their biological significance is uncertain. In general, the lesions occurred in one or more exposed groups, one sex, and were not related to exposure concentration (Tables A4 and B4). These lesions included hemorrhage of the mesenteric lymph node (vehicle control, 7/50; 50 mg/kg, 14/49; 100 mg/kg, 17/49; 200 mg/kg, 8/36; 300 mg/kg, 9/32), cystic hyperplasia of the glands of the glandular stomach (9/49, 13/50, 10/50, 15/37, 6/32), and lymphoid hyperplasia of the thymus (1/48, 1/45, 6/47, 1/33, 6/32) in males and fibrous osteodystrophy of the bone (2/50, 7/50, 9/50, 6/40, 4/42), pancreatic islet hyperplasia (2/50, 5/49, 6/49, 7/40, 10/41), nephropathy (29/50, 31/50, 41/50, 26/40, 33/42), cytoplasmic alteration of the acinar pancreas (0/50, 4/49, 0/49, 2/40, 4/41), pigmentation in the spleen (13/50, 24/50, 12/49, 10/40, 12/42), and cystic degeneration of the thyroid gland (26/50, 18/49, 39/50, 24/40, 29/42) in females.

Litter and Sire Effects

For lung neoplasms, the only exposure-related neoplasms, no litter effects were observed and no sire effects were observed (Table D2). Litter effects were detected for liver neoplasms and skin lesions when considering all pups. No sire effects were observed for liver neoplasms or skin lesions.

Genetic Toxicology

Micronucleus Frequencies in Male Pups

In independent reproductive toxicity studies conducted by NTP, Swiss (CD-1®) mouse pups exposed to AZT *in utero*, lactationally, and by gavage showed significant dose and exposure duration-dependent increases in the frequency of micronucleated polychromatic erythrocytes (MN-PCEs) in blood at all doses at all sampling times (Tables E1 and E2; Witt *et al.*, 2004). AZT-exposed pups sampled on postnatal day 8 showed a remarkable increase in MN-PCE frequency compared to pups sampled on postnatal days 1 and 4. The additional increase in the frequency of MN-PCEs in the postnatal day 8 pups is most likely the result of the direct gavage administration of AZT that began on postnatal day 4 and that supplemented the pups' lactational exposure to the chemical. Although high numbers of MN-PCEs were also observed at postnatal day 21 in the study using the Maalox TC® vehicle, the frequencies were notably lower than those observed in the pups sampled at postnatal day 8 (Table E1).

Percentage of PCEs in Male Pups

The data in Tables E1 and E2 show an extremely high percentage of PCEs in the blood of both vehicle control and treated pups. In healthy adult mice, the percentage of PCEs in peripheral blood is generally between 2% and 5%. In the newborn pups, the percentage of PCEs in blood was much higher, suggesting that at this stage of postnatal development there is a high rate of erythropoiesis. The data indicate that erythropoiesis is quite active through postnatal day 8. The reduction in the percentage of PCEs seen by postnatal day 21 (Table E1) may reflect a slowing of erythropoiesis as the pups mature.

The data in Tables E1 and E2, in addition to demonstrating a high rate of erythropoiesis in these pups, provide evidence for chemical-induced toxicity to the bone marrow. The treated pups at postnatal days 1, 4, and 8 show a decrease in the percentage of PCEs compared to the vehicle control group and this observation is typically an indication of bone marrow toxicity.

Micronucleus Frequencies and Percentage of PCEs in Dams

The micronucleus frequencies seen in the AZT-treated female mice were significantly elevated at all three dose levels, but they were notably lower than the frequencies seen in the AZT-treated pups sampled on postnatal days 8 and 21 (Tables E1 and E3; Witt *et al.*, 2004). As expected, the percentage of PCEs in the vehicle control dams was markedly lower than the percentage of PCEs in the vehicle control pups. Unlike the pups on postnatal day 8, the dams do not show a significant decrease in the percentage of PCEs with increasing dose of AZT. The small fluctuations in percentages of PCEs noted in AZT-treated adult female mice were not significant (Table E3).

DISCUSSION AND CONCLUSIONS

AZT is a transplacental carcinogen in CD-1® mice born to dams given AZT at oral doses estimated to be between 400 and 800 mg AZT/kg body weight per day (25 mg/day to the dam) on days 12 through 18 of gestation (Olivero *et al.*, 1997; Diwan *et al.*, 1999). During this time period, gestational organogenesis is being completed (Rice, 1973).

In the National Institute of Environmental Health Sciences (NIEHS) transplacental carcinogenicity study described in this report, oral doses of AZT were administered to CD-1® dams throughout pregnancy. To simulate the situation that often occurs in the clinic (USDHHS, 2004), this NIEHS study confirms that AZT is a transplacental carcinogen in CD-1® mice born to these dams and held without dosing for up to 24 months. The AZT-induced carcinogenic activity was seen at a lower dose (300 mg/kg per day) than used in a previous AZT transplacental carcinogenicity study (Olivero *et al.*, 1997; Diwan *et al.*, 1999). Increased incidences of alveolar/bronchiolar carcinoma and alveolar/bronchiolar adenoma or carcinoma (combined) were seen in the lung of AZT-treated male mice.

The increases in the incidences of alveolar/bronchiolar carcinoma and alveolar/bronchiolar adenoma or carcinoma (combined) in male mice were independent of litters. The lung neoplasms in male mice were considered evidence for a carcinogenic effect because the response was statistically significant, and there was a decreased time to the first incidence of these neoplasms in treated groups. In addition, the finding was supported by the AZT *in utero* studies where the lung was also a site for AZT treatment-related tumors (Olivero *et al.*, 1997; Diwan *et al.*, 1999). With some transplacental carcinogens Ki-*ras* mutations are seen in lung neoplasms (Miller *et al.*, 2000), but with the AZT-induced lung neoplasms reported by Olivero *et al.* (1997), there were no increases in *ras* mutations (Zhang *et al.*, 1998).

The 50, 100, 200, and 300 mg/kg doses given to F_0 mice in the present study correspond to approximately 150, 300, 600, and 900 mg/m^2 body surface area, respectively. Human doses are approximately 8 mg/kg or 296 mg/m^2 body surface area (Freireich *et al.*, 1966; PHSTF, 2004).

A previous transplacental AZT study reported treatment-related lung neoplasms in both male and female CD-1® mice (Olivero *et al.*, 1997; Diwan *et al.*, 1999). However, no dose-related increases in the incidences of lung neoplasms were seen in the AZT-treated female mice in the current study. The reason for this sex difference in the development of treatment-related lung neoplasms is not known.

In mice, transplacental carcinogenesis most often occurs in the nervous system, kidney, and lungs. For example, N-ethyl-nitrosourea and urethane are transplacental carcinogens in mice causing lung and/or brain neoplasms. Often, the site for transplacental carcinogenesis corresponds to the site where spontaneous neoplasms occur (Alexandrov, 1983). In the current study, there was a relatively high rate for spontaneous alveolar/bronchiolar adenomas and carcinomas in both male and female control mice, and this was also the site for AZT treatment-related neoplasms.

The NTP does not routinely use the CD-1® mouse; therefore, it does not have a historical control database. We are aware of two sources of historical control incidences in this strain. The Charles River Laboratories (2000) dataset reports spontaneous tumors in control CD-1® mice 78 weeks of age or more at study termination. Charles River reports the following incidences of alveolar/bronchiolar adenoma: males–mean 14.3%, range 2% to 42%; females–mean 8.5%, range 2% to 27%. For alveolar/bronchiolar carcinoma, Charles River reports the following incidences: males–mean 6.9%, range 1% to 26%; females–mean 4.1%, range 1% to 18%. The Charles River dataset does not provide a combined analysis of benign and malignant neoplasms. The Maita *et al.* (1988) dataset for CD-1® male mice indicated that 130/891 (14.5%) had lung adenoma and 168/891 (18.8%) had lung carcinoma. It is assumed that the vast majority of these lung neoplasms would be of alveolar/bronchiolar origin; they also did not include a combined analysis.

The mechanisms for the carcinogenic effects of AZT are probably related to how AZT is metabolized. AZT is metabolized by three pathways: glucuronidation, which accounts for up to 75% of the human urinary product; mixed-function oxidase-mediated reactions, giving 3′-amino-3′-deoxythymidine (AMT), a minor urinary metabolite; and phosphorylation, which occurs intracellularly. Synthesis of AMT is probably mediated by cytochrome P450 isozymes and NADPH-cytochrome P450 reductase. Phosphorylation is fundamental to the antiviral activity of AZT but accounts for only about 1% of its total disposition. Unchanged AZT constitutes about 20% of the human urinary products. In contrast, the unchanged drug in rats and mice accounts for up to 90% of the drug recovered in the urine (Doshi *et al.*, 1989; Patel *et al.*, 1989; de Miranda *et al.*, 1990).

AZT enters cells through passive diffusion. Once inside, it is converted by cellular thymidine kinase to AZT-5′-monophosphate. AZT-5′-monophosphate is then phosphorylated by thymidylate kinase to the 5′-diphosphate and then by pyrimidine nucleoside diphosphate kinase to the 5′-triphosphate. Because 5′-monophosphate is a poor substrate for thymidylate kinase, this is the rate-limiting step in the formation of AZT-triphosphate. Measurement of peripheral blood mononuclear cells (a heterogeneous population of lymphocytes and monocytes obtained from whole blood) has been used to determine AZT phosphorylation in patients. AZT-triphosphate may contribute up to 30% of the total amount of phosphorylated AZT (Stretcher, 1995). The formation of AZT-triphosphate is a complex function dependent on genetic factors and cell type.

Many studies have failed to find a correlation between profiles of AZT in plasma and clinical effects (Stretcher, 1995), because the clinical efficacy/toxicity of AZT is related to the intracellular concentration of phosphorylated AZT. This finding is supported by a number of studies that show the plasma profile of AZT provides limited information on clinical efficacy/toxicity (Stretcher, 1995). The critical step in the cancer potential of AZT is probably also related to the phosphorylation processes.

Triphosphorylated AZT is incorporated into nuclear and mitochondrial DNA in mammalian cells and causes mutations primarily by inducing large deletions. This is consistent with AZT's action as a DNA chain terminator. AZT can also cause mutations and loss of heterozygosity in mammalian cells (Meng *et al.*, 2000a,b,c). AZT has been shown to cause oxidative damage in CD-1® mice after transplacental exposure as measured by an increase in 8-oxo-2′-deoxyguanosine in the liver and kidney (but not in the lung) (Bialkowska *et al.*, 2000). These authors suggest that the oxidative damage may be a result of AZT damage to mitochondria, resulting in an increase in reactive oxygen species.

All phosphorylated forms of AZT may contribute to the toxicity of the chemical. AZT-monophosphate has been shown to interfere with protein glycosylation, exonuclease repair of DNA, and the RNAse activity of reverse transcriptase (Stretcher, 1995). *In vitro* studies indicate that AMT is also toxic to human hematopoietic progenitor cells (Veal and Back, 1995).

The current transplacental carcinogenicity study did not measure AZT incorporation into DNA. However, further studies to investigate the relationship between AZT pharmacokinetics and AZT incorporation into DNA would help in the understanding of the AZT transplacental carcinogenesis processes.

In the previous NCI study, in addition to lung neoplasms, transplacental exposure to AZT increased the incidences of liver neoplasms in male offspring and reproductive organ neoplasms in female offspring (Olivero *et al.*, 1997; Diwan *et al.*, 1999). The current transplacental carcinogenicity study did not find evidence for treatment-related liver or reproductive organ neoplasms.

AZT has a relatively high rate of incorporation into liver and lung nuclear and mitochondrial DNA after transplacental exposure (Olivero *et al.*, 1997); this information on DNA incorporation into lung and liver nuclear DNA was from a study of only one litter. In this litter, the incorporation of AZT into lung DNA was about twice the incorporation of AZT into liver DNA. This may explain why the lung, but not the liver, was a target for transplacental carcinogenicity in the current study. The exposure concentrations used in the current transplacental carcinogenicity study were lower than those used in the NCI studies; accordingly, there might not have been a sufficient exposure to AZT to reach the critical liver AZT concentrations necessary for a carcinogenic response.

There have been no reports of AZT causing cancer in humans. Cancer takes time to develop, and further follow-up of patients is ongoing to determine any association between AZT (and other retroviral drugs) and long-term adverse effects, including cancer.

Administration of AZT to pregnant female Swiss CD-1® mice also resulted in diminished reproductive parameters for the F_0 generation (see Appendix C). This included treatment-related declines in pregnancy rates, average litter size, and average number of implantation sites, and a dose-related increase in the average number of resorptions. AZT exposure *in utero* has been shown to induce significant dose-related increases in the frequency of micronucleated erythrocytes in blood of male pups born to dams dosed throughout pregnancy (Witt *et al.*, 2004). This is an indication that AZT can cause genetic damage in the fetus. This AZT-induced genetic damage in the fetus is thought to be related to the diminished reproductive endpoints in the AZT-treated dams in the current study.

CONCLUSIONS

Under the conditions of this study, there was *clear evidence of carcinogenic activity** in F_1 male mice exposed transplacentally to AZT based on increased incidences of alveolar/bronchiolar neoplasms. There was *no evidence of carcinogenic* activity in F_1 female mice exposed transplacentally to AZT at 50, 100, 200, or 300 mg/kg.

Reproductive toxicity in the form of decreased litter size and fertility rates was observed in dams in the 200 and 300 mg AZT/kg dose groups.

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

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APPENDIX A
SUMMARY OF LESIONS
IN MALE SWISS (CD-1®) MICE
IN THE TRANSPLACENTAL STUDY OF AZT

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TABLE A1
Summary of the Incidence of Neoplasms in Male Swiss (CD-1®) Mice in the Transplacental Study of AZT[a]

	Vehicle Control	50 mg/kg	100 mg/kg	200 mg/kg	300 mg/kg
Disposition Summary					
Animals initially in study	50	50	50	37	32
Early deaths					
Accidental deaths			1		2
Moribund	23	21	25	23	12
Natural deaths	8	9	11	6	10
Survivors					
Died last week of study					1
Terminal sacrifice	19	20	13	7	7
Other				1	
Animals examined microscopically	50	50	50	37	32
Alimentary System					
Gallbladder	(45)	(46)	(46)	(33)	(27)
Intestine large, colon	(48)	(50)	(49)	(37)	(32)
Intestine large, cecum	(49)	(49)	(48)	(35)	(30)
Intestine small, duodenum	(49)	(50)	(49)	(36)	(32)
Polyp adenomatous	1 (2%)				
Intestine small, jejunum	(49)	(50)	(46)	(36)	(29)
Intestine small, ileum	(49)	(48)	(47)	(35)	(30)
Liver	(50)	(50)	(50)	(37)	(32)
Hemangiosarcoma	7 (14%)	4 (8%)	3 (6%)	1 (3%)	3 (9%)
Hepatoblastoma	1 (2%)		2 (4%)		
Hepatocellular carcinoma	4 (8%)	5 (10%)	5 (10%)	2 (5%)	1 (3%)
Hepatocellular carcinoma, multiple	2 (4%)	1 (2%)	1 (2%)	2 (5%)	1 (3%)
Hepatocellular adenoma	12 (24%)	5 (10%)	5 (10%)	5 (14%)	4 (13%)
Hepatocellular adenoma, multiple	2 (4%)	6 (12%)	5 (10%)	3 (8%)	
Hepatocholangiocarcinoma					1 (3%)
Pancreas	(50)	(50)	(50)	(37)	(31)
Salivary glands	(50)	(50)	(50)	(37)	(32)
Carcinoma		1 (2%)			
Stomach, forestomach	(49)	(50)	(50)	(37)	(32)
Squamous cell papilloma				1 (3%)	
Stomach, glandular	(49)	(50)	(50)	(37)	(32)
Adenoma					1 (3%)
Cardiovascular System					
Heart	(50)	(50)	(50)	(37)	(32)
Alveolar/bronchiolar carcinoma, metastatic, lung				1 (3%)	
Sarcoma				1 (3%)	
Endocrine System					
Adrenal cortex	(50)	(50)	(50)	(37)	(32)
Adenoma	2 (4%)		1 (2%)	1 (3%)	
Subcapsular, adenoma				2 (5%)	
Adrenal medulla	(50)	(50)	(49)	(37)	(32)
Pheochromocytoma benign			1 (2%)		
Islets, pancreatic	(50)	(50)	(50)	(36)	(31)
Adenoma	1 (2%)				

Table A1
Summary of the Incidence of Neoplasms in Male Swiss (CD-1®) Mice in the Transplacental Study of AZT

	Vehicle Control	50 mg/kg	100 mg/kg	200 mg/kg	300 mg/kg
Endocrine System (continued)					
Pituitary gland	(48)	(49)	(49)	(36)	(31)
Schwannoma malignant, metastatic, brain	1 (2%)		1 (2%)		
Pars distalis, adenoma		1 (2%)			
Thyroid gland	(50)	(50)	(50)	(37)	(32)
Follicular cell, adenoma				1 (3%)	
General Body System					
None					
Genital System					
Epididymis	(50)	(50)	(50)	(37)	(32)
Prostate	(50)	(50)	(50)	(37)	(32)
Seminal vesicle	(50)	(50)	(50)	(37)	(32)
Testes	(50)	(50)	(50)	(37)	(32)
Hemangioma			1 (2%)		
Hemangiosarcoma			1 (2%)		
Bilateral, interstitial cell, carcinoma				1 (3%)	
Interstitial cell, adenoma				1 (3%)	
Hematopoietic System					
Bone marrow	(50)	(50)	(50)	(37)	(32)
Hemangiosarcoma		1 (2%)			
Lymph node	(12)	(10)	(15)	(6)	(2)
Mediastinal, alveolar/bronchiolar carcinoma, metastatic, lung				1 (17%)	
Mediastinal, hemangiosarcoma			1 (7%)		
Lymph node, mandibular	(50)	(50)	(49)	(37)	(32)
Lymph node, mesenteric	(50)	(49)	(49)	(36)	(32)
Spleen	(49)	(50)	(50)	(37)	(32)
Hemangiosarcoma	3 (6%)	2 (4%)	1 (2%)		1 (3%)
Thymus	(48)	(45)	(47)	(33)	(32)
Integumentary System					
Skin	(50)	(50)	(50)	(37)	(32)
Squamous cell papilloma				1 (3%)	
Subcutaneous tissue, basal cell carcinoma		1 (2%)			
Subcutaneous tissue, fibrosarcoma		1 (2%)			
Subcutaneous tissue, fibrous histiocytoma				1 (3%)	
Subcutaneous tissue, hemangiosarcoma			1 (2%)		
Subcutaneous tissue, schwannoma malignant			1 (2%)		
Musculoskeletal System					
Bone	(50)	(50)	(50)	(37)	(32)
Schwannoma malignant, metastatic, brain			1 (2%)		
Skeletal muscle	(1)	(2)	(1)	(3)	(2)
Alveolar/bronchiolar carcinoma, metastatic, lung		1 (50%)		1 (33%)	1 (50%)
Hemangioma		1 (50%)			
Hemangiosarcoma				1 (33%)	

Table A1
Summary of the Incidence of Neoplasms in Male Swiss (CD-1®) Mice in the Transplacental Study of AZT

	Vehicle Control		50 mg/kg		100 mg/kg		200 mg/kg		300 mg/kg	
Nervous System										
Brain	(49)		(50)		(50)		(37)		(32)	
Oligodendroglioma malignant									1	(3%)
Schwannoma malignant					1	(2%)				
Cranial nerve, schwannoma malignant	1	(2%)								
Respiratory System										
Lung	(50)		(50)		(50)		(37)		(32)	
Alveolar/bronchiolar adenoma	7	(14%)	13	(26%)	8	(16%)	8	(22%)	10	(31%)
Alveolar/bronchiolar adenoma, multiple	3	(6%)					1	(3%)	1	(3%)
Alveolar/bronchiolar carcinoma	4	(8%)	6	(12%)	5	(10%)	5	(14%)	5	(16%)
Alveolar/bronchiolar carcinoma, multiple	1	(2%)	5	(10%)	1	(2%)	6	(16%)	3	(9%)
Hepatocellular carcinoma, metastatic, liver	1	(2%)								
Nose	(50)		(50)		(50)		(36)		(32)	
Special Senses System										
Harderian gland	(50)		(50)		(49)		(37)		(32)	
Adenoma	11	(22%)	8	(16%)	9	(18%)	3	(8%)	4	(13%)
Carcinoma					1	(2%)			1	(3%)
Urinary System										
Kidney	(50)		(50)		(50)		(37)		(32)	
Renal tubule, adenoma			1	(2%)						
Urinary bladder	(50)		(50)		(50)		(37)		(32)	
Systemic Lesions										
Multiple organs[b]	(50)		(50)		(50)		(37)		(32)	
Lymphoma malignant	6	(12%)	9	(18%)	7	(14%)	4	(11%)	3	(9%)
Neoplasm Summary										
Total animals with primary neoplasms[c]	35		35		34		25		26	
Total primary neoplasms	68		71		61		51		40	
Total animals with benign neoplasms	27		23		27		18		16	
Total benign neoplasms	39		35		30		27		20	
Total animals with malignant neoplasms	19		27		20		20		17	
Total malignant neoplasms	29		36		31		24		20	
Total animals with metastatic neoplasms	2		1		1		1		1	
Total metastatic neoplasms	2		1		2		3		1	

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

TABLE A2
Individual Animal Tumor Pathology of Male Swiss (CD-1®) Mice in the Transplacental Study of AZT: Vehicle Control

Number of Days on Study	104	111	308	322	329	329	373	392	413	418	446	453	463	475	486	488	497	532	538	560	565	567	601	603	614
Carcass ID Number	216	197	198	320	209	210	331	205	325	215	334	199	330	341	204	712	217	335	200	323	319	333	329	321	328
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder	+	+	+	+	+	+	A	+	+	A	+	+	M	+	+	+	+	+	+	+	+	+	+	A	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+
Polyp adenomatous																							X		
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+
Intestine small, ileum	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma							X	X					X									X	X		X
Hepatoblastoma																X									
Hepatocellular carcinoma																	X								
Hepatocellular carcinoma, multiple								X														X			
Hepatocellular adenoma											X				X	X					X				X
Hepatocellular adenoma, multiple																									
Mesentery																									
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cardiovascular System																									
Blood vessel										+															
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma									X																
Parathyroid gland	+	M	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pituitary gland	+	I	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Schwannoma malignant, metastatic, brain																									
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
General Body System																									
None																									

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

TABLE A2
Individual Animal Tumor Pathology of Male Swiss (CD-1®) Mice in the Transplacental Study of AZT: Vehicle Control

Number of Days on Study	619	621	635	641	654	661	668	668	669	670	670	670	671	671	671	672	672	675	676	677	677	678	678	678	678	
Carcass ID Number	203	201	214	332	206	326	321	339	342	322	324	336	318	337	338	327	340	208	202	207	213	193	194	195	212	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder	+	+	+	+	I	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Polyp adenomatous																										1
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma																								X		7
Hepatoblastoma																										1
Hepatocellular carcinoma	X																		X					X		4
Hepatocellular carcinoma, multiple																										2
Hepatocellular adenoma	X						X	X					X							X			X		X	12
Hepatocellular adenoma, multiple									X										X							2
Mesentery												+														1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	49
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Cardiovascular System																										
Blood vessel																										1
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma													X	X												2
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma																										1
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Pituitary gland	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Schwannoma malignant, metastatic, brain		X																								1
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
General Body System																										
None																										

TABLE A2
Individual Animal Tumor Pathology of Male Swiss (CD-1®) Mice in the Transplacental Study of AZT: Vehicle Control

Number of Days on Study	104	111	308	322	329	329	373	392	413	418	446	453	463	475	486	488	497	532	538	560	565	567	601	603	614
Carcass ID Number	216	197	198	320	209	210	331	205	325	215	334	199	330	341	204	712	217	335	200	323	319	333	329	213	328
Genital System																									
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node		+	+	+	+	+			+	+		+				+							+		
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma							X	X														X			
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skeletal muscle										+															
Nervous System																									
Brain	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cranial nerve, schwannoma malignant																									
Peripheral nerve				+		+								+					+				+		
Spinal cord	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																				X	X			X	
Alveolar/bronchiolar adenoma, multiple																									
Alveolar/bronchiolar carcinoma																									
Alveolar/bronchiolar carcinoma, multiple																									
Hepatocellular carcinoma, metastatic, liver								X																	
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Harderian gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma												X			X	X									

TABLE A2
Individual Animal Tumor Pathology of Male Swiss (CD-1®) Mice in the Transplacental Study of AZT: Vehicle Control

Number of Days on Study	619	621	635	641	654	661	668	668	669	670	670	670	671	671	671	672	672	675	676	677	677	678	678	678	678	
Carcass ID Number	203	201	214	332	206	326	321	339	342	322	324	336	318	337	338	327	340	208	202	207	213	193	194	195	212	Total Tissues/ Tumors
Genital System																										
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node						+							+													12
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Hemangiosarcoma																										3
Thymus	M	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Skeletal muscle																										1
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Cranial nerve, schwannoma malignant		X																								1
Peripheral nerve		+			+																					7
Spinal cord	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma							X				X										X				X	7
Alveolar/bronchiolar adenoma, multiple		X	X																	X						3
Alveolar/bronchiolar carcinoma	X	X													X							X				4
Alveolar/bronchiolar carcinoma, multiple				X																						1
Hepatocellular carcinoma, metastatic, liver																										1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
Harderian gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma				X	X	X	X							X					X				X		X	11

TABLE A2
Individual Animal Tumor Pathology of Male Swiss (CD-1®) Mice in the Transplacental Study of AZT: Vehicle Control

Number of Days on Study	104	111	308	322	329	329	373	392	413	418	446	453	463	475	486	488	497	532	538	560	565	567	601	603	614
Carcass ID Number	216	197	198	320	209	210	331	205	325	215	334	199	330	341	204	712	217	335	200	323	319	333	329	211	328
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Ureter															M										
Urethra																									
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant									X							X				X			X		

TABLE A2
Individual Animal Tumor Pathology of Male Swiss (CD-1®) Mice in the Transplacental Study of AZT: Vehicle Control

Number of Days on Study	619	621	635	641	654	661	668	668	669	670	670	670	671	671	671	672	672	675	676	677	677	678	678	678	678	
Carcass ID Number	203	201	214	332	206	326	321	339	342	322	324	336	318	337	338	327	340	208	202	207	213	193	194	195	212	Total Tissues/ Tumors
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Ureter																										
Urethra				+																						1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymphoma malignant						X							X													6

Table A2
Individual Animal Tumor Pathology of Male Swiss (CD-1®) Mice in the Transplacental Study of AZT: 50 mg/kg

Number of Days on Study	045	147	157	168	229	236	254	300	322	322	329	363	385	418	432	444	467	475	479	495	523	562	567	580	588
Carcass ID Number	344	238	346	361	235	730	240	359	234	357	230	358	356	222	225	362	366	347	363	221	237	734	343	723	367
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder	+	+	+	+	+	A	+	+	A	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	+	+	+	A	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma													X											X	
Hepatocellular carcinoma																X									
Hepatocellular carcinoma, multiple																									
Hepatocellular adenoma																									
Hepatocellular adenoma, multiple																									
Mesentery												+													
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma																									
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tooth																									
Cardiovascular System																									
Blood vessel									+																
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pituitary gland	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma																									
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
General Body System																									
None																									
Genital System																									
Coagulating gland																									
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Penis																			+				+		
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

TABLE A2
Individual Animal Tumor Pathology of Male Swiss (CD-1®) Mice in the Transplacental Study of AZT: 50 mg/kg

