NIEHS AIDS Therapeutics
Toxicity Report
Number 8

NIEHS Technical Report
on the 13-Week Toxicity Study of

3′-Azido-3′-deoxythymidine (AZT) and Isoniazid Combinations

(CAS Nos. 30516-87-1 and 54-85-3)

Administered by Gavage
to B6C3F$_1$ Mice

NIH Publication 02-4411
July 2002

U.S. Department of Health and Human Services
Public Health Service
National Institutes of Health

FOREWORD

Infection with human immunodeficiency virus (HIV) causes immunosuppression and leads to acquired immunodeficiency syndrome (AIDS) with a broad spectrum of opportunistic infections. Prophylaxis and treatment of AIDS are generally combination therapies of antiretroviral agents with antimicrobial drugs specific for the opportunistic infections. The National Institute of Environmental Health Sciences (NIEHS), under the AIDS research program, is evaluating AIDS therapeutics for reproductive, developmental, and general toxicity in rodents. These evaluations may include single therapeutic agents or combination therapies when the toxic potential of these agents in animal models is not available or is incomplete.

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CONTRIBUTORS

This report on the 13-week toxicity study of 3′-azido-3′-deoxythymidine (AZT) and isoniazid combinations is based primarily on studies that began in February 1993 and ended in May 1993 at Southern Research Institute, Birmingham, AL.

National Institute of Environmental Health Sciences

Evaluated experiment, interpreted results, and reported findings

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PEER REVIEW

The draft report on the 13-week toxicity study of 3′-azido-3′-deoxythymidine (AZT) and isoniazid combinations was evaluated by the following reviewers. These reviewers served as independent scientists, not as representatives of any institution, company, or governmental agency. In this capacity, reviewers determine if the design and conditions of the study are appropriate and ensure that this 13-week toxicity study report presents the experimental results and conclusions fully and clearly. The comments of the reviewers were reviewed prior to finalization of this document. Changes were made such that the concerns of the reviewers were addressed to the extent possible.

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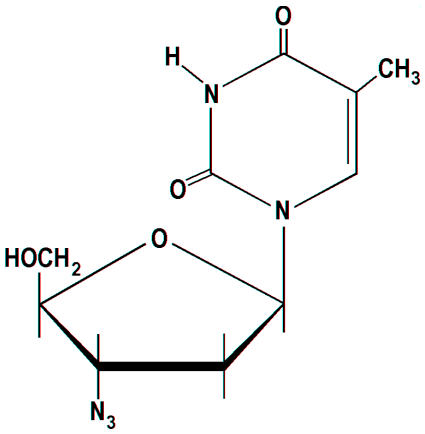
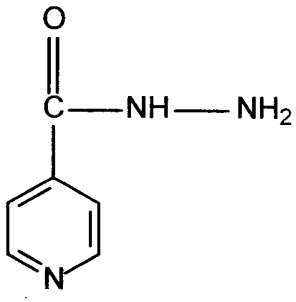
CONTENTS

ABSTRACT

3′-Azido-3′-deoxythymidine (AZT) and Isoniazid Combinations



AZT
Molecular Formula: $C_{10}H_{13}N_5O_4$
Molecular Weight: 267.24
CAS No.: 30516-87-1



Isoniazid
Molecular Formula: $C_6H_7N_3O$
Molecular Weight: 137.14
CAS No.: 54-85-3

Male and female B6C3F$_1$ mice were dosed orally with AZT alone (100, 200, or 400 mg AZT/kg body weight per day), isoniazid alone (50, 100, or 150 mg/kg per day), or combinations of AZT and isoniazid for up to 94 days. Mice were evaluated for clinical signs, mortality, body and organ weights, sperm function and vaginal cytology, and hematology and clinical chemistry parameters. Core study mice, early-death clinical pathology mice, and females from the 400 + 150 mg/kg (AZT + isoniazid) clinical pathology group were necropsied and subjected to histopathological evaluations.

The significant effects of treatment with AZT and isoniazid are summarized in the Abstract Table. The primary toxicity of AZT was bone marrow suppression. The hematopoietic toxicity was manifested by dose-related anemia, thrombocytosis, and a reticulocytopenia followed by reticulocytosis. Cellular depletion of the bone marrow was observed microscopically and was considered the major treatment-related effect. Increased

pigmentation of the skin and a slight decline in epididymal sperm motility also occurred in mice treated with AZT alone.

Administration of isoniazid alone resulted in slight hepatotoxicity manifested by hepatocellular hypertrophy and pigment deposition in the liver of male mice. Treatment with isoniazid also resulted in a slight increase in the duration of estrus.

Administration of AZT in combination with isoniazid resulted in hematopoietic toxicity of greater severity than that resulting from the administration of AZT alone. The bone marrow suppression and anemia resulted in significant mortality in female mice treated with the highest combinations of AZT and isoniazid. Combination therapy also resulted in treatment-related declines in body weight, reticulocytopenia followed by reticulocytosis, thrombocytosis, leukopenia, neutropenia, lymphopenia, and a slight increase in the duration of estrus.

Summary of Significant Treatment-Related Toxicological Parameters in the 13-Week Study of AZT and Isoniazid Combinations in B6C3F$_1$ Mice

Toxicological Parameter	Treatment Regimen		
	AZT Alone	Isoniazid Alone	AZT/Isoniazid Combinations
Mortality	No effect	No effect	Mortality in female groups receiving highest doses
Body Weight	No effect	No effect	Decline in body weight in female groups treated with AZT and 150 mg/kg isoniazid
Clinical Findings	Darkened skin in highest dose groups	No effect	Darkened skin in groups treated with highest doses of AZT Feet appear white in groups treated with highest combinations that developed anemia Paleness, hypothermia, lethargy, increased respiration rate, and hunched posture in high-dose female groups with mortality
Organ Weights	Slight decline in thymic weight	Slight decline in thymic weight	Slight decline in thymic weight
Hematology	Mild anemia with increased MCV and MCH values Slight reticulocytopenia (day 4) followed by reticulocytosis Slight increase in platelet counts	No effect	Mild to severe anemia with increased MCV and MCH values Mild reticulocytopenia (day 4) followed by reticulocytosis Mild to moderate thrombocytosis Mild leukopenia, neutropenia, and lymphopenia
Histopathology	Minimal bone marrow cell depletion Minimal to moderate splenic hematopoiesis	Minimal to mild splenic hematopoiesis in females Minimal to mild liver pigmentation in males Mild hepatocellular hypertrophy in males	Minimal to moderate bone marrow cell depletion Minimal to moderate splenic hematopoiesis Minimal to mild liver pigmentation in both sexes Mild hepatocellular hypertrophy in males
Reproductive	Slight decline in epididymal sperm motility	Slight increase in duration of estrus	Slight increase in duration of estrus

INTRODUCTION

Acquired immune deficiency syndrome (AIDS) is a lethal multisystem disease that has become a major public health problem since its recognition in 1981 (Gottlieb *et al.*, 1981; Masur *et al.*, 1981; Siegle *et al.*, 1981). The etiological agent of AIDS is a retrovirus now referred to as the human immunodeficiency virus (HIV) (Coffin, 1986). To date, the most effective single agent in the treatment of HIV has been the first dideoxynucleoside analogue used in clinical trials, zidovudine (3´-azido-3´-deoxythymidine, AZT, Retrovir, azidothymidine, compound S, BW A509U, CAS No. 30516-87-1), commonly referred to as AZT (Vince *et al.*, 1988; Amin, 1989).

AZT therapy produces numerous beneficial effects in AIDS patients, including decreases in morbidity and increases in life span (Amin, 1989; Jeffries, 1989). The most important adverse effects of AZT are anemia and granulocytopenia, which are believed to reflect bone marrow toxicity (Richman, 1988; Amin, 1989). Two types of anemia may occur with AZT therapy, macrocytic megaloblastic anemia and normocytic normochromic anemia.

Several subacute and subchronic rodent toxicity studies have demonstrated that the primary toxicity of AZT is myelosuppression. Male Swiss (CD-1®) mice were administered 100, 250, 500, or 1,000 mg AZT/kg body weight by gavage for 30 days (Mansuri *et al.*, 1990). No mortality or body weight effects were evident from AZT treatment. Erythropenia and increased mean cell volume were observed at all doses, and anemia was observed at the 1,000 mg/kg dose. Pathologic findings in the AZT-treated mice were consistent with the hematological results and included lymphoid depletion, reticuloendothelial hyperplasia in the spleen and thymus, and bone marrow hypocellularity.

In a 14-week subchronic study (NTP, 1999), B6C3F_1 mice were treated with 0, 25, 50, 100, 400, or 1,000 mg of AZT/kg body weight administered by gavage twice daily with one half the total dose in 0.5% methylcellulose. On day 5, statistically significant dose-related decreases were observed in reticulocyte counts in males and females. Dose-related anemia was evident on days 23 and 93. To evaluate the ability of treated animals to reverse any compound-related effects when treatment is stopped, additional groups were administered 0, 50, 400, or 1,000 mg/kg AZT twice daily for 14 weeks and then held without additional treatment for 29 days. Improvement of hematology parameters indicated recovery of the bone marrow after treatment stopped. An apparently nontoxic, treatment-related clinical finding that affected AZT-treated B6C3F_1 mice was a darkening of the skin on the tail, feet, and/or muzzle.

Oral bioavailability of AZT was determined in female B6C3F_1 mice by comparison of the area under the curve obtained from an oral dose to that of an intravenous dose at the same concentration (Trang *et al.*, 1993).

Bioavailability was found to be 0.86, 0.78, and 0.97 for the 15, 30, and 60 mg/kg oral doses. The mean elimination half-life values ranged from 17.3 to 19.9 minutes for the three intravenous doses and from 16.5 to 21.9 minutes for the three oral doses. Based on these results, the internal dose of AZT was linear and dose-proportional over the oral dose concentration range administered.

Standard teratology studies of AZT have been performed in rats and rabbits (Ayers, 1988). Rats were dosed orally with 125 to 500 mg/kg on gestation days 6 to 15. No fetal toxicity or teratogenicity was found. Fetal AZT concentrations 30 minutes post-dosing were 61 µg/g or 76 times the antiviral inhibitory dose for 50% of the viral population tested (ID_{50}). Rabbits were dosed orally at 125 to 500 mg/kg on gestation days 6 to 18, and no fetal toxicity or teratogenicity was found. Fetal AZT concentrations 30 minutes post-dosing were 40.2 µg/g, or 50 times the antiviral ID_{50}.

Female Wistar rats were dosed three times orally with 100 mg/kg AZT at 5-hour intervals on gestation day 10 for a total dose of 300 mg/kg (Greene *et al*., 1990). No adverse effects on maternal body weight gain, feed consumption, fertility, and hematological parameters, or growth and survival of offspring were observed. AZT concentration measurements 30 minutes after the last dose were 62.6 µg/mL in maternal plasma and 21.1 µg/g in fetal tissue.

Studies in C3H/He mice concluded that AZT has a direct toxic effect on the developing mouse embryo (Toltzis *et al*., 1991). Female mice were exposed to 0, 0.25, 0.5, or 2.5 mg AZT/mL drinking water for 8 weeks during mating and throughout gestation. All AZT groups had fewer pregnant mice per group, fewer pups per litter, and increased resorptions per mouse. Dose-related embryolethality was observed.

Because AIDS is a disease of immune suppression, the majority of AIDS patients actually die from characteristic opportunistic infections (Hardy, 1991; Harkins and Herriot, 1992). Thus, AIDS is increasingly treated with a combination of antiretroviral and antimicrobial drugs (Goldschmidt and Dong, 1992). Tuberculosis is one of the opportunistic diseases leading to mortality in AIDS patients (Nolan, 1992), and the spread of the HIV virus is one of the factors contributing to the resurgence of tuberculosis and resistant strains of the microorganisms that cause tuberculosis (Humma, 1996). The prevalence of tuberculosis in HIV-infected individuals is high, and the largest increases in tuberculosis nationally and internationally have occurred in urban areas that have a high percentage of HIV-infected individuals (Blanchard, 1996). AIDS patients with tuberculosis receive combination therapy with AZT and antituberculosis drugs (CDC, 1998; Pozniak *et al*., 1999; Murray, 1998). Treatment for tuberculosis involves combination therapy with multiple antibacterial agents in order to eliminate the strains of organisms inducing the disease, including those resistant to isoniazid, the primary drug used in treating tuberculosis. The standard regimen is isoniazid (300 mg/day), rifampin (600 mg/day or 450 mg/day for persons weighing less than

50 kg), and pyrazinamide (20 to 30 mg/kg/day) for the first 2 months of treatment. Isoniazid and rifampin are continued for another 7 months, for a total therapy duration of 9 months (CDC, 1987; Barnes *et al*., 1991).

Isoniazid is used alone for chemoprophylaxis of tuberculosis at a daily dose of 5 to 10 mg/kg for 12 months. This therapeutic regimen is relevant to AIDS in that up to 31% of new cases of tuberculosis are subsequently found to be HIV seropositive (Jacobson, 1988). Therefore, it is now recommended all HIV-seropositive patients, with or without clinical evidence of AIDS, be evaluated for the presence of latent tuberculosis infection and the need for chemoprophylaxis. In a recent study designed to evaluate the efficacy of isoniazid in individuals with HIV infection, Bucher *et al.* (1999) concluded that prophylaxis with isoniazid reduces the risk of tuberculosis in persons with HIV infection. This effect, however, was restricted to tuberculin skin-test-positive persons, and isoniazid prophylaxis showed no overall impact on mortality from tuberculosis. The authors found a trend suggesting that patients experienced more side effects, particularly related to hepatotoxicity, and suggested that any mortality reduction due to tuberculosis prevention was counterbalanced by mortality associated with drug toxicity.

Isoniazid is water soluble and is readily absorbed into all body fluids and cells following administration by any route. Peak plasma concentrations of 3 to 5 µg/mL are obtained in humans 1 to 2 hours after an oral dose of 5 mg/kg (*Goodman & Gilman's*, 2001). Thirty minutes after an oral dose of 144 mg/kg in albino mice, mean plasma concentrations of 44 µg/mL isoniazid were achieved (Rubin *et al.*, 1952). The absorption, distribution, and excretion of isoniazid appear to be similar in rodents, dogs, and humans (Rubin and Burke, 1953; Peretti *et al.*, 1987). The drug is excreted in the urine within 24 hours, primarily as acetylisoniazid and isonicotinic acid, products of acetylation and hydrolysis, respectively. Smaller quantities of isonicotinyl conjugates (*e.g.*, glycine), isonicotinyl hydrazones, and N-methylisoniazid are also detected in urine (*Goodman & Gilman's*, 2001). Isoniazid does not appear to accumulate following daily administration for up to 8 months (Rubin and Burke, 1953).

Acetylation by the enzyme N-acetyltransferase represents a major route of metabolism for isoniazid in rodents, dogs, and humans (Timbrell, 1981). The metabolism, pharmacokinetics, and toxicity of isoniazid are determined, in part, by the inheritance of a "rapid" or "slow" acetylator phenotype. The plasma concentrations of acetylisoniazid and isonicotinic acid are increased in rapid acetylators, while concentrations of unchanged isoniazid and hydrazones are increased in slow acetylators. The half-life of isoniazid in humans is approximately 3 hours in slow acetylators and 70 minutes in the rapid phenotype (*Goodman & Gilman's*, 2001). Slow acetylators are more likely to develop isoniazid neurotoxicity, which results from the competitive inhibition of pyridoxal phosphokinase (Blakemore, 1986). This enzyme phosphorylates vitamin B_6 to form an active coenzyme that participates in a variety of enzymatic reactions. Timbrell *et al.* (1980) reviewed studies showing that the association of acetylator phenotype and hepatotoxicity is less clear. The metabolite acetylhydrazine is transformed by cytochrome P_{450} to an intermediate that covalently bonds to liver proteins. Acetylhydrazine can be further

acetylated to diacetylhydrazine, a nontoxic moiety, and acetylation and P_{450}-dependent biotransformation are inhibited by isoniazid. Therefore, hepatotoxicity appears to be dependent upon acetylator phenotype, which will determine the relative concentrations of isoniazid, acetylhydrazine, and diacetylhydrazine and on the relative activities of other metabolic pathways. In mice (or rodents), the acetylator phenotype is strain specific (Tannen and Weber, 1979). Swiss (CD-1®) mice are reported to be slow acetylators compared to Wistar rats (Mate *et al.*, 1981). The authors reported that slow acetylation resulted in prolonged (18 hours) circulating levels of mono- and di-acetylhydrazine in mice; these metabolites were not detected in rats after 3 hours. The fact that mice, and not rats, develop lung tumors after long-term exposure to isoniazid led the investigators to correlate the slow acetylator phenotype with tumorigenicity.

Isoniazid has been used for the treatment of tuberculosis since 1951; clinical toxicities are fairly well known and include rash (2% incidence), fever (1.2%), jaundice (0.6%), and peripheral neuritis (0.2%) (*Goodman & Gilman's* 2001). Hypersensitivity, hematological effects (agranulocytosis, eosinophilia, thrombocytopenia, and anemia), vasculitis, arthritic symptoms, and neurologic effects occur at lesser incidences. Hepatotoxicity resulting in death can occur in some individuals (Vasudeva and Woods, 1997; Stuart and Grayson, 1999; Bucher *et al.*, 1999). There are no specific histologic features that distinguish isoniazid-related liver injury. The spectrum of microscopic findings reflects the variability of the clinical presentations and varies from extensive bridging hepatocellular necrosis, cholestasis, and fibrosis to an appearance resembling chronic active hepatitis (Vasudeva and Woods, 1997). The peripheral neuritis and hepatotoxicity observed clinically with isoniazid use are reproducible in rodents (Timbrell, 1979; Blakemore, 1986).

The following doses of isoniazid causing 50% mortality (LD_{50}) in mice were determined by Benson *et al.* (1952): oral, 133 mg/kg; subcutaneous, 177 mg/kg; intravenous, 153 mg/kg; intraperitoneal, 130 mg/kg; and intramuscular, 137 mg/kg. In rats, the oral LD_{50} was 1,435 mg/kg, and in rabbits, the oral LD_{50} was 200 mg/kg and the intravenous LD_{50} was 94 mg/kg. Male and female Sprague-Dawley rats were administered 0%, 0.025%, 0.05%, 0.25%, or 0.5% isoniazid in feed for 52 weeks (Harper and Worden, 1966). The authors reported that the 0.5% concentration was equivalent to a daily dose of 500 mg/kg; the majority of animals that received this dose died within a few weeks, and hepatic necrosis and ovarian or testicular hypertrophy were observed. Ovarian or testicular hypertrophy and reduced mean body weight gain were observed at 0.25%. No adverse effects were observed at 0.025% and 0.05%.

The carcinogenic potential of isoniazid in Swiss (CD-1®) mice has been studied by Menon and Bhide (1983). Beginning at 10 weeks of age, male and female mice were treated with 0 or 1.1 mg isoniazid by gavage in distilled water 5 days per week until death. A significant increase in the incidences of adenocarcinoma of the lung was observed in treated males and females. In a second experiment, 1.1 mg/day was administered in distilled water by gavage to pregnant mice throughout gestation and lactation. Eight weeks after weaning, F_1 males and

F_1 females were dosed with 0 (distilled water), 0.55, 1.1, or 2.2 mg isoniazid per day. Four weeks after initiation of treatment, F_1 males and F_1 females were mated. The dose of 2.2 mg/day was highly toxic to the F_1 mice and resulted in mortality; therefore, no mating occurred at this dose. Pregnant F_1 females received isoniazid treatment during gestation and lactation and were then divided into a group that was dosed postweaning and a group that was not. At study termination, the incidences of lung neoplasms were significantly increased in the F_1 mice at all three doses and in both postweaning groups. The F_2 generations from two groups were raised: a) from F_1 mice given 1.1 mg/day with no treatment postweaning, and b) from F_1 mice given 1.1 mg/day and 0.55 mg/day postweaning. The incidences of lung neoplasms were 11% in F_2 mice from the first group, 70% in F_2 mice from the second group, and 5% in the control group.

Reproductive and developmental toxicity studies of isoniazid have been conducted in Swiss (CD-1®) mice (Menon and Bhide, 1980). Groups of pregnant female mice were administered 0 (distilled water), 1.1, or 2.2 mg isoniazid per day by gavage during gestation days 1 to 4, gestation days 10 to 13, or gestation days 1 to 19. The results indicated that isoniazid induced early resorptions and embryolethality, but no teratogenicity. Hemorrhages were observed in some of the progeny from the isoniazid-treated dams. In a second experiment (Menon and Bhide, 1983), pregnant females were administered 0 (distilled water), 0.55, 1.1, or 2.2 mg isoniazid per day by gavage during gestation days 1 to 19. There were no adverse effects in the offspring of the dams administered 0.55 mg/day, while embryolethality and reduced mean body weights were observed in the offspring of the dams administered 1.1 or 2.2 mg/day. The F_1 offspring were mated and then dosed during gestation days 1 to 19. Successful mating occurred only among the F_1 offspring from dams that received 0.55 mg/day. Embryolethality was observed in the F_2 generation of the group administered 0.55 mg/day.

In another reproductive, developmental, and general toxicity study of AZT and isoniazid in Swiss (CD-1®) mice (NIEHS, 1999), doses of isoniazid up to 150 mg/kg per day caused minimal reproductive and developmental toxicity manifested by slight increases in the incidence of dams with resorptions and the percentage of dams with resorbed or dead fetuses. At these doses, isoniazid alone did not produce toxicity in adult mice. Doses of AZT up to 400 mg/kg per day caused minimal reproductive and developmental toxicity manifested by increased resorptions, reduced litter sizes, and reduced pup weights. At these doses, AZT alone caused slight anemia in adult male and female mice, slight leukopenia in female mice, and a minor decline in epididymal sperm motility. Coadministration of isoniazid and AZT exacerbated both the reproductive and the hematologic toxicity.

STUDY RATIONALE

Tuberculosis is one of the most common opportunistic infections in AIDS patients. AIDS patients with tuberculosis receive combination therapy of the antiretroviral drug AZT with antituberculosis drugs such as isoniazid. Information on the toxicity of AZT alone and isoniazid alone is available. However, information on the toxic effects of AZT and isoniazid in combination in animal models is not available. This 13-week toxicity study of the combination of AZT and isoniazid in an animal model was conducted by the NIEHS as part of the program to evaluate the toxicity of drugs, especially combination therapies used in the treatment of AIDS patients with opportunistic infections.