Number of Days on Study	592	595	624	640	668	668	670	670	670	671	671	671	672	676	677	677	678	678	678	678	679	679	679	679	679	
Carcass ID Number	239	726	365	349	352	732	353	355	725	350	354	364	360	219	228	229	218	224	233	242	227	231	232	236	241	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma	X																					X				4
Hepatocellular carcinoma	X														X		X	X								5
Hepatocellular carcinoma, multiple										X																1
Hepatocellular adenoma			X								X			X							X	X				5
Hepatocellular adenoma, multiple		X						X	X				X					X		X						6
Mesentery																+										2
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma													X													1
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Tooth																	+									1
Cardiovascular System																										
Blood vessel																										1
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pars distalis, adenoma								X																		1
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
General Body System																										
None																										
Genital System																										
Coagulating gland				+												+										2
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Penis																										2
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50

TABLE A2
Individual Animal Tumor Pathology of Male Swiss (CD-1®) Mice in the Transplacental Study of AZT: 50 mg/kg

Number of Days on Study	045	147	157	168	229	236	254	300	322	322	329	363	385	418	432	444	467	475	479	495	523	562	567	580	588
Carcass ID Number	344	238	346	361	235	730	240	359	234	357	230	358	356	222	225	362	366	347	363	221	237	734	343	723	367
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																									
Lymph node									+	+	+						+		+	+			+		+
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																								X	
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	M	+
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Subcutaneous tissue, basal cell carcinoma			X																						
Subcutaneous tissue, fibrosarcoma					X																				
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skeletal muscle																				+					
Alveolar/bronchiolar carcinoma, metastatic, lung																				X					
Hemangioma																									
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Peripheral nerve																		+						+	+
Spinal cord	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma					X									X		X	X			X				X	X
Alveolar/bronchiolar carcinoma																						X			X
Alveolar/bronchiolar carcinoma, multiple												X						X		X					
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Eye																							+		
Harderian gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																					X			X	X

TABLE A2
Individual Animal Tumor Pathology of Male Swiss (CD-1®) Mice in the Transplacental Study of AZT: 50 mg/kg

Number of Days on Study	592	595	624	640	668	668	670	670	670	671	671	671	672	676	677	677	678	678	678	678	679	679	679	679	679	
Carcass ID Number	239	726	365	349	352	732	353	355	725	350	354	364	360	219	228	229	218	224	233	242	227	231	232	236	241	Total Tissues/ Tumors
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma															X											1
Lymph node		+															+									10
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma													X													2
Thymus	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	I	+	+	+	M	+	+	+	45
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Subcutaneous tissue, basal cell carcinoma																										1
Subcutaneous tissue, fibrosarcoma																										1
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Skeletal muscle								+																		2
Alveolar/bronchiolar carcinoma, metastatic, lung																										1
Hemangioma								X																		1
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Peripheral nerve			+																							4
Spinal cord	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma				X			X	X														X		X	X	13
Alveolar/bronchiolar carcinoma							X		X	X			X													6
Alveolar/bronchiolar carcinoma, multiple				X																X						5
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
Eye																										1
Harderian gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma				X				X	X				X	X												8

TABLE A2
Individual Animal Tumor Pathology of Male Swiss (CD-1®) Mice in the Transplacental Study of AZT: 50 mg/kg

Number of Days on Study	045	147	157	168	229	236	254	300	322	322	329	363	385	418	432	444	467	475	479	495	523	562	567	580	588
Carcass ID Number	344	238	346	361	235	730	240	359	234	357	330	358	356	322	225	362	366	347	363	221	237	734	343	723	367
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Renal tubule, adenoma																									
Ureter																									
Urethra															+							+			
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant									X										X	X			X		X

TABLE A2
Individual Animal Tumor Pathology of Male Swiss (CD-1®) Mice in the Transplacental Study of AZT: 50 mg/kg

Number of Days on Study	592	595	624	640	668	668	670	670	670	671	671	671	672	676	677	677	678	678	678	678	679	679	679	679	679	
Carcass ID Number	239	726	365	349	352	732	353	355	725	350	354	364	360	219	228	229	218	224	233	242	227	231	232	236	241	Total Tissues/ Tumors
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Renal tubule, adenoma																									X	1
Ureter						+			+						+											3
Urethra						+												+								4
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymphoma malignant		X	X																	X					X	9

TABLE A2
Individual Animal Tumor Pathology of Male Swiss (CD-1®) Mice in the Transplacental Study of AZT: 100 mg/kg

Number of Days on Study	147	187	214	229	243	308	315	320	322	376	376	413	434	447	481	482	489	490	505	510	532	536	538	544	546
Carcass ID Number	373	376	383	381	252	245	390	249	391	378	727	389	728	257	250	256	255	267	264	308	377	247	261	265	384
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	A	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+
Intestine small, jejunum	+	A	+	+	+	+	+	+	+	+	A	+	M	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	A	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																X									
Hepatoblastoma												X													
Hepatocellular carcinoma																					X	X			
Hepatocellular carcinoma, multiple												X													
Hepatocellular adenoma																									
Hepatocellular adenoma, multiple																			X					X	
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cardiovascular System																									
Blood vessel																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	I	+	+	+	+	+
Pheochromocytoma benign																									
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Schwannoma malignant, metastatic, brain										X															
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
General Body System																									
None																									

TABLE A2
Individual Animal Tumor Pathology of Male Swiss (CD-1®) Mice in the Transplacental Study of AZT: 100 mg/kg

Number of Days on Study	567	570	598	605	606	607	608	627	631	633	648	651	668	668	669	670	670	670	671	671	672	675	675	678	678	
Carcass ID Number	392	385	243	388	266	246	263	387	258	375	248	251	368	370	372	369	374	386	379	382	371	244	254	253	262	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	49
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, jejunum	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Intestine small, ileum	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma						X																			X	3
Hepatoblastoma						X																				2
Hepatocellular carcinoma		X				X												X								5
Hepatocellular carcinoma, multiple																										1
Hepatocellular adenoma	X			X					X		X									X						5
Hepatocellular adenoma, multiple															X						X	X				5
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cardiovascular System																										
Blood vessel										+																1
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma							X																			1
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pheochromocytoma benign																									X	1
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	M	+	M	+	+	+	+	+	+	+	+	+	M	47
Pituitary gland	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Schwannoma malignant, metastatic, brain																										1
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
General Body System																										
None																										

TABLE A2
Individual Animal Tumor Pathology of Male Swiss (CD-1®) Mice in the Transplacental Study of AZT: 100 mg/kg

Number of Days on Study	147	187	214	229	243	308	315	320	322	376	376	413	434	447	481	482	489	490	505	510	532	536	538	544	546
Carcass ID Number	373	376	383	381	252	245	390	249	391	378	727	389	728	257	250	256	255	267	264	380	377	247	261	265	384
Genital System																									
Coagulating gland																								+	
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Penis																									
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangioma																									
Hemangiosarcoma																									
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node	+				+			+	+				+												
Mediastinal, hemangiosarcoma																									
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																									
Thymus	M	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Subcutaneous tissue, hemangiosarcoma																X									
Subcutaneous tissue, schwannoma, malignant																									
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Schwannoma malignant, metastatic, brain										X															
Skeletal muscle	+																								
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Schwannoma malignant										X															
Peripheral nerve	+												+										+		+
Spinal cord	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma									X												X				X
Alveolar/bronchiolar carcinoma																X									
Alveolar/bronchiolar carcinoma, multiple																									X
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

TABLE A2
Individual Animal Tumor Pathology of Male Swiss (CD-1®) Mice in the Transplacental Study of AZT: 100 mg/kg

Number of Days on Study	567	570	598	605	606	607	608	627	631	633	648	651	668	668	669	670	670	670	671	671	672	675	675	678	678	
Carcass ID Number	392	385	243	388	266	246	263	387	258	375	248	251	368	370	372	369	374	386	379	382	371	244	254	253	262	Total Tissues/ Tumors
Genital System																										
Coagulating gland										+																2
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Penis									+																	1
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangioma													X													1
Hemangiosarcoma																									X	1
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node	+			+		+	+	+	+		+		+						+	+						15
Mediastinal, hemangiosarcoma											X															1
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	I	+	+	+	49
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma																									X	1
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	47
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Subcutaneous tissue, hemangiosarcoma																										1
Subcutaneous tissue, schwannoma, malignant												X														1
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Schwannoma malignant, metastatic, brain																										1
Skeletal muscle																										1
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Schwannoma malignant																										1
Peripheral nerve						+	+		+																	7
Spinal cord	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma		X								X			X				X	X								8
Alveolar/bronchiolar carcinoma														X	X								X	X		5
Alveolar/bronchiolar carcinoma, multiple																										1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50

TABLE A2
Individual Animal Tumor Pathology of Male Swiss (CD-1®) Mice in the Transplacental Study of AZT: 100 mg/kg

Number of Days on Study	147	187	214	229	243	308	315	320	322	376	376	413	434	447	481	482	489	490	505	510	532	536	538	544	546
Carcass ID Number	373	376	383	381	252	245	390	249	391	378	727	389	728	257	250	256	255	267	264	380	377	247	261	265	384
Special Senses System																									
Eye																									
Harderian gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma												X										X			
Carcinoma																									
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Ureter																									
Urethra									+		+				+										+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant		X											X					X			X				

TABLE A2
Individual Animal Tumor Pathology of Male Swiss (CD-1®) Mice in the Transplacental Study of AZT: 100 mg/kg

Number of Days on Study	567	570	598	605	606	607	608	627	631	633	648	651	668	668	669	670	670	670	671	671	672	675	675	678	678	
Carcass ID Number	392	385	243	388	266	246	263	387	258	375	248	251	368	370	372	369	374	386	379	382	371	244	254	253	262	Total Tissues/ Tumors
Special Senses System																										
Eye																									+	1
Harderian gland	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenoma	X					X	X	X								X							X	X		9
Carcinoma															X											1
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Ureter																		+								1
Urethra																	+									5
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymphoma malignant	X										X							X								7

TABLE A2
Individual Animal Tumor Pathology of Male Swiss (CD-1®) Mice in the Transplacental Study of AZT: 200 mg/kg

Number of Days on Study	157	159	167	298	301	320	329	329	341	382	419	434	483	501	531	539	549	563	580	589	599	607	608	612	624
Carcass ID Number	278	273	281	398	403	276	279	280	287	402	286	285	395	397	282	274	404	275	277	406	408	271	283	268	272
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder	A	A	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	M	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																						X			
Hepatocellular carcinoma																		X							
Hepatocellular carcinoma, multiple													X												
Hepatocellular adenoma													X										X		
Hepatocellular adenoma, multiple																			X						
Mesentery												+									+				
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell papilloma																									
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cardiovascular System																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar carcinoma, metastatic, lung																							X		
Sarcoma																									
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Subcapsular, adenoma																									
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid gland	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	I	+	+	+	+	+	+
Pituitary gland	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell, adenoma																									
General Body System																									
None																									

TABLE A2
Individual Animal Tumor Pathology of Male Swiss (CD-1®) Mice in the Transplacental Study of AZT: 200 mg/kg

Number of Days on Study	625	631	631	647	662	668	670	670	671	676	678	679	
Carcass ID Number	405	270	400	399	394	396	393	407	401	284	269	288	Total Tissues/ Tumors
Alimentary System													
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	37
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	+	33
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	37
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	37
Intestine large, cecum	+	+	+	+	M	+	+	+	+	+	+	+	35
Intestine small, duodenum	+	+	+	+	+	+	M	+	+	+	+	+	36
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	36
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	35
Liver	+	+	+	+	+	+	+	+	+	+	+	+	37
Hemangiosarcoma													1
Hepatocellular carcinoma	X												2
Hepatocellular carcinoma, multiple			X										2
Hepatocellular adenoma	X					X	X						5
Hepatocellular adenoma, multiple					X						X		3
Mesentery	+												3
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	37
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	37
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	37
Squamous cell papilloma				X									1
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	37
Cardiovascular System													
Heart	+	+	+	+	+	+	+	+	+	+	+	+	37
Alveolar/bronchiolar carcinoma, metastatic, lung													1
Sarcoma				X									1
Endocrine System													
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	37
Adenoma								X					1
Subcapsular, adenoma										X		X	2
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	37
Islets, pancreatic	+	+	+	+	+	+	+	+	M	+	+	+	36
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	35
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	36
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	37
Follicular cell, adenoma					X								1
General Body System													
None													

Table A2
Individual Animal Tumor Pathology of Male Swiss (CD-1®) Mice in the Transplacental Study of AZT: 200 mg/kg

Number of Days on Study	157	159	167	298	301	320	329	329	341	382	419	434	483	501	531	539	549	563	580	589	599	607	608	612	624
Carcass ID Number	278	273	281	398	403	276	279	280	287	402	286	285	395	397	282	274	404	275	277	406	408	271	283	268	272
Genital System																									
Coagulating gland																									
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Penis									+						+						+				
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Bilateral, interstitial cell, carcinoma										X															
Interstitial cell, adenoma														X											
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node				+			+	+															+		
Mediastinal, alveolar/bronchiolar carcinoma, metastatic, lung																							X		
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	+	+	+	+	M	+	M	+	+	+	+	+	+	+	+	+	+	+	+	I	+	+
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell papilloma																									
Subcutaneous tissue, fibrous histiocytoma																									
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skeletal muscle																							+		
Alveolar/bronchiolar carcinoma, metastatic, lung																							X		
Hemangiosarcoma																									
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Peripheral nerve								+				+					+					+	+		
Spinal cord	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma			X							X			X				X		X						
Alveolar/bronchiolar adenoma, multiple																									
Alveolar/bronchiolar carcinoma																	X					X	X		
Alveolar/bronchiolar carcinoma, multiple									X			X		X					X						
Nose	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

TABLE A2
Individual Animal Tumor Pathology of Male Swiss (CD-1®) Mice in the Transplacental Study of AZT: 200 mg/kg

Number of Days on Study	625	631	631	647	662	668	670	670	671	676	678	679	
Carcass ID Number	405	270	400	399	394	396	393	407	401	284	269	268	Total Tissues/ Tumors
Genital System													
Coagulating gland											+		1
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	37
Penis													3
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	37
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	37
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	37
Testes	+	+	+	+	+	+	+	+	+	+	+	+	37
Bilateral, interstitial cell, carcinoma													1
Interstitial cell, adenoma													1
Hematopoietic System													
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	37
Lymph node	+			+									6
Mediastinal, alveolar/bronchiolar carcinoma, metastatic, lung													1
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	37
Lymph node, mesenteric	+	+	+	+	+	M	+	+	+	+	+	+	36
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	37
Thymus	+	+	M	+	+	+	+	+	+	+	+	+	33
Integumentary System													
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	37
Skin	+	+	+	+	+	+	+	+	+	+	+	+	37
Squamous cell papilloma		X											1
Subcutaneous tissue, fibrous, histiocytoma							X						1
Musculoskeletal System													
Bone	+	+	+	+	+	+	+	+	+	+	+	+	37
Skeletal muscle			+				+						3
Alveolar/bronchiolar carcinoma, metastatic, lung													1
Hemangiosarcoma							X						1
Nervous System													
Brain	+	+	+	+	+	+	+	+	+	+	+	+	37
Peripheral nerve		+	+										7
Spinal cord	+	+	+	+	+	+	+	+	+	+	+	+	37
Respiratory System													
Lung	+	+	+	+	+	+	+	+	+	+	+	+	37
Alveolar/bronchiolar adenoma		X					X	X					8
Alveolar/bronchiolar adenoma, multiple	X												1
Alveolar/bronchiolar carcinoma					X	X							5
Alveolar/bronchiolar carcinoma, multiple										X		X	6
Nose	+	+	+	+	+	+	+	+	+	+	+	+	36
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	37

TABLE A2
Individual Animal Tumor Pathology of Male Swiss (CD-1®) Mice in the Transplacental Study of AZT: 200 mg/kg

Number of Days on Study	157	159	167	298	301	320	329	329	341	382	419	434	483	501	531	539	549	563	580	589	599	607	608	612	624
Carcass ID Number	278	273	281	398	403	276	279	280	287	402	286	285	395	397	282	274	404	275	277	406	408	271	283	268	272
Special Senses System																									
Harderian gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma														X											
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Ureter																									
Urethra																				+				+	
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant																				X	X	X			

TABLE A2
Individual Animal Tumor Pathology of Male Swiss (CD-1®) Mice in the Transplacental Study of AZT: 200 mg/kg

Number of Days on Study	625	631	631	647	662	668	670	670	671	676	678	679	
Carcass ID Number	405	270	400	399	394	396	393	407	401	284	269	288	Total Tissues/ Tumors
Special Senses System													
Harderian gland	+	+	+	+	+	+	+	+	+	+	+	+	37
Adenoma		X							X				3
Urinary System													
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	37
Ureter										+			1
Urethra				+									3
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	37
Systemic Lesions													
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	37
Lymphoma malignant	X												4

TABLE A2
Individual Animal Tumor Pathology of Male Swiss (CD-1®) Mice in the Transplacental Study of AZT: 300 mg/kg

Number of Days on Study	041	041	192	229	329	329	329	376	404	473	488	495	538	539	563	569	593	627	634	635	638	640	655	661	668
Carcass ID Number	316	317	300	423	298	306	308	307	421	315	424	297	294	422	312	418	302	420	303	309	311	295	305	314	419
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder	+	+	+	+	+	+	+	A	A	+	+	+	+	A	+	+	+	+	+	+	A	A	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	A	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	A	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+
Intestine small, ileum	A	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma									X				X												
Hepatocellular carcinoma										X															
Hepatocellular carcinoma, multiple											X														
Hepatocellular adenoma																		X					X		
Hepatocholangiocarcinoma																							X		
Mesentery																									
Pancreas	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																					X				
Cardiovascular System																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islets, pancreatic	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid gland	+	M	+	+	+	+	I	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
General Body System																									
None																									
Genital System																									
Coagulating gland				+																					
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Penis																	+								
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

TABLE A2
Individual Animal Tumor Pathology of Male Swiss (CD-1®) Mice in the Transplacental Study of AZT: 300 mg/kg

Number of Days on Study	673	676	677	677	678	678	678	
Carcass ID Number	310	304	293	296	299	301	313	Total Tissues/ Tumors
Alimentary System								
Esophagus	+	+	+	+	+	+	+	32
Gallbladder	+	+	+	+	+	+	+	27
Intestine large, colon	+	+	+	+	+	+	+	32
Intestine large, rectum	+	+	+	+	+	+	+	31
Intestine large, cecum	+	+	+	+	+	+	+	30
Intestine small, duodenum	+	+	+	+	+	+	+	32
Intestine small, jejunum	+	+	+	+	+	+	+	29
Intestine small, ileum	+	+	+	+	+	+	+	30
Liver	+	+	+	+	+	+	+	32
Hemangiosarcoma				X				3
Hepatocellular carcinoma								1
Hepatocellular carcinoma, multiple								1
Hepatocellular adenoma	X						X	4
Hepatocholangiocarcinoma								1
Mesentery							+	1
Pancreas	+	+	+	+	+	+	+	31
Salivary glands	+	+	+	+	+	+	+	32
Stomach, forestomach	+	+	+	+	+	+	+	32
Stomach, glandular	+	+	+	+	+	+	+	32
Adenoma								1
Cardiovascular System								
Heart	+	+	+	+	+	+	+	32
Endocrine System								
Adrenal cortex	+	+	+	+	+	+	+	32
Adrenal medulla	+	+	+	+	+	+	+	32
Islets, pancreatic	+	+	+	+	+	+	+	31
Parathyroid gland	I	+	+	+	+	+	+	28
Pituitary gland	+	+	+	+	+	+	+	31
Thyroid gland	+	+	+	+	+	+	+	32
General Body System								
None								
Genital System								
Coagulating gland								1
Epididymis	+	+	+	+	+	+	+	32
Penis								1
Preputial gland	+	+	+	+	+	+	+	32
Prostate	+	+	+	+	+	+	+	32
Seminal vesicle	+	+	+	+	+	+	+	32
Testes	+	+	+	+	+	+	+	32

TABLE A2
Individual Animal Tumor Pathology of Male Swiss (CD-1®) Mice in the Transplacental Study of AZT: 300 mg/kg

Number of Days on Study	041	041	192	229	329	329	329	376	404	473	488	495	538	539	563	569	593	627	634	635	638	640	655	661	668
Carcass ID Number	316	317	300	423	298	306	308	307	421	315	424	297	294	422	312	418	302	420	303	309	311	295	305	314	419
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node					+														+						
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma									X																
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skeletal muscle																	+						+		
Alveolar/bronchiolar carcinoma, metastatic, lung																							X		
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Oligodendroglioma malignant																	X								
Peripheral nerve											+	+					+								
Spinal cord	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Respiratory System																									
Larynx															+										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma				X		X	X	X				X		X				X						X	
Alveolar/bronchiolar adenoma, multiple																									
Alveolar/bronchiolar carcinoma								X							X										
Alveolar/bronchiolar carcinoma, multiple																			X			X	X		
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Harderian gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma											X													X	X
Carcinoma								X																	
Lacrimal gland															+										

TABLE A2
Individual Animal Tumor Pathology of Male Swiss (CD-1®) Mice in the Transplacental Study of AZT: 300 mg/kg

Number of Days on Study	673	676	677	677	678	678	678	
Carcass ID Number	310	304	293	296	299	301	313	Total Tissues/ Tumors
Hematopoietic System								
Bone marrow	+	+	+	+	+	+	+	32
Lymph node								2
Lymph node, mandibular	+	+	+	+	+	+	+	32
Lymph node, mesenteric	+	+	+	+	+	+	+	32
Spleen	+	+	+	+	+	+	+	32
Hemangiosarcoma								1
Thymus	+	+	+	+	+	+	+	32
Integumentary System								
Mammary gland	+	+	+	+	+	+	+	32
Skin	+	+	+	+	+	+	+	32
Musculoskeletal System								
Bone	+	+	+	+	+	+	+	32
Skeletal muscle								2
Alveolar/bronchiolar carcinoma, metastatic, lung								1
Nervous System								
Brain	+	+	+	+	+	+	+	32
Oligodendroglioma malignant								1
Peripheral nerve								3
Spinal cord	+	+	+	+	+	+	+	32
Respiratory System								
Larynx								1
Lung	+	+	+	+	+	+	+	32
Alveolar/bronchiolar adenoma				X			X	10
Alveolar/bronchiolar adenoma, multiple	X							1
Alveolar/bronchiolar carcinoma		X	X			X		5
Alveolar/bronchiolar carcinoma, multiple								3
Nose	+	+	+	+	+	+	+	32
Trachea	+	+	+	+	+	+	+	32
Special Senses System								
Harderian gland	+	+	+	+	+	+	+	32
Adenoma					X			4
Carcinoma								1
Lacrimal gland								1

TABLE A2
Individual Animal Tumor Pathology of Male Swiss (CD-1®) Mice in the Transplacental Study of AZT: 300 mg/kg

Number of Days on Study	041	041	192	229	329	329	329	376	404	473	488	495	538	539	563	569	593	627	634	635	638	640	655	661	668
Carcass ID Number	316	317	300	423	298	306	308	307	421	315	424	297	294	422	312	418	302	420	303	309	311	295	305	314	419
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urethra																								+	
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant												X												X	

TABLE A2
Individual Animal Tumor Pathology of Male Swiss (CD-1®) Mice in the Transplacental Study of AZT: 300 mg/kg

Number of Days on Study	673	676	677	677	678	678	678	
Carcass ID Number	310	304	293	296	299	301	313	Total Tissues/ Tumors
Urinary System								
Kidney	+	+	+	+	+	+	+	32
Urethra	+	+						3
Urinary bladder	+	+	+	+	+	+	+	32
Systemic Lesions								
Multiple organs	+	+	+	+	+	+	+	32
Lymphoma malignant							X	3

TABLE A3
Statistical Analysis of Primary Neoplasms in Male Swiss (CD-1®) Mice in the Transplacental Study of AZT

	Vehicle Control	50 mg/kg	100 mg/kg	200 mg/kg	300 mg/kg
Adrenal Cortex: Adenoma					
Overall rate[a]	2/50 (4%)	0/50 (0%)	1/50 (2%)	3/37 (8%)	0/32 (0%)
Adjusted rate[b]	6.0%	0.0%	3.4%	14.3%	0.0%
Terminal rate[c]	2/19 (11%)	0/21 (0%)	0/13 (0%)	3/7 (43%)	0/8 (0%)
First incidence (days)	668 (T)	—[e]	608	668 (T)	—
Poly-3 test[d]	P=0.528	P=0.256N	P=0.542N	P=0.296	P=0.366N
Harderian Gland: Adenoma					
Overall rate	11/50 (22%)	8/50 (16%)	9/50 (18%)	3/37 (8%)	4/32 (13%)
Adjusted rate	31.2%	25.3%	28.6%	13.9%	20.2%
Terminal rate	5/19 (26%)	4/21 (19%)	3/13 (23%)	1/7 (14%)	2/8 (25%)
First incidence (days)	453	523	413	501	488
Poly-3 test	P=0.119N	P=0.393N	P=0.515N	P=0.122N	P=0.287N
Harderian Gland: Adenoma or Carcinoma					
Overall rate	11/50 (22%)	8/50 (16%)	10/50 (20%)	3/37 (8%)	5/32 (16%)
Adjusted rate	31.2%	25.3%	31.8%	13.9%	24.3%
Terminal rate	5/19 (26%)	4/21 (19%)	4/13 (31%)	1/7 (14%)	2/8 (25%)
First incidence (days)	453	523	413	501	376
Poly-3 test	P=0.196N	P=0.393N	P=0.586	P=0.122N	P=0.402N
Liver: Hemangiosarcoma					
Overall rate	7/50 (14%)	4/50 (8%)	3/50 (6%)	1/37 (3%)	3/32 (9%)
Adjusted rate	19.3%	12.6%	10.0%	4.7%	14.7%
Terminal rate	1/19 (5%)	1/21 (5%)	1/13 (8%)	0/7 (0%)	1/8 (13%)
First incidence (days)	373	385	482	607	404
Poly-3 test	P=0.241N	P=0.337N	P=0.240N	P=0.131N	P=0.472N
Liver: Hepatocellular Adenoma					
Overall rate	14/50 (28%)	11/50 (22%)	10/50 (20%)	8/37 (22%)	4/32 (13%)
Adjusted rate	39.0%	35.7%	32.2%	35.8%	20.7%
Terminal rate	8/19 (42%)	9/21 (43%)	4/13 (31%)	3/7 (43%)	2/8 (25%)
First incidence (days)	446	595	505	483	627
Poly-3 test	P=0.124N	P=0.488N	P=0.369N	P=0.512N	P=0.137N
Liver: Hepatocellular Carcinoma					
Overall rate	6/50 (12%)	6/50 (12%)	6/50 (12%)	4/37 (11%)	2/32 (6%)
Adjusted rate	17.1%	19.1%	19.0%	17.9%	9.8%
Terminal rate	2/19 (11%)	4/21 (19%)	1/13 (8%)	0/7 (0%)	0/8 (0%)
First incidence (days)	392	444	413	483	473
Poly-3 test	P=0.287N	P=0.542	P=0.545	P=0.607	P=0.365N
Liver: Hepatocellular Adenoma or Carcinoma					
Overall rate	18/50 (36%)	16/50 (32%)	16/50 (32%)	10/37 (27%)	6/32 (19%)
Adjusted rate	47.8%	50.2%	47.9%	43.7%	29.1%
Terminal rate	9/19 (47%)	12/21 (57%)	5/13 (39%)	3/7 (43%)	2/8 (25%)
First incidence (days)	392	444	413	483	473
Poly-3 test	P=0.083N	P=0.517	P=0.596	P=0.480N	P=0.130N
Liver: Hepatocellular Carcinoma or Hepatoblastoma					
Overall rate	7/50 (14%)	6/50 (12%)	6/50 (12%)	4/37 (11%)	2/32 (6%)
Adjusted rate	19.6%	19.1%	19.0%	17.9%	9.8%
Terminal rate	2/19 (11%)	4/21 (19%)	1/13 (8%)	0/7 (0%)	0/8 (0%)
First incidence (days)	392	444	413	483	473
Poly-3 test	P=0.219N	P=0.603N	P=0.599N	P=0.573N	P=0.282N