MATERIALS AND METHODS

PROCUREMENT AND CHARACTERIZATION OF CHEMICALS

3′-Azido-3′-deoxythymidine (AZT; Lot 1401-R-7) was manufactured by Raylo Chemicals (Edmonton, Alberta) and supplied as a powder. Isoniazid (Lot 7232-74-02 RTI,) was manufactured by Fluka Chemical Corp. (Ronkonkoma, NY) and supplied as crystals. Identification of both compounds was confirmed by nuclear magnetic resonance and infrared spectroscopy. The purity of both AZT and isoniazid was determined by high-performance liquid chromatography to be greater than 99%.

The control article was an aqueous solution containing 0.5% methylcellulose. The methylcellulose (Lot 876672) was obtained from Fisher Scientific Co. (Pittsburgh, PA).

DOSE FORMULATIONS

The test articles were combined singly or in combination with the control article. The dosing formulations were then stirred until visually homogeneous.

Stability studies indicated that AZT/isoniazid formulations were stable for at least 30 days at refrigerated and ambient temperatures. Dosing formulations of AZT and isoniazid used in this study were stored refrigerated in the dark for a maximum of 23 days after mixing.

Samples of dosing formulations from each dose level from the first, midpoint, and final mixes were analyzed for concentration prior to dosing. Residual formulations taken from the same mixes after dosing were also analyzed. AZT and isoniazid formulations were homogeneous. Prior to dosing, the found concentrations of AZT ranged from 94.2% to 107% of the target concentrations; the found concentrations of isoniazid were 87.0% to 105%. Found concentrations of the residual formulations were 93.4% to 113% for AZT and 93.2% to 118% for isoniazid.

STUDY DESIGN

Male and female B6C3F$_1$ mice were obtained from an NIEHS production colony at Taconic Laboratory Animals and Services (Germantown, NY) and were approximately 6 weeks old when placed on study. The mice were housed five per cage during quarantine before randomization and were housed individually (males) or five per cage (females) after randomization.

The mice were housed in polycarbonate cages with solid bottom and sides. The cages were suspended on stainless steel racks and heat-treated hardwood chips were used as the contact bedding. Appropriate environmental conditions, as listed in Table 1, were maintained in the animal rooms throughout quarantine and testing.

Blood samples were collected from five sentinel animals per sex at approximately 60 and 90 days as part of the Animal Disease Screening program. Results indicated that all animals were free of viral antibodies.

Acquired immune deficiency syndrome (AIDS) patients frequently receive combination therapy with isoniazid and AZT to treat tuberculosis, which is one of the complicating opportunistic infections in these immunologically suppressed individuals. At the present time, no acceptable alternatives to animal models provide adequate toxicity information regarding this combination therapy. The lowest dose level of isoniazid for the current study was set at 50 mg/kg per day because it was close to the clinically relevant therapeutic dose. The medium and high dose levels of isoniazid were set at 100 and 150 mg/kg per day to induce some measure of toxicity. Even though the reported LD_{50} dose for the mouse was 133 mg/kg (Benson *et al.*, 1952), in a previous study with Swiss (CD-1®) mice, doses of isoniazid alone up to 150 mg/kg administered for 30 days did not cause significant toxicity. However, when administered in combination with AZT, the above doses of isoniazid increased the toxic effects of AZT (NIEHS, 1999). The selected AZT doses for this study were 100, 200, and 400 mg/kg per day. The human therapeutic dose for AZT is 10 mg/kg per day (PDR, 1999). The selected doses for the current study were 10, 20, and 40 times human doses, but on a body surface area basis, the doses were close to 1, 2, and 4 times the therapeutic dose (Freireich, *et al.*, 1966). Results of previous toxicity studies conducted in mice have also demonstrated that measurable evidence of toxicity would be obtained at the levels of 100, 200, and 400 mg/kg AZT (NTP, 1999).

A brief summary of the study design is provided in Table 1. The B6C3F$_1$ mouse was selected as the experimental animal because this animal model has previously been utilized for toxicity evaluations of this type by the NIEHS. The route of administration selected for this study was oral because this is the clinically relevant route used in humans. AZT and isoniazid were administered as a single dose formulation. The total daily dose was divided into

two equal doses administered by gavage approximately 6 hours apart. Each group consisted of 20 mice per sex. Core animals (10/sex) were dosed daily for 92 to 95 consecutive days until the day prior to sacrifice. Clinical pathology animals (10/sex) were dosed until day 59. All mice were observed twice daily (morning and afternoon) for signs of mortality/moribundity.

On days 4, 30, and 60 for all clinical pathology animals and prior to sacrifice on days 92 to 95 for the core animals, blood was drawn from the retroorbital sinus for clinical pathology determinations. Vaginal cytology evaluations were conducted on all core study females on days 78 to 89, and sperm count, function, and motility were assessed on core study males on days 92 to 95. Surviving clinical pathology animals were euthanized on day 60 using 100% CO_2 and discarded; surviving core study animals were sacrificed on days 92 to 95 using 100% CO_2. A complete necropsy was conducted on all core study mice, early death clinical pathology animals, and females in the 400 + 150 mg/kg clinical pathology group. Selected organs (see Table 1) from core study animals were weighed.

Reproductive Tissue Evaluation and Estrous Cycle Characterization

Samples of vaginal fluid were taken from females using a medicine dropper, moistened with 0.9% saline if necessary. Samples from 12 consecutive days per group were placed on two slides per animal and evaluated for relative frequency of estrous phases and the estrous cycle length. The left testis from each male was removed at necropsy and weighed. The left epididymis was weighed, then sperm samples were collected and mixed with modified Tyrode's Solution on two prewarmed slides per animal. Slides were maintained at approximately 37° C and viewed under a light microscope to assess sperm motility. The distal cauda of the epididymis was weighed then placed in a petri dish containing phosphate-buffered saline, and the tissue was teased to release the contents. The final caudal epididymal sperm suspension was incubated for at least 15 minutes. An aliquot was then further diluted with saline solution and placed in a bath of hot water for at least one minute to kill the sperm. Sperm density was determined using a hemocytometer. To quantify spermatogenesis, testicular spermatid head count was determined by removing the tunica albuginea and homogenizing the left testis in phosphate-buffered saline containing 10% dimethyl sulfoxide. Homogenization-resistant spermatid nuclei were counted with a hemocytometer.

Clinical Pathology

Blood was drawn on days 4, 30, and 60 from all mice in the clinical pathology groups and at terminal sacrifice from all mice in the core study groups for hematology and clinical chemistry determinations. All blood samples were taken from the retroorbital sinus under CO_2/O_2 (70/30) anesthesia and collected into tubes containing EDTA (hematology) or no anticoagulant (clinical chemistry). Animals were selected in random order for blood

collection, and samples were analyzed in the order collected. Erythrocyte, platelet, and leukocyte counts, hematocrit, hemoglobin, mean corpuscular hemoglobin, mean corpuscular volume, mean corpuscular hemoglobin concentration, and leukocyte differentials were determined on whole blood using a Technicon H·1™ automated hematology analyzer. Reticulocyte counts were conducted using a Coulter Model Elite™ Flow Cytometer. Blood smears were prepared to evaluate erythrocyte and platelet morphologies and to manually verify leukocyte differentials and morphologies if necessary; platelet and erythrocyte morphological alterations were reported only in the raw data. Alanine aminotransferase (ALT), sorbitol dehydrogenase (SDH), alkaline phosphatase (ALP), aspartate aminotransferase (AST), and total bile acids (BILA) were determined using a Roche Cobas Fara™ automated analyzer.

Histopathology

Histopathologic examination was performed on tissues listed in Table 1. A complete examination was performed on all core study control animals, all animals in the core groups that received the highest dose of each test article alone or in combination, core study females in the next lower combination dose groups, clinical pathology females in the highest dose combination group, and early deaths in all dose groups. Designated target organs and gross lesions were examined histopathologically for core study animals in the lower dose groups. Tissues were trimmed, embedded in paraffin, sectioned at 4 to 6 μm, and mounted on glass microscope slides. Slides were stained with hematoxylin and eosin or with periodic acid-Schiff (testes). All tissues were examined by light microscopy and results were described using a standard nomenclature.

TABLE 1
Experimental Design and Materials and Methods for the 13-Week Toxicity Study of AZT and Isoniazid Combinations in B6C3F$_1$ Mice

Study Laboratory	Southern Research Institute, Birmingham, AL
Strain and Species	B6C3F$_1$ mice
Animal Source	Taconic Laboratory Animals and Services, Germantown, NY
Time Held Before Study	11-12 days (core study males and females, and clinical pathology males) or 18-19 days (clinical pathology females)
Age When Placed on Study	42-43 days
Date of First Dose	Core study groups: 8 February 1993 Clinical pathology groups: 15 or 16 February 1993 (males) or 22 or 23 February 1993 (females)
Date of Last Dose	Day prior to terminal sacrifice
Date of Necropsy	Core study groups: 10-13 May 1993 Clinical pathology groups: 15 or 16 April 1993 (males) and 22 or 23 April 1993 (females)
Age at Terminal Necropsy	Core study groups: 133-136 days Clinical pathology groups: 101-102 days
Size of Study Groups	10 males and 10 females per core study group and 10 males and 10 females per clinical pathology study group
Method of Animal Distribution	Animals were assigned to groups using a stratified weight method and then assigned to study groups in random order
Method of Animal Identification	Microchip implant (Biomedic Data Systems, Inc., Maywood, NJ)
Diet	NIH-07 pelleted feed (Zeigler Bothers, Inc.; Gardners, PA) available *ad libitum*; fresh feed provided weekly or as neeeded
Water	Tap water (Birmingham municipal supply) via automated watering system (Edstrom Industries, Inc.; Waterford, WI) available *ad libitum*
Cages	Polycarbonate cages with solid bottom and sides (Lab Products, Inc.; Maywood, NJ); changed once weekly (individually housed mice) or twice weekly (group-housed mice)
Bedding	Heat-treated hardwood-chip bedding (P.J. Murphy Forest Products Corporation; Montville, NJ); changed once weekly (individually housed mice) or twice weekly (group-housed mice)

TABLE 1
Experimental Design and Materials and Methods for the 13-Week Toxicity Study of AZT and Isoniazid Combinations in B6C3F$_1$ Mice

Cage Filters
Reemay spun-bonded polyester (Andico; Birmingham, AL), changed once every 2 weeks

Racks
Stainless steel racks (Lab Products, Inc.; Maywood, NJ), changed once every 2 weeks

Animal Room Environment
Temperature: 70.6° F ± 1.2° F
Relative humidity: 49.2% ± 5.2%
Fluorescent light: 12 hours fluorescent light/day
Room air: minimum of 10 changes per hour

Doses
15 combinations of AZT + isoniazid (mg per kg body weight per day) and a control group:

0 + 0	100 + 0	200 + 0	400 + 0
0 + 50	100 + 50	200 + 50	400 + 50
0 + 100	100 + 100	200 + 100	400 + 100
0 + 150	100 + 150	200 + 150	400 + 150

Type and Frequency of Observations
Mortality/moribundity: twice daily
Clinical findings: once weekly (core study mice only)
Body weights: once weekly (recorded for the clinical pathology mice only for determination of dosing volumes and not used for interpretation of body weight effects)

Clinical Pathology
Hematology and clinical chemistry evaluations were conducted on all core study animals at terminal sacrifice and on all clinical pathology animals on days 4, 30, and 60.

Reproductive Tissue Evaluation
Conducted on all core study males at terminal sacrifice

Estrous Cycle Characterization
Conducted on all core study females on days 78-89

Necropsy and Histopathologic Examinations
Complete necropsies were performed on all core study animals, early death clinical pathology animals, and females in the 400 + 150 mg/kg clinical pathology group. All tissues were saved in formalin, except the right testis, which was saved in Bouin's. The liver, right kidney, heart, lungs, thymus, and right testis of all core study mice sacrificed at the end of the study were weighed. Complete histopathologic processing was performed on all animals in the core control group, all early deaths in all dose groups, all animals in the 0 + 0, 0 + 150, 400 + 0, and 400 + 150 mg/kg core study groups, females in the 200 + 150 and 400 + 100 mg/kg core study groups, and females in the 400 + 150 mg/kg clinical pathology group. Tissues examined for a complete evaluation were adrenal glands, brain, clitoral glands, esophagus, femur, gallbladder, gross lesions, heart and aorta, large intestines, small intestines, kidneys, liver, lungs and bronchi, mandibular and mesenteric lymph nodes, mammary gland, nose, ovaries, pancreas, parathyroid glands, pituitary gland, preputial glands, prostate, salivary glands, seminal vesicle, spleen, stomach, right testis with epididymis, thymus, thyroid gland, tissue masses with regional lymph nodes, trachea, urinary bladder, and uterus. Gross lesions, bone marrow, liver, and spleen were processed in remaining core study dose groups.

STATISTICAL METHODS

Group means and standard deviations were calculated for body weights, clinical pathology parameters, and terminal body and organ weights. Organ/body weight ratios were also calculated. Mean terminal body weights, mean organ weights, and organ/body weight ratios for each treated group were compared to those of the control group by a two-tailed Student's *t*-test for each sex. The standard deviations used in the *t*-tests were obtained by pooling the individual values for the control and treated groups. Terminal body weights were also evaluated using Jonckheere's (1954) test for trend; if there was a trend, Williams' (1971, 1972) test was applied, but if there was no trend in the data, Dunnett's (1955) test was used. Dunnett's test was also used for evaluation of differences in clinical pathology parameters for treated and control groups.

Organ weights associated with reproductive tissue evaluations, along with terminal body weights, were analyzed using a two-way analysis of variance. The primary evidence for a treatment-related effect was taken to be the statistical significance of a main effect in the analysis of variance, with no evidence of differences in the effects of AZT over the levels of isoniazid as indicated by the absence of a significant AZT by isoniazid interaction. Sperm measurements were first analyzed using a nonparametric test for interaction. If the interaction was not statistically significant, averages were taken for each drug over the levels of the other drug, and control and treated group means were compared using either Williams' (1971, 1972) or Dunnett's (1955) multiple comparison procedures. The choice between the two tests was based on the evidence of a dose-related trend in the data as assessed by Jonckheere's test (1954). Williams' test was applied if there was an indication of a trend ($P<0.01$), and Dunnett's test was used in the absence of a trend. The outlier test of Dixon and Massey (1951) was employed to detect extreme values. No value selected by the outlier test was eliminated unless it was at least twice the next largest value or at most half of the next smallest value.

Treatment effects on estrous cycle data were investigated by applying a multivariate analysis of variance (using Wilke's Criterion [Stevens, 1986] as the test statistic) to test for the simultaneous equality of measurements across dose levels. Since the data are proportions (the proportion of the observation period that an animal was in a given estrous phase), an arcsine transformation was used to bring the data into closer conformance with the normality assumptions required for the multivariate analysis of variance.

For histopathology data, the presence of dose effects and interaction between AZT and isoniazid was assessed using methods of generalized linear models (McCullagh and Nelder, 1989; Fahrmeir and Tutz, 1994). The dependent variables used were graded histopathological lesions indexed as 0 through 4. These indices were assumed to follow a multinomial distribution. A cumulative logit link function was used to relate a lesion to dose and interaction effects. When only two graded lesion indices were observed, the multinomial distribution reduced to a binomial distribution, in which case a logit link function was used. AZT and isoniazid dose effects and their interaction were investigated by analysis of deviance (Jonckheere, 1954). Statistical significance of main and interaction effects was assessed using P values obtained from likelihood ratio tests (Dunn, 1964; Shirley, 1977).

RESULTS

SURVIVAL AND CLINICAL FINDINGS

In the core study, a total of six early deaths or moribund sacrifices occurred prior to terminal sacrifice. A single male mouse treated with 100 mg/kg 3′-azido-3′-deoxythymidine (AZT) alone died on day 67 (week 10). All five of the early deaths in female mice occurred on day 43 (week 7). One female mouse treated with 400 mg/kg AZT + 50 mg/kg isoniazid and three females in the group treated with 400 mg/kg AZT + 150 mg/kg isoniazid were sacrificed due to a moribund condition. One additional female mouse treated with 400 mg/kg AZT + 150 mg/kg isoniazid was found dead. Prominent clinical findings occurring prior to these deaths included paleness, hypothermia, lethargy, increased respiration rate, and hunched posture.

In the clinical pathology groups, a total of nine early deaths or moribund sacrifices occurred, and all were female mice treated with 200 or 400 mg/kg AZT + 150 mg/kg isoniazid. One female mouse in the 200 mg/kg AZT + 150 mg/kg isoniazid group was sacrificed moribund on day 39 (week 6). Seven female mice treated with 400 mg/kg AZT + 150 mg/kg isoniazid were sacrificed moribund or found dead on days 31 and 32 (week 5), and one additional mouse in this group was found dead on day 39 (week 6). The majority of these deaths occurred shortly after the interim clinical pathology evaluation on day 30 and were attributed to the blood sampling procedure in combination with an underlying anemia.

Other clinical signs related to treatment consisted of darkened skin on the muzzle, tail, and feet, and feet appearing white. Darkened skin occurred in mice treated with the higher doses of AZT alone or in combination with isoniazid from week 7 until the end of the study. The darkened skin was believed to reflect increased pigmentation subsequent to the administration of AZT and was consistent with clinical findings reported previously (NTP, 1999). The clinical finding of feet appearing white occurred in groups treated with the highest combinations of AZT and isoniazid and was considered to be a reflection of anemia from treatment and/or the blood sampling procedure.

BODY AND ORGAN WEIGHTS

Administration of AZT (100, 200, or 400 mg/kg) alone, isoniazid (50, 100, or 150 mg/kg) alone, and combinations of AZT and isoniazid to male mice did not result in significant ($P \leq 0.05$) declines in body weights (Figure 1; Table A1). For the male group treated with 100 mg/kg AZT + 50 mg/kg isoniazid, the mean terminal body weight was approximately 12% (38.86 grams; $P \leq 0.05$) higher than the mean (34.62 grams) in the controls (Table A2). The increased terminal body weights in this group were not considered to be biologically significant as a dose-related pattern did not occur.

Although not statistically significant ($P \leq 0.05$), administration of 100, 200, or 400 mg/kg AZT to female mice resulted in slight declines in terminal body weights (Table A2). Respective mean terminal body weights were approximately 3% (27.39 grams), 4% (27.02 grams), and 3% (27.26 grams) lower than the mean (28.18 grams) in the control group. Administration of 50 or 100 mg/kg isoniazid alone to female mice did not result in diminished body weights (Figure 2; Table A1). Although not statistically significant ($P \leq 0.05$), the mean terminal body weight in the group treated with 150 mg/kg isoniazid alone was approximately 5% (26.78 grams) lower than the mean (28.18 grams) in the controls (Table A2). Administration of AZT and isoniazid combinations to female mice did not result in statistically significant ($P \leq 0.05$) alterations in body weight (Figure 2; Table A1); however, slight declines did occur in the female groups receiving AZT + 150 mg/kg isoniazid. Respective mean terminal body weights for female groups treated with 100 or 200 mg/kg AZT + 150 mg/kg isoniazid (Table A2) were approximately 5% (26.87 grams) and 8% (25.85 grams) lower than the mean (28.18 grams) in the controls. For the female group treated with 400 mg/kg AZT + 150 mg/kg isoniazid, a marked decline in mean body weight occurred on day 39 (Figure 2; Table A1). After this date, significant mortality (4 deaths during week 7) occurred in this group and the mean terminal body weight of the survivors was similar to that of the control group.

With the exception of the male group treated with 200 mg/kg AZT + 50 mg/kg isoniazid and the female group treated with 100 mg/kg isoniazid alone, mean thymic weights in all treatment groups were slightly lower than mean thymic weights in male and female control groups (Table A2). The slight declines in absolute thymic weights were significant ($P \leq 0.05$) in the male groups treated with 200 mg/kg AZT alone, 200 mg/kg AZT + 50 mg/kg isoniazid, or 200 mg/kg AZT + 100 mg/kg isoniazid and in female groups treated with 100 mg/kg AZT alone, 400 mg/kg AZT + 50 mg/kg isoniazid, or 400 mg/kg AZT + 150 mg/kg isoniazid. Relative thymic weights (thymus weight/body weight ratio) were lower in mice of both sexes when compared to controls (Table A2). Declines in relative thymic weights were significant ($P \leq 0.05$) in male groups treated with 200 mg/kg AZT alone, 50 mg/kg isoniazid alone, 100 or 400 mg/kg AZT + 50 mg/kg isoniazid, 200 mg/kg AZT + 100 mg/kg isoniazid, or 100 or 400 mg/kg AZT + 150 mg/kg isoniazid. For the female mice, the declines in relative thymic weights were significant ($P \leq 0.05$) in groups treated with 200 or 400 mg/kg AZT in combination with 50 mg/kg isoniazid. The reductions in absolute and relative thymic weights may be a reflection of stress as opposed to a direct toxic effect. Minor statistically significant ($P \leq 0.05$) alterations in other

organ weight or organ-to-body-weight ratios (liver, kidney, heart, lungs, and testicle) occurred in a random or sporadic distribution (Table A2) and, as such, were not considered to be treatment related.