Table A3
Statistical Analysis of Primary Neoplasms in Male Swiss (CD-1®) Mice in the Transplacental Study of AZT

	Vehicle Control	50 mg/kg	100 mg/kg	200 mg/kg	300 mg/kg
Liver: Hepatocellular Adenoma, Hepatocellular Carcinoma, or Hepatoblastoma					
Overall rate	18/50 (36%)	16/50 (32%)	16/50 (32%)	10/37 (27%)	6/32 (19%)
Adjusted rate	47.8%	50.2%	47.9%	43.7%	29.1%
Terminal rate	9/19 (47%)	12/21 (57%)	5/13 (39%)	3/7 (43%)	2/8 (25%)
First incidence (days)	392	444	413	483	473
Poly-3 test	P=0.083N	P=0.517	P=0.596	P=0.480N	P=0.130N
Lung: Alveolar/bronchiolar Adenoma					
Overall rate	10/50 (20%)	13/50 (26%)	8/50 (16%)	9/37 (24%)	11/32 (34%)
Adjusted rate	29.0%	37.3%	25.4%	36.8%	45.9%
Terminal rate	5/19 (26%)	5/21 (24%)	3/13 (23%)	2/7 (29%)	3/8 (38%)
First incidence (days)	560	229	322	167	229
Poly-3 test	P=0.109	P=0.311	P=0.480N	P=0.361	P=0.137
Lung: Alveolar/bronchiolar Carcinoma					
Overall rate	5/50 (10%)	11/50 (22%)	6/50 (12%)	11/37 (30%)	8/32 (25%)
Adjusted rate	14.9%	33.0%	19.9%	45.1%	38.7%
Terminal rate	2/19 (11%)	5/21 (24%)	4/13 (31%)	3/7 (43%)	3/8 (38%)
First incidence (days)	619	363	482	341	376
Poly-3 test	P=0.014	P=0.068	P=0.422	P=0.009	P=0.043
Lung: Alveolar/bronchiolar Adenoma or Carcinoma					
Overall rate	14/50 (28%)	20/50 (40%)	13/50 (26%)	18/37 (49%)	18/32 (56%)
Adjusted rate	40.2%	54.5%	40.5%	66.3%	72.9%
Terminal rate	7/19 (37%)	9/21 (43%)	7/13 (54%)	5/7 (71%)	6/8 (75%)
First incidence (days)	560	229	322	167	229
Poly-3 test	P=0.002	P=0.156	P=0.592	P=0.027	P=0.007
Spleen: Hemangiosarcoma					
Overall rate	3/49 (6%)	2/50 (4%)	1/50 (2%)	0/37 (0%)	1/32 (3%)
Adjusted rate	8.8%	6.5%	3.4%	0.0%	5.0%
Terminal rate	0/18 (0%)	1/21 (5%)	1/13 (8%)	0/7 (0%)	0/8 (0%)
First incidence (days)	373	580	668 (T)	—	404
Poly-3 test	P=0.215N	P=0.549N	P=0.362N	P=0.222N	P=0.511N
All Organs: Hemangiosarcoma					
Overall rate	7/50 (14%)	6/50 (12%)	4/50 (8%)	2/37 (5%)	3/32 (9%)
Adjusted rate	19.3%	18.9%	13.3%	9.4%	14.7%
Terminal rate	1/19 (5%)	3/21 (14%)	1/13 (8%)	1/7 (14%)	1/8 (13%)
First incidence (days)	373	385	482	607	404
Poly-3 test	P=0.247N	P=0.604N	P=0.374N	P=0.274N	P=0.472N
All Organs: Hemangioma or Hemangiosarcoma					
Overall rate	7/50 (14%)	7/50 (14%)	5/50 (10%)	2/37 (5%)	3/32 (9%)
Adjusted rate	19.3%	22.0%	16.6%	9.4%	14.7%
Terminal rate	1/19 (5%)	4/21 (19%)	2/13 (15%)	1/7 (14%)	1/8 (13%)
First incidence (days)	373	385	482	607	404
Poly-3 test	P=0.218N	P=0.510	P=0.515N	P=0.274N	P=0.472N
All Organs: Malignant Lymphoma					
Overall rate	6/50 (12%)	9/50 (18%)	7/50 (14%)	4/37 (11%)	3/32 (9%)
Adjusted rate	17.0%	26.7%	21.6%	18.2%	15.2%
Terminal rate	1/19 (5%)	2/21 (10%)	1/13 (8%)	0/7 (0%)	1/8 (13%)
First incidence (days)	413	322	187	589	495
Poly-3 test	P=0.358N	P=0.246	P=0.434	P=0.595	P=0.578N

TABLE A3
Statistical Analysis of Primary Neoplasms in Male Swiss (CD-1®) Mice in the Transplacental Study of AZT

	Vehicle Control	50 mg/kg	100 mg/kg	200 mg/kg	300 mg/kg
All Organs: Benign Neoplasms					
Overall rate	27/50 (54%)	23/50 (46%)	27/50 (54%)	18/37 (49%)	16/32 (50%)
Adjusted rate	69.6%	64.2%	76.4%	70.8%	64.6%
Terminal rate	11/19 (58%)	12/21 (57%)	11/13 (85%)	7/7 (100%)	5/8 (63%)
First incidence (days)	413	229	322	167	229
Poly-3 test	P=0.451N	P=0.398N	P=0.330	P=0.573	P=0.444N
All Organs: Malignant Neoplasms					
Overall rate	19/50 (38%)	27/50 (54%)	20/50 (40%)	20/37 (54%)	17/32 (53%)
Adjusted rate	48.4%	67.9%	55.1%	73.3%	70.5%
Terminal rate	5/19 (26%)	10/21 (48%)	6/13 (46%)	4/7 (57%)	5/8 (63%)
First incidence (days)	373	157	187	341	376
Poly-3 test	P=0.036	P=0.056	P=0.358	P=0.030	P=0.064
All Organs: Benign or Malignant Neoplasms					
Overall rate	35/50 (70%)	35/50 (70%)	34/50 (68%)	25/37 (68%)	26/32 (81%)
Adjusted rate	83.2%	83.9%	86.8%	88.0%	94.1%
Terminal rate	14/19 (74%)	15/21 (71%)	12/13 (92%)	7/7 (100%)	8/8 (100%)
First incidence (days)	373	157	187	167	229
Poly-3 test	P=0.070	P=0.585	P=0.434	P=0.404	P=0.137

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

Table A4
Summary of the Incidence of Nonneoplastic Lesions in Male Swiss (CD-1®) Mice in the Transplacental Study of AZT[a]

	Vehicle Control		50 mg/kg		100 mg/kg		200 mg/kg		300 mg/kg	
Disposition Summary										
Animals initially in study	50		50		50		37		32	
Early deaths										
Accidental deaths					1				2	
Moribund	23		21		25		23		12	
Natural deaths	8		9		11		6		10	
Survivors										
Died last week of study									1	
Terminal sacrifice	19		20		13		7		7	
Other							1			
Animals examined microscopically	50		50		50		37		32	
Alimentary System										
Intestine large, colon	(48)		(50)		(49)		(37)		(32)	
Edema					2	(4%)	1	(3%)		
Intestine large, cecum	(49)		(49)		(48)		(35)		(30)	
Edema	13	(27%)	11	(22%)	8	(17%)	14	(40%)	2	(7%)
Infiltration cellular, lymphocyte	1	(2%)								
Intestine small, duodenum	(49)		(50)		(49)		(36)		(32)	
Amyloid deposition	1	(2%)								
Epithelium, hyperplasia	3	(6%)	4	(8%)	4	(8%)	1	(3%)	1	(3%)
Intestine small, jejunum	(49)		(50)		(46)		(36)		(29)	
Amyloid deposition	1	(2%)								
Epithelium, hyperplasia	4	(8%)	2	(4%)			1	(3%)	1	(3%)
Intestine small, ileum	(49)		(48)		(47)		(35)		(30)	
Amyloid deposition	1	(2%)								
Liver	(50)		(50)		(50)		(37)		(32)	
Amyloid deposition									1	(3%)
Angiectasis	1	(2%)	1	(2%)					1	(3%)
Basophilic focus	2	(4%)	4	(8%)	2	(4%)	2	(5%)		
Cholangiofibrosis					1	(2%)				
Clear cell focus	1	(2%)	1	(2%)						
Cyst					2	(4%)	1	(3%)		
Eosinophilic focus	3	(6%)	2	(4%)	2	(4%)	1	(3%)	2	(6%)
Hematopoietic cell proliferation	9	(18%)	7	(14%)	12	(24%)	6	(16%)	5	(16%)
Hemorrhage			1	(2%)	1	(2%)			1	(3%)
Hyperplasia, lymphoid					1	(2%)				
Infarct									1	(3%)
Infiltration cellular, mixed cell	10	(20%)	7	(14%)	2	(4%)	5	(14%)	2	(6%)
Necrosis, focal	8	(16%)	9	(18%)	7	(14%)	4	(11%)	3	(9%)
Regeneration					1	(2%)			1	(3%)
Tension lipidosis					1	(2%)			1	(3%)
Centrilobular, necrosis	2	(4%)			1	(2%)				
Hepatocyte, hypertrophy	15	(30%)	15	(30%)	9	(18%)	6	(16%)	15	(47%)
Hepatocyte, vacuolization cytoplasmic	1	(2%)	1	(2%)	2	(4%)			1	(3%)
Hepatocyte, centrilobular, vacuolization cytoplasmic									1	(3%)
Kupffer cell, hyperplasia	2	(4%)					1	(3%)	1	(3%)
Kupffer cell, pigmentation	2	(4%)	3	(6%)			2	(5%)	3	(9%)

[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 Swiss (CD-1®) Mice in the Transplacental Study of AZT

	Vehicle Control		50 mg/kg		100 mg/kg		200 mg/kg		300 mg/kg	
Alimentary System (continued)										
Mesentery	(1)		(2)		(3)		(1)			
Hemorrhage			1	(50%)					1	(100%)
Fat, necrosis			1	(50%)			3	(100%)		
Pancreas	(50)		(50)		(50)		(37)		(31)	
Atrophy					1	(2%)				
Cyst									1	(3%)
Edema	1	(2%)			2	(4%)	2	(5%)		
Infiltration cellular, mixed cell									1	(3%)
Acinus, cytoplasmic alteration	1	(2%)	2	(4%)	1	(2%)	1	(3%)	1	(3%)
Salivary glands	(50)		(50)		(50)		(37)		(32)	
Atrophy	1	(2%)					1	(3%)		
Hyperplasia, lymphoid									1	(3%)
Infiltration cellular, lymphoid	1	(2%)							5	(16%)
Infiltration cellular, mixed cell	1	(2%)			1	(2%)	2	(5%)		
Stomach, forestomach	(49)		(50)		(50)		(37)		(32)	
Diverticulum							1	(3%)		
Edema	1	(2%)			2	(4%)	1	(3%)		
Ulcer	1	(2%)								
Epithelium, hyperplasia	2	(4%)			1	(2%)	1	(3%)	1	(3%)
Stomach, glandular	(49)		(50)		(50)		(37)		(32)	
Edema			1	(2%)	2	(4%)	2	(5%)		
Erosion	2	(4%)	2	(4%)	1	(2%)			1	(3%)
Glands, hyperplasia, cystic	9	(18%)	13	(26%)	10	(20%)	15	(41%)	6	(19%)
Tooth			(1)							
Malformation			1	(100%)						
Cardiovascular System										
Blood vessel	(1)		(1)		(1)					
Inflammation, chronic	1	(100%)								
Heart	(50)		(50)		(50)		(37)		(32)	
Amyloid deposition	1	(2%)								
Cardiomyopathy	12	(24%)	7	(14%)	19	(38%)	13	(35%)	7	(22%)
Inflammation	1	(2%)								
Inflammation, chronic	1	(2%)	5	(10%)	3	(6%)	2	(5%)	1	(3%)
Mineralization			2	(4%)	1	(2%)	1	(3%)		
Thrombosis	2	(4%)	4	(8%)	5	(10%)	3	(8%)	3	(9%)
Endocrine System										
Adrenal cortex	(50)		(50)		(50)		(37)		(32)	
Accessory adrenal cortical nodule	8	(16%)	9	(18%)	7	(14%)	6	(16%)	6	(19%)
Amyloid deposition	1	(2%)								
Hyperplasia, focal	2	(4%)	5	(10%)	3	(6%)	2	(5%)		
Hypertrophy, focal	6	(12%)	5	(10%)	4	(8%)	4	(11%)	4	(13%)
Capsule, hyperplasia	2	(4%)	2	(4%)	1	(2%)	3	(8%)	2	(6%)
Adrenal medulla	(50)		(50)		(49)		(37)		(32)	
Hyperplasia	2	(4%)			1	(2%)			1	(3%)
Islets, pancreatic	(50)		(50)		(50)		(36)		(31)	
Hyperplasia	15	(30%)	13	(26%)	12	(24%)	6	(17%)	6	(19%)
Pituitary gland	(48)		(49)		(49)		(36)		(31)	
Pars distalis, cyst	1	(2%)	2	(4%)	3	(6%)	2	(6%)	1	(3%)
Thyroid gland	(50)		(50)		(50)		(37)		(32)	
Amyloid deposition	1	(2%)								
Degeneration, cystic	29	(58%)	23	(46%)	33	(66%)	15	(41%)	15	(47%)
Follicular cell, hyperplasia	3	(6%)			2	(4%)				

Table A4
Summary of the Incidence of Nonneoplastic Lesions in Male Swiss (CD-1®) Mice in the Transplacental Study of AZT

	Vehicle Control		50 mg/kg		100 mg/kg		200 mg/kg		300 mg/kg	
General Body System										
None										
Genital System										
Coagulating gland			(2)		(2)		(1)		(1)	
Bilateral, dilatation			1	(50%)						
Epididymis	(50)		(50)		(50)		(37)		(32)	
Atypia cellular	1	(2%)	3	(6%)	3	(6%)	3	(8%)	3	(9%)
Granuloma sperm			1	(2%)						
Inflammation, chronic	1	(2%)			1	(2%)				
Spermatocele					2	(4%)			1	(3%)
Penis			(2)		(1)		(3)		(1)	
Inflammation, chronic active			2	(100%)	1	(100%)	1	(33%)		
Preputial gland	(50)		(50)		(50)		(37)		(32)	
Cyst	6	(12%)	7	(14%)	6	(12%)	6	(16%)	2	(6%)
Inflammation, chronic	11	(22%)	11	(22%)	18	(36%)	8	(22%)	9	(28%)
Prostate	(50)		(50)		(50)		(37)		(32)	
Inflammation, chronic	8	(16%)	3	(6%)	12	(24%)	6	(16%)	5	(16%)
Seminal vesicle	(50)		(50)		(50)		(37)		(32)	
Degeneration			1	(2%)			1	(3%)	1	(3%)
Dilatation	2	(4%)							3	(9%)
Inflammation, chronic	2	(4%)	3	(6%)			3	(8%)		
Testes	(50)		(50)		(50)		(37)		(32)	
Germinal epithelium, atrophy	4	(8%)	7	(14%)	5	(10%)	3	(8%)	4	(13%)
Hematopoietic System										
Bone marrow	(50)		(50)		(50)		(37)		(32)	
Hyperplasia	43	(86%)	29	(58%)	35	(70%)	27	(73%)	24	(75%)
Infiltration cellular, mast cell	1	(2%)								
Myelofibrosis									1	(3%)
Lymph node	(12)		(10)		(15)		(6)		(2)	
Hematopoietic cell proliferation	3	(25%)	2	(20%)	1	(7%)				
Hyperplasia, lymphoid	1	(8%)	3	(30%)	2	(13%)	2	(33%)		
Hyperplasia, plasma cell	3	(25%)							2	(100%)
Bronchial, hyperplasia, lymphoid			1	(10%)						
Iliac, hyperplasia, lymphoid					1	(7%)	1	(17%)		
Iliac, pigmentation					1	(7%)				
Inguinal, hematopoietic cell proliferation	1	(8%)			1	(7%)	1	(17%)		
Inguinal, hyperplasia, lymphoid	2	(17%)	1	(10%)	6	(40%)	1	(17%)		
Inguinal, hyperplasia, plasma cell	2	(17%)								
Inguinal, pigmentation					1	(7%)				
Lumbar, pigmentation					1	(7%)				
Mediastinal, hemorrhage	1	(8%)								
Mediastinal, hyperplasia, lymphoid					3	(20%)				
Renal, hyperplasia, lymphoid	1	(8%)					1	(17%)		
Renal, hyperplasia, plasma cell	1	(8%)								
Lymph node, mandibular	(50)		(50)		(49)		(37)		(32)	
Atrophy					1	(2%)	3	(8%)		
Ectasia	2	(4%)			1	(2%)	1	(3%)	2	(6%)
Hematopoietic cell proliferation	7	(14%)			6	(12%)	4	(11%)	5	(16%)
Hemorrhage					3	(6%)				
Hyperplasia, lymphoid	11	(22%)	7	(14%)	9	(18%)	6	(16%)	9	(28%)
Hyperplasia, plasma cell	11	(22%)	9	(18%)	6	(12%)	3	(8%)	4	(13%)
Pigmentation			1	(2%)	1	(2%)				

TABLE A4
Summary of the Incidence of Nonneoplastic Lesions in Male Swiss (CD-1®) Mice in the Transplacental Study of AZT

	Vehicle Control		50 mg/kg		100 mg/kg		200 mg/kg		300 mg/kg	
Hematopoietic System (continued)										
Lymph node, mesenteric	(50)		(49)		(49)		(36)		(32)	
Atrophy	1	(2%)			2	(4%)	3	(8%)		
Ectasia	2	(4%)	7	(14%)	3	(6%)	6	(17%)	2	(6%)
Hematopoietic cell proliferation	12	(24%)	3	(6%)	8	(16%)	3	(8%)	4	(13%)
Hemorrhage	7	(14%)	14	(29%)	17	(35%)	8	(22%)	9	(28%)
Hyperplasia, lymphoid	15	(30%)	16	(33%)	9	(18%)	10	(28%)	6	(19%)
Infiltration cellular, histiocyte	1	(2%)								
Necrosis	1	(2%)	1	(2%)	3	(6%)				
Pigmentation	1	(2%)	1	(2%)	1	(2%)			1	(3%)
Spleen	(49)		(50)		(50)		(37)		(32)	
Hematopoietic cell proliferation	31	(63%)	29	(58%)	27	(54%)	18	(49%)	20	(63%)
Pigmentation	2	(4%)	3	(6%)	4	(8%)	2	(5%)		
Lymphoid follicle, atrophy	4	(8%)	5	(10%)	5	(10%)	7	(19%)	2	(6%)
Lymphoid follicle, hyperplasia			6	(12%)	5	(10%)	2	(5%)	1	(3%)
Thymus	(48)		(45)		(47)		(33)		(32)	
Atrophy	15	(31%)	12	(27%)	15	(32%)	13	(39%)	7	(22%)
Cyst	2	(4%)	1	(2%)	2	(4%)	1	(3%)	1	(3%)
Hyperplasia, lymphoid	1	(2%)	1	(2%)	6	(13%)	1	(3%)	6	(19%)
Integumentary System										
Skin	(50)		(50)		(50)		(37)		(32)	
Cyst epithelial inclusion			2	(4%)			1	(3%)		
Edema	10	(20%)	2	(4%)	7	(14%)	7	(19%)	1	(3%)
Ulcer	14	(28%)	14	(28%)	13	(26%)	7	(19%)	6	(19%)
Epidermis, hyperplasia	13	(26%)	12	(24%)	12	(24%)	8	(22%)	5	(16%)
Epidermis, inflammation	1	(2%)			1	(2%)				
Epidermis, ulcer					1	(2%)				
Subcutaneous tissue, edema			1	(2%)	1	(2%)				
Musculoskeletal System										
Bone	(50)		(50)		(50)		(37)		(32)	
Fibrous osteodystrophy					1	(2%)	1	(3%)	1	(3%)
Fracture									1	(3%)
Femur, osteopetrosis			1	(2%)					2	(6%)
Scapula, osteopetrosis									1	(3%)
Skeletal muscle	(1)		(2)		(1)		(3)		(2)	
Hemorrhage	1	(100%)								
Pigmentation							1	(33%)		
Nervous System										
Brain	(49)		(50)		(50)		(37)		(32)	
Hydrocephalus			1	(2%)						
Necrosis									1	(3%)
Spinal cord	(50)		(50)		(50)		(37)		(32)	
Cyst epithelial inclusion	1	(2%)							1	(3%)
Demyelination									1	(3%)
Infiltration cellular, mast cell	1	(2%)								
Necrosis	1	(2%)	1	(2%)					1	(3%)

Table A4
Summary of the Incidence of Nonneoplastic Lesions in Male Swiss (CD-1®) Mice in the Transplacental Study of AZT

	Vehicle Control		50 mg/kg		100 mg/kg		200 mg/kg		300 mg/kg	
Respiratory System										
Lung	(50)		(50)		(50)		(37)		(32)	
Congestion							1	(3%)		
Edema			1	(2%)	2	(4%)	4	(11%)		
Fibrosis, focal					1	(2%)				
Foreign body	1	(2%)			1	(2%)	1	(3%)	1	(3%)
Hemorrhage	5	(10%)	3	(6%)	7	(14%)	5	(14%)	2	(6%)
Hyperplasia, lymphoid	1	(2%)					1	(3%)	1	(3%)
Infiltration cellular, histiocyte	12	(24%)	16	(32%)	13	(26%)	16	(43%)	14	(44%)
Inflammation, chronic	2	(4%)	1	(2%)	5	(10%)	2	(5%)	1	(3%)
Thrombosis	1	(2%)	1	(2%)						
Alveolar epithelium, hyperplasia	6	(12%)	3	(6%)			1	(3%)	4	(13%)
Nose	(50)		(50)		(50)		(36)		(32)	
Foreign body	1	(2%)	1	(2%)	1	(2%)				
Inflammation, chronic	5	(10%)	5	(10%)	5	(10%)	3	(8%)	4	(13%)
Special Senses System										
Harderian gland	(50)		(50)		(49)		(37)		(32)	
Hyperplasia, focal	2	(4%)			1	(2%)	1	(3%)	1	(3%)
Hypertrophy, focal			1	(2%)						
Inflammation	1	(2%)								
Urinary System										
Kidney	(50)		(50)		(50)		(37)		(32)	
Amyloid deposition	3	(6%)								
Cyst	27	(54%)	23	(46%)	26	(52%)	24	(65%)	17	(53%)
Hydronephrosis	30	(60%)	20	(40%)	17	(34%)	16	(43%)	14	(44%)
Infarct	1	(2%)					1	(3%)	1	(3%)
Infiltration cellular, mixed cell	9	(18%)	11	(22%)	17	(34%)	9	(24%)	12	(38%)
Inflammation, chronic	1	(2%)	2	(4%)	1	(2%)	2	(5%)		
Inflammation, suppurative	4	(8%)								
Metaplasia, osseous	1	(2%)	1	(2%)	1	(2%)				
Mineralization			1	(2%)			1	(3%)		
Nephropathy	40	(80%)	40	(80%)	42	(84%)	30	(81%)	23	(72%)
Renal tubule, dilatation			1	(2%)	5	(10%)	2	(5%)	1	(3%)
Renal tubule, necrosis	3	(6%)					1	(3%)		
Renal tubule, pigmentation			1	(2%)	2	(4%)	2	(5%)		
Ureter			(3)		(1)		(1)			
Dilatation			2	(67%)	1	(100%)	1	(100%)		
Urethra	(1)		(4)		(5)		(3)		(3)	
Angiectasis	1	(100%)			3	(60%)	1	(33%)	1	(33%)
Inflammation, chronic	1	(100%)	1	(25%)	3	(60%)	1	(33%)		
Bulbourethral gland, cyst			1	(25%)	2	(40%)	1	(33%)	2	(67%)
Urinary bladder	(50)		(50)		(50)		(37)		(32)	
Edema					1	(2%)			2	(6%)
Hemorrhage					3	(6%)	2	(5%)	2	(6%)
Inflammation, chronic	4	(8%)			2	(4%)	1	(3%)	1	(3%)
Transitional epithelium, hyperplasia	4	(8%)	1	(2%)	3	(6%)	1	(3%)	1	(3%)

APPENDIX B
SUMMARY OF LESIONS
IN FEMALE SWISS (CD-1®) MICE
IN THE TRANSPLACENTAL STUDY OF AZT

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TABLE B1
Summary of the Incidence of Neoplasms in Female Swiss (CD-1®) Mice in the Transplacental Study of AZT[a]

	Vehicle Control	50 mg/kg	100 mg/kg	200 mg/kg	300 mg/kg
Disposition Summary					
Animals initially in study	50	50	50	40	42
Early deaths					
Accidental death		1			
Moribund	16	18	11	10	15
Natural deaths	14	13	15	9	9
Survivors					
Died last week of study	1	1		1	
Terminal sacrifice	19	17	24	20	18
Animals examined microscopically	50	50	50	40	42
Alimentary System					
Intestine large, rectum	(49)	(48)	(49)	(40)	(40)
Intestine large, cecum	(47)	(48)	(45)	(38)	(40)
Leiomyosarcoma					1 (3%)
Intestine small, duodenum	(50)	(50)	(48)	(40)	(42)
Intestine small, jejunum	(46)	(49)	(46)	(40)	(40)
Histiocytic sarcoma		1 (2%)			1 (3%)
Intestine small, ileum	(47)	(48)	(45)	(38)	(40)
Liver	(50)	(50)	(50)	(40)	(42)
Alveolar/bronchiolar carcinoma, metastatic, lung			1 (2%)		
Hemangiosarcoma	1 (2%)		1 (2%)		
Hepatocellular carcinoma	2 (4%)	1 (2%)			2 (5%)
Hepatocellular adenoma	2 (4%)	3 (6%)	4 (8%)	2 (5%)	2 (5%)
Hepatocellular adenoma, multiple	1 (2%)	1 (2%)	1 (2%)		2 (5%)
Histiocytic sarcoma		1 (2%)	1 (2%)	1 (3%)	2 (5%)
Osteosarcoma, metastatic, bone		1 (2%)			
Plasma cell tumor malignant		1 (2%)	1 (2%)		
Mesentery	(4)	(8)	(7)	(3)	(5)
Fibrosarcoma, metastatic, skin		1 (13%)			
Hemangioma			1 (14%)		
Histiocytic sarcoma					1 (20%)
Plasma cell tumor malignant		1 (13%)			
Pancreas	(50)	(49)	(49)	(40)	(41)
Histiocytic sarcoma					1 (2%)
Salivary glands	(50)	(49)	(49)	(40)	(42)
Stomach, forestomach	(50)	(50)	(49)	(40)	(42)
Squamous cell papilloma	1 (2%)		1 (2%)		
Stomach, glandular	(50)	(50)	(49)	(40)	(42)
Carcinoid tumor malignant					1 (2%)
Cardiovascular System					
Blood vessel	(3)	(2)			
Heart	(50)	(49)	(50)	(40)	(42)
Alveolar/bronchiolar carcinoma, metastatic, lung			1 (2%)		
Plasma cell tumor malignant		1 (2%)	1 (2%)		