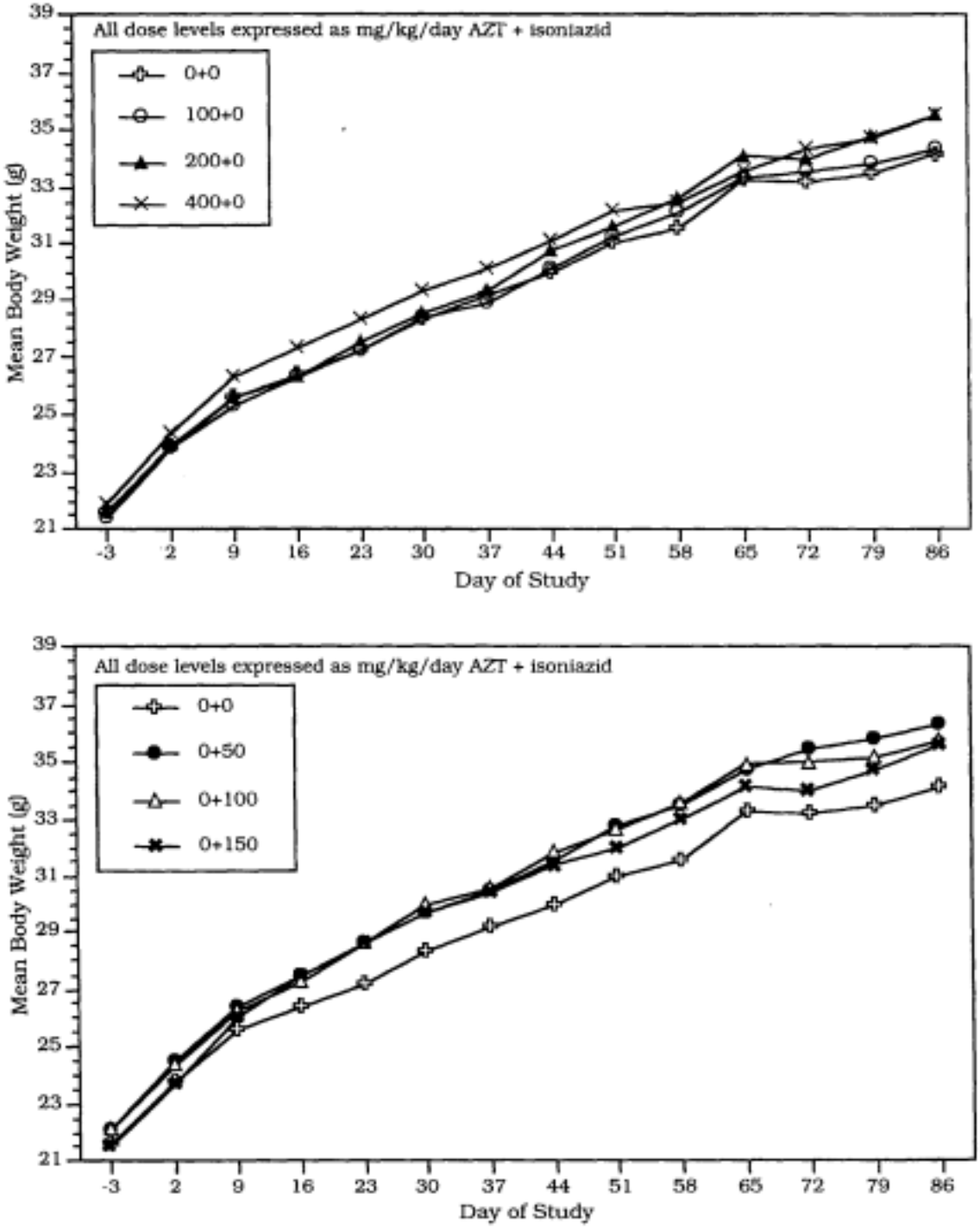


FIGURE 1
Mean Body Weights of Male (Core) Mice in the 13-Week Toxicity Study of AZT and Isoniazid Combinations

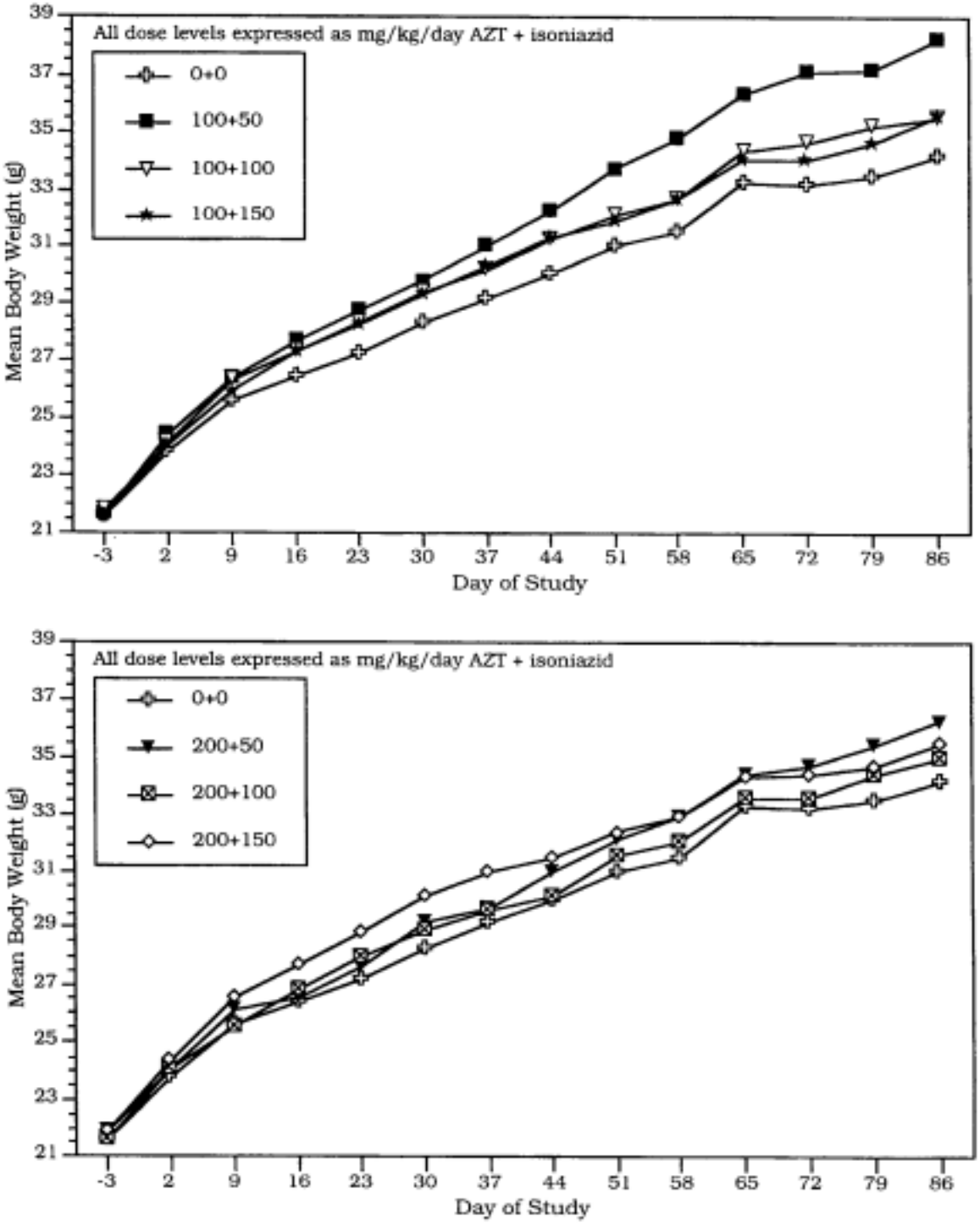


FIGURE 1 (continued)
Mean Body Weights of Male (Core) Mice in the 13-Week Toxicity Study of AZT and Isoniazid Combinations

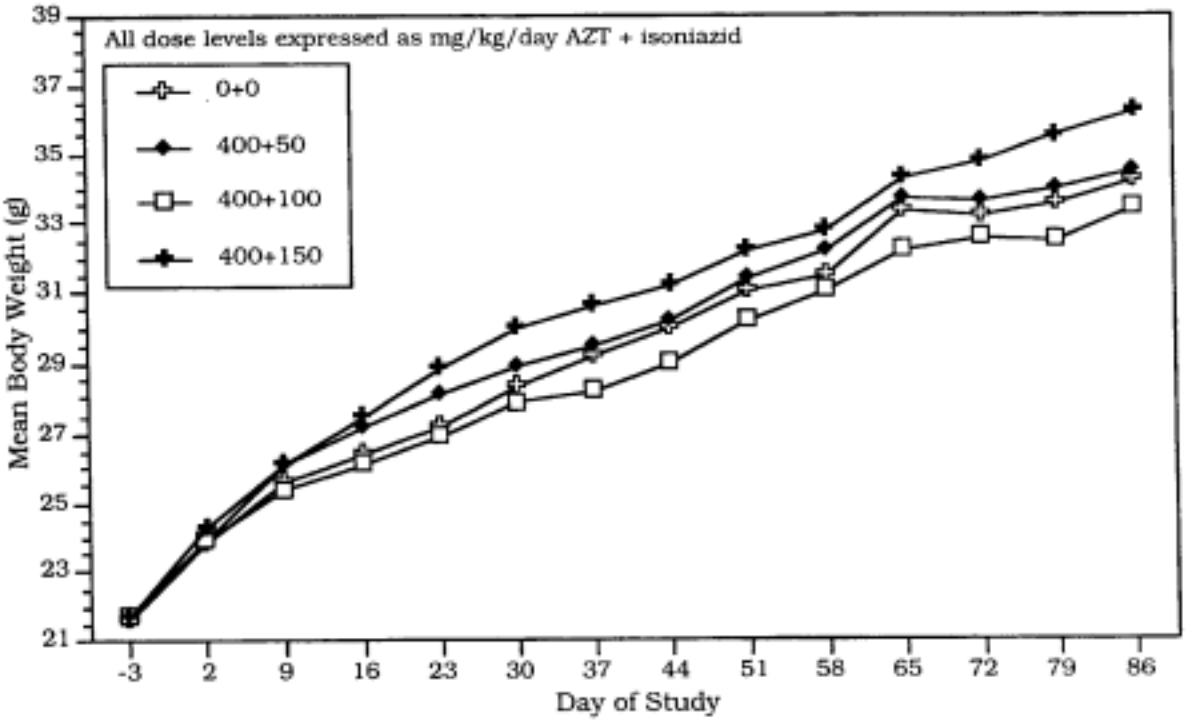


FIGURE 1 (continued)
Mean Body Weights of Male (Core) Mice in the 13-Week Toxicity Study of AZT and Isoniazid Combinations

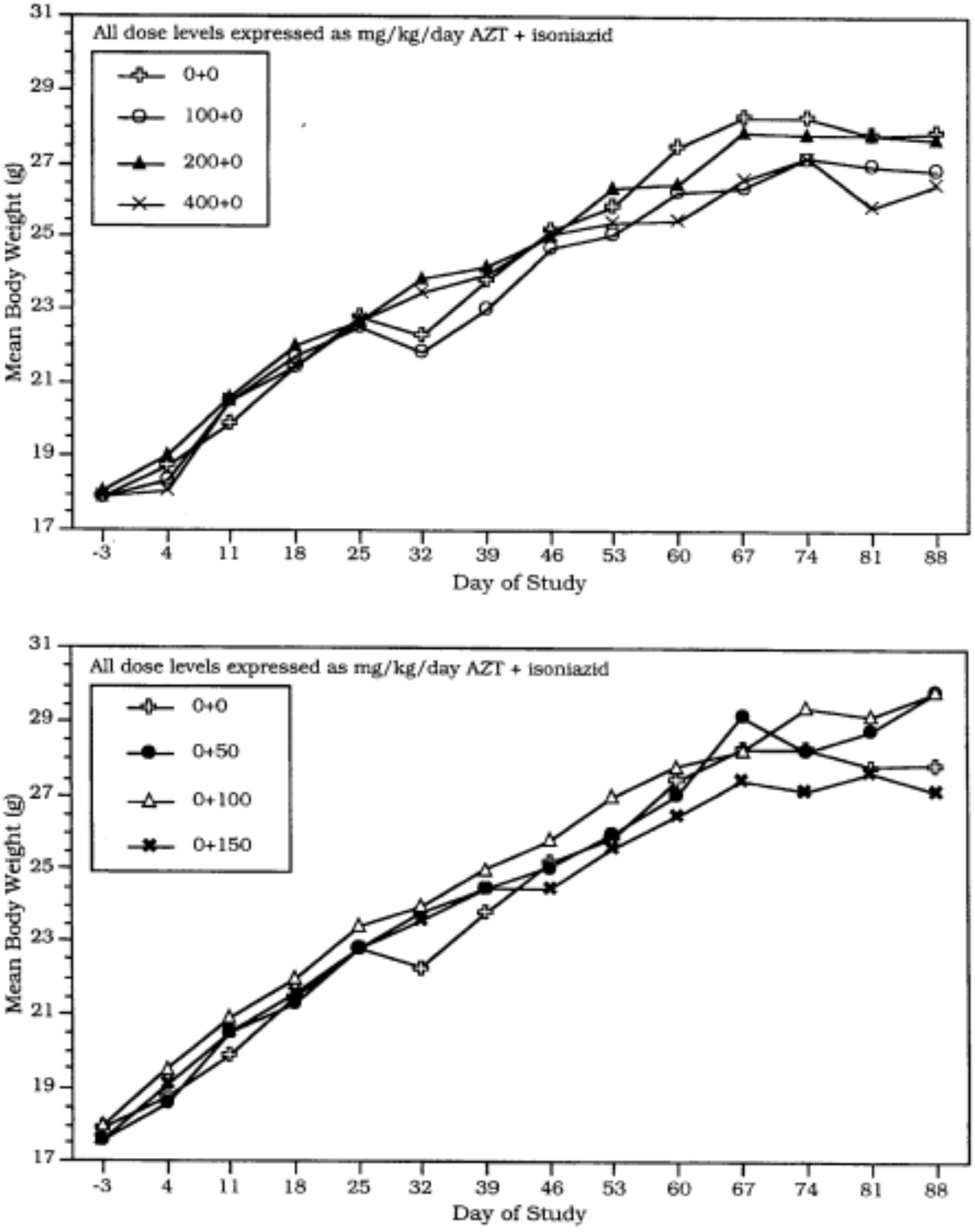


FIGURE 2
Mean Body Weights of Female (Core) Mice in the 13-Week Toxicity Study of AZT and Isoniazid Combinations

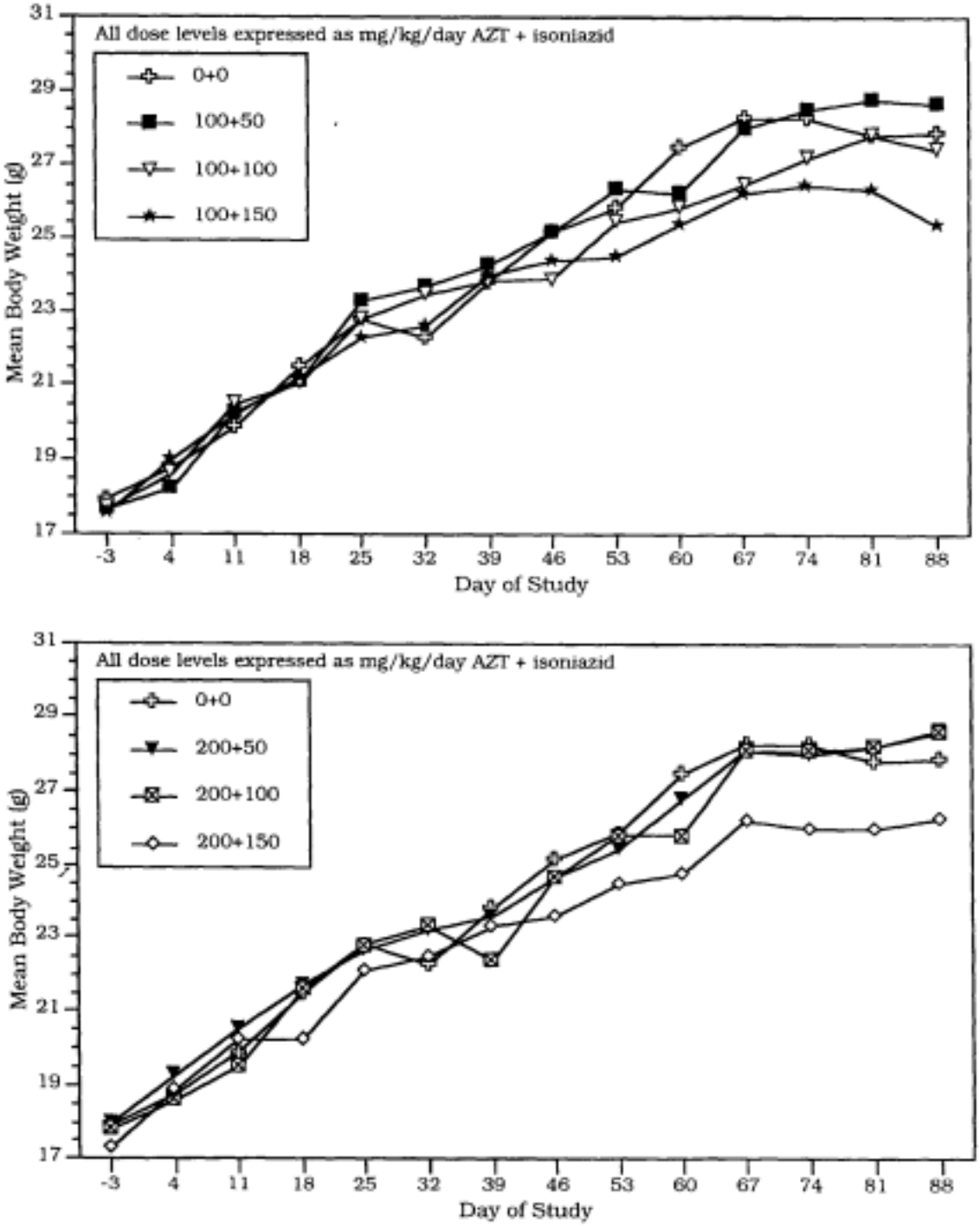
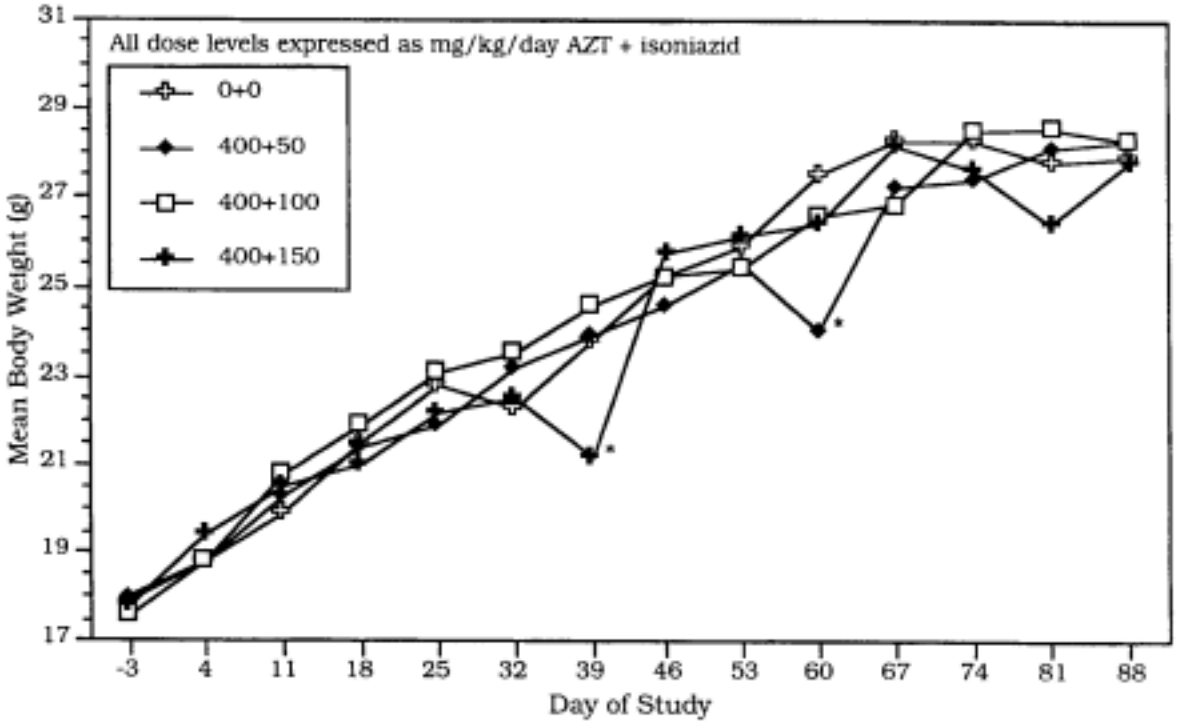


FIGURE 2 (continued)
Mean Body Weights of Female (Core) Mice in the 13-Week Toxicity Study of AZT and Isoniazid Combinations



* Moribund mice lowered the mean body weight for the group.

FIGURE 2 (continued)
Mean Body Weights of Female (Core) Mice in the 13-Week Toxicity Study of AZT and Isoniazid Combinations

CLINICAL PATHOLOGY

Hematology

AZT Alone

Administration of 100, 200, or 400 mg AZT per kg body weight alone to male and female mice produced dose- and duration-of-treatment-related anemia, thrombocytosis, and a transient reticulocytopenia followed by reticulocytosis. In general, the hematological alterations were slightly more prevalent in female mice than in males. The anemia was accompanied by elevations in mean corpuscular volume (MCV) and mean corpuscular hemoglobin (MCH) values and, as such, could be classified as macrocytic.

On day 4, marginal declines in red blood cell (RBC) counts occurred only in female mice. Respective mean RBC counts (Figure 4; Table B1) for female groups treated with 100, 200, or 400 mg/kg AZT were approximately 7% (9.10×10^6/_L; P≤0.01), 5% (9.25×10^6/_L; P≤0.05), and 6% (9.23×10^6/_L; P≤0.05) lower than the mean RBC count (9.77×10^6/_L) in the control group. On day 30, dose-related declines in RBC counts occurred in mice of both sexes. Respective mean RBC counts on day 30 (Figure 3; Table B1) for male mice treated with 100, 200, or 400 mg/kg AZT were approximately 13% (8.62×10^6/_L; P≤0.01), 14% (8.50×10^6/_L; P≤0.01), and 21% (7.80×10^6/_L; P≤0.01) lower than the mean RBC count (9.91×10^6/_L) in the male control group. Respective mean RBC counts on day 30 (Figure 4; Table B1) for the female groups treated with the same doses were approximately 16% (7.96×10^6/_L; P≤0.01), 20% (7.63×10^6/_L; P≤0.01), and 25% (7.15×10^6/_L; P≤0.01) lower than the mean (9.49×10^6/_L) in the female control group. Similar dose-related declines in RBC counts occurred in male and female mice on day 60. Respective mean RBC counts on day 60 for male mice (Figure 3; Table B1) treated with 100, 200, or 400 mg/kg AZT were approximately 16% (8.63×10^6/_L; P≤0.01), 21% (8.10×10^6/_L; P≤0.01), and 27% (7.46×10^6/_L) lower than the mean (10.27×10^6/_L) for the male controls. Female groups treated identically (Figure 4; Table B1) had respective mean RBC counts approximately 13% (8.26×10^6/_L; P≤0.01), 21% (7.45×10^6/_L; P≤0.01), and 24% (7.20×10^6/_L; P≤0.01) lower than the mean RBC count (9.48×10^6/_L) for the female controls. An anemia of similar severity was present in male and female mice at the time of terminal sacrifice on days 92 to 95. For the male mice treated with 100, 200, or 400 mg/kg AZT, respective mean RBC counts (Figure 3; Table B1) were approximately 13% (8.54×10^6/_L; P≤0.01), 20% (7.91×10^6/_L; P≤0.01), and 27% (7.18×10^6/_L; P≤0.01) lower than the mean (9.83×10^6/_L) in the control group. For the female mice treated with the same AZT doses, respective mean RBC counts (Figure 4; Table B1) were approximately 20% (7.73×10^6/_L; P≤0.01), 24% (7.35×10^6/_L; P≤0.01), and 29% (6.84×10^6/_L; P≤0.01) lower than the mean (9.63×10^6/_L) in the control group. In general for mice of both sexes, declines in hemoglobin (HGB) and hematocrit (HCT) values (Table B1) accompanied the dose-related declines in RBC counts at all of the bleeding

intervals (days 4, 30, 60, and 92 to 95). However, the declines in HGB and HCT values were not as marked as the RBC counts because of macrocytic erythrocytes.