Table B1
Summary of the Incidence of Neoplasms in Female Swiss (CD-1®) Mice in the Transplacental Study of AZT

	Vehicle Control	50 mg/kg	100 mg/kg	200 mg/kg	300 mg/kg
Endocrine System					
Adrenal cortex	(50)	(49)	(50)	(38)	(42)
Carcinoma				1 (3%)	
Plasma cell tumor malignant		1 (2%)			
Subcapsular, adenoma	1 (2%)	1 (2%)			
Adrenal medulla	(50)	(49)	(50)	(38)	(42)
Plasma cell tumor malignant		1 (2%)			
Islets, pancreatic	(50)	(49)	(49)	(40)	(41)
Adenoma				1 (3%)	2 (5%)
Parathyroid gland	(45)	(45)	(48)	(37)	(36)
Adenoma			1 (2%)		
Pituitary gland	(50)	(49)	(50)	(40)	(42)
Pars distalis, adenoma		1 (2%)	1 (2%)	1 (3%)	1 (2%)
Pars intermedia, adenoma		1 (2%)			
Thyroid gland	(50)	(49)	(50)	(40)	(42)
Follicular cell, adenoma		1 (2%)			
General Body System					
None					
Genital System					
Clitoral gland	(50)	(50)	(50)	(40)	(42)
Ovary	(50)	(50)	(49)	(40)	(42)
Cystadenoma	2 (4%)	1 (2%)	2 (4%)		1 (2%)
Granulosa cell tumor malignant				2 (5%)	1 (2%)
Hemangioma				1 (3%)	
Hemangiosarcoma					1 (2%)
Luteoma		1 (2%)			
Plasma cell tumor malignant			1 (2%)		
Sertoli cell tumor benign			1 (2%)		
Uterus	(50)	(50)	(49)	(40)	(42)
Hemangioma		1 (2%)		1 (3%)	
Hemangiosarcoma	1 (2%)				
Histiocytic sarcoma	1 (2%)			2 (5%)	
Leiomyoma		1 (2%)	1 (2%)		
Leiomyosarcoma			1 (2%)		
Polyp stromal	1 (2%)	1 (2%)	1 (2%)	1 (3%)	1 (2%)
Vagina	(49)	(49)	(47)	(40)	(41)
Plasma cell tumor malignant		1 (2%)			
Hematopoietic System					
Bone marrow	(50)	(50)	(50)	(40)	(42)
Histiocytic sarcoma		1 (2%)	1 (2%)		1 (2%)
Plasma cell tumor malignant		1 (2%)			
Lymph node	(14)	(23)	(16)	(12)	(16)
Histiocytic sarcoma		1 (4%)			
Plasma cell tumor malignant			1 (6%)		
Deep cervical, plasma cell tumor malignant			1 (6%)		
Iliac, histiocytic sarcoma		1 (4%)			
Iliac, plasma cell tumor malignant			1 (6%)		

TABLE B1
Summary of the Incidence of Neoplasms in Female Swiss (CD-1®) Mice in the Transplacental Study of AZT

	Vehicle Control	50 mg/kg	100 mg/kg	200 mg/kg	300 mg/kg
Hematopoietic System (continued)					
Lymph node (continued)	(14)	(23)	(16)	(12)	(16)
Inguinal, plasma cell tumor malignant			1 (6%)		
Mediastinal, histiocytic sarcoma			1 (6%)		1 (6%)
Mediastinal, plasma cell tumor malignant		2 (9%)	1 (6%)		
Pancreatic, hemangioma			1 (6%)		
Pancreatic, plasma cell tumor malignant			1 (6%)		
Popliteal, plasma cell tumor malignant			1 (6%)		
Renal, histiocytic sarcoma		1 (4%)			
Renal, plasma cell tumor malignant		1 (4%)	1 (6%)		
Lymph node, mandibular	(49)	(47)	(49)	(40)	(42)
Histiocytic sarcoma		1 (2%)	1 (2%)		
Plasma cell tumor malignant		1 (2%)	1 (2%)		
Lymph node, mesenteric	(50)	(48)	(46)	(40)	(42)
Histiocytic sarcoma		1 (2%)	1 (2%)		2 (5%)
Plasma cell tumor malignant		1 (2%)	1 (2%)		
Spleen	(50)	(50)	(49)	(40)	(42)
Hemangiosarcoma	1 (2%)				
Histiocytic sarcoma		1 (2%)	1 (2%)		1 (2%)
Osteosarcoma, metastatic, bone		1 (2%)			
Plasma cell tumor malignant		1 (2%)	1 (2%)		
Sarcoma, metastatic, skeletal muscle	1 (2%)				
Thymus	(49)	(44)	(46)	(36)	(42)
Alveolar/bronchiolar carcinoma, metastatic, lung			1 (2%)	1 (3%)	
Histiocytic sarcoma		1 (2%)	1 (2%)		2 (5%)
Plasma cell tumor malignant		2 (5%)	1 (2%)		
Integumentary System					
Mammary gland	(50)	(50)	(49)	(40)	(42)
Carcinoma	2 (4%)	2 (4%)	2 (4%)	1 (3%)	1 (2%)
Skin	(50)	(50)	(49)	(40)	(42)
Squamous cell carcinoma	1 (2%)				
Squamous cell papilloma		1 (2%)			
Subcutaneous tissue, fibrosarcoma	1 (2%)	1 (2%)		1 (3%)	
Subcutaneous tissue, fibrous histiocytoma	1 (2%)				
Subcutaneous tissue, hemangiosarcoma		1 (2%)	1 (2%)	1 (3%)	
Musculoskeletal System					
Bone	(50)	(50)	(50)	(40)	(42)
Osteoma		1 (2%)		1 (3%)	
Osteosarcoma		1 (2%)			
Skeletal muscle	(5)	(2)	(1)	(1)	(4)
Sarcoma	1 (20%)				
Nervous System					
Brain	(50)	(50)	(50)	(40)	(42)
Alveolar/bronchiolar carcinoma, metastatic, lung			1 (2%)		
Spinal cord	(50)	(50)	(50)	(40)	(42)

TABLE B1
Summary of the Incidence of Neoplasms in Female Swiss (CD-1®) Mice in the Transplacental Study of AZT

	Vehicle Control		50 mg/kg		100 mg/kg		200 mg/kg		300 mg/kg	
Respiratory System										
Lung	(50)		(49)		(50)		(40)		(42)	
Alveolar/bronchiolar adenoma	7	(14%)	3	(6%)	7	(14%)	4	(10%)	7	(17%)
Alveolar/bronchiolar adenoma, multiple			3	(6%)	1	(2%)				
Alveolar/bronchiolar carcinoma	4	(8%)	6	(12%)	6	(12%)	4	(10%)	3	(7%)
Alveolar/bronchiolar carcinoma, multiple	1	(2%)			2	(4%)	4	(10%)	2	(5%)
Carcinoma, metastatic, harderian gland					1	(2%)				
Carcinoma, metastatic, mammary gland					1	(2%)				
Granulosa cell tumor malignant, metastatic, lung							1	(3%)		
Hemangiosarcoma									1	(2%)
Hepatocellular carcinoma, metastatic, liver									1	(2%)
Histiocytic sarcoma					1	(2%)	1	(3%)		
Osteosarcoma, metastatic, bone			1	(2%)						
Plasma cell tumor malignant			1	(2%)	1	(2%)				
Sarcoma, metastatic, skeletal muscle	1	(2%)								
Nose	(50)		(50)		(50)		(40)		(42)	
Histiocytic sarcoma							1	(3%)		
Special Senses System										
Harderian gland	(49)		(49)		(50)		(40)		(41)	
Adenoma	4	(8%)	6	(12%)	9	(18%)	4	(10%)	7	(17%)
Carcinoma					1	(2%)			1	(2%)
Histiocytic sarcoma							1	(3%)		
Urinary System										
Kidney	(50)		(50)		(50)		(40)		(42)	
Histiocytic sarcoma							1	(3%)		
Plasma cell tumor malignant			1	(2%)	1	(2%)				
Urinary bladder	(50)		(50)		(49)		(40)		(42)	
Histiocytic sarcoma							1	(3%)		
Systemic Lesions										
Multiple organs[b]	(50)		(50)		(50)		(40)		(42)	
Histiocytic sarcoma	1	(2%)	1	(2%)	1	(2%)	2	(5%)	2	(5%)
Leukemia granulocytic					1	(2%)			1	(2%)
Lymphoma malignant	19	(38%)	19	(38%)	20	(40%)	16	(40%)	17	(40%)
Neoplasm Summary										
Total animals with primary neoplasms[c]	35		33		38		31		33	
Total primary neoplasms	55		76		85		48		57	
Total animals with benign neoplasms	17		17		23		14		16	
Total benign neoplasms	19		27		32		16		23	
Total animals with malignant neoplasms	30		28		31		25		27	
Total malignant neoplasms	36		49		53		32		34	
Total animals with metastatic neoplasms	1		2		3		2		1	
Total metastatic neoplasms	2		4		6		2		1	

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

TABLE B2
Individual Animal Tumor Pathology of Female Swiss (CD-1®) Mice in the Transplacental Study of AZT: Vehicle Control

Number of Days on Study	105	179	248	255	287	352	372	391	443	443	460	497	510	535	558	573	577	581	588	588	593	598	598	599	609
Carcass ID Number	585	448	449	463	719	461	589	572	545	693	591	462	575	466	581	458	467	452	580	590	465	453	456	583	578
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+
Gallbladder	A	+	+	+	+	A	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	A
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	A
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	A	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	A
Intestine small, ileum	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																									
Hepatocellular carcinoma																									
Hepatocellular adenoma																									
Hepatocellular adenoma, multiple																									
Mesentery																+		+		+					
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell papilloma														X											
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cardiovascular System																									
Blood vessel					+	+																			
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Subcapsular, adenoma																		X							
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid gland	+	+	+	+	+	+	M	+	M	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
General Body System																									
None																									

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

TABLE B2
Individual Animal Tumor Pathology of Female Swiss (CD-1®) Mice in the Transplacental Study of AZT: Vehicle Control

Number of Days on Study	612	644	648	651	658	668	668	669	669	670	671	671	671	671	672	672	674	675	675	675	675	676	678	678	679	
Carcass ID Number	586	573	451	443	570	579	584	576	577	571	574	582	588	592	587	694	644	450	457	460	464	454	459	721	445	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	I	+	+	+	+	+	+	49
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, jejunum	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma																X										1
Hepatocellular carcinoma															X				X							2
Hepatocellular adenoma					X								X													2
Hepatocellular adenoma, multiple																		X								1
Mesentery		+																								4
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Squamous cell papilloma																										1
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cardiovascular System																										
Blood vessel		+																								3
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Subcapsular, adenoma																										1
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	M	+	+	+	+	45
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
General Body System																										
None																										

TABLE B2
Individual Animal Tumor Pathology of Female Swiss (CD-1®) Mice in the Transplacental Study of AZT: Vehicle Control

Number of Days on Study	105	179	248	255	287	352	372	391	443	443	460	497	510	535	558	573	577	581	588	588	593	598	598	599	609
Carcass ID Number	585	448	449	463	719	461	589	572	455	693	591	462	575	466	581	458	467	452	580	590	465	453	456	583	578
Genital System																									
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cystadenoma													X									X			
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																	X								
Histiocytic sarcoma																									
Polyp stromal																									
Vagina	I	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node		+	+		+	+		+		+	+	+	+		+			+			+	+			
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																								X	
Sarcoma, metastatic, skeletal muscle																				X					
Thymus	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma																X									
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell carcinoma																									
Subcutaneous tissue, fibrosarcoma																									
Subcutaneous tissue, fibrous, histiocytoma																									
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skeletal muscle		+				+		+												+			+		
Sarcoma																				X					
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Peripheral nerve		+									+	+			+				+		+				
Spinal cord	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																X					X				
Alveolar/bronchiolar carcinoma																									
Alveolar/bronchiolar carcinoma, multiple																								X	
Sarcoma, metastatic, skeletal muscle																				X					
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

TABLE B2
Individual Animal Tumor Pathology of Female Swiss (CD-1®) Mice in the Transplacental Study of AZT: Vehicle Control

Number of Days on Study	612	644	648	651	658	668	668	669	669	670	671	671	671	671	672	672	674	675	675	675	675	676	678	678	679	
Carcass ID Number	586	573	451	443	570	579	584	576	577	571	574	582	588	592	587	694	644	450	457	460	464	454	459	721	445	Total Tissues/ Tumors
Genital System																										
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cystadenoma																										2
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma																										1
Histiocytic sarcoma																				X						1
Polyp stromal																		X								1
Vagina	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node		+																								14
Lymph node, mandibular	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma																										1
Sarcoma, metastatic, skeletal muscle																										1
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma		X																								2
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Squamous cell carcinoma		X																								1
Subcutaneous tissue, fibrosarcoma	X																									1
Subcutaneous tissue, fibrous, histiocytoma																								X		1
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Skeletal muscle																										5
Sarcoma																										1
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Peripheral nerve			+																							7
Spinal cord	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma				X			X									X	X							X		7
Alveolar/bronchiolar carcinoma		X					X															X		X		4
Alveolar/bronchiolar carcinoma, multiple																										1
Sarcoma, metastatic, skeletal muscle																										1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50

TABLE B2
Individual Animal Tumor Pathology of Female Swiss (CD-1®) Mice in the Transplacental Study of AZT: Vehicle Control

Number of Days on Study	105	179	248	255	287	352	372	391	443	443	460	497	510	535	558	573	577	581	588	588	593	598	598	599	609
Carcass ID Number	585	448	449	463	719	461	589	572	455	693	591	462	575	466	581	458	467	452	580	590	465	453	456	583	578
Special Senses System																									
Harderian gland	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma															X						X				
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																									
Lymphoma malignant						X		X					X		X			X	X		X		X		X

TABLE B2
Individual Animal Tumor Pathology of Female Swiss (CD-1®) Mice in the Transplacental Study of AZT: Vehicle Control

Number of Days on Study	612	644	648	651	658	668	668	669	669	670	671	671	671	671	672	672	674	675	675	675	675	676	678	678	679	
Carcass ID Number	586	573	451	443	570	579	584	576	577	571	574	582	588	592	587	694	644	450	457	460	464	454	459	721	445	Total Tissues/ Tumors
Special Senses System																										
Harderian gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenoma	X														X											4
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																				X						1
Lymphoma malignant	X	X						X	X	X		X	X					X			X				X	19

TABLE B2
Individual Animal Tumor Pathology of Female Swiss (CD-1®) Mice in the Transplacental Study of AZT: 50 mg/kg

Number of Days on Study	207	219	290	326	341	350	369	395	402	412	417	441	472	475	475	476	500	500	521	536	539	549	556	559	560
Carcass ID Number	614	485	613	600	489	611	471	616	608	606	731	483	596	607	617	482	472	484	733	599	488	491	481	490	597
Alimentary System																									
Esophagus	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	A	+
Intestine large, colon	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	A	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																							X		
Intestine small, ileum	+	+	A	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular carcinoma																									
Hepatocellular adenoma																									
Hepatocellular adenoma, multiple																									
Histiocytic sarcoma																							X		
Osteosarcoma, metastatic, bone																									
Plasma cell tumor malignant												X													
Mesentery												+				+		+						+	
Fibrosarcoma, metastatic, skin																									
Plasma cell tumor malignant												X													
Pancreas	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cardiovascular System																									
Heart	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Plasma cell tumor malignant												X													
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Plasma cell tumor malignant												X													
Subcapsular, adenoma																									
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Plasma cell tumor malignant												X													
Islets, pancreatic	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid gland	+	+	M	+	M	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+
Pituitary gland	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma																									
Pars intermedia, adenoma																									
Thyroid gland	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell, adenoma																									X
General Body System																									
None																									

TABLE B2
Individual Animal Tumor Pathology of Female Swiss (CD-1®) Mice in the Transplacental Study of AZT: 50 mg/kg

Number of Days on Study	560	565	577	577	600	644	655	668	668	669	671	671	672	672	675	675	676	677	677	677	677	677	678	679	679	
Carcass ID Number	615	487	473	478	610	593	594	612	735	736	602	603	605	609	474	475	486	468	477	479	480	724	476	469	492	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	48
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Histiocytic sarcoma																										1
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular carcinoma																								X		1
Hepatocellular adenoma									X			X								X						3
Hepatocellular adenoma, multiple																									X	1
Histiocytic sarcoma																										1
Osteosarcoma, metastatic, bone		X																								1
Plasma cell tumor malignant																										1
Mesentery						+			+								+							+		8
Fibrosarcoma, metastatic, skin						X																				1
Plasma cell tumor malignant																										1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cardiovascular System																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Plasma cell tumor malignant																										1
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Plasma cell tumor malignant																										1
Subcapsular, adenoma																X										1
Adrenal medulla	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Plasma cell tumor malignant																										1
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Parathyroid gland	+	+	+	+	+	+	+	M	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pars distalis, adenoma																									X	1
Pars intermedia, adenoma										X																1
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Follicular cell, adenoma																										1
General Body System																										
None																										

TABLE B2
Individual Animal Tumor Pathology of Female Swiss (CD-1®) Mice in the Transplacental Study of AZT: 50 mg/kg

Number of Days on Study	207	219	290	326	341	350	369	395	402	412	417	441	472	475	475	476	500	500	521	536	539	549	556	559	560
Carcass ID Number	614	485	613	600	489	611	471	616	608	606	731	483	596	607	617	482	472	484	733	599	488	491	481	490	597
Genital System																									
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cystadenoma																									
Luteoma																									
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangioma																									
Leiomyoma																									
Polyp stromal																									
Vagina	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Plasma cell tumor malignant												X													
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																							X		
Plasma cell tumor malignant												X													
Lymph node	+	+			+			+				+	+	+	+	+				+	+	+	+	+	+
Histiocytic sarcoma																							X		
Iliac, histiocytic sarcoma																							X		
Mediastinal, plasma cell tumor, malignant												X												X	
Renal, histiocytic sarcoma																							X		
Renal, plasma cell tumor malignant												X													
Lymph node, mandibular	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	I	+	+	+	+
Histiocytic sarcoma																							X		
Plasma cell tumor malignant												X													
Lymph node, mesenteric	+	+	M	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																							X		
Plasma cell tumor malignant												X													
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																							X		
Osteosarcoma, metastatic, bone																									
Plasma cell tumor malignant												X													
Thymus	M	M	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	M
Histiocytic sarcoma																							X		
Plasma cell tumor malignant												X												X	
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma																									
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell papilloma																									
Subcutaneous tissue, fibrosarcoma																									
Subcutaneous tissue, hemangiosarcoma																									

TABLE B2
Individual Animal Tumor Pathology of Female Swiss (CD-1®) Mice in the Transplacental Study of AZT: 50 mg/kg

Number of Days on Study	560	565	577	577	600	644	655	668	668	669	671	671	672	672	675	675	676	677	677	677	677	677	678	679	679	
Carcass ID Number	615	487	473	478	610	593	594	612	735	736	602	603	605	609	474	475	486	468	477	479	480	724	476	469	492	Total Tissues/ Tumors
Genital System																										
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cystadenoma																		X								1
Luteoma							X																			1
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangioma	X																									1
Leiomyoma							X																			1
Polyp stromal													X													1
Vagina	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	49
Plasma cell tumor malignant																										1
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																										1
Plasma cell tumor malignant																										1
Lymph node	+	+	+				+	+		+				+											+	23
Histiocytic sarcoma																										1
Iliac, histiocytic sarcoma																										1
Mediastinal, plasma cell tumor, malignant																										2
Renal, histiocytic sarcoma																										1
Renal, plasma cell tumor malignant																										1
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	I	+	47
Histiocytic sarcoma																										1
Plasma cell tumor malignant																										1
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Histiocytic sarcoma																										1
Plasma cell tumor malignant																										1
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																										1
Osteosarcoma, metastatic, bone		X																								1
Plasma cell tumor malignant																										1
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	I	+	+	44
Histiocytic sarcoma																										1
Plasma cell tumor malignant																										2
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma															X	X										2
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Squamous cell papilloma																									X	1
Subcutaneous tissue, fibrosarcoma						X																				1
Subcutaneous tissue, hemangiosarcoma													X													1

TABLE B2
Individual Animal Tumor Pathology of Female Swiss (CD-1®) Mice in the Transplacental Study of AZT: 50 mg/kg

Number of Days on Study	207	219	290	326	341	350	369	395	402	412	417	441	472	475	475	476	500	500	521	536	539	549	556	559	560
Carcass ID Number	614	485	613	600	489	611	471	616	608	606	731	483	596	607	617	482	472	484	733	599	488	491	481	490	597
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Osteoma																										
Osteosarcoma																										
Skeletal muscle				+			+																			
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Peripheral nerve				+			+							+												
Spinal cord	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Respiratory System																										
Lung	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																										
Alveolar/bronchiolar adenoma, multiple																										
Alveolar/bronchiolar carcinoma																										X
Osteosarcoma, metastatic, bone																										
Plasma cell tumor malignant												X														
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																										
Harderian gland	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																										
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Plasma cell tumor malignant												X														
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																							X		
Lymphoma malignant					X		X	X	X						X	X		X							X

TABLE B2
Individual Animal Tumor Pathology of Female Swiss (CD-1®) Mice in the Transplacental Study of AZT: 50 mg/kg

Number of Days on Study	560	565	577	577	600	644	655	668	668	669	671	671	672	672	675	675	676	677	677	677	677	677	678	679	679	
Carcass ID Number	615	487	473	478	610	593	594	612	735	736	602	603	605	609	474	475	486	468	477	479	480	724	476	469	492	Total Tissues/ Tumors
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Osteoma			X																							1
Osteosarcoma		X																								1
Skeletal muscle																										2
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Peripheral nerve		+		+																						5
Spinal cord	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Alveolar/bronchiolar adenoma						X	X									X										3
Alveolar/bronchiolar adenoma, multiple															X						X				X	3
Alveolar/bronchiolar carcinoma		X		X																X	X		X			6
Osteosarcoma, metastatic, bone		X																								1
Plasma cell tumor malignant																										1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Special Senses System																										
Harderian gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenoma				X										X	X			X		X					X	6
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Plasma cell tumor malignant																										1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																										1
Lymphoma malignant	X	X	X					X		X			X	X			X			X		X	X			19

TABLE B2
Individual Animal Tumor Pathology of Female Swiss (CD-1®) Mice in the Transplacental Study of AZT: 100 mg/kg

Number of Days on Study	181	182	237	322	328	332	362	425	432	460	490	495	514	524	537	574	585	590	612	619	621	631	640	650	654
Carcass ID Number	508	506	511	637	631	499	620	622	510	498	635	629	497	633	623	493	639	500	501	509	517	640	729	628	513
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder	+	+	+	A	+	A	+	+	+	+	+	+	+	+	+	+	A	A	+	+	+	A	+	+	+
Intestine large, colon	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	A	A	+	+	+	+	+	+	+	+	+	+	+	A	+	A	+	+	A	+	+	+
Intestine small, duodenum	+	+	+	A	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	A	A	+	+	+	+	A	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	+	A	A	+	+	+	A	+	+	+	+	+	+	+	M	+	+	+	+	M	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar carcinoma, metastatic, lung													X												
Hemangiosarcoma																									
Hepatocellular adenoma													X		X										
Hepatocellular adenoma, multiple																					X				
Histiocytic sarcoma																						X			
Plasma cell tumor malignant		X																							
Mesentery							+							+		+						+			
Hemangioma																						X			
Pancreas	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+
Stomach, forestomach	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell papilloma																									
Stomach, glandular	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cardiovascular System																									
Blood vessel		+														+									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar carcinoma, metastatic, lung													X												
Plasma cell tumor malignant		X																							
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islets, pancreatic	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid gland	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma																									X
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
General Body System																									
None																									

TABLE B2
Individual Animal Tumor Pathology of Female Swiss (CD-1®) Mice in the Transplacental Study of AZT: 100 mg/kg

Number of Days on Study	666	668	669	669	670	670	670	670	670	671	671	671	671	672	675	675	675	675	677	677	678	678	678	679	679	
Carcass ID Number	624	737	619	642	621	625	627	632	738	626	636	641	739	634	494	496	503	504	495	507	502	505	514	515	516	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar carcinoma, metastatic, lung																										1
Hemangiosarcoma			X																							1
Hepatocellular adenoma																	X								X	4
Hepatocellular adenoma, multiple																										1
Histiocytic sarcoma																										1
Plasma cell tumor malignant																										1
Mesentery													+	+	+											7
Hemangioma																										1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Squamous cell papilloma															X											1
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Cardiovascular System																										
Blood vessel																										2
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar carcinoma, metastatic, lung																										1
Plasma cell tumor malignant																										1
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	48
Adenoma					X																					1
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pars distalis, adenoma																										1
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
General Body System																										
None																										

TABLE B2
Individual Animal Tumor Pathology of Female Swiss (CD-1®) Mice in the Transplacental Study of AZT: 100 mg/kg

Number of Days on Study	181	182	237	322	328	332	362	425	432	460	490	495	514	524	537	574	585	590	612	619	621	631	640	650	654
Carcass ID Number	508	506	511	637	631	499	620	622	510	498	635	629	497	633	623	493	639	500	501	509	517	640	729	628	513
Genital System																									
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Ovary	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cystadenoma																									X
Plasma cell tumor malignant		X																							
Sertoli cell tumor benign																									
Uterus	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leiomyoma																									
Leiomyosarcoma																							X		
Polyp stromal																									
Vagina	+	+	M	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																						X			
Lymph node		+						+	+	+		+		+			+		+			+	+	+	+
Plasma cell tumor malignant		X																							
Deep cervical, plasma cell tumor, malignant		X																							
Iliac, plasma cell tumor malignant		X																							
Inguinal, plasma cell tumor malignant		X																							
Mediastinal, histiocytic sarcoma																						X			
Mediastinal, plasma cell tumor, malignant		X																							
Pancreatic, hemangioma																									
Pancreatic, plasma cell tumor, malignant		X																							
Popliteal, plasma cell tumor, malignant		X																							
Renal, plasma cell tumor malignant		X																							
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+
Histiocytic sarcoma																						X			
Plasma cell tumor malignant		X																							
Lymph node, mesenteric	+	+	+	A	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																						X			
Plasma cell tumor malignant		X																							
Spleen	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																						X			
Plasma cell tumor malignant		X																							
Thymus	+	+	+	+	+	M	+	M	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar carcinoma, metastatic, lung													X												
Histiocytic sarcoma																						X			
Plasma cell tumor malignant		X																							
Integumentary System																									
Mammary gland	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma								X																X	
Skin	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Subcutaneous tissue, hemangiosarcoma																									X

TABLE B2
Individual Animal Tumor Pathology of Female Swiss (CD-1®) Mice in the Transplacental Study of AZT: 100 mg/kg