Elevations in MCV and MCH values accompanied the dose-related declines in RBC counts in male and female mice on days 30, 60, and 92 to 95 (Table B1). On day 30, respective mean MCV values in male mice (Figure 5) treated with 100, 200, or 400 mg/kg AZT were approximately 8% (52.2 fL; P≤0.01), 12% (54.2 fL; P≤0.01), and 16% (56.5 fL; P≤0.01) higher than the mean MCV value (48.5 fL) in the control group. Respective mean MCH values (Table B1) for the same groups were approximately 9% (17.7 pg; P≤0.01), 10% (17.9 pg; P≤0.01), and 14% (18.6 pg; P≤0.01) higher than the mean (16.3 pg) for the controls. For the female mice treated with 100, 200, or 400 mg/kg AZT alone, respective mean MCV values on day 30 (Figure 6) were approximately 11% (54.9 fL; P≤0.01), 15% (56.7 fL; P≤0.01), and 18% (58.5 fL; P≤0.01) higher than the mean MCV value (49.5 fL) in the control group. Corresponding MCH values (Table B1) were approximately 10% (18.2 pg; P≤0.01), 12% (18.5 pg; P≤0.01), and 15% (18.9 pg; P≤0.01) higher than the mean MCH value (16.5 pg) in the control group. The severity of the macrocytosis was greater on day 60 in mice of both sexes (Table B1). Respective mean MCV values on day 60 for male mice (Figure 5) treated with 100, 200, or 400 mg/kg AZT were approximately 11% (53.4 fL; P≤0.01), 16% (56.1 fL; P≤0.01), and 21% (58.5 fL; P≤0.01) higher than the mean (48.3 fL) for the controls. Corresponding mean MCH values were approximately 9% (17.7 pg; P≤0.01), 14% (18.4 pg; P≤0.01), and 18% (19.1 pg; P≤0.01) higher than the mean MCH value (16.2 pg) for the controls. For the female groups treated identically, respective mean MCV values (Figure 6) were approximately 15% (54.4 fL; P≤0.01), 20% (56.8 fL; P≤0.01), and 25% (59.4 fL; P≤0.01) higher than the mean MCV value (47.5 fL) in the female control group. Corresponding mean MCH values for the female groups were approximately 13% (18.1 pg; P≤0.01), 18% (18.8 pg; P≤0.01), and 22% (19.5 pg; P≤0.01) higher than the mean (16.0 pg) for the controls. A dose-related macrocytosis also occurred in mice of both sexes at terminal sacrifice (days 92 to 95). Respective mean MCV values on days 92 to 95 for male mice (Figure 5) treated with 100, 200, or 400 mg/kg AZT were approximately 13% (52.7 fL; P≤0.01), 18% (55.1 fL; P≤0.01), and 25% (58.4 fL; P≤0.01) higher than the mean MCV value (46.7 fL) for the male control group. Corresponding mean MCH values were approximately 11% (17.5 pg; P≤0.01), 16% (18.3 pg; P≤0.01), and 20% (19.0 pg; P≤0.01) higher than the mean MCH value (15.8 pg) for the controls. For the female groups treated identically, respective mean MCV values were approximately 17% (54.6 fL; P≤0.01), 21% (56.4 fL; P≤0.01), and 26% (58.9 fL; P≤0.01) higher than the mean MCV value (46.8 fL) in the female control group. Corresponding mean MCH values for the female groups were approximately 15% (18.3 pg; P≤0.01), 17% (18.6 pg; P≤0.01), and 21% (19.3 pg; P≤0.01) higher than the mean MCH value (15.9 pg) for the controls. Marginal statistically significant declines (P≤0.01 to P≤0.05) in mean corpuscular hemoglobin concentration (MCHC) occurring in the higher dose male groups (days 30 and 92 to 95) and female groups (days 60 and 92 to 95) were not

considered to be biologically significant (Table B1).

Administration of AZT alone to male and female mice resulted in an initial reticulocytopenia (day 4) followed by reticulocytosis at the day 30, 60, and 92 to 95 bleeding intervals (Table B1). Respective mean reticulocytic counts on day 4 in male mice (Figure 7) treated with 100, 200, or 400 mg/kg AZT alone were approximately 28% (2.8×10^5/_L; P≤0.01), 36% (2.5×10^5/_L; P≤0.01), and 44% (2.2×10^5/_L) lower than the mean reticulocyte count (3.9×10^5/_L) in the control group. For female mice treated with the same AZT doses (Figure 8), reticulocyte counts on day 4 were approximately 44% (1.5×10^5/_L; P≤0.01), 52% (1.3×10^5/_L; P≤0.01), and 52% (1.3×10^5/_L; P≤0.01) lower than the mean (2.7×10^5/_L) in the female control group. Reticulocyte counts rebounded in mice of both sexes by day 30. Respective mean reticulocyte counts on day 30 for male mice treated with 100, 200, or 400 mg/kg AZT alone (Figure 7) were approximately 1.1 times (3.4×10^5/_L), 1.2 times (3.6×10^5/_L; P≤0.05), and 1.4 times (4.1×10^5/_L; P≤0.01) the mean reticulocyte count (3.0×10^5/_L) in the controls. For the female groups (Figure 8) treated identically, respective mean reticulocyte counts were approximately 1.2 times (3.5×10^5/_L), 1.5 times (4.6×10^5/_L; P≤0.05), and 1.6 times (4.8×10^5/_L; P≤0.01) the mean reticulocyte count (3.0×10^5/_L) in the control group. A dose-related increase in reticulocytes was observed in mice of both sexes on day 60. Respective mean reticulocyte counts on day 60 in male groups (Figure 7) treated with 100, 200, or 400 mg/kg AZT alone were approximately 1.1 times (3.5×10^5/_L; P≤0.05), 1.3 times (3.9×10^5/_L; P≤0.01), and 1.5 times (4.6×10^5/_L; P≤0.01) the mean (3.1×10^5/_L) in the controls. For the female groups (Figure 8) treated identically, respective mean reticulocyte counts on day 60 were approximately 1.2 times (4.0×10^5/_L), 1.2 times (3.8×10^5/_L), and 1.4 times (4.6×10^5/_L; P≤0.01) the mean reticulocyte count (3.3×10^5/_L) in the control group. A dose-related reticulocytosis also occurred in mice of both sexes at terminal sacrifice (days 92 to 95). On days 92 to 95, respective mean reticulocyte counts in the male groups treated with 100, 200, or 400 mg/kg AZT alone (Figure 7) were approximately 1.1 times (4.0×10^5/_L), 1.3 times (4.8×10^5/_L; P≤0.01), and 1.5 times (5.4×10^5/_L; P≤0.01) the mean reticulocyte count (3.7×10^5/_L) in the male control group. For the female groups treated identically (Figure 8), respective mean reticulocyte counts were approximately 1.2 times (3.9×10^5/_L), 1.5 times (4.9×10^5/_L; P≤0.05), and 1.8 times (6.2×10^5/_L; P≤0.01) the mean (3.3×10^5/_L) in the female control group.

In general, for the male and female groups treated with the highest doses of AZT, significant (P≤0.01) increases in reticulocyte counts correlated with significant (P≤0.01) increases in MCV values on days 30, 60, and 92 to 95. However, for the male (days 30 and 92 to 95) and female groups (days 30, 60, and 92 to 95) treated with

100 mg/kg AZT alone, significant ($P \leq 0.01$) increases in MCV values were not accompanied by elevated reticulocyte counts ($P > 0.05$), suggesting that the macrocytosis was not proportional to the reticulocytosis.

Administration of AZT alone to male and female mice resulted in treatment-related increases in platelet counts (Table B1). For the male mice in the 400 mg/kg group, the mean platelet count (Figure 9) on days 92 to 95 was approximately 1.3 times ($1,568 \times 10^3$/_L; $P \leq 0.01$) the mean ($1,222 \times 10^3$/_L) in the control group. For the female mice on day 60, the mean platelet count (Figure 10) in the 400 mg/kg AZT group was approximately 1.3 times ($1,461 \times 10^3$/_L; $P \leq 0.01$) the mean ($1,158 \times 10^3$/_L) in the control group. On days 92 to 95, the mean platelet count in the high-dose female group (Figure 10) was approximately 1.3 times ($1,517 \times 10^3$/_L; $P \leq 0.01$) the mean platelet count ($1,214 \times 10^3$/_L) in the control group. Although not statistically significant when compared to control groups, platelet counts were also elevated in the high-dose male and female groups on day 30 and in the high-dose male group on day 60.

With the exception of the 400 mg/kg female group on day 30, significant ($P \leq 0.05$) declines in white blood cell (WBC) counts did not occur with AZT therapy alone (Table B1). The mean WBC count on day 30 in the high-dose female group was approximately 23% (6.09×10^3/_L; $P \leq 0.05$) lower than the mean WBC count (7.91×10^3/_L) in the controls. Evaluation of the corresponding differential data (Table B1) revealed slight declines in all types of the WBC. The significant decline ($P \leq 0.05$) in the monocyte counts was not believed to be biologically significant because of the low numbers of this cell type normally present in the differential. No other statistically significant ($P \leq 0.05$) alterations occurred in the differential data.

Isoniazid Alone

Administration of 50, 100, or 150 mg isoniazid/kg body weight alone to male and female mice did not result in consistent biologically significant hematological alterations (Table B1).

On day 4, a marginal decline in RBC counts occurred in the high-dose female group. The mean RBC count on day 4 in the female group treated with 150 mg/kg isoniazid (Figure 4) was approximately 6% (9.16×10^6/_L; $P \leq 0.01$) lower than the mean (9.77×10^6/_L) in the control group. This slight decline in the erythrocyte count was not believed to be biologically significant as no other alterations occurred in any of the other erythrocyte parameters evaluated in female mice on days 30, 60, or 92 to 95.

At the day 60 bleeding interval, minor declines in HGB and HCT values occurred in male groups treated with 100 or 150 mg/kg isoniazid alone (Table B1). Respective mean HGB values for the 100 and 150 mg/kg dose groups were approximately 5% (15.7 g/dL; P≤0.05) and 5% (15.7 g/dL; P≤0.01) lower than the mean (16.6 g/dL) for the control group. HCT values paralleled the HGB values. These minor declines were not believed to be biologically significant as RBC counts were within a normal range and significant (P≤0.05) alterations in RBC, HGB, or HCT values did not occur in male mice at terminal sacrifice.

On days 92 to 95, minor alterations in MCH and reticulocyte values occurred in the male group treated with 150 mg/kg isoniazid alone (Table B1). The mean MCH value was approximately 4% (15.2 pg; P≤0.05) lower than the mean (15.8 pg) for the control group, and the mean reticulocyte count was approximately 1.1 times (4.2×10^5/_L; P≤0.05) the mean (3.7×10^5/_L) for the control group. These statistically significant alterations in MCH and reticulocyte values were not believed to be biologically significant as anemia did not occur and there were no biologically significant alterations in any of the other hematology parameters evaluated.

AZT and Isoniazid Combinations

Administration of 100, 200, or 400 mg AZT/kg body weight in combination with 50, 100, or 150 mg isoniazid/kg body weight resulted in some hematological alterations of greater severity than those detected subsequent to the administration of AZT alone. In general, the macrocytic anemia, thrombocytosis, reticulocytopenia, and reticulocytosis that occurred subsequent to combination therapy were more prevalent in female mice than in males and were usually most evident in groups treated with 100, 200, or 400 mg/kg AZT in combination with 150 mg/kg isoniazid.

Significant declines in RBC counts occurred in mice of both sexes on day 4 (Table B1). The mean RBC count on day 4 in the male group treated with 400 mg/kg AZT + 150 mg/kg isoniazid (Figure 3) was approximately 8% (8.32×10^6/_L; P≤0.01) lower than the mean (9.00×10^6/_L) for the controls. On day 4, respective mean RBC counts (Figure 4) in female mice treated with 100, 200, or 400 mg/kg AZT + 150 mg/kg isoniazid were approximately 7% (9.09×10^6/_L; P≤0.01), 6% (9.17×10^6/_L; P≤0.01), and 9% (8.89×10^6/_L; P≤0.01) lower than the mean RBC count (9.77×10^6/_L) for the female controls. The anemia was considerably more severe in both sexes on day 30 (Table B1). Respective mean RBC counts on day 30 in male mice (Figure 3) treated with 100, 200, or 400 mg/kg AZT + 150 mg/kg isoniazid were approximately 15% (8.44×10^6/_L; P≤0.01), 20% (7.89×10^6/_L; P≤0.01), and 29% (7.02×10^6/_L; P≤0.01) lower than the mean RBC count

(9.91×10^6/_L) for the control group. For the female groups treated identically, mean RBC counts (Figure 4) were approximately 19% (7.71×10^6/_L; P≤0.01), 38% (5.86×10^6/_L; P≤0.01), and 77% (2.17×10^6/_L; P≤0.01) lower than the mean (9.49×10^6/_L) in the controls. The majority of the female mice in the high-dose combination group had severe anemia and died after the bleeding procedure on day 30. Anemia was also prominent in mice of both sexes on day 60. Respective mean RBC counts in male mice on day 60 (Figure 3) treated with 100, 200, or 400 mg/kg AZT + 150 mg/kg isoniazid were approximately 18% (8.38×10^6/_L; P≤0.01), 26% (7.62×10^6/_L; P≤0.01), and 34% (6.81×10^6/_L; P≤0.01) lower than the mean (10.27×10^6/_L) in the control group. Respective mean RBC counts on day 60 for female mice (Figure 4) treated with the same combinations were approximately 16% (7.94×10^6/_L; P≤0.01), 28% (6.83×10^6/_L; P≤0.01), and 26% (6.97×10^6/_L; P≤0.01) lower than the mean RBC count (9.48×10^6/_L) for the control group. Only one blood sample was available for evaluation on day 60 in the female high-dose combination group due to mortality. At the time of terminal sacrifice (days 92 to 95), the anemia in mice of both sexes was similar to that on day 60. On days 92 to 95, respective mean RBC counts in male mice (Figure 3) treated with 100, 200, or 400 mg/kg AZT + 150 mg/kg isoniazid were approximately 22% (7.70×10^6/_L; P≤0.01), 27% (7.19×10^6/_L; P≤0.01), and 33% (6.59×10^6/_L; P≤0.01) lower than the mean RBC count (9.83×10^6/_L) for the controls. Respective mean RBC counts for the female groups treated with the same doses were approximately 23% (7.40×10^6/_L; P≤0.01), 27% (7.07×10^6/_L; P≤0.01), and 35% (6.26×10^6/_L; P≤0.01) lower than the mean (9.63×10^6/_L) in the control group. In general, lower HGB and HCT values paralleled the treatment-related declines in RBC counts at all of the bleeding intervals (Table B1). However, the declines in HGB and HCT values were not as marked as the RBC counts because of macrocytic erythrocytes.

In general, treatment-related elevations in MCV and MCH values accompanied the anemia in male and female mice on days 30, 60, and 92 to 95 (Table B1). On day 30, respective mean MCV values in male mice (Figure 5) treated with 100, 200, or 400 mg/kg AZT + 150 mg/kg isoniazid were approximately 8% (52.3 fL; P≤0.01), 13% (54.9 fL; P≤0.01), and 15% (55.9 fL; P≤0.01) higher than the mean MCV value (48.5 fL) in the control group. Corresponding MCH values were approximately 7% (17.4 pg; P≤0.01), 11% (18.1 pg; P≤0.01), and 13% (18.4 pg; P≤0.01) higher than the mean (16.3 pg) for the controls. For the female groups treated with 100 or 200 mg/kg AZT + 150 mg/kg isoniazid, respective mean MCV values (Figure 6) were approximately 12% (55.3 fL; P≤0.01) and 13% (55.7 fL; P≤0.01) higher than the mean MCV value (49.5 fL) in the control group. Corresponding mean MCH values were approximately 8% (17.9 pg) and 5% (17.3 pg) higher than the mean MCH value (16.5 pg) for the controls. Significant (P≤0.05) increases in MCV and MCH values did not occur in the high-dose female combination group on day 30. A treatment-related macrocytosis was also prevalent in mice of both sexes on day 60. Respective mean MCV values on day 60 for male mice (Figure 5) treated with 100, 200, or 400 mg/kg AZT + 150 mg/kg isoniazid were approximately 9% (52.6 fL; P≤0.01), 14% (55.3 fL;

P≤0.01), and 20% (58.0 fL; P≤0.01) higher than the mean MCV value (48.3 fL) in the control group. Corresponding mean MCH values were approximately 7% (17.3 pg; P≤0.01), 10% (17.9 pg; P≤0.01), and 15% (18.7 pg; P≤0.01) higher than the mean MCH value (16.2 pg) in the control group. For the female groups treated identically, respective mean MCV values (Figure 6) were approximately 15% (54.7 fL; P≤0.01), 20% (57.2 fL; P≤0.01), and 23% (58.3 fL; P≤0.01) higher than the mean MCV value (47.5 fL) in the female control group. Corresponding mean MCH values were approximately 13% (18.0 pg; P≤0.01), 18% (18.9 pg; P≤0.01), and 21% (19.4 pg; P≤0.01) higher than the mean MCH value (16.0 pg) for the controls. The macrocytosis was even more pronounced at the time of terminal sacrifice (days 92 to 95). Respective mean MCV values on days 92 to 95 in male groups (Figure 5) treated with 100, 200, or 400 mg/kg AZT + 150 mg/kg isoniazid were approximately 14% (53.4 fL; P≤0.01), 18% (55.1 fL; P≤0.01), and 26% (58.8 fL; P≤0.01) higher than the mean MCV value (46.7 fL) in the control group. Corresponding mean MCH values were approximately 11% (17.5 pg; P≤0.01), 15% (18.1 pg; P≤0.01), and 20% (18.9 pg; P≤0.01) higher than the mean MCH value (15.8 pg) in the control group. For the female groups treated identically, respective mean MCV values (Figure 6) were approximately 17% (54.8 fL; P≤0.01), 20% (56.3 fL; P≤0.01), and 30% (60.8 fL; P≤0.01) higher than the mean (46.8 fL) for the control group. Corresponding mean MCH values were approximately 12% (17.8 pg; P≤0.01), 16% (18.4 pg; P≤0.01), and 21% (19.3 pg; P≤0.01) higher than the mean MCH value (15.9 pg) for the controls. Minor statistically significant (P≤0.05 to P≤0.01) declines in MCHC values occurring in mice of both sexes (Table B1) were not considered to be biologically significant.

Administration of AZT + isoniazid resulted in an initial reticulocytopenia (day 4) in all combination treatment groups of both sexes, followed by a rebound in reticulocyte counts on days 30, 60, and 92 to 95 (Table B1). The severity of the reticulocytopenia was greater than that induced by AZT alone. Respective mean reticulocyte counts on day 4 in male mice (Figure 7) treated with 100, 200, or 400 mg/kg AZT + 150 mg/kg isoniazid were approximately 33% (2.6×10^5/_L; P≤0.01), 38% (2.4×10^5/_L; P≤0.01), and 64% (1.4×10^5/_L; P≤0.01) lower than the mean reticulocyte count (3.9×10^5/_L) in the control group. For the female groups (Figure 8) treated identically, respective mean reticulocyte counts were approximately 41% (1.6×10^5/_L; P≤0.01), 63% (1.0×10^5/_L; P≤0.01), and 74% (0.7×10^5/_L; P≤0.01) lower than the mean reticulocyte count (2.7×10^5/_L) in the control group. Reticulocyte counts rebounded in mice of both sexes by day 30. Respective mean reticulocyte counts on day 30 for male mice (Figure 7) treated with 100, 200, or 400 mg/kg AZT + 150 mg/kg isoniazid were approximately 1.2 times (3.5×10^5/_L), 1.3 times (4.0×10^5/_L; P≤0.01), and 1.6 times (4.7×10^5/_L; P≤0.01) the mean (3.0×10^5/_L) in the male control group. For the female groups treated identically (Figure 8), respective mean reticulocyte counts had returned to a normal range for all groups except the group treated with 400 mg/kg AZT + 100 mg/kg isoniazid; this group had approximately 2.1 times (6.4×10^5/_L; P≤0.01) more reticulocytes than the mean (3.0×10^6/_L) in the control group. On day 60, the

rebound in reticulocyte counts was more pronounced in male mice than in female mice. Respective mean reticulocyte counts on day 60 (Figure 7) for male groups treated with 100, 200, or 400 mg/kg AZT + 150 mg/kg isoniazid were approximately 1.3 times (4.0×10^5/_L; $P \leq 0.01$), 1.3 times (4.1×10^5/_L; $P \leq 0.01$), and 1.4 times (4.2×10^5/_L; $P \leq 0.01$) the mean reticulocyte count (3.1×10^5/_L) in the control group. Female groups treated identically did not have significant ($P \leq 0.05$) elevations in reticulocyte counts, although prominent macrocytosis (elevated MCV values) was present. On day 60, significant increases in reticulocyte counts only occurred in the female group (Figure 8) treated with 400 mg/kg AZT + 50 mg/kg isoniazid, which had a reticulocyte count approximately 1.5 times (4.9×10^5/_L; $P \leq 0.01$) the mean (3.3×10^5/_L) in the controls. Reticulocytosis also occurred in mice of both sexes at the time of terminal sacrifice. Respective mean reticulocyte counts on days 92 to 95 (Figure 7) for male mice treated with 100, 200, or 400 mg/kg AZT + 150 mg/kg isoniazid were approximately 1.4 times (5.0×10^5/_L; $P \leq 0.01$), 1.5 times (5.4×10^5/_L; $P \leq 0.01$), and 1.5 times (5.5×10^5/_L; $P \leq 0.01$) the mean reticulocyte count (3.7×10^5/_L) in the controls. For the female groups treated identically (Figure 8), respective mean reticulocyte counts on days 92 to 95 were approximately 1.3 times (4.2×10^5/_L), 1.5 times (4.9×10^5/_L; $P \leq 0.05$), and 2.1 times (7.1×10^5/_L; $P \leq 0.01$) the mean reticulocyte count (3.3×10^5/_L) in the control group.

In general for the male groups treated with combinations of AZT and isoniazid, significant ($P \leq 0.05$ to $P \leq 0.01$) increases in reticulocyte counts correlated well with significant elevations ($P \leq 0.01$) in MCV values on days 30, 60, and 92 to 95. All male combination treatment groups had significant ($P \leq 0.01$) increases in MCV values at all three bleeding intervals and only four of these combination treatment groups did not have significant ($P \leq 0.05$) increases in reticulocyte counts. Significant ($P \leq 0.05$) increases in reticulocyte counts did not occur in male groups on day 30 treated with 100 mg/kg AZT + 50, 100, or 150 mg/kg isoniazid and on day 60 in the group treated with 100 mg/kg AZT + 100 mg/kg isoniazid.

The correlation between macrocytosis and reticulocytosis was not as good in female mice treated with combinations of AZT and isoniazid. With the exception of the highest dose combination group on day 30, significant ($P \leq 0.01$) increases in MCV values occurred in all female combination groups at all bleeding intervals. On day 30, significant increases in reticulocyte counts did not occur in the female groups treated with 100 mg/kg AZT + 50, 100, or 150 mg/kg isoniazid, 200 mg/kg AZT + 150 mg/kg isoniazid, or 400 mg/kg AZT + 150 mg/kg isoniazid. On day 60, with the exception of the female group treated with 400 mg/kg AZT + 50 mg/kg isoniazid, significant increases ($P \leq 0.05$) in reticulocyte counts did not occur with combination therapy. At the time of terminal sacrifice, the female groups treated with 100 mg/kg AZT + 50, 100, or 150 mg/kg isoniazid and the groups treated with 200 mg/kg AZT + 50 or 100 mg/kg isoniazid did not have significant increases ($P > 0.05$) in reticulocyte counts. The lack of correlation between elevated MCV values and elevated reticulocyte counts implies an etiology other than increased reticulocyte counts for the macrocytosis.

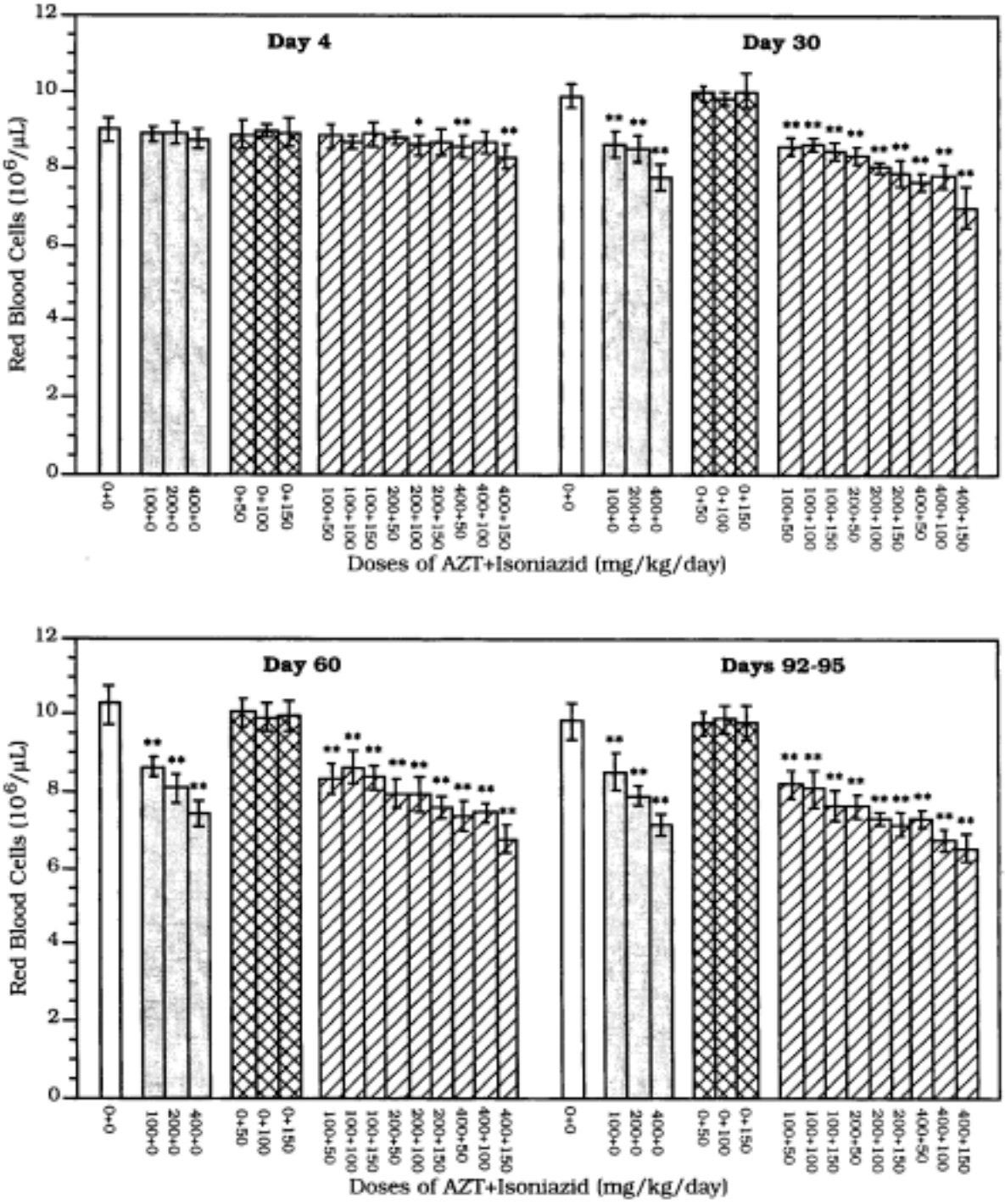
Administration of AZT and isoniazid combinations to male and female mice resulted in elevated platelet counts on days 30, 60, and 92 to 95 (Table B1). In general, the incidence and severity of the thrombocytosis were greater than induced by AZT therapy alone. On day 30, thrombocytosis occurred in two of the three male groups treated with AZT + 150 mg/kg isoniazid. Respective mean platelet counts on day 30 in the male groups (Figure 9) treated with 100 or 400 mg/kg AZT + 150 mg/kg isoniazid were approximately 1.2 times ($1,411 \times 10^3$/_L; $P \leq 0.05$) and 1.4 times ($1,664 \times 10^3$/_L; $P \leq 0.01$) the mean platelet count ($1,165 \times 10^3$/_L) for the controls. Thrombocytosis occurred on day 30 in the three female groups (Figure 10) treated with 400 mg/kg AZT + 50, 100, or 150 mg/kg isoniazid. Respective mean platelet counts were approximately 1.4 times ($1,408 \times 10^3$/_L; $P \leq 0.05$), 1.3 times ($1,379 \times 10^3$/_L; $P \leq 0.05$), and 2.2 times ($2,273 \times 10^3$/_L; $P \leq 0.01$) the mean platelet count ($1,023 \times 10^3$/_L) for the female controls. Thrombocytosis was more prominent on day 60 in mice of both sexes. Respective mean platelet counts on day 60 in male groups (Figure 9) treated with 100, 200, or 400 mg/kg AZT + 150 mg/kg isoniazid were approximately 1.2 times ($1,456 \times 10^3$/_L), 1.3 times ($1,666 \times 10^3$/_L; $P \leq 0.01$), and 1.5 times ($1,822 \times 10^3$/_L; $P \leq 0.01$) the mean platelet count ($1,257 \times 10^3$/_L) in the male control group. Significant ($P \leq 0.05$ to $P \leq 0.01$) elevations in platelet counts also occurred on day 60 in the male groups treated with 100 or 200 mg/kg AZT + 100 mg/kg isoniazid and with 400 mg/kg AZT + 50 or 100 mg/kg isoniazid. Respective mean platelet counts on day 60 for female mice (Figure 10) treated with 100, 200, or 400 mg/kg AZT + 150 mg/kg isoniazid were approximately 1.1 times ($1,286 \times 10^3$/_L), 1.3 times ($1,458 \times 10^3$/_L; $P \leq 0.01$), and 1.3 times ($1,502 \times 10^3$/_L) the mean platelet count ($1,158 \times 10^3$/_L) for the female controls. Significant elevations ($P \leq 0.05$ to $P \leq 0.01$) in platelet counts also occurred on day 60 in female groups treated with 400 mg/kg AZT + 50 and 100 mg/kg isoniazid. Treatment-related elevations in platelet counts also occurred in mice of both sexes at the time of terminal sacrifice (days 92 to 95). Respective mean platelet counts on days 92 to 95 in male groups (Figure 9) treated with 100, 200, or 400 mg/kg AZT + 150 mg/kg isoniazid were approximately 1.2 times ($1,442 \times 10^3$/_L), 1.2 times ($1,456 \times 10^3$/_L; $P \leq 0.05$), and 1.2 times ($1,518 \times 10^3$/_L; $P \leq 0.01$) the mean platelet count ($1,222 \times 10^3$/_L) in the male controls. Significant ($P \leq 0.05$ to $P \leq 0.01$) elevations also occurred in the male groups treated with 200 or 400 mg/kg AZT in combination with 50 or 100 mg/kg isoniazid. For the female mice (Figure 10) receiving combination therapy, thrombocytosis occurred in the groups treated with 400 mg/kg AZT + 50, 100, or 150 mg/kg isoniazid. Respective mean platelet counts were approximately 1.3 times ($1,547 \times 10^3$/_L; $P \leq 0.01$), 1.3 times ($1,543 \times 10^3$/_L; $P \leq 0.01$) and 1.3 times ($1,628 \times 10^3$/_L; $P \leq 0.01$) the mean platelet count ($1,214 \times 10^3$/_L) in the female control group.

Although not statistically ($P \leq 0.05$) significant, white blood cell (WBC) counts in the male combination treatment groups tended to be low (Table B1). On days 30, 60, and 92 to 95, respective mean WBC counts for male mice treated with 400 mg/kg AZT + 150 mg/kg isoniazid were approximately 20% (7.20×10^3/_L), 24% (4.20×10^3/_L), and 32% (3.75×10^3/_L) lower than the respective means (8.99, 5.53, and 5.49×10^3/_L) for

the male controls. Evaluation of the differential data revealed slight declines in granulocytes and mononuclear cells. For the female mice receiving combination therapy (Table B1), a compound-related leukopenia occurred on day 30. Respective mean WBC counts in female groups treated with 200 or 400 mg/kg AZT + 150 mg/kg isoniazid were approximately 27% (5.74×10^3/_L; $P \leq 0.05$) and 40% (4.75×10^3/_L; $P \leq 0.01$) lower than the mean (7.91×10^3/_L) in the female controls. Evaluation of the differential data revealed that the leukopenia involved predominantly lymphocytes, monocytes, and neutrophils. Respective mean lymphocyte counts for the same treatment groups were approximately 27% (4.81×10^3/_L; $P \leq 0.05$) and 38% (4.08×10^3/_L; $P \leq 0.01$) lower than the mean lymphocyte count (6.59×10^3/_L) for the control group. Although not statistically ($P \leq 0.05$) significant, the mean neutrophil count in the high-dose combination group was approximately 39% (0.51×10^3/_L) lower than the mean (0.83×10^3/_L) in the control group. The significant ($P \leq 0.05$) declines in monocyte counts were not believed to be biologically significant because of the low number of this cell type normally present in the differential. Significant ($P \leq 0.05$) declines in WBC, neutrophil, and lymphocyte counts did not occur in female combination groups on days 60 and 92 to 95; however, slight downward trends were present.

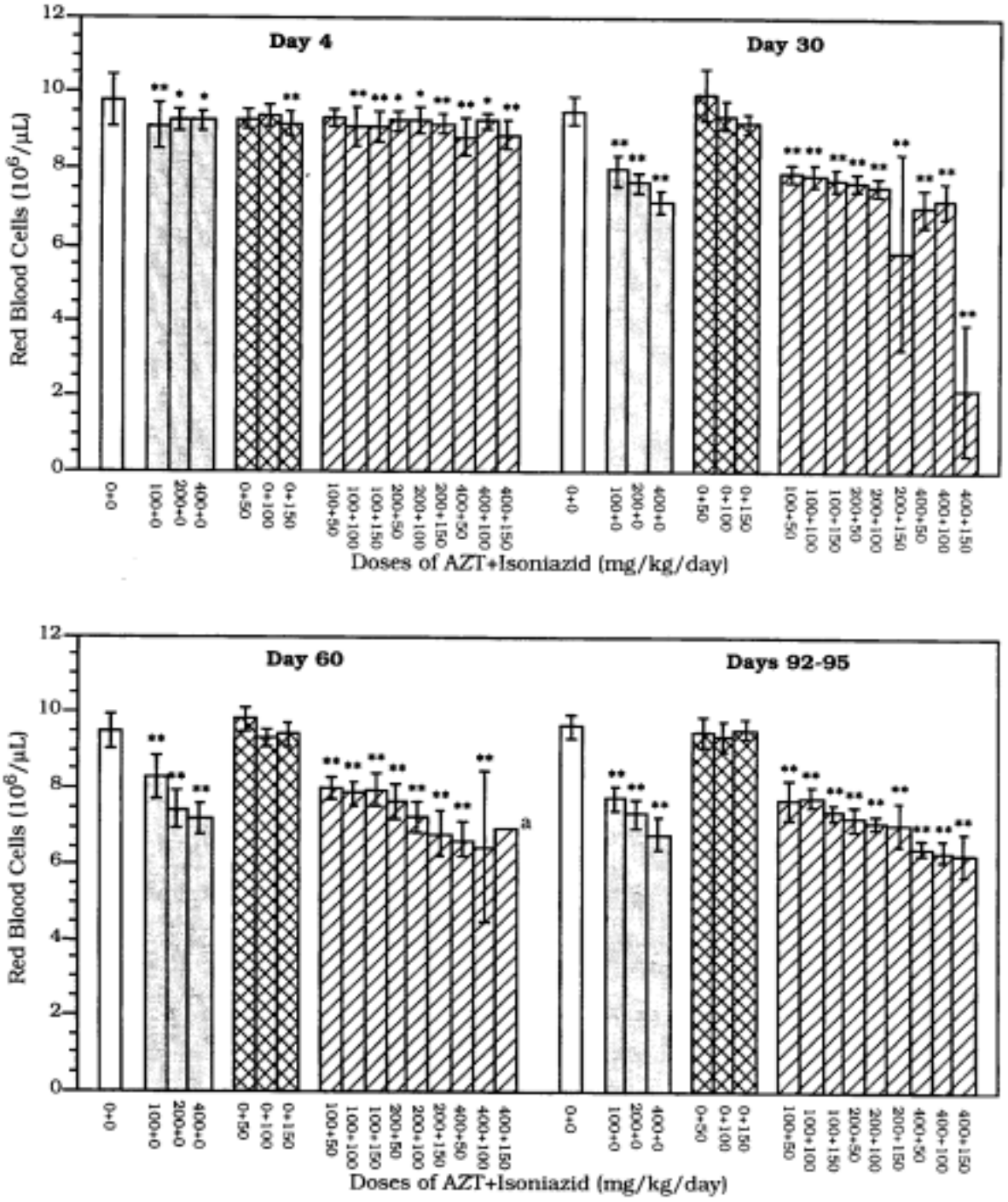
Clinical Chemistry

Administration of AZT (100, 200, and 400 mg/kg per day) and isoniazid (50, 100, and 150 mg/kg per day) separately and in various combinations did not result in any biologically significant alterations in the clinical chemistry parameters (Table B2) evaluated in male or female mice at any of the scheduled bleeding intervals (days 4, 30, 60, and terminal sacrifice).



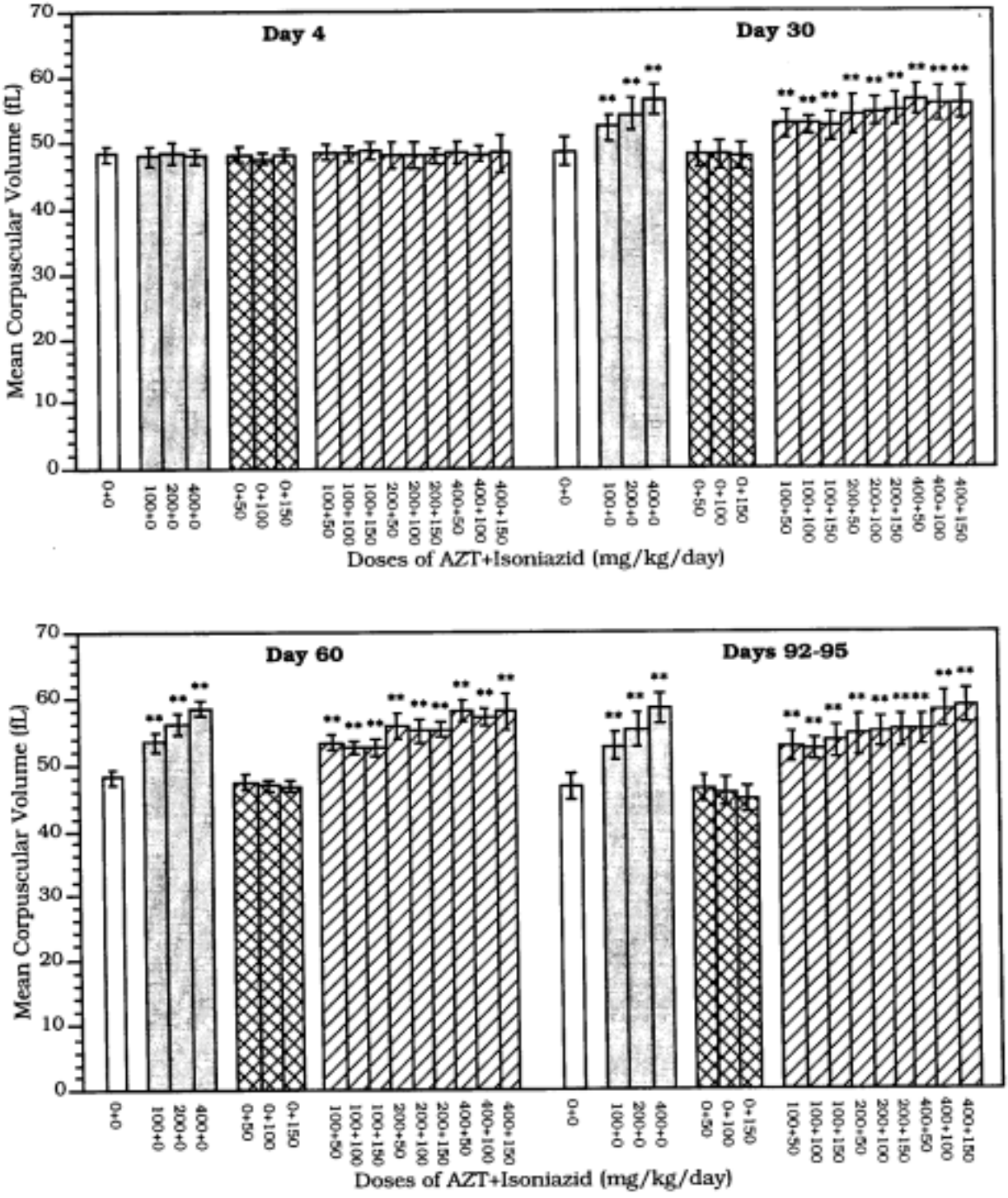
Bars indicate standard deviation
* Significantly different (P<0.05) from control group using ANOVA followed by Dunnett's procedure
** Significantly different (P<0.01) from control group using ANOVA followed by Dunnett's procedure

FIGURE 3
Mean Red Blood Cell Counts for Male Mice in the 13-Week Toxicity Study of AZT and Isoniazid Combinations



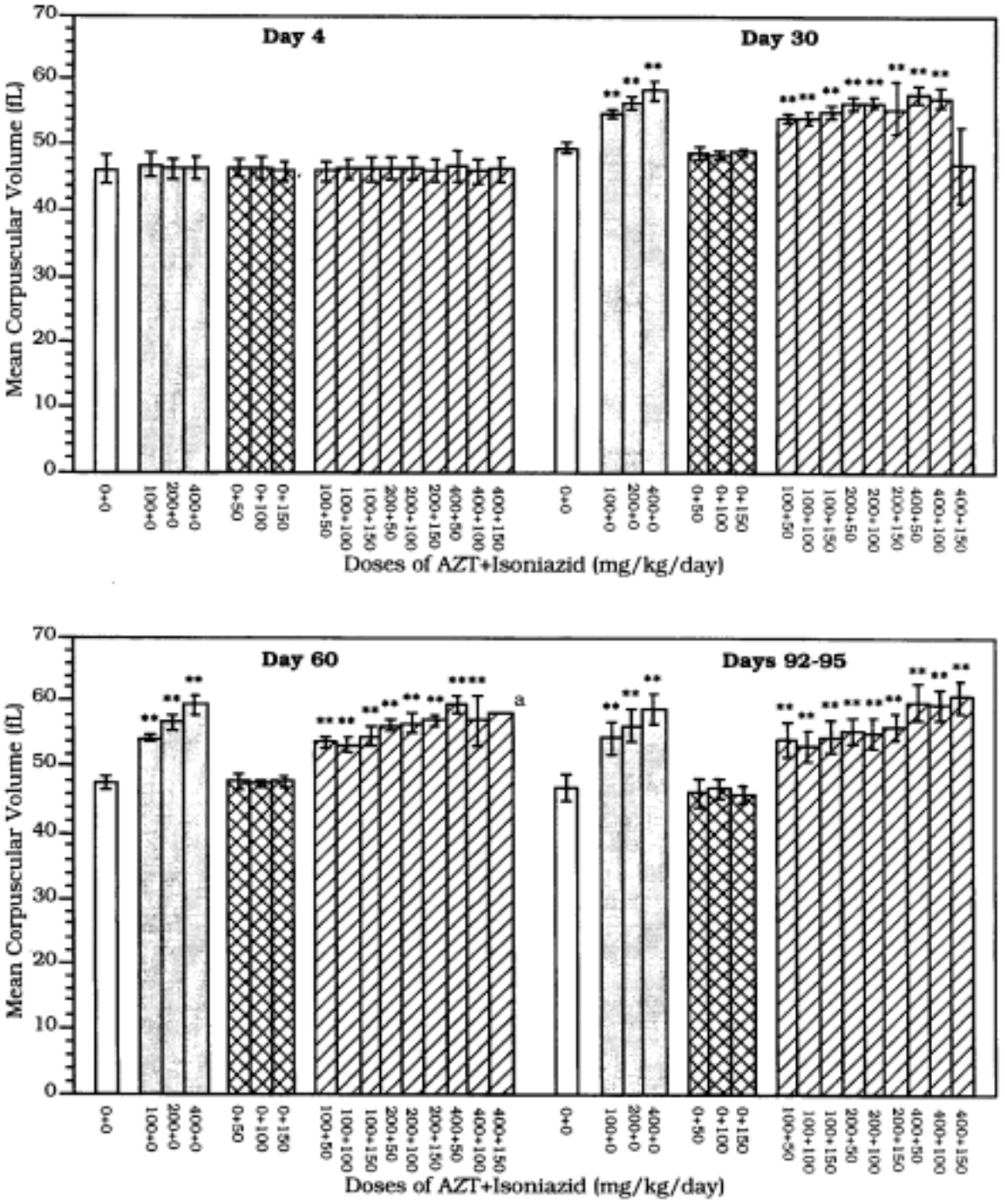
Bars indicate standard deviation
* Significantly different (P<0.05) from control group using ANOVA followed by Dunnett's procedure
** Significantly different (P<0.01) from control group using ANOVA followed by Dunnett's procedure
a Value for one mouse that survived to Day 60