Number of Days on Study	666	668	669	669	670	670	670	670	670	671	671	671	671	672	675	675	675	675	677	677	678	678	678	679	679	
Carcass ID Number	624	737	619	642	621	625	627	632	738	626	636	641	739	634	494	496	503	504	495	507	502	505	514	515	516	Total Tissues/ Tumors
Genital System																										
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Cystadenoma				X																						2
Plasma cell tumor malignant																										1
Sertoli cell tumor benign																			X							1
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Leiomyoma															X											1
Leiomyosarcoma																										1
Polyp stromal																									X	1
Vagina	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	47
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																										1
Lymph node			+				+	+								+										16
Plasma cell tumor malignant																										1
Deep cervical, plasma cell tumor, malignant																										1
Iliac, plasma cell tumor malignant																										1
Inguinal, plasma cell tumor malignant																										1
Mediastinal, histiocytic sarcoma																										1
Mediastinal, plasma cell tumor, malignant																										1
Pancreatic, hemangioma								X																		1
Pancreatic, plasma cell tumor, malignant																										1
Popliteal, plasma cell tumor, malignant																										1
Renal, plasma cell tumor malignant																										1
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Histiocytic sarcoma																										1
Plasma cell tumor malignant																										1
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	M	+	+	+	+	+	+	46
Histiocytic sarcoma																										1
Plasma cell tumor malignant																										1
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Histiocytic sarcoma																										1
Plasma cell tumor malignant																										1
Thymus	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Alveolar/bronchiolar carcinoma, metastatic, lung																										1
Histiocytic sarcoma																										1
Plasma cell tumor malignant																										1
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Carcinoma																										2
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Subcutaneous tissue, hemangiosarcoma																										1

TABLE B2
Individual Animal Tumor Pathology of Female Swiss (CD-1®) Mice in the Transplacental Study of AZT: 100 mg/kg

Number of Days on Study	181	182	237	322	328	332	362	425	432	460	490	495	514	524	537	574	585	590	612	619	621	631	640	650	654
Carcass ID Number	508	506	511	637	631	499	620	622	510	498	635	629	497	633	623	493	639	500	501	509	517	640	729	628	513
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skeletal muscle																	+								
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar carcinoma, metastatic, lung													X												
Peripheral nerve										+											+		+		
Spinal cord	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma									X										X	X					
Alveolar/bronchiolar adenoma, multiple																								X	
Alveolar/bronchiolar carcinoma																									
Alveolar/bronchiolar carcinoma, multiple													X												
Carcinoma, metastatic, harderian gland																X									
Carcinoma, metastatic, mammary gland								X																	
Histiocytic sarcoma																						X			
Plasma cell tumor malignant		X																							
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																										
Eye																+									
Harderian gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma															X										
Carcinoma																X									
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Plasma cell tumor malignant		X																							
Urinary bladder	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																						X			
Leukemia granulocytic															X										
Lymphoma malignant								X				X		X							X			X	

TABLE B2
Individual Animal Tumor Pathology of Female Swiss (CD-1®) Mice in the Transplacental Study of AZT: 100 mg/kg

Number of Days on Study	666	668	669	669	670	670	670	670	670	671	671	671	671	672	675	675	675	675	677	677	678	678	678	679	679	
Carcass ID Number	624	737	619	442	621	625	627	632	738	626	636	641	739	634	494	496	503	504	495	507	502	505	514	515	516	Total Tissues/ Tumors
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Skeletal muscle																										1
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar carcinoma, metastatic, lung																										1
Peripheral nerve																										3
Spinal cord	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma				X					X					X							X					7
Alveolar/bronchiolar adenoma, multiple																										1
Alveolar/bronchiolar carcinoma			X	X				X	X		X	X														6
Alveolar/bronchiolar carcinoma, multiple																		X								2
Carcinoma, metastatic, harderian gland																										1
Carcinoma, metastatic, mammary gland																										1
Histiocytic sarcoma																										1
Plasma cell tumor malignant																										1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
Eye	+																									2
Harderian gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma		X	X	X	X	X		X											X					X		9
Carcinoma																										1
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Plasma cell tumor malignant																										1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																										1
Leukemia granulocytic																										1
Lymphoma malignant			X			X	X	X		X		X	X	X	X	X	X			X	X	X			X	20

TABLE B2
Individual Animal Tumor Pathology of Female Swiss (CD-1®) Mice in the Transplacental Study of AZT: 200 mg/kg

Number of Days on Study	359	414	448	497	510	510	523	530	539	541	561	565	572	603	608	614	641	646	662	667	668	669	669	669	670
Carcass ID Number	524	654	647	526	649	664	645	655	532	525	660	623	657	530	518	662	659	651	652	653	661	644	656	663	643
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	A	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular adenoma			X																						
Histiocytic sarcoma																	X								
Mesentery			+											+											
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cardiovascular System																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma																									
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Parathyroid gland	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma																									
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
General Body System																									
None																									
Genital System																									
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Granulosa cell tumor malignant												X						X							
Hemangioma																			X						
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangioma																		X							
Histiocytic sarcoma																	X								
Polyp stromal																									
Vagina	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

TABLE B2
Individual Animal Tumor Pathology of Female Swiss (CD-1®) Mice in the Transplacental Study of AZT: 200 mg/kg

Number of Days on Study	670	671	671	672	672	675	675	675	676	677	677	677	678	679	679	
Carcass ID Number	650	646	658	648	665	522	531	534	520	521	527	528	529	519	533	Total Tissues/ Tumor
Alimentary System																
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	40
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	39
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	39
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	40
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	38
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	40
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	40
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	38
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	40
Hepatocellular adenoma		X														2
Histiocytic sarcoma																1
Mesentery								+								3
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	40
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	40
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	40
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	40
Cardiovascular System																
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	40
Endocrine System																
Adrenal cortex	+	+	+	+	+	+	+	+	M	+	M	+	+	+	+	38
Carcinoma			X													1
Adrenal medulla	+	+	+	+	+	+	+	+	M	+	M	+	+	+	+	38
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	40
Adenoma	X															1
Parathyroid gland	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	37
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	40
Pars distalis, adenoma					X											1
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	40
General Body System																
None																
Genital System																
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	40
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	40
Granulosa cell tumor malignant																2
Hemangioma																1
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	40
Hemangioma																1
Histiocytic sarcoma												X				2
Polyp stromal			X													1
Vagina	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	40

TABLE B2
Individual Animal Tumor Pathology of Female Swiss (CD-1®) Mice in the Transplacental Study of AZT: 200 mg/kg

Number of Days on Study	359	414	448	497	510	510	523	530	539	541	561	565	572	603	608	614	641	646	662	667	668	669	669	669	670
Carcass ID Number	524	654	647	526	649	664	645	655	532	525	660	623	657	530	518	662	659	651	652	653	661	644	656	663	643
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node	+		+		+								+						+	+					
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	M	+	+	M	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar carcinoma, metastatic, lung															X										
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma																		X							
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Subcutaneous tissue, fibrosarcoma							X																		
Subcutaneous tissue, hemangiosarcoma		X																							
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Osteoma																									
Skeletal muscle					+																				
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Peripheral nerve			+				+						+			+									
Spinal cord	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma	X															X									
Alveolar/bronchiolar carcinoma															X						X				
Alveolar/bronchiolar carcinoma, multiple									X		X														
Granulosa cell tumor malignant, metastatic, lung												X													
Histiocytic sarcoma																	X								
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																	X								
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Eye						+																			
Harderian gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma												X													
Histiocytic sarcoma																	X								

TABLE B2
Individual Animal Tumor Pathology of Female Swiss (CD-1®) Mice in the Transplacental Study of AZT: 200 mg/kg

Number of Days on Study	670	671	671	672	672	675	675	675	676	677	677	677	678	679	679	
Carcass ID Number	650	646	658	648	665	522	531	534	520	521	527	528	529	519	533	Total Tissues/ Tumor
Hematopoietic System																
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	40
Lymph node				+					+	+	+	+		+		12
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	40
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	40
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	40
Thymus	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	36
Alveolar/bronchiolar carcinoma, metastatic, lung																1
Integumentary System																
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	40
Carcinoma																1
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	40
Subcutaneous tissue, fibrosarcoma																1
Subcutaneous tissue, hemangiosarcoma																1
Musculoskeletal System																
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	40
Osteoma	X															1
Skeletal muscle																1
Nervous System																
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	40
Peripheral nerve												+				5
Spinal cord	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	40
Respiratory System																
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	40
Alveolar/bronchiolar adenoma										X				X		4
Alveolar/bronchiolar carcinoma				X			X									4
Alveolar/bronchiolar carcinoma, multiple								X				X				4
Granulosa cell tumor malignant, metastatic, lung																1
Histiocytic sarcoma																1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	40
Histiocytic sarcoma																1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	40
Special Senses System																
Eye																1
Harderian gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	40
Adenoma						X						X		X		4
Histiocytic sarcoma																1

TABLE B2
Individual Animal Tumor Pathology of Female Swiss (CD-1®) Mice in the Transplacental Study of AZT: 200 mg/kg

Number of Days on Study	359	414	448	497	510	510	523	530	539	541	561	565	572	603	608	614	641	646	662	667	668	669	669	669	670
Carcass ID Number	524	654	647	526	649	664	645	555	532	525	660	523	657	530	518	662	659	651	652	653	661	644	656	663	643
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																	X								
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																	X								
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																	X								
Lymphoma malignant	X				X	X					X	X	X			X			X		X		X		

TABLE B2
Individual Animal Tumor Pathology of Female Swiss (CD-1®) Mice in the Transplacental Study of AZT: 200 mg/kg

Number of Days on Study	670	671	671	672	672	675	675	675	676	677	677	677	678	679	679	
Carcass ID Number	650	646	658	648	665	522	531	534	520	521	527	528	529	519	533	Total Tissues/ Tumor
Urinary System																
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	40
Histiocytic sarcoma																1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	40
Histiocytic sarcoma																1
Systemic Lesions																
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	40
Histiocytic sarcoma												X				2
Lymphoma malignant				X			X		X	X	X				X	16

TABLE B2
Individual Animal Tumor Pathology of Female Swiss (CD-1®) Mice in the Transplacental Study of AZT: 300 mg/kg

Number of Days on Study	043	049	207	325	332	412	453	455	467	474	479	482	482	530	539	565	580	585	593	593	598	641	645	668	668
Carcass ID Number	568	550	545	678	548	546	565	559	564	563	544	558	566	553	567	569	562	571	547	557	561	555	549	675	679
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder	+	A	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	I	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+
Leiomyosarcoma																									
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	A	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																									
Intestine small, ileum	+	A	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular carcinoma													X												
Hepatocellular adenoma																									
Hepatocellular adenoma, multiple																X									
Histiocytic sarcoma																									X
Mesentery						+																			+
Histiocytic sarcoma																									X
Pancreas	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																									X
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoid tumor malignant																							X		
Cardiovascular System																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islets, pancreatic	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																X									
Parathyroid gland	M	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma																									
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
General Body System																									
None																									

TABLE B2
Individual Animal Tumor Pathology of Female Swiss (CD-1®) Mice in the Transplacental Study of AZT: 300 mg/kg

Number of Days on Study	669	669	669	670	670	670	671	671	671	671	672	672	676	677	677	678	678	
Carcass ID Number	556	672	673	669	670	677	668	680	681	682	674	676	560	551	554	543	552	Total Tissues/ Tumors
Alimentary System																		
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	42
Gallbladder	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	39
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	42
Intestine large, rectum	I	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	40
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	40
Leiomyosarcoma	X																	1
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	42
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	40
Histiocytic sarcoma																	X	1
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	40
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	42
Hepatocellular carcinoma										X								2
Hepatocellular adenoma				X	X													2
Hepatocellular adenoma, multiple		X																2
Histiocytic sarcoma																	X	2
Mesentery					+											+	+	5
Histiocytic sarcoma																		1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	41
Histiocytic sarcoma																		1
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	42
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	42
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	42
Carcinoid tumor malignant																		1
Cardiovascular System																		
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	42
Endocrine System																		
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	42
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	42
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	41
Adenoma					X													2
Parathyroid gland	I	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	M	36
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	42
Pars distalis, adenoma									X									1
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	42
General Body System																		
None																		

TABLE B2
Individual Animal Tumor Pathology of Female Swiss (CD-1®) Mice in the Transplacental Study of AZT: 300 mg/kg

Number of Days on Study	043	049	207	325	332	412	453	455	467	474	479	482	482	530	539	565	580	585	593	593	598	641	645	668	668
Carcass ID Number	568	550	545	678	548	546	565	559	564	563	544	558	566	553	567	569	562	671	547	557	561	555	549	675	679
Genital System																									
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cystadenoma																							X		
Granulosa cell tumor malignant																									
Hemangiosarcoma												X													
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Polyp stromal																									
Vagina	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																									X
Lymph node				+			+						+	+	+		+	+			+			+	+
Mediastinal, histiocytic sarcoma																									X
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																									X
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																									X
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																									X
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma																	X								
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skeletal muscle			+	+							+											+			
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Peripheral nerve			+						M			+	+						+	+		+			
Spinal cord	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma							X			X															
Alveolar/bronchiolar carcinoma																				X					
Alveolar/bronchiolar carcinoma, multiple																									
Hemangiosarcoma																									
Hepatocellular carcinoma, metastatic, liver													X												
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

TABLE B2
Individual Animal Tumor Pathology of Female Swiss (CD-1®) Mice in the Transplacental Study of AZT: 300 mg/kg

Number of Days on Study	669	669	669	670	670	670	671	671	671	671	672	672	676	677	677	678	678	
Carcass ID Number	556	672	673	669	670	677	668	680	681	682	674	676	560	551	554	543	552	Total Tissues/ Tumors
Genital System																		
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	42
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	42
Cystadenoma																		1
Granulosa cell tumor malignant				X														1
Hemangiosarcoma																		1
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	42
Polyp stromal															X			1
Vagina	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	41
Hematopoietic System																		
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	42
Histiocytic sarcoma																		1
Lymph node				+			+			+	+			+		+		16
Mediastinal, histiocytic sarcoma																		1
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	42
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	42
Histiocytic sarcoma																	X	2
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	42
Histiocytic sarcoma																		1
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	42
Histiocytic sarcoma																	X	2
Integumentary System																		
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	42
Carcinoma																		1
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	42
Musculoskeletal System																		
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	42
Skeletal muscle																		4
Nervous System																		
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	42
Peripheral nerve																		6
Spinal cord	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	42
Respiratory System																		
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	42
Alveolar/bronchiolar adenoma					X	X		X	X			X						7
Alveolar/bronchiolar carcinoma								X					X					3
Alveolar/bronchiolar carcinoma, multiple	X	X																2
Hemangiosarcoma												X						1
Hepatocellular carcinoma, metastatic, liver																		1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	42
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	42

TABLE B2
Individual Animal Tumor Pathology of Female Swiss (CD-1®) Mice in the Transplacental Study of AZT: 300 mg/kg

Number of Days on Study	043	049	207	325	332	412	453	455	467	474	479	482	482	530	539	565	580	585	593	593	598	641	645	668	668
Carcass ID Number	568	550	545	678	548	546	565	559	564	563	544	558	566	553	567	569	562	571	547	557	561	555	549	675	679
Special Senses System																									
Eye													+												M
Harderian gland	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma							X									X	X		X						X
Carcinoma																									
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																									X
Leukemia granulocytic																					X				
Lymphoma malignant				X				X						X			X	X					X	X	

TABLE B2
Individual Animal Tumor Pathology of Female Swiss (CD-1®) Mice in the Transplacental Study of AZT: 300 mg/kg

Number of Days on Study	669	669	669	670	670	670	671	671	671	671	672	672	676	677	677	678	678	
Carcass ID Number	556	672	673	669	670	677	668	680	681	682	674	676	560	551	554	543	552	Total Tissues/ Tumors
Special Senses System																		
Eye							+											2
Harderian gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	41
Adenoma			X			X												7
Carcinoma													X					1
Urinary System																		
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	42
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	42
Systemic Lesions																		
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	42
Histiocytic sarcoma																	X	2
Leukemia granulocytic																		1
Lymphoma malignant			X	X	X	X	X			X	X		X	X		X		17

TABLE B3
Statistical Analysis of Primary Neoplasms in Female Swiss (CD-1®) Mice in the Transplacental Study of AZT

	Vehicle Control	50 mg/kg	100 mg/kg	200 mg/kg	300 mg/kg
Harderian Gland: Adenoma					
Overall rate[a]	4/50 (8%)	6/50 (12%)	9/50 (18%)	4/40 (10%)	7/42 (17%)
Adjusted rate[b]	11.1%	19.1%	24.2%	12.4%	22.9%
Terminal rate[c]	1/20 (5%)	5/18 (28%)	8/24 (33%)	3/20 (15%)	3/19 (16%)
First incidence (days)	558	577	537	565	453
Poly-3 test[d]	P=0.294	P=0.283	P=0.121	P=0.587	P=0.167
Harderian Gland: Adenoma or Carcinoma					
Overall rate	4/50 (8%)	6/50 (12%)	10/50 (20%)	4/40 (10%)	8/42 (19%)
Adjusted rate	11.1%	19.1%	26.7%	12.4%	26.2%
Terminal rate	1/20 (5%)	5/18 (28%)	8/24 (33%)	3/20 (15%)	4/19 (21%)
First incidence (days)	558	577	537	565	453
Poly-3 test	P=0.211	P=0.283	P=0.078	P=0.587	P=0.098
Liver: Hepatocellular Adenoma					
Overall rate	3/50 (6%)	4/50 (8%)	5/50 (10%)	2/40 (5%)	4/42 (10%)
Adjusted rate	8.6%	12.9%	13.2%	6.1%	13.7%
Terminal rate	2/20 (10%)	4/18 (22%)	2/24 (8%)	1/20 (5%)	3/19 (16%)
First incidence (days)	658	668 (T)	514	488	565
Poly-3 test	P=0.511	P=0.433	P=0.399	P=0.533N	P=0.400
Liver: Hepatocellular Carcinoma					
Overall rate	2/50 (4%)	1/50 (2%)	0/50 (0%)	0/40 (0%)	2/42 (5%)
Adjusted rate	5.7%	3.2%	0.0%	0.0%	6.8%
Terminal rate	2/20 (10%)	1/18 (6%)	0/24 (0%)	0/20 (0%)	1/19 (5%)
First incidence (days)	668 (T)	668 (T)	—[e]	—	482
Poly-3 test	P=0.562	P=0.542N	P=0.226N	P=0.255N	P=0.632
Liver: Hepatocellular Adenoma or Carcinoma					
Overall rate	5/50 (10%)	5/50 (10%)	5/50 (10%)	2/40 (5%)	6/42 (14%)
Adjusted rate	14.3%	16.1%	13.2%	6.1%	20.1%
Terminal rate	4/20 (20%)	5/18 (28%)	2/24 (8%)	1/20 (5%)	4/19 (21%)
First incidence (days)	658	668 (T)	514	488	482
Poly-3 test	P=0.501	P=0.555	P=0.582N	P=0.241N	P=0.385
Lung: Alveolar/bronchiolar Adenoma					
Overall rate	7/50 (14%)	6/49 (12%)	8/50 (16%)	4/40 (10%)	7/42 (17%)
Adjusted rate	19.6%	19.3%	21.1%	12.1%	23.2%
Terminal rate	4/20 (20%)	4/18 (22%)	4/24 (17%)	2/20 (10%)	5/19 (26%)
First incidence (days)	573	644	432	359	453
Poly-3 test	P=0.522N	P=0.609N	P=0.551	P=0.301N	P=0.478
Lung: Alveolar/bronchiolar Carcinoma					
Overall rate	5/50 (10%)	6/49 (12%)	8/50 (16%)	8/40 (20%)	5/42 (12%)
Adjusted rate	14.2%	18.7%	21.5%	24.2%	17.2%
Terminal rate	3/20 (15%)	3/18 (17%)	7/24 (29%)	5/20 (25%)	4/19 (21%)
First incidence (days)	599	560	514	539	593
Poly-3 test	P=0.356	P=0.431	P=0.304	P=0.225	P=0.504
Lung: Alveolar/bronchiolar Adenoma or Carcinoma					
Overall rate	10/50 (20%)	11/49 (22%)	14/50 (28%)	12/40 (30%)	11/42 (26%)
Adjusted rate	27.7%	34.1%	36.4%	35.1%	36.1%
Terminal rate	5/20 (25%)	6/18 (33%)	9/24 (38%)	7/20 (35%)	8/19 (42%)
First incidence (days)	573	560	432	359	453
Poly-3 test	P=0.296	P=0.377	P=0.286	P=0.338	P=0.315

TABLE B3
Statistical Analysis of Primary Neoplasms in Female Swiss (CD-1®) Mice in the Transplacental Study of AZT

	Vehicle Control	50 mg/kg	100 mg/kg	200 mg/kg	300 mg/kg
Ovary: Granulosa Cell Tumor Malignant					
Overall rate	0/50 (0%)	0/50 (0%)	0/49 (0%)	2/40 (5%)	1/42 (2%)
Adjusted rate	0.0%	0.0%	0.0%	6.2%	3.5%
Terminal rate	0/20 (0%)	0/18 (0%)	0/24 (0%)	0/20 (0%)	1/19 (5%)
First incidence (days)	—	—[f]	—	565	668 (T)
Poly-3 test	P=0.059	—	—	P=0.219	P=0.461
Pancreatic Islets: Adenoma					
Overall rate	0/50 (0%)	0/49 (0%)	0/49 (0%)	1/40 (3%)	2/41 (5%)
Adjusted rate	0.0%	0.0%	0.0%	3.1%	6.9%
Terminal rate	0/20 (0%)	0/18 (0%)	0/24 (0%)	1/20 (5%)	1/19 (5%)
First incidence (days)	—	—	—	668 (T)	565
Poly-3 test	P=0.020	—	—	P=0.482	P=0.195
Thymus: Plasma Cell Tumor Malignant					
Overall rate	0/49 (0%)	2/44 (5%)	1/46 (2%)	0/36 (0%)	0/42 (0%)
Adjusted rate	0.0%	6.7%	2.8%	0.0%	0.0%
Terminal rate	0/20 (0%)	0/17 (0%)	0/23 (0%)	0/19 (0%)	0/19 (0%)
First incidence (days)	—	441	182	—	—
Poly-3 test	P=0.270N	P=0.202	P=0.505	—	—
All Organs: Hemangioma					
Overall rate	0/50 (0%)	1/50 (2%)	2/50 (4%)	2/40 (5%)	0/42 (0%)
Adjusted rate	0.0%	3.2%	5.4%	6.2%	0.0%
Terminal rate	0/20 (0%)	0/18 (0%)	1/24 (4%)	0/20 (0%)	0/19 (0%)
First incidence (days)	—	560	631	646	—
Poly-3 test	P=0.520	P=0.479	P=0.248	P=0.216	—
All Organs: Hemangiosarcoma					
Overall rate	3/50 (6%)	1/50 (2%)	2/50 (4%)	1/40 (3%)	2/42 (5%)
Adjusted rate	8.4%	3.2%	5.5%	3.1%	6.8%
Terminal rate	1/20 (5%)	1/18 (6%)	1/24 (4%)	0/20 (0%)	1/19 (5%)
First incidence (days)	577	668 (T)	654	414	482
Poly-3 test	P=0.460N	P=0.354N	P=0.486N	P=0.334N	P=0.587N
All Organs: Hemangioma or Hemangiosarcoma					
Overall rate	3/50 (6%)	2/50 (4%)	4/50 (8%)	3/40 (8%)	2/42 (5%)
Adjusted rate	8.4%	6.4%	10.9%	9.1%	6.8%
Terminal rate	1/20 (5%)	1/18 (6%)	2/24 (8%)	0/20 (0%)	1/19 (5%)
First incidence (days)	577	560	631	414	482
Poly-3 test	P=0.514N	P=0.557N	P=0.519	P=0.627	P=0.587N
All Organs: Histiocytic Sarcoma					
Overall rate	1/50 (2%)	1/50 (2%)	1/50 (2%)	2/40 (5%)	2/42 (5%)
Adjusted rate	2.9%	3.2%	2.7%	6.2%	6.9%
Terminal rate	1/20 (5%)	0/18 (0%)	0/24 (0%)	1/20 (5%)	2/19 (11%)
First incidence (days)	668 (T)	556	631	641	668 (T)
Poly-3 test	P=0.201	P=0.738	P=0.750N	P=0.470	P=0.432

TABLE B3
Statistical Analysis of Primary Neoplasms in Female Swiss (CD-1®) Mice in the Transplacental Study of AZT

	Vehicle Control	50 mg/kg	100 mg/kg	200 mg/kg	300 mg/kg
All Organs: Malignant Lymphoma					
Overall rate	19/50 (38%)	19/50 (38%)	20/50 (40%)	16/40 (40%)	17/42 (40%)
Adjusted rate	48.2%	50.3%	51.6%	45.3%	53.7%
Terminal rate	8/20 (40%)	8/18 (44%)	15/24 (63%)	8/20 (40%)	11/19 (58%)
First incidence (days)	352	341	425	359	325
Poly-3 test	P=0.463	P=0.517	P=0.471	P=0.491N	P=0.409
All Organs: Benign Neoplasms					
Overall rate	17/50 (34%)	17/50 (34%)	23/50 (46%)	14/40 (35%)	16/42 (38%)
Adjusted rate	44.7%	51.9%	58.5%	41.0%	51.2%
Terminal rate	7/20 (35%)	11/18 (61%)	14/24 (58%)	8/20 (40%)	10/19 (53%)
First incidence (days)	510	560	432	359	453
Poly-3 test	P=0.492N	P=0.349	P=0.153	P=0.468N	P=0.380
All Organs: Malignant Neoplasms					
Overall rate	30/50 (60%)	28/50 (56%)	31/50 (62%)	25/40 (63%)	27/42 (64%)
Adjusted rate	73.7%	70.4%	74.7%	66.6%	80.6%
Terminal rate	15/20 (75%)	12/18 (67%)	19/24 (79%)	11/20 (55%)	17/19 (90%)
First incidence (days)	352	341	182	359	325
Poly-3 test	P=0.374	P=0.468N	P=0.560	P=0.323N	P=0.318
All Organs: Benign or Malignant Neoplasms					
Overall rate	35/50 (70%)	33/50 (66%)	38/50 (76%)	31/40 (78%)	33/42 (79%)
Adjusted rate	84.1%	82.9%	89.1%	81.2%	92.9%
Terminal rate	16/20 (80%)	16/18 (89%)	23/24 (96%)	16/20 (80%)	19/19 (100%)
First incidence (days)	352	341	182	359	325
Poly-3 test	P=0.207	P=0.568N	P=0.347	P=0.481N	P=0.167

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

TABLE B4
Summary of the Incidence of Nonneoplastic Lesions in Female Swiss CD-1® Mice in the Transplacental Study of AZT[a]