FIGURE 4
Mean Red Blood Cell Counts for Female Mice in the 13-Week Toxicity Study of AZT and Isoniazid Combinations



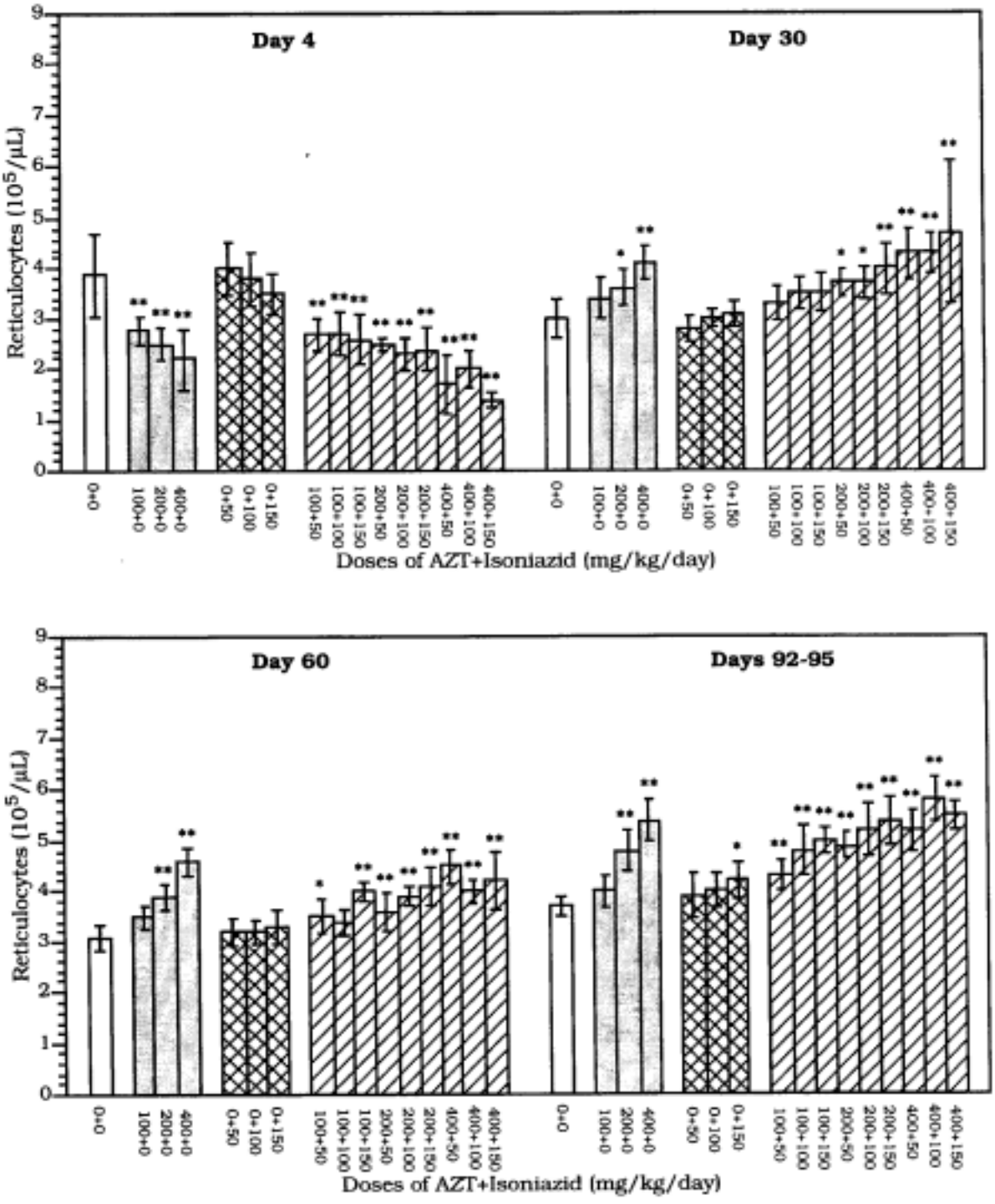
Bars indicate standard deviation
* Significantly different (P<0.05) from control group using ANOVA followed by Dunnett's procedure
** Significantly different (P<0.01) from control group using ANOVA followed by Dunnett's procedure

FIGURE 5
Mean Corpuscular Volume for Male Mice in the 13-Week Toxicity Study of AZT and Isoniazid Combinations



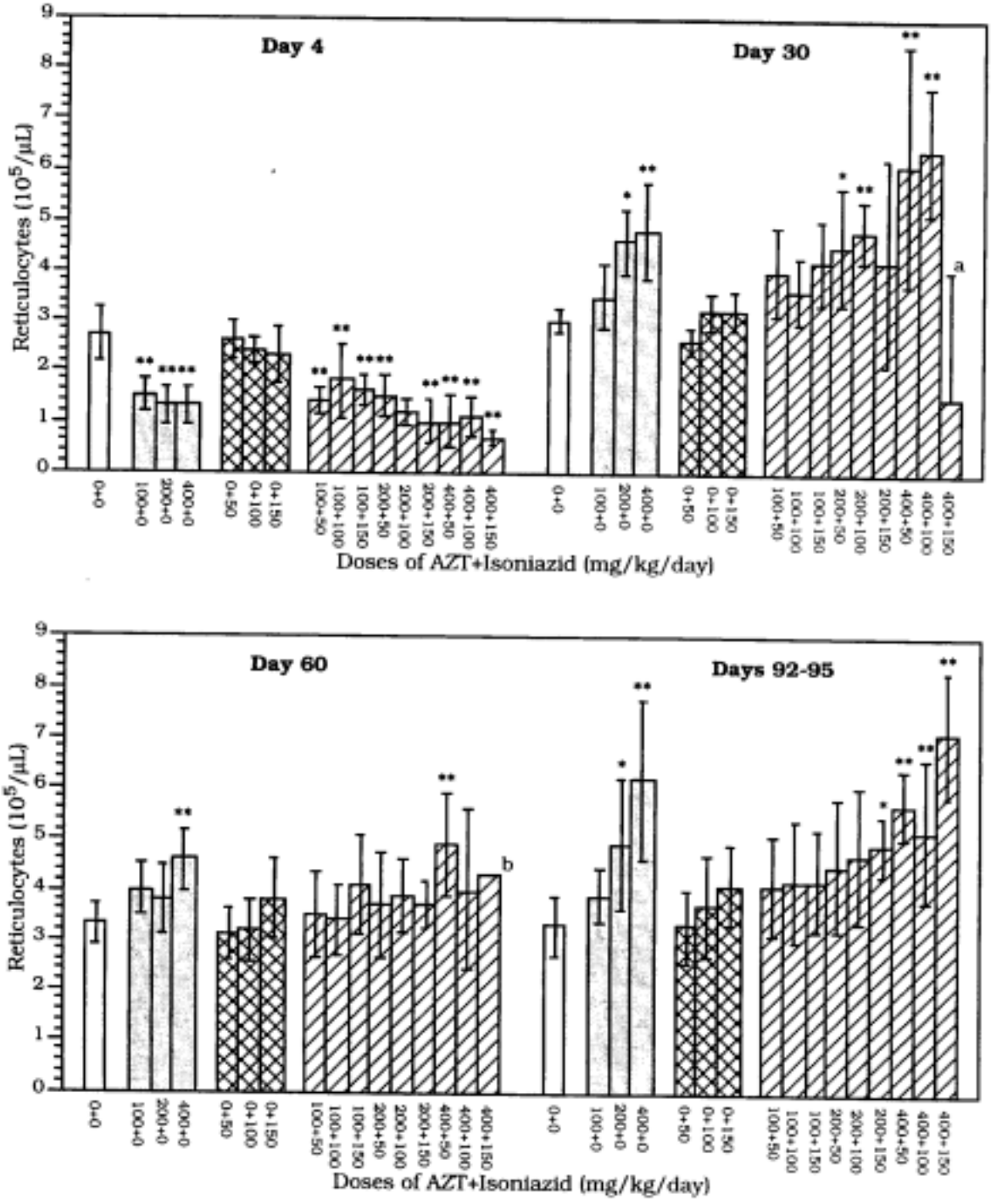
Bars indicate standard deviation
* Significantly different (P<0.05) from control group using ANOVA followed by Dunnett's procedure
** Significantly different (P<0.01) from control group using ANOVA followed by Dunnett's procedure
a Value for one mouse that survived to Day 60

FIGURE 6
Mean Corpuscular Volume for Female Mice in the 13-Week Toxicity Study of AZT and Isoniazid Combinations



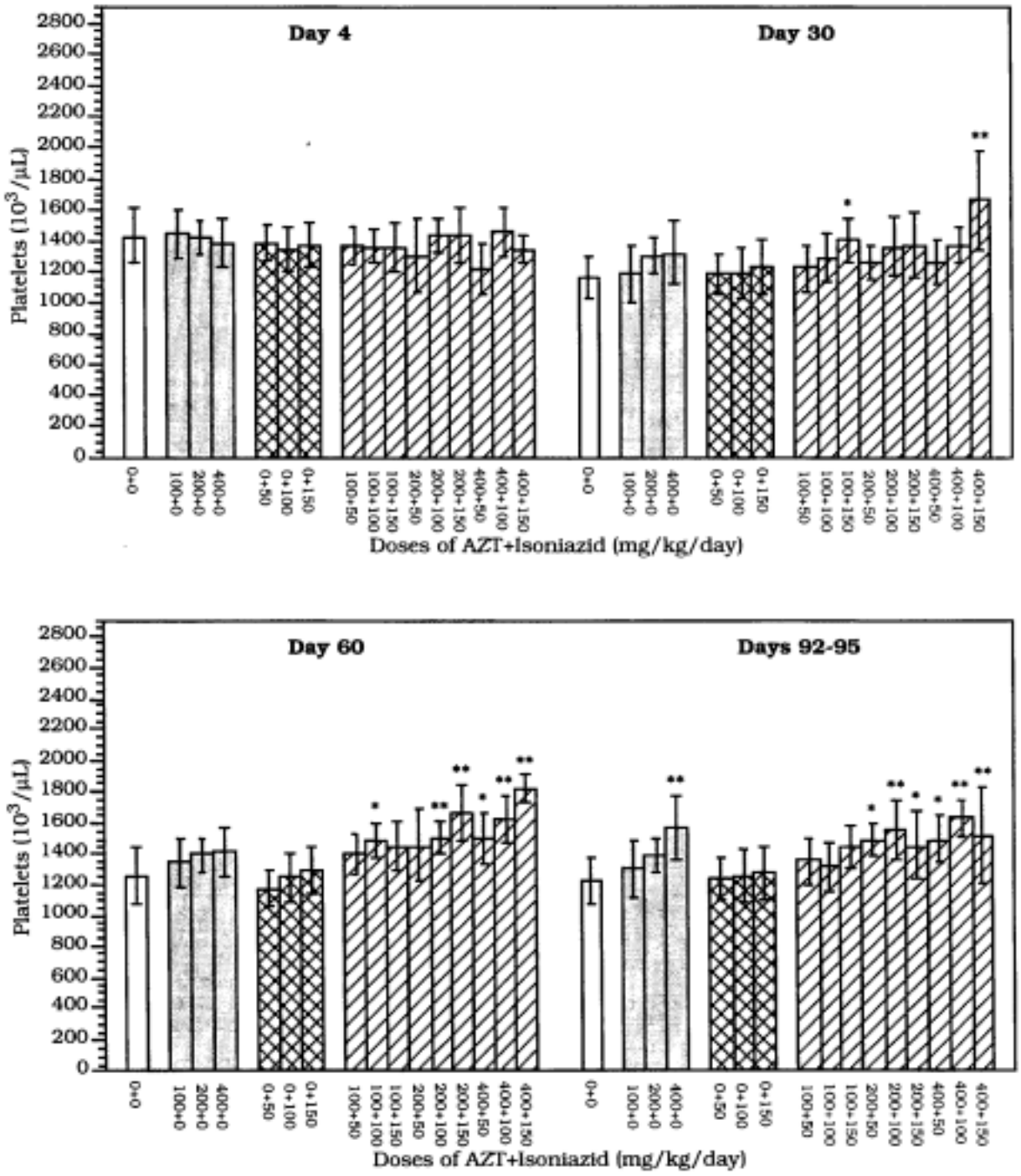
Bars indicate standard deviation
* Significantly different (P<0.05) from control group using ANOVA followed by Dunnett's procedure
** Significantly different (P<0.01) from control group using ANOVA followed by Dunnett's procedure

FIGURE 7
Mean Reticulocyte Counts for Male Mice in the 13-Week Toxicity Study of AZT and Isoniazid Combinations



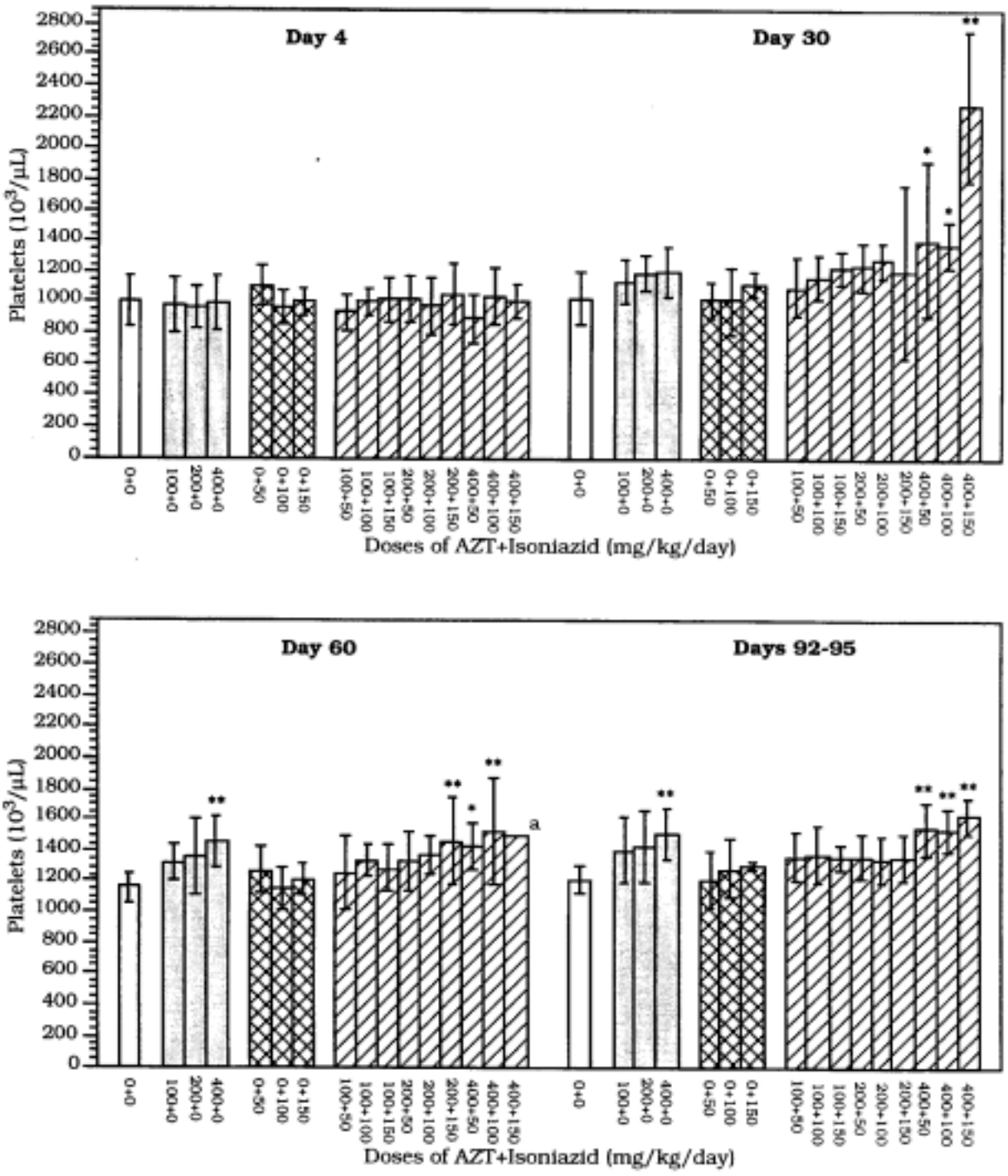
Bars indicate standard deviation
* Significantly different (P<0.05) from control group using ANOVA followed by Dunnett's procedure
** Significantly different (P<0.01) from control group using ANOVA followed by Dunnett's procedure
a Negative standard deviation not shown as it extends beyond the chart boundaries
b Value for one mouse that survived to Day 60

FIGURE 8
Mean Reticulocyte Counts for Female Mice in the 13-Week Toxicity Study of AZT and Isoniazid Combinations



Bars indicate standard deviation
* Significantly different (P<0.05) from control group using ANOVA followed by Dunnett's procedure
** Significantly different (P<0.01) from control group using ANOVA followed by Dunnett's procedure

FIGURE 9
Mean Platelet Counts for Male Mice in the 13-Week Toxicity Study of AZT and Isoniazid Combinations



Bars indicate standard deviation
* Significantly different (P<0.05) from control group using ANOVA followed by Dunnett's procedure
** Significantly different (P<0.01) from control group using ANOVA followed by Dunnett's procedure
a Value for one mouse that survived to Day 60

FIGURE 10
Mean Platelet Counts for Female Mice in the 13-Week Toxicity Study of AZT and Isoniazid Combinations

REPRODUCTIVE TISSUE EVALUATION AND ESTROUS CYCLE CHARACTERIZATION

Administration of AZT alone, isoniazid alone, or combinations of AZT and isoniazid had no significant effect ($P \leq 0.05$) on left caudal, epididymal, or testicular weights, total spermatid heads per gram of testis, epididymal sperm density, or epididymal sperm motility (Table C1). Although not statistically significant, marginal declines in epididymal sperm motility occurred in male groups treated with 200 or 400 mg/kg AZT alone.

For female mice, the administration of AZT alone, isoniazid alone, or combinations of AZT and isoniazid had no effect on the average estrous cycle length (Table C2). Results of a two-way analysis of variance, however, indicated a significant ($P \leq 0.0025$) increase in the duration of estrus due to isoniazid treatment.

NECROPSY OBSERVATIONS

Necropsy findings possibly attributable to treatment were limited to thin, pale carcass in three female mice and small spleen in one female mouse in the group treated with 400 mg/kg AZT + 150 mg/kg isoniazid. Other findings occurring with a random distribution and believed to be incidental were focus on the spleen, focus on the liver, nodule on the liver, small testis, cyst on the ovary, dark clitoral gland, mass in the lung, diverticulum of the jejunum, alopecia, and opaque eye.

HISTOPATHOLOGIC OBSERVATIONS

Representative microscopic lesions resulting from administration of AZT and isoniazid are illustrated in Plates 1 through 6, which are summarized in Table 2. Target tissues included the bone marrow, liver, and spleen of male and female mice. Statistical results include dose-response effects of AZT and isoniazid compared to the vehicle control group as well as significant dose-response effects compared to AZT or isoniazid alone.