	Vehicle Control		50 mg/kg		100 mg/kg		200 mg/kg		300 mg/kg	
Disposition Summary										
Animals initially in study	50		50		50		40		42	
Early deaths										
Accidental death			1							
Moribund	16		18		11		10		15	
Natural deaths	14		13		15		9		9	
Survivors										
Died last week of study	1		1				1			
Terminal sacrifice	19		17		24		20		18	
Animals examined microscopically	50		50		50		40		42	
Alimentary System										
Intestine large, colon	(50)		(49)		(49)		(39)		(42)	
Edema			1	(2%)	1	(2%)			1	(2%)
Intestine large, cecum	(47)		(48)		(45)		(38)		(40)	
Amyloid deposition	1	(2%)								
Edema	3	(6%)	3	(6%)	4	(9%)	4	(11%)	8	(20%)
Intestine small, duodenum	(50)		(50)		(48)		(40)		(42)	
Amyloid deposition	1	(2%)								
Erosion	1	(2%)	1	(2%)					2	(5%)
Ulcer					2	(4%)			1	(2%)
Epithelium, hyperplasia	12	(24%)	7	(14%)	12	(25%)	4	(10%)	9	(21%)
Intestine small, jejunum	(46)		(49)		(46)		(40)		(40)	
Amyloid deposition	1	(2%)								
Epithelium, hyperplasia			1	(2%)	1	(2%)			1	(3%)
Intestine small, ileum	(47)		(48)		(45)		(38)		(40)	
Amyloid deposition	1	(2%)								
Liver	(50)		(50)		(50)		(40)		(42)	
Amyloid deposition	1	(2%)					1	(3%)		
Angiectasis	1	(2%)								
Basophilic focus					1	(2%)			1	(2%)
Cyst	2	(4%)			1	(2%)	1	(3%)		
Eosinophilic focus	1	(2%)	2	(4%)	3	(6%)	1	(3%)	3	(7%)
Hematopoietic cell proliferation	8	(16%)	5	(10%)	5	(10%)	5	(13%)	8	(19%)
Hyperplasia, lymphoid							3	(8%)		
Infiltration cellular, mixed cell	7	(14%)	6	(12%)	6	(12%)	9	(23%)	9	(21%)
Necrosis, focal	6	(12%)	8	(16%)	5	(10%)	4	(10%)	6	(14%)
Regeneration			1	(2%)					1	(2%)
Thrombosis	1	(2%)								
Hepatocyte, hypertrophy	1	(2%)	6	(12%)	3	(6%)	2	(5%)	2	(5%)
Hepatocyte, vacuolization cytoplasmic			1	(2%)	3	(6%)			2	(5%)
Kupffer cell, hyperplasia	1	(2%)			1	(2%)	1	(3%)	2	(5%)
Kupffer cell, pigmentation	4	(8%)	4	(8%)	2	(4%)	6	(15%)	6	(14%)
Mesentery	(4)		(8)		(7)	(3)		(5)		
Angiectasis					1	(14%)				
Hemorrhage	1	(25%)	1	(13%)			1	(33%)		
Thrombosis	1	(25%)								
Fat, necrosis			5	(63%)	4	(57%)	2	(67%)	3	(60%)

[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 Swiss CD-1® Mice in the Transplacental Study of AZT

	Vehicle Control		50 mg/kg		100 mg/kg		200 mg/kg		300 mg/kg	
Alimentary System (continued)										
Pancreas	(50)		(49)		(49)		(40)		(41)	
Atrophy			1	(2%)			1	(3%)		
Edema			2	(4%)	1	(2%)			1	(2%)
Necrosis, focal	1	(2%)								
Acinus, cytoplasmic alteration			4	(8%)			2	(5%)	4	(10%)
Salivary glands	(50)		(49)		(49)		(40)		(42)	
Hyperplasia, lymphoid	2	(4%)	6	(12%)	3	(6%)	1	(3%)	4	(10%)
Stomach, forestomach	(50)		(50)		(49)		(40)		(42)	
Edema	1	(2%)	5	(10%)	3	(6%)	2	(5%)	4	(10%)
Erosion									2	(5%)
Epithelium, hyperplasia	4	(8%)	3	(6%)			2	(5%)	4	(10%)
Stomach, glandular	(50)		(50)		(49)		(40)		(42)	
Amyloid deposition	1	(2%)								
Cyst			2	(4%)						
Edema			2	(4%)	1	(2%)			2	(5%)
Erosion	1	(2%)	2	(4%)	1	(2%)				
Infiltration cellular, mixed cell									1	(2%)
Glands, hyperplasia, cystic	6	(12%)	12	(24%)	8	(16%)	10	(25%)	6	(14%)
Cardiovascular System										
Blood vessel	(3)				(2)					
Inflammation, chronic	1	(33%)								
Heart	(50)		(49)		(50)		(40)		(42)	
Amyloid deposition	1	(2%)								
Cardiomyopathy	3	(6%)	2	(4%)	6	(12%)	1	(3%)	2	(5%)
Inflammation, chronic	7	(14%)	1	(2%)	2	(4%)	2	(5%)	2	(5%)
Mineralization	2	(4%)	3	(6%)	2	(4%)	1	(3%)	2	(5%)
Thrombosis					3	(6%)			1	(2%)
Endocrine System										
Adrenal cortex	(50)		(49)		(50)		(38)		(42)	
Accessory adrenal cortical nodule	10	(20%)	8	(16%)	11	(22%)	7	(18%)	6	(14%)
Amyloid deposition	1	(2%)								
Hyperplasia, diffuse			2	(4%)					1	(2%)
Hypertrophy, focal									1	(2%)
Capsule, hyperplasia	1	(2%)	1	(2%)			2	(5%)	2	(5%)
Adrenal medulla	(50)		(49)		(50)		(38)		(42)	
Hyperplasia	1	(2%)	3	(6%)	1	(2%)				
Islets, pancreatic	(50)		(49)		(49)		(40)		(41)	
Hyperplasia	2	(4%)	5	(10%)	6	(12%)	7	(18%)	10	(24%)
Pituitary gland	(50)		(49)		(50)		(40)		(42)	
Pars distalis, angiectasis					1	(2%)	1	(3%)	2	(5%)
Pars distalis, cyst	3	(6%)					3	(8%)		
Pars distalis, hyperplasia, focal	3	(6%)	4	(8%)	1	(2%)	2	(5%)	4	(10%)
Pars distalis, hyperplasia	1	(2%)			1	(2%)				
Thyroid gland	(50)		(49)		(50)		(40)		(42)	
Amyloid deposition	1	(2%)					1	(3%)		
Degeneration, cystic	26	(52%)	18	(37%)	39	(78%)	24	(60%)	29	(69%)
Follicular cell, hyperplasia	4	(8%)	2	(4%)	5	(10%)	4	(10%)	1	(2%)

TABLE B4
Summary of the Incidence of Nonneoplastic Lesions in Female Swiss CD-1® Mice in the Transplacental Study of AZT

	Vehicle Control		50 mg/kg		100 mg/kg		200 mg/kg		300 mg/kg	
General Body System										
None										
Genital System										
Clitoral gland	(50)		(50)		(50)		(40)		(42)	
Cyst	22	(44%)	18	(36%)	25	(50%)	14	(35%)	12	(29%)
Infiltration cellular, lymphocyte							1	(3%)		
Inflammatioin, chronic	23	(46%)	19	(38%)	17	(34%)	14	(35%)	16	(38%)
Ovary	(50)		(50)		(49)		(40)		(42)	
Amyloid deposition	1	(2%)							1	(2%)
Angiectasis	1	(2%)	1	(2%)	4	(8%)	3	(8%)	4	(10%)
Cyst	38	(76%)	35	(70%)	37	(76%)	28	(70%)	29	(69%)
Hematocyst	1	(2%)								
Hemorrhage	2	(4%)	2	(4%)	7	(14%)	5	(13%)	4	(10%)
Thrombosis					2	(4%)	1	(3%)	1	(2%)
Bilateral, cyst							1	(3%)		
Corpus luteum, hyperplasia	1	(2%)			1	(2%)	1	(3%)	1	(2%)
Uterus	(50)		(50)		(49)		(40)		(42)	
Angiectasis	1	(2%)			4	(8%)			1	(2%)
Hemorrhage			1	(2%)	1	(2%)				
Infiltration cellular, histiocyte									1	(2%)
Inflammation, chronic	1	(2%)	1	(2%)					1	(2%)
Thrombosis	2	(4%)			3	(6%)			1	(2%)
Endometrium, hyperplasia, cystic	22	(44%)	27	(54%)	29	(59%)	24	(60%)	22	(52%)
Vagina	(49)		(49)		(47)		(40)		(41)	
Cyst	2	(4%)			1	(2%)				
Epithelium, hyperplasia	1	(2%)	1	(2%)	2	(4%)				
Hematopoietic System										
Bone marrow	(50)		(50)		(50)		(40)		(42)	
Hyperplasia	33	(66%)	24	(48%)	30	(60%)	22	(55%)	26	(62%)
Myelofibrosis			1	(2%)					1	(2%)
Lymph node	(14)		(23)		(16)		(12)		(16)	
Hematopoietic cell proliferation	1	(7%)	1	(4%)	2	(13%)				
Hemorrhage					1	(6%)				
Hyperplasia, lymphoid	1	(7%)	3	(13%)			1	(8%)		
Hyperplasia, plasma cell	2	(14%)							1	(6%)
Pigmentation									1	(6%)
Bronchial, hemorrhage			1	(4%)						
Iliac, hematopoietic cell proliferatioin	1	(7%)	1	(4%)	1	(6%)				
Iliac, hemorrhage									1	(6%)
Iliac, hyperplasia, lymphoid			2	(9%)	2	(13%)				
Inguinal, hematopoietic cell proliferation			1	(4%)					1	(6%)
Inguinal, hyperplasia, lymphoid	2	(14%)	4	(17%)	2	(13%)	1	(8%)	2	(13%)
Inguinal, hyperplasia, plasma cell	1	(7%)								
Inguinal, pigmentation			1	(4%)						
Lumbar, hematopoietic cell proliferation	1	(7%)								
Lumbar, hyperplasia, lymphoid			1	(4%)					1	(6%)
Mediastinal, hematopoietic cell proliferation	1	(7%)								
Mediastinal, hemorrhage	1	(7%)	1	(4%)	2	(13%)			1	(6%)
Mediastinal, hyperplasia, lymphoid	1	(7%)	2	(9%)			1	(8%)		
Mediastinal, pigmentation			1	(4%)						
Pancreatic, hyperplasia, lymphoid							1	(8%)		
Popliteal, hyperplasia					1	(6%)				

Table B4
Summary of the Incidence of Nonneoplastic Lesions in Female Swiss CD-1® Mice in the Transplacental Study of AZT

	Vehicle Control		50 mg/kg		100 mg/kg		200 mg/kg		300 mg/kg	
Hematopoietic System (continued)										
Lymph node (continued)	(14)		(23)		(16)		(12)		(16)	
Popliteal, hyperplasia, lymphoid							1	(8%)		
Renal, ectasia			1	(4%)						
Renal, hematopoietic cell proliferation			1	(4%)						
Renal, hemorrhage			2	(9%)	1	(6%)				
Renal, hyperplasia, lymphoid			3	(13%)	2	(13%)				
Lymph node, mandibular	(49)		(47)		(49)		(40)		(42)	
Amyloid deposition	1	(2%)								
Atrophy	2	(4%)	2	(4%)	1	(2%)			4	(10%)
Ectasia	2	(4%)	1	(2%)			3	(8%)	2	(5%)
Hematopoietic cell proliferation	7	(14%)	3	(6%)	2	(4%)	4	(10%)	6	(14%)
Hemorrhage	3	(6%)	4	(9%)	5	(10%)	5	(13%)	7	(17%)
Hyperplasia, lymphoid	9	(18%)	10	(21%)	17	(35%)	10	(25%)	4	(10%)
Hyperplasia, plasma cell	5	(10%)							3	(7%)
Infiltration cellular, plasma cell	2	(4%)								
Pigmentation	5	(10%)	4	(9%)	2	(4%)	4	(10%)	6	(14%)
Lymph node, mesenteric	(50)		(48)		(46)		(40)		(42)	
Atrophy	2	(4%)	4	(8%)	2	(4%)	1	(3%)	5	(12%)
Ectasia	2	(4%)	3	(6%)	2	(4%)	3	(8%)	1	(2%)
Hematopoietic cell proliferation	6	(12%)	6	(13%)	2	(4%)	3	(8%)	8	(19%)
Hemorrhage	12	(24%)	10	(21%)	9	(20%)	9	(23%)	11	(26%)
Hyperplasia, lymphoid	6	(12%)	7	(15%)	9	(20%)	10	(25%)	7	(17%)
Pigmentation	2	(4%)	7	(15%)	3	(7%)	2	(5%)	4	(10%)
Spleen	(50)		(50)		(49)		(40)		(42)	
Amyloid deposition							1	(3%)		
Hematopoietic cell proliferation	31	(62%)	21	(42%)	32	(65%)	26	(65%)	29	(69%)
Pigmentation	13	(26%)	24	(48%)	12	(24%)	10	(25%)	12	(29%)
Lymphoid follicle, atrophy	4	(8%)	6	(12%)	5	(10%)	6	(15%)	4	(10%)
Lymphoid follicle, hyperplasia	7	(14%)	3	(6%)	7	(14%)	6	(15%)	7	(17%)
Thymus	(49)		(44)		(46)		(36)		(42)	
Atrophy	7	(14%)	3	(7%)	5	(11%)	2	(6%)	4	(10%)
Hemorrhage	1	(2%)	4	(9%)	2	(4%)			3	(7%)
Hyperplasia, lymphoid	7	(14%)	3	(7%)	3	(7%)	7	(19%)	2	(5%)
Thrombosis							1	(3%)		
Integumentary System										
Mammary gland	(50)		(50)		(49)		(40)		(42)	
Hyperplasia	9	(18%)	9	(18%)	8	(16%)	6	(15%)	7	(17%)
Skin	(50)		(50)		(49)		(40)		(42)	
Cyst epithelial inclusion							1	(3%)	2	(5%)
Edema	3	(6%)	7	(14%)	7	(14%)	6	(15%)	5	(12%)
Inflammation, chronic	1	(2%)			1	(2%)	1	(3%)	1	(2%)
Ulcer	8	(16%)	5	(10%)	1	(2%)	5	(13%)	3	(7%)
Epidermis, hyperplasia	7	(14%)	5	(10%)	3	(6%)	4	(10%)	3	(7%)
Musculoskeletal System										
Bone	(50)		(50)		(50)		(40)		(42)	
Fibrous osteodystrophy	2	(4%)	7	(14%)	9	(18%)	6	(15%)	4	(10%)
Hyperostosis					1	(2%)	1	(3%)		
Myelofibrosis							1	(3%)		
Cranium, hyperostosis			1	(2%)						
Femur, callus									1	(2%)
Femur, hyperostosis							1	(3%)		

TABLE B4
Summary of the Incidence of Nonneoplastic Lesions in Female Swiss CD-1® Mice in the Transplacental Study of AZT

	Vehicle Control		50 mg/kg		100 mg/kg		200 mg/kg		300 mg/kg	
Musculoskeletal System (continued)										
Skeletal muscle	(5)		(2)		(1)		(1)		(4)	
Inflammation, chronic	1	(20%)			1	(100%)				
Thrombosis									1	(25%)
Nervous System										
Brain	(50)		(50)		(50)		(40)		(42)	
Compression			1	(2%)						
Hemorrhage			1	(2%)	1	(2%)				
Necrosis			1	(2%)						
Peripheral nerve	(7)		(5)		(3)		(5)		(6)	
Atrophy			1	(20%)	1	(33%)	1	(20%)		
Spinal cord	(50)		(50)		(50)		(40)		(42)	
Cyst epithelial inclusion					1	(2%)	1	(3%)	1	(2%)
Necrosis	1	(2%)	1	(2%)			1	(3%)		
Respiratory System										
Lung	(50)		(49)		(50)		(40)		(42)	
Amyloid deposition									1	(2%)
Edema	1	(2%)	3	(6%)	4	(8%)	1	(3%)	3	(7%)
Fibrosis, focal					1	(2%)				
Foreign body	3	(6%)								
Hemorrhage	7	(14%)	6	(12%)	6	(12%)	2	(5%)	8	(19%)
Hyperplasia, lymphoid	1	(2%)	1	(2%)	3	(6%)	4	(10%)	1	(2%)
Infiltration cellular, histiocyte	12	(24%)	11	(22%)	21	(42%)	12	(30%)	10	(24%)
Infiltration cellular, mixed cell	2	(4%)					1	(3%)	1	(2%)
Inflammation, chronic	1	(2%)					2	(5%)	2	(5%)
Alveolar epithelium, hyperplasia	2	(4%)	2	(4%)	10	(20%)	3	(8%)	2	(5%)
Nose	(50)		(50)		(50)		(40)		(42)	
Foreign body	2	(4%)								
Inflammation, chronic	11	(22%)	2	(4%)	7	(14%)	2	(5%)	4	(10%)
Special Senses System										
Eye					(2)		(1)		(2)	
Atrophy					1	(50%)	1	(100%)		
Cataract									1	(50%)
Inflammation, chronic					1	(50%)				
Harderian gland	(49)		(49)		(50)		(40)		(41)	
Atrophy					1	(2%)			1	(2%)
Hyperplasia, focal					1	(2%)	2	(5%)	1	(2%)
Urinary System										
Kidney	(50)		(50)		(50)		(40)		(42)	
Amyloid deposition	2	(4%)			1	(2%)			2	(5%)
Cyst	2	(4%)	7	(14%)	5	(10%)	7	(18%)	5	(12%)
Hydronephrosis	2	(4%)	7	(14%)	5	(10%)	5	(13%)	3	(7%)
Infarct			1	(2%)	3	(6%)	2	(5%)		
Infiltration cellular, mixed cell	10	(20%)	20	(40%)	15	(30%)	14	(35%)	15	(36%)
Inflammation, chronic	3	(6%)								
Metaplasia, osseous	1	(2%)							2	(5%)

TABLE B4
Summary of the Incidence of Nonneoplastic Lesions in Female Swiss CD-1® Mice in the Transplacental Study of AZT

	Vehicle Control		50 mg/kg		100 mg/kg		200 mg/kg		300 mg/kg	
Urinary System (continued)										
Kidney (continued)	(50)		(50)		(50)		(40)		(42)	
Nephropathy	29	(58%)	31	(62%)	41	(82%)	26	(65%)	33	(79%)
Renal tubule, accumulation, hyaline droplet	1	(2%)	2	(4%)	2	(4%)	3	(8%)	3	(7%)
Renal tubule, dilatation	1	(2%)	3	(6%)			1	(3%)		
Renal tubule, necrosis					1	(2%)	1	(3%)		
Renal tubule, pigmentation	1	(2%)	1	(2%)	1	(2%)	2	(5%)	2	(5%)
Urinary bladder	(50)		(50)		(49)		(40)		(42)	
Hyperplasia, lymphoid	1	(2%)	1	(2%)	3	(6%)	2	(5%)	3	(7%)
Inflammation, chronic	1	(2%)	1	(2%)						

APPENDIX C
REPRODUCTIVE PERFORMANCE OF SWISS (CD-1®) MICE IN THE TRANSPLACENTAL STUDY OF AZT

TABLE C1 Survival of Swiss (CD-1®) Mouse Dams in the Transplacental Study of AZT 146
TABLE C2 Mean Body Weights of Swiss (CD-1®) Mouse Dams in the Transplacental Study of AZT 146
TABLE C3 Mean Body Weights of Swiss (CD-1®) Mouse Dams at Necropsy in the Transplacental Study of AZT 147
TABLE C4 Fertility Rates of Swiss (CD-1®) Mouse Dams in the Transplacental Study of AZT 147
TABLE C5 Number of Implantation Sites, Births, and *In Utero* Losses in Swiss (CD-1®) Mouse Dams in the Transplacental Study of AZT 148
TABLE C6 Litter Parameters for Swiss (CD-1®) Mouse Litters at Postnatal Day 0 in the Transplacental Study of AZT 148
TABLE C7 Litter Parameters for Swiss (CD-1®) Mouse Litters at Postnatal Day 4 in the Transplacental Study of AZT 149

TABLE C1
Survival of Swiss (CD-1®) Mouse Dams in the Transplacental Study of AZT

	Vehicle Control	100 mg/kg	200 mg/kg	300 mg/kg
Animals initially in study	19	23	30	39
Accidental deaths[a]	0	2	1	2
Moribund	1	0	0	0
Natural deaths[b]	2	0	0	0
Animals surviving to study termination	16	21	29	37
Percent probability of survival at end of study[c]	82	100	100	100
Mean survival (days)[d]	55	52	49	45
Survival analysis[e]	P=0.003	P=0.062N	P=0.057N	P=0.064N

[a] Gavage accidents; censored from survival analysis
[b] Cause of deaths undetermined
[c] Kaplan-Meier determinations
[d] Mean of all deaths (uncensored, censored, and terminal sacrifice)
[e] 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 lower mortality in a dosed group is indicated by **N**.

TABLE C2
Mean Body Weights of Swiss (CD-1®) Mouse Dams in the Transplacental Study of AZT[a]

Days on Study	Vehicle Control	50 mg/kg	100 mg/kg	200 mg/kg	300 mg/kg	ANOVA P Value
–1	29.8 ± 0.3 (22)	29.7 ± 0.3 (22)	29.5 ± 0.2 (28)	29.6 ± 0.2 (34)	29.6 ± 0.2 (46)	0.89
0	30.1 ± 0.3 (22)	30.0 ± 0.3 (22)	30.0 ± 0.3 (28)	30.1 ± 0.3 (34)	30.0 ± 0.2 (46)	0.99
4	30.6 ± 0.3 (22)	30.0 ± 0.4 (22)	30.4 ± 0.4 (28)	30.3 ± 0.3 (34)	30.2 ± 0.2 (46)	0.88
12	29.9 ± 0.5 (22)	29.2 ± 0.3 (22)	29.3 ± 0.3 (26)	29.2 ± 0.3 (34)	29.0 ± 0.3 (45)	0.46
16	31.0 ± 0.5 (22)	30.2 ± 0.4 (22)	30.3 ± 0.4 (26)	30.0 ± 0.3 (34)	29.8 ± 0.3 (45)	0.23
20	33.3 ± 0.7 (22)	32.4 ± 0.4 (22)	31.8 ± 0.5 (26)	31.5 ± 0.4* (33)	31.2 ± 0.3** (45)	0.01
23	35.7 ± 1.5 (11)	35.9 ± 1.1 (11)	32.2 ± 1.1 (14)	32.7 ± 0.9 (16)	31.4 ± 0.5** (23)	0.002
25	38.8 ± 1.7 (11)	35.8 ± 0.5 (11)	35.8 ± 1.2 (12)	32.3 ± 0.6** (17)	32.7 ± 0.6** (21)	<0.0001
26	43.5 ± 1.8 (22)	41.9 ± 0.9 (22)	38.3 ± 1.2** (26)	34.4 ± 0.8** (33)	32.9 ± 0.6** (44)	<0.0001

* Significantly different (P<0.05) from the vehicle control group by Dunnett's test (Dunnett, 1955)
** P<0.01
[a] Mean ± standard error of the mean in grams (sample size)

TABLE C3
Mean Body Weights of Swiss (CD-1®) Mouse Dams at Necropsy in the Transplacental Study of AZT[a]

Days on Study	Vehicle Control	100 mg/kg	200 mg/kg	300 mg/kg	P Value[b]
Less than 30[c]	— (0)	27.4 ± 1.8 (2)	25.3 (1)	27.8 ± 6.2 (2)	0.95
30 to 44[d]	29.9 (1)	28.8 ± 0.4 (2)	29.9 ± 0.8 (10)	30.6 ± 0.3 (19)	0.57
More than 44	38.0 ± 1.4 (18)	37.6 ± 0.8 (19)	35.4 ± 0.7 (19)	35.0 ± 0.6 (18)	0.055
Total	37.6 ± 1.4 (19)	35.9 ± 1.0 (23)	33.0 ± 0.7** (30)	32.7 ± 0.6** (39)	0.0002

** Significantly different (P≤0.01) from the vehicle control group by Dunnett's test (Dunnett, 1955)
[a] Mean ± standard error of the mean in grams (sample size)
[b] P value for equality of weights across dose groups from ANOVA
[c] These dams died early due to gavage accidents.
[d] These dams did not produce pups.

TABLE C4
Fertility Rates of Swiss (CD-1®) Mouse Dams in the Transplacental Study of AZT

	Vehicle Control	50 mg/kg	100 mg/kg	200 mg/kg	300 mg/kg	P Value[a]
Number of dams in group	22	22	28	34	46	
Number of dams sperm positive[b]	13	17	18	26	36	
Percent of dams sperm positive	59	77	64	76	78	0.13
Number of dams pregnant[c]	18	21	19	19*	18**	
Percent of dams pregnant	82	95	68	56*	39**	<0.0001

* Significantly different (P<0.05) from the vehicle control group by Fisher's exact test (Gart *et al.*, 1979)
** P<0.01
[a] Cochran-Armitage trend test (Armitage, 1971)
[b] Number of dams with vaginal plug *in situ*
[c] Number of dams delivering one or more pups

TABLE C5
Number of Implantation Sites, Births, and *In Utero* Losses in Swiss (CD-1®) Mouse Dams in the Transplacental Study of AZT

	Vehicle Control[a]	50 mg/kg	100 mg/kg	200 mg/kg	300 mg/kg	P Value[b]
Number of dams examined for implants[c]	19	0	23	30	39	
Number of implants per dam	12.2	—	9.6	6.7**	5.6**	<0.0001
Number of dams with no implants	1 (6%)	—	4 (17%)	8 (27%)	15** (38%)[d]	0.0002
Number of dams with at least one implant but having no litter information	0	—	0	3	6	
Number of dams having litter information	17	21	19	19	18	
Number of implants per dam[e]	13.0 ± 0.6	—	11.6 ± 0.6	8.8 ± 0.6**	9.3 ± 0.6**	<0.0001
Number of births per dam[e]	12.2 ± 0.8	9.5 ± 0.7*	8.7 ± 0.8**	4.9 ± 0.6**	4.3 ± 0.7**	<0.0001
Number of *in utero* losses per dam[e]	0.9 ± 0.3	—	2.8 ± 0.4*	3.9 ± 0.5**	5.0 ± 0.8**	<0.0001

* Significantly different at (P<0.05) from the vehicle control group by Dunnett's test (Dunnett, 1955)
** P<0.01
[a] One vehicle control dam is excluded in all rows below row one because the number of implants (10) was less than the number of births (14).
[b] Probability of overall difference across dose groups via parametric ANOVA, except *in utero* losses via nonparametric ANOVA and Dunn's test
[c] More dams were used in the higher dose groups to ensure that adequate numbers of pups would be produced.
[d] Cochran-Armitage trend test (Armitage, 1971) followed by Fisher's exact test (Gart *et al.*, 1979) comparing percentages in the dosed and vehicle control groups
[e] Mean ± standard error of the mean

TABLE C6
Litter Parameters for Swiss (CD-1®) Mouse Litters at Postnatal Day 0 in the Transplacental Study of AZT

	Vehicle Control	50 mg/kg	100 mg/kg	200 mg/kg	300 mg/kg	P Value[a]
Number of litters in group	17	21	19	19	18	
Males per litter						
Number live	5.8	4.3	3.5**	1.9**	1.7**	<0.0001
Number found dead	0.1	0.1	0.1	0.0	0.0	0.38
Total number per litter	5.9	4.4	3.6**	1.9**	1.7**	<0.0001
Females per litter						
Number live	5.1	4.8	4.6	2.4**	2.4**	<0.0001
Number found dead	0.05	0.1	0.05	0.0	0.05	0.78
Total number per litter	5.2	4.9	4.7	2.4**	2.5**	<0.0001
Unknown sex						
Number found dead	0.9	0.05	0.4	0.5	0.1	0.43
All pups per litter						
Number live[b]	10.9 ± 1.1	9.1 ± 0.7	8.2 ± 0.9	4.4 ± 0.7**	4.1 ± 0.7**	<0.0001
Number found dead[b]	1.1 ± 0.8	0.2 ± 0.1	0.6 ± 0.2	0.5 ± 0.2	0.2 ± 0.1	0.41

** Statistically different (P<0.01) from the vehicle control group by Dunn's (Dunn, 1964) or Dunnett's test (Dunnett, 1955)
[a] Probability of overall difference across dose groups via nonparametric or parametric ANOVA
[b] Mean ± standard error of the mean

TABLE C7
Litter Parameters for Swiss (CD-1®) Mouse Litters at Postnatal Day 4 in the Transplacental Study of AZT

	Vehicle Control	50 mg/kg	100 mg/kg	200 mg/kg	300 mg/kg	P Value[a]
Number of litters with at least one pup after postnatal day 0	16	21	18	15	17	
Males per litter						
Number culled	1.4	0.2**	0.3**	0.0**	0.0**	<0.0001
Number found dead or missing	0.1	0.1	0.1	0.1	0.1	0.99
Number remaining	4.8	4.1	3.4*	2.4**	1.8**	<0.0001
Females per litter						
Number culled	0.9	0.6	0.6	0.0	0.0	0.07
Number found dead or missing	0.1	0.05	0.2	0.1	0.0	0.49
Number remaining	4.6	4.1	4.2	3.0*	2.6**	0.003
All pups per litter						
Number culled	2.2	0.8*	0.8*	0.0**	0.0**	<0.0001
Number found dead[b]	0.1	0.1	0.3	0.1	0.1	0.83
Number remaining[c]	9.4 ± 0.4	8.3 ± 0.5	7.5 ± 0.7	5.4 ± 0.7**	4.3 ± 0.7**	<0.0001

* Significantly different P<0.05 from the vehicle control group by Dunn's (Dunn, 1964) or Dunnett's test (Dunnett, 1955)
** P<0.01
[a] Probability of overall difference via nonparametric or parametric ANOVA
[b] Includes pups that died on postnatal days 1 through 4; excludes culled pups
[c] Mean ± standard error of the mean

APPENDIX D
INCIDENCES OF SELECTED NEOPLASMS AND NONNEOPLASTIC LESIONS IN LITTERMATES

TABLE D1 **Incidence of Lung and Liver Neoplasms and Progressive Necrotizing Dermatitis in Littermates** 152
TABLE D2 **P Values for Litter and Sire Effects on Selected Neoplasm and Nonneoplastic Lesion Incidences in Swiss (CD-1®) Mice in the Transplacental Study of AZT** 161

TABLE D1
Incidence of Lung and Liver Neoplasms and Progressive Necrotizing Dermatitis in Littermates

Dam	Sire	Dose (mg/kg)	Sex	F_1 Pup ID Number	Lung: Alveolar/ bronchiolar Adenoma	Lung: Alveolar/ bronchiolar Carcinoma	Liver: Hepato-cellular Adenoma	Liver: Hepato-cellular Carcinoma	Skin: Ulcer	Skin: Chronic Inflammation
45	3	0	F	443	X				X	
45	3	0	F	444	X					
45	3	0	F	445					X	
47	4	0	F	448						
47	4	0	F	449						
47	4	0	F	450			X[a]		X	
51	6	0	F	451						
51	6	0	F	452						
51	6	0	F	453					X	
51	6	0	F	454		X				
48	4	0	F	455						
42	1	0	F	456						X
42	1	0	F	457				X		
42	1	0	F	458	X					
42	1	0	F	459						
44	2	0	F	460					X	
44	2	0	F	461						
44	2	0	F	462					X	
44	2	0	F	463					X	
46	3	0	F	464						
46	3	0	F	465	X					
46	3	0	F	466						
46	3	0	F	467						
120	2	0	F	570			X			
120	2	0	F	571						
120	2	0	F	572						
120	2	0	F	573		X				
117	1	0	F	574						
117	1	0	F	575						
117	1	0	F	576						
117	1	0	F	577						
119	2	0	F	578						
119	2	0	F	579						
119	2	0	F	580						
119	2	0	F	581						
123	4	0	F	582						
123	4	0	F	583		X[a]				
123	4	0	F	584	X	X				
123	4	0	F	585						
124	4	0	F	586						
124	4	0	F	587				X		
124	4	0	F	588			X			
124	4	0	F	589						
126	5	0	F	590						
126	5	0	F	591					X	
127	6	0	F	592						
127	6	0	F	693						
127	6	0	F	694	X					
48	4	0	F	719						
48	4	0	F	721	X	X				
57	9	50	F	468						

TABLE D1
Incidence of Lung and Liver Neoplasms and Progressive Necrotizing Dermatitis in Littermates

Dam	Sire	Dose (mg/kg)	Sex	F_1 Pup ID Number	Lung: Alveolar/ bronchiolar Adenoma	Lung: Alveolar/ bronchiolar Carcinoma	Liver: Hepato-cellular Adenoma	Liver: Hepato-cellular Carcinoma	Skin: Ulcer	Skin: Chronic Inflammation
57	9	50	F	469				X		
53	7	50	F	471						
53	7	50	F	472						
53	7	50	F	473						
55	8	50	F	474	X[a]					
54	8	50	F	475	X					
54	8	50	F	476		X				
54	8	50	F	477						
58	10	50	F	478		X				
58	10	50	F	479		X	X			
58	10	50	F	480	X[a]	X				
60	11	50	F	481						
60	11	50	F	482						
60	11	50	F	483						
56	9	50	F	484						
56	9	50	F	485						
56	9	50	F	486						
59	10	50	F	487		X				
59	10	50	F	488						
59	10	50	F	489						
62	12	50	F	490						
62	12	50	F	491						
62	12	50	F	492	X[a]		X[a]			
135	10	50	F	593	X					
135	10	50	F	594	X				X	
138	12	50	F	596						
138	12	50	F	597		X			X	
129	7	50	F	599						
129	7	50	F	600						
131	8	50	F	602						
131	8	50	F	603			X			
132	9	50	F	605						
132	9	50	F	606						
132	9	50	F	607					X	
133	9	50	F	608						
133	9	50	F	609						
133	9	50	F	610						
134	10	50	F	611						
134	10	50	F	612						
134	10	50	F	613	m[b]	m[b]				
136	11	50	F	614					X	
136	11	50	F	615					X	
137	11	50	F	616						
137	11	50	F	617						
61	11	50	F	724						
128	7	50	F	731						
128	7	50	F	733						
130	8	50	F	735			X			
130	8	50	F	736						
63	13	100	F	493						
63	13	100	F	494						

TABLE D1
Incidence of Lung and Liver Neoplasms and Progressive Necrotizing Dermatitis in Littermates

Dam	Sire	Dose (mg/kg)	Sex	F_1 Pup ID Number	Lung: Alveolar/ bronchiolar Adenoma	Lung: Alveolar/ bronchiolar Carcinoma	Liver: Hepato-cellular Adenoma	Liver: Hepato-cellular Carcinoma	Skin: Ulcer	Skin: Chronic Inflammation
63	13	100	F	495						
65	14	100	F	496						
65	14	100	F	497		X[a]	X			
65	14	100	F	498						
70	16	100	F	499						
70	16	100	F	500						
70	16	100	F	501	X					
66	14	100	F	502	X					
66	14	100	F	503			X			
67	15	100	F	504		X[a]				
67	15	100	F	505						
67	15	100	F	506						
69	16	100	F	507						
69	16	100	F	508						
74	18	100	F	509	X					
74	18	100	F	510	X					
74	18	100	F	511						
73	18	100	F	513						
73	18	100	F	514						
73	18	100	F	515						
73	18	100	F	516			X			
71	17	100	F	517			X[a]			
146	16	100	F	619		X				
146	16	100	F	620						
146	16	100	F	621						
140	13	100	F	622						
140	13	100	F	623			X			
145	16	100	F	624						
145	16	100	F	625						
145	16	100	F	626						
147	17	100	F	627					X	
147	17	100	F	628	X[a]					
147	17	100	F	629						X
141	14	100	F	631						
141	14	100	F	632		X				
141	14	100	F	633						
141	14	100	F	634	X					
149	18	100	F	635						
149	18	100	F	636		X				
149	18	100	F	637						
152	19	100	F	639						
152	19	100	F	640						
152	19	100	F	641		X				
152	19	100	F	642	X	X				
66	14	100	F	729						
139	13	100	F	737						
139	13	100	F	738	X	X				
139	13	100	F	739						
81	22	200	F	518		X				
93	28	200	F	519	X					
93	28	200	F	520						

TABLE D1
Incidence of Lung and Liver Neoplasms and Progressive Necrotizing Dermatitis in Littermates

Dam	Sire	Dose (mg/kg)	Sex	F_1 Pup ID Number	Lung: Alveolar/ bronchiolar Adenoma	Lung: Alveolar/ bronchiolar Carcinoma	Liver: Hepato-cellular Adenoma	Liver: Hepato-cellular Carcinoma	Skin: Ulcer	Skin: Chronic Inflammation
80	21	200	F	521	X				X	
80	21	200	F	522						
80	21	200	F	523						
80	21	200	F	524	X					
78	20	200	F	525						
78	20	200	F	526						
78	20	200	F	527						
78	20	200	F	528		X[a]				
78	20	200	F	529						
87	25	200	F	530						
87	25	200	F	531		X				
87	25	200	F	532		X[a]				
83	23	200	F	533						
83	23	200	F	534		X[a]				
153	20	200	F	643						
153	20	200	F	644					X	
162	24	200	F	645					X	
162	24	200	F	646			X			
162	24	200	F	647			X		X	
155	21	200	F	648		X				
155	21	200	F	649						
157	22	200	F	650						
157	22	200	F	651						
157	22	200	F	652						X
159	23	200	F	653						
159	23	200	F	654						
159	23	200	F	655						
159	23	200	F	656						
159	23	200	F	657					X	
159	23	200	F	658						
159	23	200	F	659						
160	23	200	F	660		X[a]				
160	23	200	F	661		X				
161	24	200	F	662	X					
161	24	200	F	663						
161	24	200	F	664						
161	24	200	F	665						
110	37	300	F	543						
96	30	300	F	544						
96	30	300	F	545						
96	30	300	F	546						
100	32	300	F	547						
100	32	300	F	548						
100	32	300	F	549						
101	32	300	F	550						
114	39	300	F	551						
114	39	300	F	552						
115	39	300	F	553						
115	39	300	F	554						
115	39	300	F	555						
115	39	300	F	556		X[a]				

TABLE D1
Incidence of Lung and Liver Neoplasms and Progressive Necrotizing Dermatitis in Littermates

Dam	Sire	Dose (mg/kg)	Sex	F_1 Pup ID Number	Lung: Alveolar/ bronchiolar Adenoma	Lung: Alveolar/ bronchiolar Carcinoma	Liver: Hepato-cellular Adenoma	Liver: Hepato-cellular Carcinoma	Skin: Ulcer	Skin: Chronic Inflammation
115	39	300	F	557		X				
115	39	300	F	558						
100	32	300	F	559						
100	32	300	F	560		X				
100	32	300	F	561						
97	30	300	F	562						
97	30	300	F	563	X					
103	33	300	F	564					X	
103	33	300	F	565	X				X	
103	33	300	F	566				X		X
102	33	300	F	567						
102	33	300	F	568						
102	33	300	F	569			X[a]			
191	39	300	F	668					X	
192	40	300	F	669			X			
192	40	300	F	670	X		X			
192	40	300	F	671						
192	40	300	F	672		X[a]	X[a]			
182	35	300	F	673						
182	35	300	F	674						
182	35	300	F	675						
188	38	300	F	676	X					
171	29	300	F	677	X					
171	29	300	F	678						
187	37	300	F	679						
187	37	300	F	680	X	X				
187	37	300	F	681	X					
187	37	300	F	682				X		
45	3	0	M	193		X				
45	3	0	M	194			X			
45	3	0	M	195				X		
47	4	0	M	197					X	
47	4	0	M	198					X	
47	4	0	M	199					X	
47	4	0	M	200					X	
51	6	0	M	201	X[a]	X				
51	6	0	M	202			X[a]	X		
51	6	0	M	203		X	X	X		
51	6	0	M	204			X		X	
48	4	0	M	205				X[a]		
42	1	0	M	206						
42	1	0	M	207	X[a]		X		X	
42	1	0	M	208						
42	1	0	M	209					X	
44	2	0	M	210					X	
44	2	0	M	211	X					
44	2	0	M	212	X		X			
44	2	0	M	213	X				X	
46	3	0	M	214	X[a]					
46	3	0	M	215						
46	3	0	M	216						

TABLE D1
Incidence of Lung and Liver Neoplasms and Progressive Necrotizing Dermatitis in Littermates

Dam	Sire	Dose (mg/kg)	Sex	F_1 Pup ID Number	Lung: Alveolar/ bronchiolar Adenoma	Lung: Alveolar/ bronchiolar Carcinoma	Liver: Hepato-cellular Adenoma	Liver: Hepato-cellular Carcinoma	Skin: Ulcer	Skin: Chronic Inflammation
46	3	0	M	217				X		
120	2	0	M	318			X		X	
120	2	0	M	319	X		X		X	
120	2	0	M	320					X	
120	2	0	M	321	X		X			
117	1	0	M	322						
117	1	0	M	323	X					
117	1	0	M	324	X					
117	1	0	M	325						
119	2	0	M	326						
119	2	0	M	327						
123	4	0	M	328			X			
123	4	0	M	329						
123	4	0	M	330						
123	4	0	M	331						
124	4	0	M	332		X[a]				
124	4	0	M	333				X[a]		
124	4	0	M	334			X		X	
124	4	0	M	335					X	
126	5	0	M	336						
126	5	0	M	337						
126	5	0	M	338		X				
127	6	0	M	339			X			
127	6	0	M	340						
127	6	0	M	341						
127	6	0	M	342			X[a]			
45	3	0	M	712			X			
57	9	50	M	218				X		
57	9	50	M	219			X			
53	7	50	M	221	X	X[a]				
53	7	50	M	222	X					
55	8	50	M	224			X[a]	X	X	
55	8	50	M	225						
54	8	50	M	227			X			
54	8	50	M	228				X		
54	8	50	M	229						
58	10	50	M	230					X	
58	10	50	M	231	X		X			
58	10	50	M	232						
60	11	50	M	233						
60	11	50	M	234						
60	11	50	M	235	X					
56	9	50	M	236	X					
56	9	50	M	237						
56	9	50	M	238					X	
59	10	50	M	239				X		
59	10	50	M	240					X	
59	10	50	M	241	X				X	
62	12	50	M	242		X[a]	X[a]			
135	10	50	M	343						
135	10	50	M	344						

TABLE D1
Incidence of Lung and Liver Neoplasms and Progressive Necrotizing Dermatitis in Littermates

Dam	Sire	Dose (mg/kg)	Sex	F_1 Pup ID Number	Lung: Alveolar/ bronchiolar Adenoma	Lung: Alveolar/ bronchiolar Carcinoma	Liver: Hepato-cellular Adenoma	Liver: Hepato-cellular Carcinoma	Skin: Ulcer	Skin: Chronic Inflammation
138	12	50	M	346						
138	12	50	M	347		X[a]				
129	7	50	M	349	X	X[a]			X	
129	7	50	M	350		X		X[a]		
131	8	50	M	352					X	
131	8	50	M	353	X	X				
132	9	50	M	354			X			
132	9	50	M	355	X		X[a]			
132	9	50	M	356					X	
133	9	50	M	357					X	
133	9	50	M	358		X[a]			X	
133	9	50	M	359					X	
134	10	50	M	360		X	X[a]			
134	10	50	M	361						
136	11	50	M	362	X			X		
136	11	50	M	363						
136	11	50	M	364					X	
137	11	50	M	365			X			
137	11	50	M	366	X				X	
137	11	50	M	367	X	X			X	
61	11	50	M	723	X					
61	11	50	M	725		X	X[a]			
62	12	50	M	726			X[a]			
130	8	50	M	730						
130	8	50	M	732						
62	12	50	M	734		X				
63	13	100	M	243					X	
63	13	100	M	244			X[a]			
63	13	100	M	245					X	
65	14	100	M	246				X		
65	14	100	M	247				X		
65	14	100	M	248			X			
70	16	100	M	249					X	
70	16	100	M	250						
70	16	100	M	251						
66	14	100	M	252					X	
67	15	100	M	253		X				
67	15	100	M	254		X				
67	15	100	M	255						
67	15	100	M	256		X				
69	16	100	M	257						
69	16	100	M	258			X			
74	18	100	M	261						
74	18	100	M	262						
74	18	100	M	263						
73	18	100	M	264			X[a]			
69	16	100	M	265			X[a]			
69	16	100	M	266						
71	17	100	M	267					X	
146	16	100	M	368	X				X	
146	16	100	M	369						

TABLE D1
Incidence of Lung and Liver Neoplasms and Progressive Necrotizing Dermatitis in Littermates

Dam	Sire	Dose (mg/kg)	Sex	F_1 Pup ID Number	Lung: Alveolar/ bronchiolar Adenoma	Lung: Alveolar/ bronchiolar Carcinoma	Liver: Hepato-cellular Adenoma	Liver: Hepato-cellular Carcinoma	Skin: Ulcer	Skin: Chronic Inflammation
146	16	100	M	370		X				
140	13	100	M	371			X[a]			
140	13	100	M	372		X	X[a]			
145	16	100	M	373						
145	16	100	M	374	X					
143	15	100	M	375	X				X	
143	15	100	M	376						
143	15	100	M	377	X			X	X	
147	17	100	M	378					X	
147	17	100	M	379						
147	17	100	M	380					X	
147	17	100	M	381					X	
141	14	100	M	382			X			
141	14	100	M	383						
149	18	100	M	384	X	X[a]				
149	18	100	M	385	X			X		
149	18	100	M	386	X			X		
149	18	100	M	387					X	
152	19	100	M	388			X			
152	19	100	M	389				X[a]		
152	19	100	M	390						
139	13	100	M	391	X				X	
139	13	100	M	392			X			
63	13	100	M	727						
65	14	100	M	728						
81	22	200	M	268						
81	22	200	M	269			X[a]			
81	22	200	M	270	X					
93	28	200	M	271		X				
93	28	200	M	272						
80	21	200	M	273						
80	21	200	M	274					X	
80	21	200	M	275				X		
78	20	200	M	276						
78	20	200	M	277	X	X[a]	X[a]			
78	20	200	M	278						
87	25	200	M	279					X	
87	25	200	M	280					X	
87	25	200	M	281	X				X	
83	23	200	M	282						
83	23	200	M	283		X	X			
83	23	200	M	284		X[a]				
83	23	200	M	285		X[a]				
83	23	200	M	286						
83	23	200	M	287		X[a]				
83	23	200	M	288		X[a]				
162	24	200	M	393	X		X			
162	24	200	M	394		X	X[a]			
162	24	200	M	395	X		X	X[a]		
162	24	200	M	396		X	X			
155	21	200	M	397		X[a]				

TABLE D1
Incidence of Lung and Liver Neoplasms and Progressive Necrotizing Dermatitis in Littermates

Dam	Sire	Dose (mg/kg)	Sex	F_1 Pup ID Number	Lung		Liver		Skin	
					Alveolar/ bronchiolar Adenoma	Alveolar/ bronchiolar Carcinoma	Hepato-cellular Adenoma	Hepato-cellular Carcinoma	Ulcer	Chronic Inflammation
157	22	200	M	398					X	
157	22	200	M	399						
157	22	200	M	400				X[a]	X	
159	23	200	M	401						
154	20	200	M	402	X					
154	20	200	M	403					X	
160	23	200	M	404	X	X				
160	23	200	M	405	X[a]		X	X		
161	24	200	M	406						
161	24	200	M	407	X					
161	24	200	M	408						
110	37	300	M	293		X				
96	30	300	M	294						
96	30	300	M	295		X[a]				
96	30	300	M	296	X					
100	32	300	M	297	X					
101	32	300	M	298					X	
115	39	300	M	299						
115	39	300	M	300					X	
115	39	300	M	301		X				
115	39	300	M	302						
115	39	300	M	303		X[a]			X	
115	39	300	M	304		X				
108	36	300	M	305		X[a]	X	X[c]		
108	36	300	M	306	X				X	
108	36	300	M	307	X	X				
108	36	300	M	308	X				X	
97	30	300	M	309						
97	30	300	M	310	X[a]		X			
97	30	300	M	311						
97	30	300	M	312		X				
97	30	300	M	313	X		X			
97	30	300	M	314	X					
97	30	300	M	315				X		
103	33	300	M	316						
103	33	300	M	317						
191	39	300	M	418						
192	40	300	M	419					X	
192	40	300	M	420	X		X			
182	35	300	M	421						
171	29	300	M	422	X					
187	37	300	M	423	X					
187	37	300	M	424				X[a]		

[a] Indicates "multiple"
[b] m indicates missing tissue
[c] Indicates "hepatocholangiocarcinoma"

TABLE D2
P Values for Litter and Sire Effects on Selected Neoplasm and Nonneoplastic Lesion Incidences in Swiss (CD-1®) Mice in the Transplacental Study of AZT[a]

	Lung[b]	Liver[c]	Skin[d]
Litter Effects			
Male pups	0.33	0.29	0.10
Female pups	0.58	0.31	0.08
All pups	0.68	0.04	0.04
Sire Effects			
Male pups	0.31	0.99	0.45
Female pups	0.92	0.55	0.99
All pups	0.98	0.33	0.64

[a] Probabilities derived using a mixed effects logistic regression model (McCullagh and Nelder, 1989)
[b] Includes alveolar/bronchiolar adenoma and carcinoma
[c] Includes hepatocellular adenoma, hepatocellular carcinoma, and hepatocholangiocarcinoma
[d] Includes ulcer and chronic inflammation

APPENDIX E
GENETIC TOXICOLOGY

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GENETIC TOXICOLOGY

Mouse Peripheral Blood Micronucleus Test Protocol

In a reproductive toxicity investigation of AZT, conducted independently from the transplacental carcinogenicity study that is the subject of this Technical Report, micronucleus assessments were measured in Swiss (CD-1®) mouse pups exposed to AZT. The protocols for these studies and the data were published by Witt *et al.* (2004).

AZT (Raylo Chemicals Division of Terochem Laboratories Ltd., Edmonton, Alberta, Canada) lot batch 1401-R-7 was obtained from the NTP chemical repository at Research Triangle Institute, NC. Maalox TC® (Novartis; obtained from Triangle Pharmacy, Durham, NC) was used as the vehicle. Maalox TC® formulations of AZT were stored at room temperature in glass containers sealed with Teflon® lids and protected from light. Solutions were stable for 30 days. Prior to dosing, solutions were stirred with a large magnetic stir bar until completely mixed. Stirring was continued during the dosing process to maintain a uniform suspension; during dosing procedures, solutions were stable for 3 hours. Control mice were given Maalox TC® only.

Swiss (CD-1®) female mice were acclimated for 7 days after receipt from Charles River Laboratories (Portage, MI). They were 5 to 6 weeks of age at the beginning of treatment. Mice were maintained in constant temperature rooms (71° ± 3° F) with relative humidity of 30% to 70% on a 12:12 (5 a.m. to 5 p.m.) light:dark cycle. Except for the period of mating, females were housed individually in polycarbonate cages with Sanichip hardwood bedding (P.J. Murphy Forest Products Corp., Montvale, NJ) and fed NIH-07 pellets (Harlan Teklad, Madison, WI). Filtered tap water was given *ad libitum*. Animals were handled strictly in accordance with institutional guidelines for humane treatment.

Females and males were dosed for 2 weeks prior to the initiation of cohabitation. Female mice were randomized into four treatment groups with 20 females per group. Equally divided doses of AZT or Maalox TC® alone were administered twice daily by gavage, 6 hours apart, 7 days a week throughout gestation. After delivery, females continued to receive two daily gavage treatments of AZT or Maalox TC®. Pups were thus exposed postnatally via nursing, and beginning on the afternoon of postnatal day 4, pups received AZT or Maalox TC® via direct gavage, twice daily, on the same schedule and at the same doses as the adults. To determine dosing dilution, an entire litter was weighed, not individual pups, in order to reduce the amount of handling. Dams were dosed for a total of 53 days.

In addition to the studies just described, another mouse pup study was conducted as described above, but using AZT in a 0.1% polysorbate/0.2% methylcellulose vehicle, rather than Maalox TC®.

Peripheral blood slides were prepared from randomly selected male pups, one each from five different litters on postnatal days 1, 4, 8, and 21 for determining the frequency of micronucleated (MN) polychromatic erythrocytes (PCEs). Peripheral blood slides were also prepared from the treated dams within 24 hours of the last dosing. Dams selected for micronucleus assessment were those that provided pups for the micronucleus test. Slides were fixed in absolute methanol and transported to Integrated Laboratory Systems, Inc. (Research Triangle Park, NC), for scoring. Slides were stained with acridine orange. For each pup, 2,000 uniformly stained PCEs were scored to determine the frequency of MN cells. In addition, 200 erythrocytes were scored for each pup to establish the percentage of PCEs among total erythrocytes, providing a measure of chemical-induced hematopoietic toxicity. For each treated dam, 2,000 PCEs and 2,000 normochromatic erythrocytes (NCEs) were scored to determine the frequency of MN immature and mature erythrocytes, respectively. The percentage of PCEs was based on scoring 1,000 erythrocytes per dam. Using acridine orange, PCEs and NCEs can be easily distinguished by their staining properties, which differ based on the presence or absence of residual RNA.

The micronucleus results were tabulated as the mean frequency of MN erythrocytes per 1,000 cells per animal within a treatment group, plus or minus the standard error of the mean among animals. The frequencies of micronucleated PCEs or NCEs were analyzed by a statistical software package (ILS, 1990) that tested for increasing trend over dose groups using a one-tailed Cochran-Armitage trend test. The trend test was followed by pairwise comparisons between each dosed group and the control group using an unadjusted one-tailed Pearson chi-squared test. 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. An individual trial is considered positive if the trend test P value is less than or equal to 0.025, and the P value for any single dosed group is less than or equal to 0.025 divided by the number of dosed groups. The percentage of PCE data were analyzed by an analysis of variance (ANOVA) test based on individual animal data; pairwise comparisons between the dosed and control groups were made using a two-tailed Student's t-test. Significance for each test was set at the 0.05 level.

Evaluation Protocol

These are the basic guidelines for arriving at an overall assay result for assays performed by the National Toxicology Program. Statistical as well as biological factors are considered. For an individual assay, the statistical procedures for data analysis have been described in the preceding protocol. There have been instances, however, in which multiple aliquots of a chemical were tested in the same assay, and different results were obtained among aliquots and/or among laboratories. Results from more than one aliquot or from more than one laboratory are not simply combined into an overall result. Rather, all the data are critically evaluated, particularly with regard to pertinent protocol variations, in determining the weight of evidence for an overall conclusion of chemical activity in an assay. The summary table in the Abstract of this Technical Report presents a result that represents a scientific judgement of the overall evidence for activity of the chemical in an assay.

Results

Micronucleus Frequencies in Male Pups

Pups exposed to AZT showed significant dose and exposure duration-dependent increases in the frequency of MN-PCEs in blood at all doses at all sampling times (Tables E1 and E2; Witt *et al.*, 2004). AZT-exposed pups sampled on postnatal day 8 showed a remarkable increase in MN-PCE frequency compared to pups sampled on postnatal days 1 and 4. The additional increase in the frequency of MN-PCEs in the postnatal day 8 pups is most likely the result of the direct gavage administration of AZT that began on postnatal day 4 and that supplemented the pups' lactational exposure to the chemical. Although high numbers of MN-PCEs were also observed at postnatal day 21 in the study using the Maalox TC® vehicle, the frequencies were notably lower than those observed in the pups sampled at postnatal day 8 (Table E1).