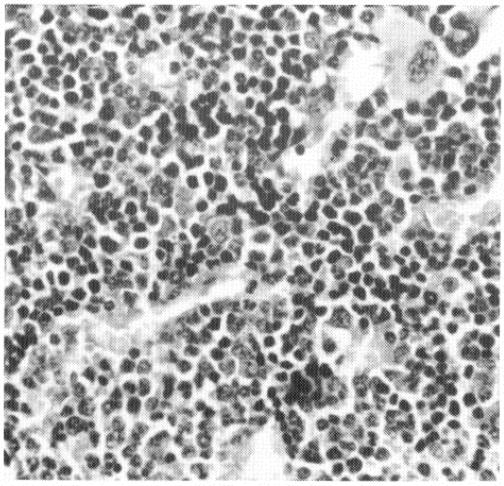


PLATE 1
Bone marrow from a control female mouse showing no treatment-related lesions. (×400)

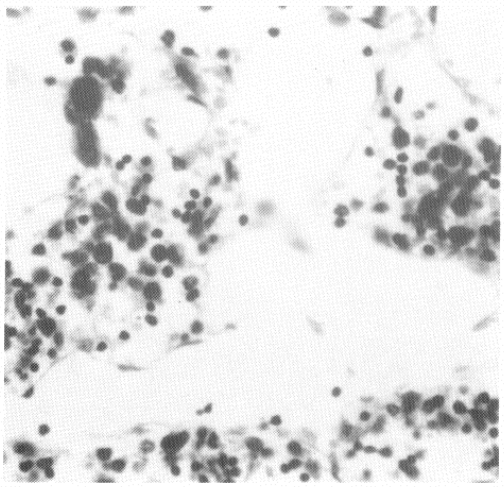


PLATE 2
Bone marrow from a female mouse treated with 400 mg/kg AZT + 150 mg/kg isoniazid showing moderate cellular depletion. (×400)

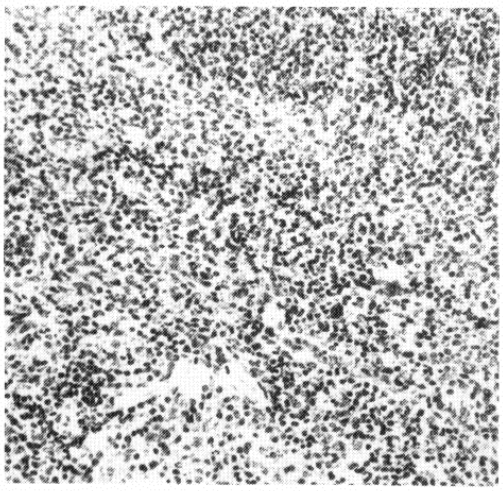


PLATE 3
Spleen from a control female mouse showing no treatment-related lesions. (×200)

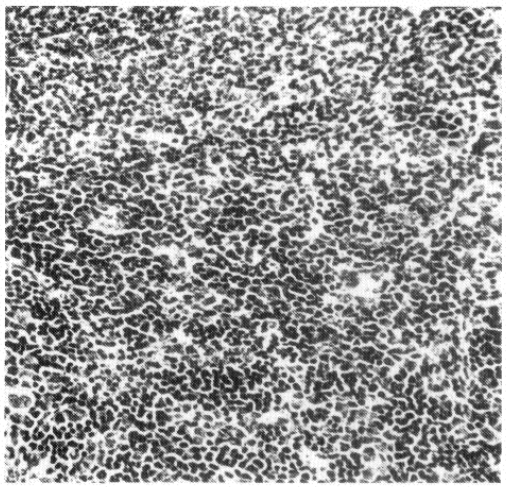


PLATE 4
Spleen from a female mouse treated with 400 mg/kg AZT + 150 mg/kg isoniazid showing moderate hematopoietic cell proliferation. (×200)

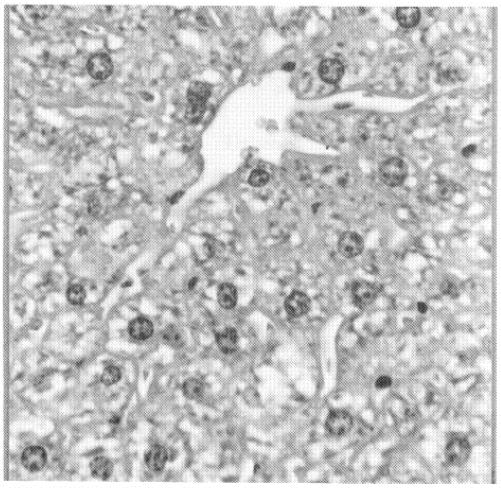


PLATE 5
Liver from a control male mouse showing no treatment-related lesions. (×400)

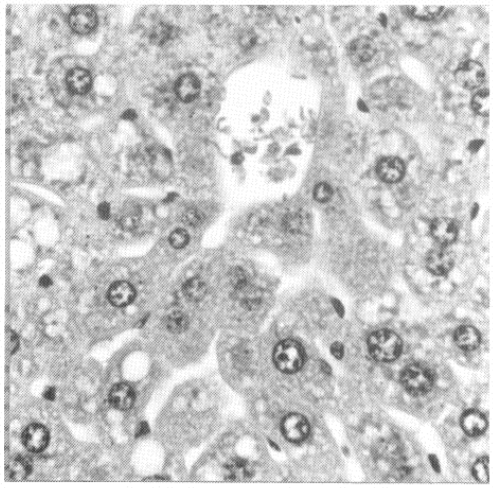


PLATE 6
Liver from a male mouse treated with 400 mg/kg AZT + 150 mg/kg isoniazid showing mild hepatocellular hypertrophy. (×400)

TABLE 2
List of Photomicrographs (Plates) of Treatment-Related Lesions in B6C3F$_1$ Mice from the 13-Week Toxicity Study of AZT and Isoniazid Combinations

Dose[a]	Tissue	Magnification	Plate Number	Lesion
0 + 0	Bone Marrow	×400	1	None (control)
400 + 150	Bone Marrow	×400	2	Cellular depletion, moderate
0 + 0	Spleen	×200	3	None (control)
400 + 150	Spleen	×200	4	Hematopoietic cell proliferation, moderate
0 + 0	Liver	×400	5	None (control)
400 + 150	Liver	×400	6	Hepatocellular hypertrophy, mild

[a] AZT + isoniazid in mg/kg/day

Bone Marrow Lesions

Cellular depletion of the bone marrow occurred in male and female mice treated with 400 mg/kg AZT alone (Table 3). Administration of isoniazid alone did not result in bone marrow depletion. Administration of AZT and isoniazid combinations to male and female mice resulted in an increase in the incidence (Table 3) of bone marrow depletion as well as an increase in the severity in females (Tables 3 and 4). Criteria for severity of bone marrow lesions were as follows:

Minimal - Depletion of approximately 5% of the hematopoietic cells of the bone marrow

Mild - Depletion of approximately 6% to 20% of the hematopoietic cells of the bone marrow

Moderate - Depletion of approximately 21% to 50% of the hematopoietic cells of the bone marrow

Marked - Depletion of more than 50% of the hematopoietic cells of the bone marrow.

TABLE 3
Incidence and Severity of Cellular Depletion of Bone Marrow in B6C3F$_1$ Mice from the 13-Week Toxicity Study of AZT and Isoniazid Combinations

	Males		Females	
Dose[a]	Group Incidence[b]	Mean Severity[c]	Group Incidence[b]	Mean Severity[c]
0+0	0/10	—	0/10	—
100+0	0/10	—	0/10	—
200+0	0/10	—	0/10	—
400+0	4/10	1.0	8/10	1.1
0+50	0/10	—	0/10	—
100+50	0/10	—	1/10	1.0
200+50	3/10	1.0	4/10	1.0
400+50	8/10	1.0	8/10	1.3
0+100	0/10	—	0/10	—
100+100	1/10	1.0	0/10	—
200+100	3/10	1.0	6/10	1.0
400+100	10/10	1.0	8/10	1.1
0+150	0/10	—	0/10	—
100+150	3/10	1.0	5/10	1.0
200+150	9/10	1.0	9/10	1.0
400+150	8/10	1.0	8/10	2.1

[a] AZT + isoniazid in mg/kg/day
[b] Number of animals in group with lesion/number of animals with tissue examined microscopically
[c] Mean severity (1=minimal, 2=mild, 3=moderate, 4=marked) for mice with the lesion

When compared to groups treated with AZT alone (100, 200, or 400 mg/kg), significant increases in severity ($P \leq 0.05$ to $P \leq 0.01$) occurred in female mice treated with 100 mg/kg AZT + 150 mg/kg isoniazid, female mice treated with 200 mg/kg AZT + 50 or 100 mg/kg isoniazid, male and female groups treated with 200 mg/kg AZT + 150 mg/kg isoniazid, and the male group treated with 400 mg/kg AZT + 100 mg/kg isoniazid (Table 4). Compared to groups treated with isoniazid alone (50, 100, or 150 mg/kg), significant increases in severity ($P \leq 0.05$ to $P \leq 0.01$) occurred in male and female groups treated with 200 or 400 mg/kg AZT + 50 or 150 mg/kg isoniazid, males treated with 400 mg/kg AZT + 100 mg/kg isoniazid, and female groups receiving 200 or 400 mg/kg AZT + 100 mg/kg isoniazid (Table 4). The peak mean severity occurred in the female group treated with 400 mg/kg AZT + 150 mg/kg isoniazid. In general, the enhanced severity of bone marrow depletion ($P \leq 0.05$ to $P \leq 0.01$) in groups receiving combination therapy corresponded with the increased severity of anemia.

TABLE 4
Statistical Analysis of Mean Severity of Cellular Depletion of Bone Marrow in B6C3F$_1$ Mice from the 13-Week Toxicity Study of AZT and Isoniazid Combinations

	Severity in Males[a]			Severity in Females[a]		
Dose[b]	Mean[c]	S.E.	Ratio[d]	Mean[c]	S.E.	Ratio[d]
0+0	0.000	0.000	—	0.000	0.000	—
100+0	0.000	0.000		0.000	0.000	
200+0	0.000	0.000		0.000	0.000	
400+0	**0.400	0.163		**0.900	0.180	
	Trend[e]	+ (P=0.005)		Trend[e]	+ (P≤0.001)	
	Test Used[f]	Shirley		Test Used[f]	Shirley	
100+0	0.000	0.000	—	0.000	0.000	—
100+50	0.000	0.000		0.100	0.100	
100+100	0.100	0.100		0.000	0.000	
100+150	0.300	0.153		**0.500	0.167	
	Trend[e]	+ (P=0.020)		Trend[e]	+ (P=0.006)	
	Test Used[f]	Dunn		Test Used[f]	Shirley	
200+0	0.000	0.000	—	0.000	0.000	—
200+50	0.300	0.153		*0.400	0.163	
200+100	0.300	0.153		**0.600	0.163	
200+150	**0.900	0.100		**0.900	0.100	
	Trend[e]	+ (P≤0.001)		Trend[e]	+ (P≤0.001)	
	Test Used[f]	Shirley		Test Used[f]	Shirley	
400+0	0.400	0.163	—	0.900	0.180	—
400+50	0.800	0.133	200	1.000	0.258	111
400+100	**1.000	0.000	250	0.900	0.180	100
400+150	0.800	0.133	200	1.700	0.396	189
	Trend[e]	+ (P=0.024)		Trend[e]	+ (P=0.157)	
	Test Used[f]	Dunn		Test Used[f]	Dunn	
0+50	0.000	0.000	—	0.000	0.000	—
100+50	0.000	0.000		0.100	0.100	
200+50	*0.300	0.153		*0.400	0.163	
400+50	**0.800	0.133		**1.000	0.258	
	Trend[e]	+ (P≤0.001)		Trend[e]	+ (P≤0.001)	
	Test Used[f]	Shirley		Test Used[f]	Shirley	

TABLE 4
Statistical Analysis of Mean Severity of Cellular Depletion of Bone Marrow in B6C3F$_1$ Mice from the 13-Week Toxicity Study of AZT and Isoniazid Combinations

	Severity in Males[a]			Severity in Females[a]		
Dose[b]	Mean[c]	S.E.	Ratio[d]	Mean[c]	S.E.	Ratio[d]
0+100	0.000	0.000	—	0.000	0.000	—
100+100	0.100	0.100		0.000	0.000	
200+100	0.300	0.153		**0.600	0.163	
400+100	**1.000	0.000		**0.900	0.180	
	Trend[e]	+ (P≤0.001)		Trend[e]	+ (P≤0.001)	
	Test Used[f]	Shirley		Test Used[f]	Shirley	
0+150	0.000	0.000	—	0.000	0.000	—
100+150	0.300	0.153		*0.500	0.167	
200+150	**0.900	0.100		**0.900	0.100	
400+150	**0.800	0.133		**1.700	0.396	
	Trend[e]	+ (P≤0.001)		Trend[e]	+ (P≤0.001)	
	Test Used[f]	Shirley		Test Used[f]	Shirley	

[a] Severity grade presented as mean severity (0=not present, 1=minimal, 2=mild, 3=moderate, 4=marked) and standard error (S.E.) for all mice in the group, including those with no lesion.
[b] AZT + isoniazid in mg/kg/day
[c] n=10
[d] (Dosed group mean/control group mean) × 100
[e] Direction and significance of trend (Jonckheere's test)
[f] Multiple comparisons test comparing dose group to control group
* Significantly different from the control group (P≤0.05)
** Significantly different from the control group (P≤0.01)

Spleen Lesions

Hematopoietic cell proliferation or hyperplasia in the red pulp of the spleen (above background levels of normal extramedullary hematopoiesis) occurred in all male and female groups treated with AZT alone or in combination with isoniazid and in all female groups treated with isoniazid alone (Table 5). Extramedullary hematopoiesis (grade 0 for hematopoietic cell proliferation) consisting of megakaryocytes, foci of erythroid precursors, and large granulocytic precursors is a normal occurrence in the red pulp of the spleen of mice (Maronpot *et al.*, 1999). Criteria for severity grades for hematopoietic cell proliferation in the spleen were as follows:

Minimal - Approximately 15% of the red pulp is occupied by hematopoietic cells

Mild - Approximately 16% to 50% of the red pulp is occupied by hematopoietic cells

Moderate - Approximately 51% to 90% of the red pulp is occupied by hematopoietic cells

Marked - Approximately 91% to 100% of the red pulp is occupied by hematopoietic cells.

Compared to the vehicle control groups, the degree of severity (Table 6) of splenic hematopoietic cell proliferation was significant ($P \leq 0.01$) in male groups treated with 100, 200, or 400 mg/kg AZT alone and in female groups treated with 200 or 400 mg/kg AZT alone. For mice treated with isoniazid alone, splenic hematopoiesis was significant ($P \leq 0.01$) only in the female group treated with 50 mg/kg when compared to the vehicle controls. When compared to groups treated with AZT alone (100, 200, or 400 mg/kg), splenic hematopoiesis was significant ($P \leq 0.05$ to $P \leq 0.01$) in male mice treated with 100 or 200 mg/kg AZT in combination with 100 or 150 mg/kg isoniazid and in female mice treated with 100 mg/kg AZT + 150 mg/kg isoniazid (Table 6). When compared to groups treated with isoniazid alone (50, 100, or 150 mg/kg), splenic hematopoiesis was significant ($P \leq 0.01$) in all male groups receiving combination therapy and in female groups treated with 100, 200, or 400 mg/kg AZT + 100 mg/kg isoniazid and with 100 mg/kg AZT + 150 mg/kg isoniazid (Table 6). In general, splenic hematopoiesis occurred with increased severity in groups with anemia and likely reflected a compensatory response to the anemia.

TABLE 5
Incidence and Severity of Hematopoietic Cell Proliferation in the Spleen in B6C3F$_1$ Mice from the 13-Week Toxicity Study of AZT and Isoniazid Combinations

	Males		Females	
Dose[a]	Group Incidence[b]	Mean Severity[c]	Group Incidence[b]	Mean Severity[c]
0+0	0/10	—	1/10	1.0
100+0	7/10	1.1	4/10	1.8
200+0	8/10	1.0	8/10	1.6
400+0	10/10	1.6	9/10	2.1
0+50	0/10	—	8/10	1.5
100+50	7/10	1.6	8/10	2.1
200+50	10/10	1.4	8/10	2.0
400+50	10/10	1.8	8/10	2.5
0+100	0/10	—	5/10	1.0
100+100	10/10	1.9	9/10	2.0
200+100	10/10	2.1	10/10	2.2
400+100	10/10	1.6	9/10	2.1
0+150	0/10	—	2/10	1.0
100+150	10/10	1.9	9/10	2.2
200+150	10/10	1.7	9/10	1.1
400+150	9/10	2.0	6/10	2.7

[a] AZT + isoniazid in mg/kg/day
[b] Number of animals in group with lesion/number of animals with tissue examined microscopically.
[c] Mean severity (1=minimal, 2=mild, 3=moderate, and 4=marked) for mice with the lesion.

TABLE 6
Statistical Analysis of Mean Severity of Hematopoietic Cell Proliferation in the Spleen in B6C3F$_1$ Mice from the 13-Week Toxicity Study of AZT and Isoniazid Combinations

	Severity in Males[a]			Severity in Females[a]		
Dose[b]	Mean[c]	S.E.	Ratio[d]	Mean[c]	S.E.	Ratio[d]
0+0	0.000	0.000	—	0.100	0.100	—
100+0	**0.800	0.200		0.700	0.335	700
200+0	**1.000	0.211		**1.300	0.260	1300
400+0	**1.600	0.163		**1.900	0.314	1900
	Trend[e]	+ (P≤0.001)		Trend[e]	+ (P≤0.001)	
	Test Used[f]	Shirley		Test Used[f]	Shirley	
0+0	0.000	0.000	—	0.100	0.100	—
0+50	0.000	0.000		**1.300	0.300	1300
0+100	0.000	0.000		0.500	0.167	500
0+150	0.000	0.000		0.200	0.133	200
	Trend[e]	(P=1.000)		Trend[e]	- (P=0.739)	
	Test Used[f]	Dunn		Test Used[f]	Dunn	
100+0	0.800	0.200	—	0.700	0.335	—
100+50	1.100	0.277	138	1.700	0.396	243
100+100	**1.900	0.233	238	1.800	0.291	257
100+150	**2.000	0.149	250	*2.000	0.258	286
	Trend[e]	+ (P≤0.001)		Trend[e]	+ (P=0.014)	
	Test Used[f]	Shirley		Test Used[f]	Dunn	
200+0	1.000	0.211	—	1.300	0.260	—
200+50	1.400	0.163	140	1.600	0.371	123
200+100	**2.100	0.100	210	2.200	0.249	169
200+150	**1.700	0.153	170	1.200	0.200	92
	Trend[e]	+ (P=0.002)		Trend[e]	+ (P=0.960)	
	Test Used[f]	Shirley		Test Used[f]	Dunn	
400+0	1.600	0.163	—	1.900	0.314	—
400+50	1.800	0.133	113	2.000	0.394	105
400+100	1.600	0.163	100	1.900	0.277	100
400+150	1.800	0.291	113	1.400	0.476	74
	Trend[e]	+ (P=0.571)		Trend[e]	- (P=0.470)	
	Test Used[f]	Dunn		Test Used[f]	Dunn	
0+50	0.000	0.000	—	1.300	0.300	—
100+50	**1.100	0.277		1.700	0.396	131
200+50	**1.400	0.163		1.600	0.371	123
400+50	**1.800	0.133		2.000	0.394	154
	Trend[e]	+ (P≤0.001)		Trend[e]	+ (P=0.215)	
	Test Used[f]	Shirley		Test Used[f]	Dunn	

TABLE 6
Statistical Analysis of Mean Severity of Hematopoietic Cell Proliferation in the Spleen in B6C3F$_1$ Mice from the 13-Week Toxicity Study of AZT and Isoniazid Combinations

	Severity in Males[a]			Severity in Females[a]		
Dose[b]	Mean[c]	S.E.	Ratio[d]	Mean[c]	S.E.	Ratio[d]
0+100	0.000	0.000	—	0.500	0.167	—
100+100	**1.900	0.233		**1.800	0.291	360
200+100	**2.100	0.100		**2.200	0.249	440
400+100	**1.600	0.163		**1.900	0.277	380
	Trend[e]	+ (P=0.001)		Trend[e]	+ (P=0.001)	
	Test Used[f]	Shirley		Test Used[f]	Shirley	
0+150	0.000	0.000	—	0.200	0.133	—
100+150	**2.000	0.149		**2.000	0.258	1000
200+150	**1.700	0.153		1.200	0.200	600
400+150	**1.800	0.291		1.400	0.476	700
	Trend[e]	+ (P=0.001)		Trend[e]	+ (P=0.096)	
	Test Used[f]	Shirley		Test Used[f]	Dunn	

[a] Severity grade presented as mean severity (0=not present, 1=minimal, 2=mild, 3=moderate, 4=marked) and standard error (S.E.) for all mice in the group, including those with no lesion.
[b] AZT + isoniazid in mg/kg/day
[c] n=10
[d] (Dosed group mean/control group mean) × 100
[e] Direction and significance of trend (Jonckheere's test)
[f] Multiple comparisons test comparing dose group to control group
* Significantly different from the control group (P≤0.05)
** Significantly different from the control group (P≤0.01)

Liver Lesions

A treatment-related pigmentation of the liver occurred in male groups treated with 100 or 150 mg/kg isoniazid alone or in combination with AZT and in female mice treated with 400 mg/kg AZT + 150 mg/kg isoniazid (Table 7). The liver pigmentation did not occur in groups treated with 50 mg/kg isoniazid alone or in groups treated with AZT alone or in combination with 50 mg/kg isoniazid. The pigment consisted of fine to coarse brown granules within the cytoplasm of hepatocytes and, to a lesser extent, Kupffer cells. The pigment resembled hemosiderin with routine hematoxylin and eosin stains, but when stained with Prussian Blue, was negative for iron (Sheehan and Hrapchak, 1980). The pigment occurred primarily in the paracentral and midzonal portions of the hepatic lobules with relative sparing of the periportal areas. Criteria for grading the pigmentation were as follows:

Minimal - approximately 5% of the cytoplasm occupied by pigment

Mild - approximately 6 to 15% of the cytoplasm occupied by pigment.

Compared to the vehicle control male group, the liver pigmentation was significant ($P \leq 0.01$) in male groups treated with 100 or 150 mg/kg isoniazid alone (Table 8). When compared to groups treated with AZT alone (100, 200, or 400 mg/kg), significant increases in pigmentation ($P \leq 0.01$) occurred in male groups treated with 100 or 200 mg/kg AZT in combination with 100 or 150 mg/kg isoniazid and in male and female groups treated with 400 mg/kg AZT + 150 mg/kg isoniazid. When compared to the male group treated with 100 mg/kg isoniazid alone, a significant decline ($P \leq 0.01$) in pigmentation occurred in the male group treated with 400 mg/kg AZT + 100 mg/kg isoniazid. The pigment was not identified but was considered possibly a metabolite of isoniazid.

Hypertrophy of hepatocytes occurred in male groups treated with 150 mg/kg isoniazid alone or in combination with 100, 200, or 400 mg/kg AZT (Table 7). The hypertrophy occurred in the same areas of the liver lobules as the pigmentation. Criteria for grading the severity of hypertrophy were as follows:

Minimal - an increase in the size of hepatocytes by approximately 15%

Mild - an increase in the size of hepatocytes by approximately 16% to 25%.

Hepatocellular hypertrophy was significant ($P \leq 0.05$) only in the group treated with 400 mg/kg AZT + 150 mg/kg isoniazid when compared to the group treated with 400 mg/kg AZT alone (Table 9).