Percentage of PCEs in Male Pups

The data in Tables E1 and E2 show an extremely high percentage of PCEs in the blood of both vehicle control and treated pups. In healthy adult mice, the percentage of PCEs in peripheral blood is generally between 2% and 5%. In the newborn pups, the percentage of PCEs in blood was much higher, suggesting that at this stage of postnatal development there is a high rate of erythropoiesis. The data indicate that erythropoiesis is quite active through postnatal day 8. The reduction in the percentage of PCEs seen by postnatal day 21 (Table E1) may reflect a slowing of erythropoiesis as the pups mature.

The data in Tables E1 and E2, in addition to demonstrating a high rate of erythropoiesis in these pups, provide evidence for chemical-induced toxicity to the bone marrow. The treated pups at postnatal days 1, 4, and 8 show a decrease in the percentage of PCEs compared to the vehicle control group and this observation is typically an indication of bone marrow toxicity.

Micronucleus Frequencies and Percentage of PCEs in Dams

The micronucleus frequencies seen in AZT-treated female mice were significantly elevated at all three dose levels, but they were notably lower than the frequencies seen in the AZT-treated pups sampled on postnatal days 8 and 21 (Tables E1 and E3; Witt *et al.*, 2004). As expected, the percentage of PCEs in the vehicle control dams was markedly lower than the percentage of PCEs in the vehicle control pups. Unlike the pups on postnatal day 8, the dams do not show a significant decrease in the percentage of PCEs with increasing dose of AZT. The small fluctuations in percentages of PCEs noted in AZT-treated adult female mice were not significant (Table E3).

TABLE E1
Frequency of Micronucleated Polychromatic Erythrocytes (PCEs) and Percentage of PCEs in Peripheral Blood of Male Swiss (CD-1®) Mouse Pups Exposed to AZT Transplacentally, Lactationally, and by Gavage[a]

	Vehicle Control[b]	50 mg/kg	75 mg/kg	150 mg/kg	Statistical Test[c]
Frequency of MN-PCE					
Postnatal day 1	1.40 ± 0.19	14.90 ± 4.61	21.30 ± 3.54	19.90 ± 2.19	P<0.0001
Postnatal day 4	2.70 ± 0.51	17.90 ± 8.28[d]	31.90 ± 12.11	75.90 ± 21.19	P<0.0001
Postnatal day 8	3.70 ± 0.75	59.30 ± 17.82	76.60 ± 17.50	219.60 ± 34.82	P<0.0001
Postnatal day 21	1.10 ± 0.29	17.80 ± 5.49	25.00 ± 8.08	15.80 ± 2.39	P=0.012
Percentage of PCEs					
Postnatal day 1	51 ± 4.8	46 ± 3.2	37 ± 3.6	43 ± 3.9	P=0.114
Postnatal day 4	43 ± 1.7	33 ± 2.9	38 ± 2.9	32 ± 3.7	P=0.062
Postnatal day 8	35 ± 3.3	27 ± 2.0	31 ± 2.8	24 ± 1.2	P=0.015
Postnatal day 21	25 ± 4.0	21 ± 1.8	16 ± 1.8	15 ± 1.8	P=0.034

[a] The detailed protocol and these data are presented in Witt *et al.*, 2004. Data are expressed as micronucleated PCEs/1,000 PCEs ± standard error of the mean, 5 pups per treatment were examined. For each treated group, pairwise comparison to the concurrent vehicle control is highly significant (P<0.005) unless otherwise indicated.
[b] Maalox TC®
[c] One-tailed trend test; statistically significant at P≤0.025 (frequency of MN-PCE) or ANOVA, analysis of variance; statistically significant at P≤0.05 (percentage of PCEs)
[d] Not significant; P=0.039

TABLE E2
Frequency of Micronucleated Polychromatic Erythrocytes (PCEs) and Percentage of PCEs in Peripheral Blood of Male Swiss (CD-1®) Mouse Pups Exposed to AZT Transplacentally, Lactationally, and by Gavage[a]

	Vehicle Control[b]	50 mg/kg	100 mg/kg	150 mg/kg	Statistical Test[c]
Frequency of MN-PCE					
Postnatal day 1	1.20 ± 0.51	9.40 ± 1.25	17.87 ± 3.67	18.30 ± 4.94	P<0.001
Postnatal day 4	2.20 ± 0.66	14.00 ± 4.69	28.80 ± 8.61	19.30 ± 2.27	P<0.001
Postnatal day 8	3.50 ± 1.01	26.10 ± 5.06	39.00 ± 8.01	65.60 ± 16.07	P<0.001
Percentage of PCEs					
Postnatal day 1	38 ± 3.6	30 ± 2.7	25 ± 6.7	25 ± 5.3	P=0.221
Postnatal day 4	29 ± 3.6	19 ± 2.9	24 ± 4.5	20 ± 1.8	P=0.174
Postnatal day 8	32 ± 0.8	16 ± 2.3	15 ± 3.1	16 ± 2.4	P<0.001

[a] Data are expressed as micronucleated PCEs/1,000 PCEs ± standard error of the mean. Five pups per treatment were examined, except in the PND 8 100 mg/kg dose group, where only 3 pups were examined. For each treated group, pairwise comparison to the concurrent vehicle control is highly significant (P<0.001).
[b] 0.1% polysorbate/0.2% methylcellulose
[c] One-tailed trend test; statistically significant at P≤0.025 (frequency of MN-PCE) or ANOVA, analysis of variance; statistically significant at P≤0.05 (percentage of PCEs)

TABLE E3
Frequency of Micronucleated Erythrocytes and Percentage of PCEs in Female Swiss (CD-1®) Mouse Dams Administered AZT by Gavage for 53 Days[a]

	Vehicle Control[b]	50 mg/kg	75 mg/kg	150 mg/kg	Statistical Test[c]
Number of mice with erythrocytes scored	8	10	9	9	
MN-PCEs/1,000 PCEs	1.19 ± 0.30	9.10 ± 1.40	10.61 ± 3.09	29.89 ± 9.01	P<0.001
MN-NCEs/1,000 NCEs	2.13 ± 0.41	9.65 ± 1.91	12.44 ± 1.25	23.94 ± 2.61	P<0.001
Percentage of PCEs	5.4 ± 1.2	6.0 ± 0.9	3.9 ± 0.6	3.2 ± 0.5	P=0.076

[a] The detailed protocol and these data are presented in Witt *et al.*, 2004. Data are expressed as micronucleated cells/1,000 cells ± standard error of the mean. MN-PCE = micronucleated polychromatic erythrocyte, MN-NCE = micronucleated normochromatic erthrocyte. For each treated group compared to the vehicle control group, the pairwise P values for frequencies of MN-NCEs were <0.001. For MN-PCEs, all values were ≤0.01.
[b] Maalox TC®
[c] One-tailed trend test, statistically significant at P≤0.025 (frequency of MN-PCE) or ANOVA, analysis of variance; statistically significant at P≤0.05 (percentage of PCEs)

APPENDIX F
CHEMICAL CHARACTERIZATION AND DOSE FORMULATION STUDIES

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CHEMICAL CHARACTERIZATION AND DOSE FORMULATION STUDIES

Procurement and Characterization

AZT

A single lot of AZT (A980427A) was obtained from Raylo Chemicals (Edmonton, Alberta, Canada) by the analytical chemistry laboratory, Research Triangle Institute (Research Triangle Park, NC), and used during the gestational exposure phase of the study. Identity and purity analyses were conducted by the analytical chemistry laboratory. Stability analyses were conducted by Midwest Research Institute (Kansas City, MO) on a separate lot of AZT (809796) obtained from Burroughs Wellcome Company (Research Triangle Park, NC). Reports on analyses performed in support of the AZT studies are on file at the National Institute of Environmental Health Sciences. The study was conducted by Southern Research Institute (Birmingham, AL).

Lot A980427A of the chemical, an white crystalline powder, was identified as AZT by infrared and nuclear magnetic resonance spectroscopy. All spectra were consistent with the literature spectra (Horowitz, 1964; *Aldrich,* 1993) and with the structure of AZT. The infrared and nuclear magnetic resonance spectra are presented in Figures F1 and F2.

The purity of Lot A980427A was determined by high-performance liquid chromatography (HPLC) with systems similar to System A. The purity of lot A980427A was determined to be greater than 99%.

A) Waters (Millford, MA) HPLC, a Waters Symmetry C18 column (15 cm × 3.9 mm ID; 5 µm particle size) and a mobile phase of A) water and B) methanol. Following 5 minutes 90% A:10% B, the mobile phase was linearly changed to 10% A:90% B in 25 minutes and then held for 10 minutes. The flow rate was 1.0 mL/minute with ultraviolet detection at 254 nm.

B) Waters HPLC, a Waters Symmetry C18 column (15 cm × 3.9 mm ID; 5 µm particle size) and a mobile phase of A) 0.05% triethylamine, pH 5.0 and B) acetonitrile. Following 5 minutes 80% A:20% B, the mobile phase was linearly changed to 40% A:60% B in 5 minutes and then held for 5 minutes. The flow rate was 1.0 mL/minute with ultraviolet detection at 280 nm.

Stability studies of lot 809796 were conducted by Midwest Research Institute using HPLC by systems similar to system A. AZT stored in amber septum vials was stable for at least 2 weeks at temperatures up to 60° C. To ensure stability, the bulk chemical was stored protected from light at approximately 5° C.

Methylcellulose

A lot of methylcellulose (986713) was obtained from Fisher Scientific (Pittsburgh, PA) for use as the vehicle.

Preparation and Analysis of Dose Formulations

The dose formulations were prepared twice during the gestational phase of the study by mixing AZT with 0.5% methylcellulose (Table F1). Formulations were stored refrigerated and protected from light for up to 35 days.

Homogeneity studies of the 2.5 and 15.0 mg/mL dose formulations were performed by the analytical chemistry laboratory using HPLC by system B. Stability studies of 2 mg/g AZT in 0.5% methylcellulose were performed by Midwest Research Institute using lot 809796 with HPLC by systems similar to system B. Homogeneity was

confirmed and stability was confirmed for at least 3 weeks for dose formulations stored protected from light at room temperature and for up to 3 hours when stored exposed to light and air at room temperatures. Stability was checked during the course of the study. Formulations of 15 mg AZT/mL in 0.5% methylcellulose were found to be stable for 85 days when stored refrigerated and protected from light.

Periodic analyses of the dose formulations of AZT were conducted by the analytical chemistry laboratory using HPLC by system B (Table F2). The dose formulations were analyzed prospectively and during use; the highest dose formulation was also analyzed after use. All dose formulations were within 10% of the target concentration at each analysis point.

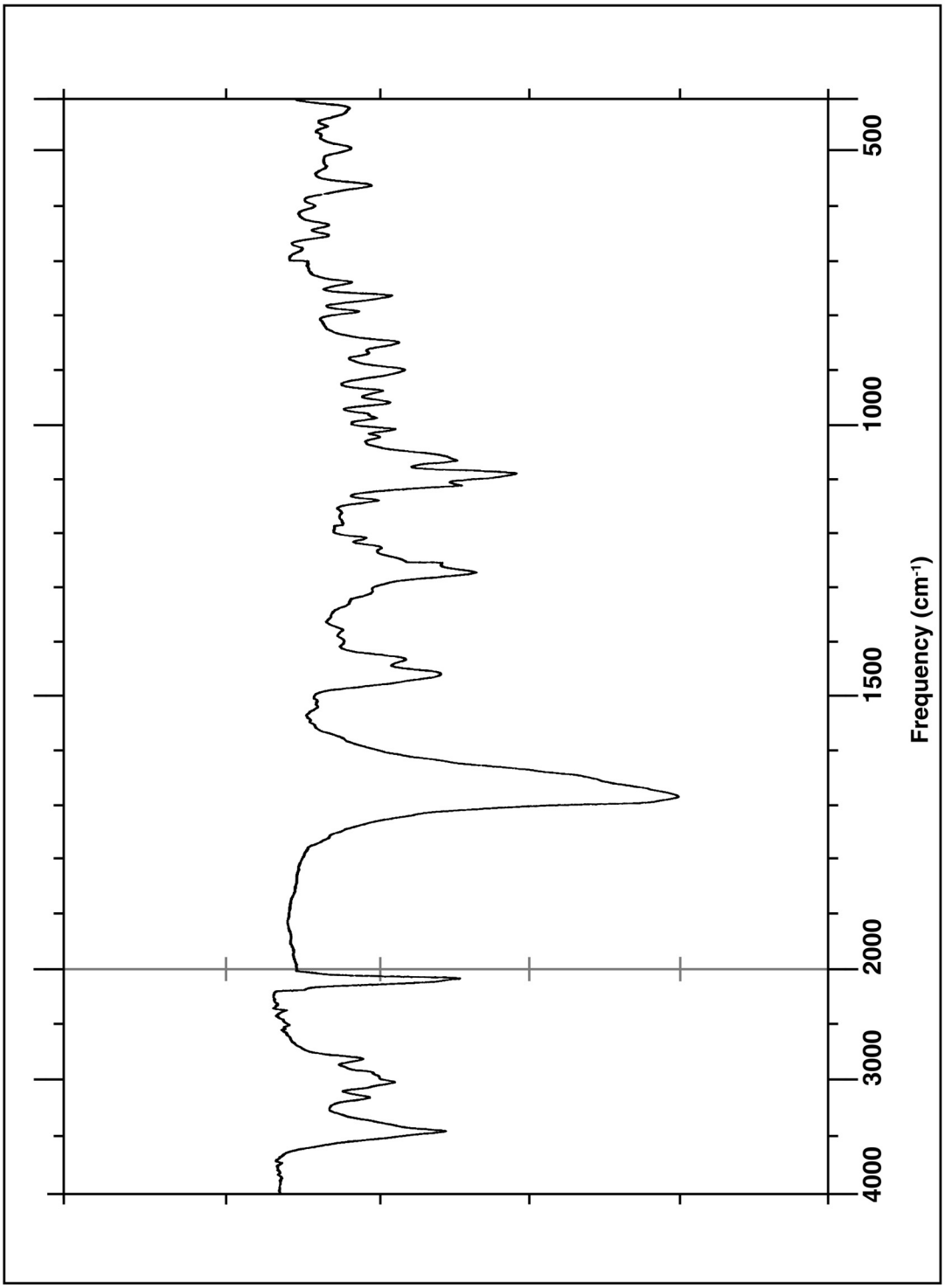

FIGURE F1
Infrared Absorption Spectrum of AZT

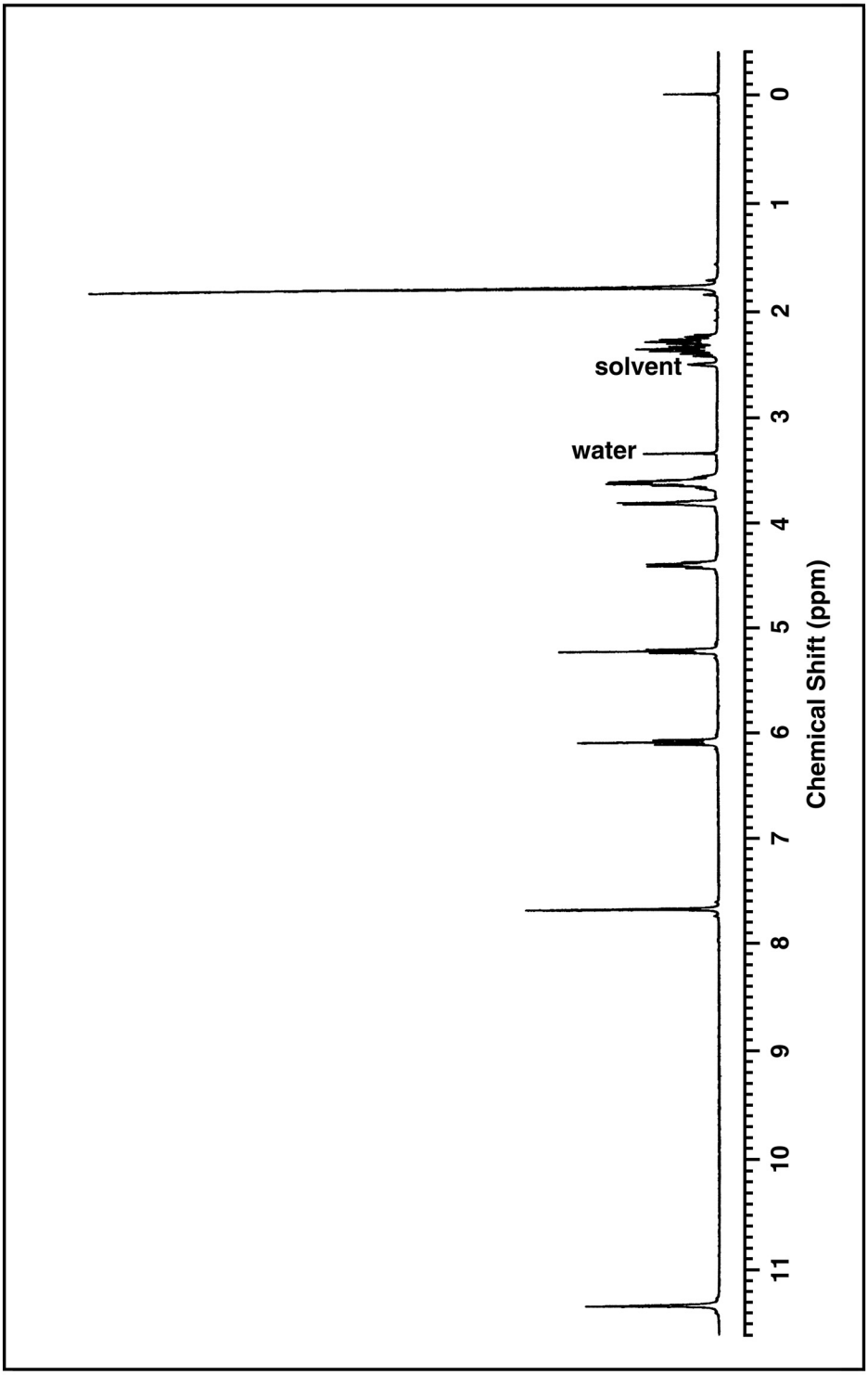

FIGURE F2
Nuclear Magnetic Resonance Spectrum of AZT

TABLE F1
Preparation and Storage of Dose Formulations in the Transplacental Study of AZT

Preparation
AZT was weighed and combined with the appropriate volume of 0.5% methylcellulose in a beaker and stirred for at least 30 minutes or until the AZT was completely in solution or visibly homogeneous. The dose formulations were prepared twice during the gestational phase of the study.

Chemical Lot Number
A980427A

Maximum Storage Time
85 days

Storage Conditions
Stored protected from light and refrigerated

Study Laboratory
Southern Research Institute (Birmingham, AL)

TABLE F2
Results of Analyses of Dose Formulations Administered to Mouse Dams in the Transplacental Study of AZT

Date Prepared	Date Analyzed	Target Concentration (mg/mL)[a]	Determined Concentration[b] (mg/mL)	Difference from Target (%)
May 12, 1999	May 14, 17, and 18, 1999	0	ND[c]	
		2.5	2.61[d]	4
		5.0	5.00	0
		10.0	9.37	–6
		15.0	14.7[d]	–2
	June 9, 10, 14, and 15, 1999[e]	0	ND	
		2.5	2.70	8
		5.0	5.23	5
		10.0	9.95	0
		15.0	15.2	1
	August 5, 6, and 10, 1999[f]	15.0	14.3	–5
June 1, 1999	June 3, 4, 7, 8, 16, and 17, 1999	0	ND	
		2.5	2.52	1
		5.0	5.21	5
		10.0	10.2	–1
		15.0	15.4	1
	June 29 and July 1 and 2, 1999[e]	0	ND	
		2.5	2.32	–7
		5.0	4.59	–8
		10.0	9.97	0
		15.0	14.6	–3
	August 5, 6, and 10, 1999[f]	15.0	14.8	–1

[a] Dosing volume = 10 mL/kg twice daily; 2.5 mg/mL = 50 mg/kg; 5.0 mg/mL = 100 mg/kg; 10.0 mg/mL = 200 mg/kg; 15 mg/mL = 300 mg/kg.
[b] Results of duplicate analyses
[c] Not detected
[d] Homogeneity samples
[e] Animal room samples
[f] Stability samples

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

TABLE G1 Ingredients of NIH-07 Rat and Mouse Ration 178
TABLE G2 Vitamins and Minerals in NIH-07 Rat and Mouse Ration 178
TABLE G3 Nutrient Composition of NIH-07 Rat and Mouse Ration 179
TABLE G4 Contaminant Levels in NIH-07 Rat and Mouse Ration 180

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

Ingredients[b]	Percent by Weight
Ground #2 yellow shelled corn	24.50
Ground hard winter wheat	23.00
Soybean meal (49% protein)	12.00
Fish meal (60% protein)	10.00
Wheat middlings	10.00
Dried skim milk	5.00
Alfalfa meal (dehydrated, 17% protein)	4.00
Corn gluten meal (60% protein)	3.00
Soy oil	2.50
Dried brewer's yeast	2.00
Dry molasses	1.50
Dicalcium phosphate	1.25
Ground limestone	0.50
Salt	0.50
Premixes vitamin	0.125
Premixes mineral	0.125

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

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

	Amount	Source
Vitamins		
A	5,500,000 IU	Stabilized vitamin A palmitate or acetate
D_3	4,600,000 IU	D-activated animal sterol
K_3	2.8 g	Menadione
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 mg	
Pyridoxine	1.7 g	Pyridoxine hydrochloride
Biotin	140.0 mg	*d*-Biotin
Minerals		
Iron	120.0 g	Iron sulfate
Manganese	60.0 g	Manganous oxide
Zinc	16.0 g	Zinc oxide
Copper	4.0 g	Copper sulfate
Iodine	1.4 g	Calcium iodate
Cobalt	0.4 g	Cobalt carbonate

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

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

Nutrient	Mean ± Standard Deviation	Range	Number of Samples
Protein (% by weight)	22.74 ± 0.98	21.1 – 26.2	22
Crude fat (% by weight)	5.22 ± 0.31	4.80 – 6.20	22
Crude fiber (% by weight)	3.18 ± 0.17	2.80 – 3.60	22
Ash (% by weight)	6.51 ± 0.35	6.0 – 7.50	22
Selected Vitamins and Minerals			
Vitamin A (IU/kg)	6,432 ± 910	4,390 – 7,950	22
Thiamine (ppm)	16.84 ± 3.87	11.1 – 24.4	22
Calcium (%)	1.27 ± 0.12	1.13 – 1.62	22
Phosphorus (%)	0.98 ± 0.06	0.91 – 1.17	22

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

	Mean ± Standard Deviation[b]	Range	Number of Samples
Contaminants			
Arsenic (ppm)	0.37 ± 0.17	0.10 – 0.72	22
Cadmium (ppm)	0.05 ± 0.01	0.04 – 0.06	22
Lead (ppm)	0.15 ± 0.09	0.06 – 0.43	22
Mercury (ppm)	< 0.2		22
Selenium (ppm)	0.34 ± 0.06	0.25 – 0.46	22
Aflatoxins (ppm)	< 5.00		22
Nitrate nitrogen (ppm)[c]	14.55 ± 4.53	10.0 – 29.1	22
Nitrite nitrogen (ppm)[c]	0.61 ± 0.02	0.61 – 0.68	22
BHA (ppm)[d]	1.01 ± 0.06	1.0 – 1.3	22
BHT (ppm)[d]	1.20 ± 0.40	1.0 – 2.4	22
Aerobic plate count (CFU/g)	53,112 ± 132,929	670 – 530,000	22
Coliform (MPN/g)	25 ± 97	0 – 460	22
Escherichia coli (MPN/g)	9.5 ± 2.1	0 – 10	22
Salmonella (MPN/g)	Negative		22
Total nitrosoamines (ppb)[e]	10.04 ± 2.69	4.90 – 14.2	22
N–Nitrosodimethylamine (ppb)[e]	7.63 ± 2.20	3.7 – 11.9	22
N–Nitrosopyrrolidine (ppb)[e]	2.41 ± 1.01	1.00 – 4.80	22
Pesticides (ppm)			
α–BHC	<0.01		22
β–BHC	<0.02		22
γ–BHC	<0.01		22
δ–BHC	<0.01		22
Heptachlor	<0.01		22
Aldrin	<0.01		22
Heptachlor epoxide	<0.01		22
DDE	<0.01		22
DDD	<0.01		22
DDT	<0.01		22
HCB	<0.01		22
Mirex	<0.01		22
Methoxychlor	<0.05		22
Dieldrin	<0.01		22
Endrin	<0.01		22
Telodrin	<0.01		22
Chlordane	<0.05		22
Toxaphene	<0.10		22
Estimated PCBs	<0.20		22
Ronnel	<0.01		22
Ethion	<0.02		22
Trithion	<0.05		22
Diazinon	<0.10		22
Methyl chlorpyrifos	0.13 ± 0.125	0.031 – 0.50	22
Methyl parathion	<0.02		22
Ethyl parathion	<0.02		22
Malathion	0.19 ± 0.16	0.02 – 0.54	22
Endosulfan I	<0.01		22
Endosulfan II	<0.01		22
Endosulfane sulfate	<0.03		22

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

APPENDIX H
SENTINEL ANIMAL PROGRAM

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SENTINEL ANIMAL PROGRAM

METHODS

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

Serum samples were collected from five male and 10 female F_0 mice at termination, five male and five female F_1 mice exposed to 50 mg/kg at culling (study start), five male and five female sentinel mice at 6 and 12 months, one male and five female F_1 mice sacrificed moribund at approximately 18 months, and five male and five female F_1 mice at the end of the study. In addition, fecal and liver samples from two male and two female F_1 mice at study termination were sent to BioReliance Corporation for *Helicobacter spp.* determination. Blood from each animal was collected and allowed to clot, and the serum was separated. The samples were processed appropriately and sent to BioReliance Corporation (Rockville, MD) for determination of antibody titers. The laboratory serology methods and bacterial 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
MICE	
F_0 generation	
ELISA	
Ectromelia virus	Termination of F_0 generation
EDIM (epizootic diarrhea of infant mice)	Termination of F_0 generation
GDVII (mouse encephalomyelitis virus)	Termination of F_0 generation
LCM (lymphocytic choriomeningitis virus)	Termination of F_0 generation
Mouse adenoma-virus FL	Termination of F_0 generation
MHV (mouse hepatitis virus)	Termination of F_0 generation
Mycoplasma arthritidis	Termination of F_0 generation
Mycoplasma pulmonis	Termination of F_0 generation
PVM (pneumonia virus of mice)	Termination of F_0 generation
Reovirus 3	Termination of F_0 generation
Sendai	Termination of F_0 generation
Immunofluorescence Assay	
Helicobacter hepaticus sp.	Upon receipt and termination of F_0 generation
Parvovirus	Termination of F_0 generation

Method and Test	Time of Analysis
MICE	
F_1 generation	
ELISA	
Ectromelia virus	Study start, 6, 12, & 18 months, study termination
EDIM	Study start, 6, 12, & 18 months, study termination
GDVII	Study start, 6, 12, & 18 months, study termination
LCM	Study start, 6, 12, & 18 months, study termination
Mouse adenoma virus-FL	Study start, 6, 12, & 18 months, study termination
MHV	Study start, 6, 12, & 18 months, study termination
M. arthritidis	Study start, 6, 12, & 18 months, study termination
M. pulmonis	Study start, 6, 12, & 18 months, study termination
PVM	Study start, 6, 12, & 18 months, study termination
Reovirus 3	Study start, 6, 12, & 18 months, study termination
Sendai	Study start, 6, 12, & 18 months, study termination
Immunofluorescence Assay	
H. hepaticus	Study termination
Parvovirus	Study start, 6, 12, & 18 months, study termination

RESULTS

All tests were negative.