TABLE 7
Incidence and Severity of Hepatocyte Pigmentation and Hypertrophy in B6C3F$_1$ Mice from the 13-Week Toxicity Study of AZT and Isoniazid Combinations

	Pigmentation				Hypertrophy			
	Males		Females		Males		Females	
Dose[a]	Group Incidence[b]	Mean Severity[c]	Group Incidence[b]	Mean Severity[c]	Group Incidence[b]	Mean Severity[c]	Group Incidence[b]	Mean Severity[c]
0+0	0/10	—	0/10	—	0/10	—	0/10	—
0+100	6/10	1.2	0/10	—	0/10	—	0/10	—
100+100	6/10	1.0	0/10	—	0/10	—	0/10	—
200+100	6/10	1.0	0/10	—	0/10	—	0/10	—
400+100	0/10	—	0/10	—	0/10	—	0/10	—
0+150	10/10	2.0	0/10	—	2/10	2.0	0/10	—
100+150	10/10	1.7	0/10	—	2/10	2.0	0/10	—
200+150	9/10	1.8	0/10	—	2/10	2.0	0/10	—
400+150	9/10	1.7	4/10	1.0	3/10	2.0	0/10	—

[a] AZT + isoniazid in mg/kg/day. Groups treated with AZT alone or AZT + 50 mg/kg isoniazid are not listed because lesions did not occur.
[b] Number of animals in group with lesion/number of animals with tissue examined microscopically.
[c] Mean severity (1=minimal, 2=mild, 3=moderate, and 4=marked) for mice with the lesion.

TABLE 8
Statistical Analysis of Mean Severity of Hepatocyte Pigmentation in B6C3F$_1$ Mice from the 13-Week Toxicity Study of AZT and Isoniazid Combinations

	Severity in Males[a]			Severity in Females[a]		
Dose[b]	Mean[c]	S.E.	Ratio[d]	Mean[c]	S.E.	Ratio[d]
0+0	0.000	0.000	—	0.000	0.000	—
100+0	0.000	0.000		0.000	0.000	
200+0	0.000	0.000		0.000	0.000	
400+0	0.000	0.000		0.000	0.000	
	Trend[e]	(P=1.000)		Trend[e]	(P=1.000)	
	Test Used[f]	Dunn		Test Used[f]	Dunn	
0+0	0.000	0.000	—	0.000	0.000	—
0+50	0.000	0.000		0.000	0.000	
0+100	**0.700	0.213		0.000	0.000	
0+150	**2.000	0.149		0.000	0.000	
	Trend[e]	+ (P≤0.001)		Trend[e]	(P=1.000)	
	Test Used[f]	Shirley		Test Used[f]	Dunn	
100+0	0.000	0.000	—	0.000	0.000	—
100+50	0.000	0.000		0.000	0.000	
100+100	**0.600	0.163		0.000	0.000	
100+150	**1.700	0.260		0.000	0.000	
	Trend[e]	+ (P≤0.001)		Trend[e]	(P=1.000)	
	Test Used[f]	Shirley		Test Used[f]	Dunn	
200+0	0.000	0.000	—	0.000	0.000	—
200+50	0.000	0.000		0.000	0.000	
200+100	**0.600	0.163		0.000	0.000	
200+150	**1.600	0.267		0.000	0.000	
	Trend[e]	+ (P≤0.001)		Trend[e]	(P=1.000)	
	Test Used[f]	Shirley		Test Used[f]	Dunn	
400+0	0.000	0.000	—	0.000	0.000	—
400+50	0.000	0.000		0.000	0.000	
400+100	0.000	0.000		0.000	0.000	
400+150	**1.500	0.224		**0.400	0.163	
	Trend[e]	+ (P≤0.001)		Trend[e]	+ (P=0.005)	
	Test Used[f]	Shirley		Test Used[f]	Shirley	

TABLE 8
Statistical Analysis of Mean Severity of Hepatocyte Pigmentation in B6C3F$_1$ Mice from the 13-Week Toxicity Study of AZT and Isoniazid Combinations

	Severity in Males[a]			Severity in Females[a]		
Dose[b]	Mean[c]	S.E.	Ratio[d]	Mean[c]	S.E.	Ratio[d]
0+100	0.700	0.213	—	0.000	0.000	—
100+100	0.600	0.163	86	0.000	0.000	
200+100	0.600	0.163	86	0.000	0.000	
400+100	**0.000	0.000	0	0.000	0.000	
	Trend[e]	- (P=0.008)		Trend[e]	(P=1.000)	
	Test Used[f]	Shirley		Test Used[f]	Dunn	
0+150	2.000	0.149	—	0.000	0.000	—
100+150	1.700	0.260	85	0.000	0.000	
200+150	1.600	0.267	80	0.000	0.000	
400+150	1.500	0.224	75	**0.400	0.163	
	Trend[e]	- (P=0.150)		Trend[e]	+ (P=0.005)	
	Test Used[f]	Dunn		Test Used[f]	Shirley	

[a] Severity grade presented as mean severity (0=not present, 1=minimal, 2=mild) and standard error (S.E.) for all mice in the group, including those with no lesion.
[b] AZT + isoniazid in mg/kg/day
[c] n=10
[d] (Dosed group mean/control group mean) ×100
[e] Direction and significance of trend (Jonckheere's test)
[f] Multiple comparisons test comparing dose group to control group
* Significantly different from the control group ($P \leq 0.05$)
** Significantly different from the control group ($P \leq 0.01$)

TABLE 9
Statistical Analysis of Mean Severity of Hepatocyte Hypertrophy in Male B6C3F$_1$ Mice from the 13-Week Toxicity Study of AZT and Isoniazid Combinations

	Severity in Males[a]		
Dose[b]	Mean[c]	S.E.	Ratio[d]
0+0	0.000	0.000	—
100+0	0.000	0.000	
200+0	0.000	0.000	
400+0	0.000	0.000	
	Trend[e]	(P=1.000)	
	Test Used[f]	Dunn	
0+0	0.000	0.000	—
0+50	0.000	0.000	
0+100	0.000	0.000	
0+150	0.400	0.267	
	Trend[e]	+ (P=0.055)	
	Test Used[f]	Dunn	
100+0	0.000	0.000	—
100+50	0.000	0.000	
100+100	0.000	0.000	
100+150	0.400	0.267	
	Trend[e]	+ (P=0.055)	
	Test Used[f]	Dunn	
200+0	0.000	0.000	—
200+50	0.000	0.000	
200+100	0.000	0.000	
200+150	0.400	0.267	
	Trend[e]	+ (P=0.055)	
	Test Used[f]	Dunn	
400+0	0.000	0.000	—
400+50	0.000	0.000	
400+100	0.000	0.000	
400+150	*0.600	0.306	
	Trend[e]	+ (P=0.017)	
	Test Used[f]	Dunn	
0+150	0.400	0.267	—
100+150	0.400	0.267	100
200+150	0.400	0.267	100
400+150	0.600	0.306	150
	Trend[e]	+ (P=0.616)	
	Test Used[f]	Dunn	

[a] Severity grade presented as mean severity (0=not present, 1=minimal, 2=mild) and standard error (S.E.) for all mice in the group, including those with no lesion.
[b] AZT + isoniazid in mg/kg/day
[c] n=10
[d] (Dosed group mean/control group mean) × 100
[e] Direction and significance of trend (Jonckheere's test)
[f] Multiple comparisons test comparing dose group to control group
* Significantly different from the control group (P≤0.05)
** Significantly different from the control group (P≤0.01)

Other Lesions

Other lesions occurred with a random distribution across all treatment groups and were not believed to be related to treatment. Two female mice had benign teratomas of the ovary. Examples of nonneoplastic lesions believed to be incidental were suppurative inflammation in the lung, chronic inflammation in the skin and liver, bone marrow hyperplasia, perforated esophagus, pigment in the spleen, focal necrosis of the liver, cyst in the ovary and parathyroid, hydrometra, hemmorhage in the esophagus, accessory adrenal cortical nodule, epithelial hyperplasia in the forestomach, and atrophy of germinal epithelium in the testicle.

DISCUSSION AND CONCLUSIONS

A 13-week toxicity study was conducted in which male and female B6C3F$_1$ mice were treated with 3′-azido-3′-deoxythymidine (AZT) alone (100, 200, or 400 mg/kg per day), isoniazid alone (50, 100, or 150 mg/kg/day), or combinations of AZT and isoniazid. The test articles were administered by oral gavage for approximately 13 weeks.

Measurable evidence of hematopoietic toxicity occurred in mice of both sexes treated with AZT alone, and the most significant alteration consisted of a mild anemia. The anemia was accompanied by elevations in MCV and MCH values and, therefore, could be classified as macrocytic. The mild macrocytic anemia was accompanied microscopically by splenic hematopoiesis and bone marrow depression. Elevated reticulocyte counts also occurred in mice of both sexes treated with AZT alone; however, the extent of the reticulocytosis was not as great as the extent of the macrocytosis. The mild macrocytic anemia that occurred with AZT treatment is compatible with the anemia previously reported in mice (Thompson *et al.*, 1991). Macrocytic anemia is a common observation in humans treated with AZT (Snower and Weil, 1993; Richman *et al.*, 1987). The exact mechanism of the erythrocyte macrocytosis is unclear but it likely reflects inhibition of DNA synthesis in erythroid precursors. AZT is directly toxic to erythroid blast forming units (BFU-E) and erythroid colony forming units (CFU-E) *in vitro* at high concentrations and is antiproliferative in CFU-E at lower concentrations (Gogu *et al.*, 1995). In *in vivo* studies, AZT has been shown to increase splenic and bone marrow BFU-E in mice and to increase the sensitivity of both splenic and bone marrow BFU-E to erythropoietin (Chow *et al.*, 1991); both effects occur in the absence of an appreciable regenerative response (reticulocytosis), suggesting a maturation block in the erythroid series due to a block in terminal differentiation. AZT has since been shown to down-regulate the erythropoietin receptor in CFU-E and inhibit erythropoietin receptor-mediated signal transduction (Gogu *et al.*, 1995). These mechanisms could inhibit CFU-E proliferation and possibly affect erythropoietin-regulated maturation (Bick, 1993). The disproportionate reticulocyte response, when compared to the extent of the macrocytosis observed in this study, suggests that the anemia caused by AZT administration is compatible with depression of erythroid precursors due to impaired DNA synthesis. Other alterations associated with AZT therapy in mice consisted of a slight increase in platelet counts, increased pigmentation of the skin, and a slight decline in epididymal sperm motility.

Administration of isoniazid alone resulted in slight hepatotoxicity manifested by minimal to mild paracentral and midzonal hepatocellular hypertrophy and cytoplasmic pigment deposition in the liver of male mice. In human patients, isoniazid-related hepatotoxicity ranges from asymptomatic elevations in serum enzymes indicative of liver toxicity to fulminant hepatic failure and death (Vasudeva and Woods, 1997). Microscopic findings reported

in the liver of human patients with isoniazid toxicity consist of acute hepatocellular injury with ballooning degeneration, sinusoidal acidophilic bodies, focal necrosis, patchy hepatitis with inflammation, multilobular necrosis, and cirrhosis (Maddrey and Boitnott, 1973; Black *et al.*, 1975; Mitchell *et al.*, 1976). The manifestations of liver toxicity in mice in this study, even at three times the human therapeutic dose (adjusted for body surface area), are different from those described in human patients as necrosis and inflammation did not occur and there were no increases in serum enzymes indicative of liver toxicity. The absence of serum enzyme alterations with isoniazid treatment in this study is consistent with the results from a previous study conducted in Swiss (CD-1®) mice treated with the same dose levels of isoniazid for up to 30 days (NIEHS, 1999).

Administration of AZT in combination with isoniazid to male and female B6C3F$_1$ mice resulted in hematopoietic toxicity of greater severity than that resulting from the administration of AZT alone. Bone marrow suppression and severe anemia resulted in significant mortality in female mice treated with the highest combinations of AZT and isoniazid. The higher mortality rate in the female clinical pathology groups, as compared to core study animals, likely reflects the underlying treatment-related anemia in combination with the repeated blood sampling procedure. Since isoniazid administration resulted in alterations in hepatocyte morphology, the exacerbation of hematopoietic toxicity subsequent to combination therapy may be the result of isoniazid interfering with the metabolism of AZT. The liver is considered the major site for AZT catabolism and some AZT catabolites are five- to sevenfold more toxic than AZT (Cretton *et al.*, 1991). Exacerbation of hematopoietic toxicity with the higher combinations of AZT and isoniazid in this study is consistent with the enhanced hematological toxicity that occurred in a previous study (NIEHS, 1999) conducted in Swiss (CD-1®) mice treated with the same doses for up to 30 days. Other less dramatic alterations occurring in mice treated with combination therapy consisted of diminished body weight, reticulocytopenia followed by reticulocytosis, thrombocytosis, leukopenia, neutropenia, lymphopenia, and a slight increase in the duration of estrus.

CONCLUSIONS

Administration of AZT alone to B6C3F$_1$ mice resulted in dose- and duration-of-treatment-related hematopoietic toxicity manifested primarily by a mild macrocytic anemia. Administration of isoniazid alone did not cause hematopoietic toxicity but caused minimal to mild hepatotoxicity manifested by hepatocellular hypertrophy and pigment deposition in the liver. However, isoniazid, when administered in combination with AZT, increased the hematopoietic toxicity induced by AZT, resulting in treatment-related mortality. Results of this study indicate that toxicological effects of combination therapy can be considerably more severe than the toxicity of individual therapies and isoniazid may have potentiated the hematopoietic toxicity of AZT.

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APPENDIX A
BODY WEIGHTS AND ORGAN WEIGHTS

TABLE A1
Summary Body Weight Data for B6C3F$_1$ Mice from the 13-Week Toxicity Study of AZT and Isoniazid Combinations
Core Study Males

	Mean Body Weight (grams) on Day of Study						
Dose[a]	**-3**	**2**	**9**	**16**	**23**	**30**	**37**
0+0	21.6	23.8	25.6	26.4	27.2	28.3	29.2
100+0	21.4	23.8	25.3	26.3	27.2	28.4	28.9
200+0	21.6	23.9	25.6	26.3	27.5	28.5	29.3
400+0	21.9	24.3	26.3	27.3	28.3	29.3	30.1
0+50	22.1	24.5	26.4	27.5	28.6	29.7	30.5
0+100	22.1	24.3	26.2	27.3	28.6	30.0	30.6
0+150	21.5	23.7	26.0	27.5	28.6	29.7	30.4
100+50	21.7	24.4	26.3	27.6	28.7	29.8	31.0
100+100	21.8	24.1	26.2	27.3	28.3	29.4	30.1
100+150	21.6	24.0	25.9	27.3	28.2	29.3	30.3
200+50	21.9	24.1	26.1	26.5	27.6	29.2	29.7
200+100	21.6	24.1	25.5	26.8	28.0	28.9	29.6
200+150	21.9	24.4	26.5	27.7	28.8	30.1	31.0
400+50	21.8	23.9	26.1	27.2	28.1	28.9	29.5
400+100	21.7	23.9	25.4	26.1	26.9	27.9	28.2
400+150	21.7	24.3	26.1	27.5	28.8	30.0	30.6

	Mean Body Weight (grams) on Day of Study						
Dose[a]	**44**	**51**	**58**	**65**	**72**	**79**	**86**
0+0	30.0	31.0	31.5	33.3	33.2	33.5	34.2
100+0	30.1	31.2	32.1	33.4	33.6	33.9	34.3
200+0	30.7	31.6	32.6	34.1	34.0	34.8	35.5
400+0	31.1	32.2	32.5	33.6	34.3	34.7	35.5
0+50	31.5	32.8	33.5	34.8	35.4	35.8	36.3
0+100	31.8	32.6	33.6	34.9	35.0	35.1	35.7
0+150	31.4	32.0	33.0	34.2	34.0	34.8	35.6
100+50	32.3	33.7	34.8	36.3	37.1	37.2	38.2
100+100	31.2	32.1	32.7	34.3	34.6	35.2	35.5
100+150	31.3	31.9	32.7	34.0	34.0	34.6	35.6
200+50	31.0	32.2	32.9	34.4	34.7	35.4	36.2
200+100	30.1	31.6	32.1	33.6	33.6	34.4	35.0
200+150	31.5	32.4	32.9	34.3	34.4	34.7	35.5
400+50	30.2	31.4	32.2	33.7	33.6	34.0	34.5
400+100	29.0	30.2	31.0	32.2	32.6	32.5	33.4
400+150	31.2	32.2	32.8	34.3	34.8	35.5	36.2

[a] AZT + isoniazid in mg/kg/day

TABLE A1
Summary Body Weight Data for B6C3F$_1$ Mice from the 13-Week Toxicity Study of AZT and Isoniazid Combinations
Core Study Females

	Mean Body Weight (grams) on Day of Study						
Dose[a]	**-3**	**4**	**11**	**18**	**25**	**32**	**39**
0+0	17.9	18.8	19.9	21.5	22.8	22.3	23.8
100+0	17.9	18.4	20.5	21.7	22.5	21.8	23.0
200+0	18.1	19.0	20.6	22.0	22.7	23.9	24.2
400+0	17.9	18.1	20.5	21.5	22.7	23.5	24.0
0+50	17.6	18.6	20.5	21.3	22.8	23.8	24.5
0+100	18.0	19.5	20.9	22.0	23.4	24.0	25.0
0+150	17.6	19.1	20.5	21.6	22.8	23.6	24.5
100+50	17.7	18.2	20.3	21.1	23.3	23.7	24.3
100+100	17.7	18.6	20.5	21.0	22.8	23.5	23.8
100+150	17.6	19.0	20.2	21.2	22.3	22.6	24.0
200+50	18.0	19.3	20.5	21.7	22.7	23.2	23.6
200+100	17.8	18.6	19.5	21.6	22.8	23.3	22.4
200+150	17.3	18.9	20.2	20.2	22.1	22.5	23.3
400+50	18.0	18.8	20.3	21.4	21.9	23.2	23.9
400+100	17.6	18.8	20.8	21.9	23.1	23.5	24.6
400+150	17.8	19.4	20.5	21.0	22.2	22.5	21.2

	Mean Body Weight (grams) on Day of Study						
Dose[a]	**46**	**53**	**60**	**67**	**74**	**81**	**88**
0+0	25.2	25.9	27.5	28.3	28.3	27.8	27.9
100+0	24.7	25.1	26.3	26.4	27.2	27.0	26.9
200+0	25.0	26.4	26.5	27.9	27.8	27.8	27.7
400+0	25.1	25.4	25.5	26.6	27.2	25.9	26.5
0+50	25.1	26.0	27.1	29.2	28.2	28.8	29.9
0+100	25.8	27.0	27.8	28.2	29.4	29.2	29.9
0+150	24.5	25.6	26.5	27.5	27.2	27.7	27.2
100+50	25.2	26.4	26.3	28.0	28.5	28.8	28.7
100+100	23.9	25.5	25.9	26.5	27.2	27.8	27.4
100+150	24.4	24.5	25.4	26.3	26.5	26.4	25.4
200+50	24.7	25.5	26.8	28.1	28.0	28.2	28.7
200+100	24.7	25.8	25.8	28.1	28.1	28.2	28.6
200+150	23.6	24.5	24.8	26.2	26.0	26.0	26.3
400+50	24.6	25.5	24.0	27.2	27.4	28.1	28.3
400+100	25.2	25.4	26.6	26.8	28.5	28.6	28.3
400+150	25.7	26.1	26.4	28.2	27.6	26.4	27.8

[a] AZT + isoniazid in mg/kg/day

TABLE A2
Summary Organ Weight Data for B6C3F$_1$ Mice from the 13-Week Toxicity Study of AZT and Isoniazid Combinations

Core-Study Males

Dose[a]	Mean Body Weight (g)	n	Organ Weight (g)[b]	Organ to Body Ratio × 1,000[b]	Organ Weight (g)[b]	Organ to Body Ratio × 1,000[b]
			Liver		Right Kidney	
0+0	34.62	10	1.5256 ± 0.1503(—)[c]	43.9 ± 4.4(—)[c]	0.2830 ± 0.0250(—)	8.2 ± 0.7(—)
100+0	34.93	9	1.5200 ± 0.1295(-0.4)	43.7 ± 3.9(-0.4)	0.2900 ± 0.0218(+2.5)	8.4 ± 0.9(+1.4)
200+0	35.98	10	1.5250 ± 0.1606(+0.0)	42.5 ± 2.5(-3.2)	0.2760 ± 0.0237(-2.5)	7.7 ± 0.7(-6.5)
400+0	36.60[c]	10	1.5970 ± 0.1210(+4.7)	44.0 ± 2.8(+0.3)[c]	0.2880 ± 0.0274(+1.8)	8.0 ± 0.7(-2.7)[c]
0+50	37.36	10	1.6530 ± 0.1587(+8.4)	44.2 ± 3.3(+0.8)	0.2990 ± 0.0273(+5.7)	8.0 ± 0.6(-3.0)
100+50	38.86*[c]	10	1.6890 ± 0.1368(+10.7)*	43.2 ± 3.2(-1.5)[c]	0.2890 ± 0.0223(+2.1)	7.4 ± 0.7(-9.7)*[c]
200+50	37.09	10	1.5400 ± 0.1372(+0.9)[c]	42.2 ± 1.7(-3.7)[c]	0.2800 ± 0.0302(-1.1)	7.5 ± 0.5(-8.5)*
400+50	35.49	10	1.5610 ± 0.1859(+2.3)	44.0 ± 2.6(+0.2)	0.2778 ± 0.0249(-1.8)[c]	8.0 ± 0.7(-2.5)[c]
0+100	36.38	10	1.5620 ± 0.1586(+2.4)	43.0 ± 2.3(-1.9)	0.2770 ± 0.0245(-2.1)	7.6 ± 0.5(-7.3)*
100+100	35.91	10	1.5710 ± 0.0989(+3.0)	43.8 ± 2.4(-0.1)	0.2810 ± 0.0233(-0.7)	7.8 ± 0.5(-5.0)
200+100	35.15	10	1.5430 ± 0.1345(+1.1)	44.0 ± 2.8(+0.2)	0.2670 ± 0.0170(-5.7)	7.6 ± 0.7(-7.5)*
400+100	33.80	10	1.5689 ± 0.1769(+2.8)[c]	45.4 ± 3.4(+3.5)[c]	0.2610 ± 0.0300(-7.8)*	7.7 ± 0.5(-6.4)
0+150	34.15	10	1.6070 ± 0.1541(+5.3)	47.6 ± 7.3(+8.5)*	0.2870 ± 0.0177(+1.4)	8.5 ± 1.2(+3.3)
100+150	35.68	10	1.6170 ± 0.1948(+6.0)	45.2 ± 2.4(+3.1)	0.2770 ± 0.0221(-2.1)	7.8 ± 0.4(-5.7)
200+150	35.10	10	1.6040 ± 0.1841(+5.1)	45.6 ± 3.3(+4.0)	0.2789 ± 0.0293(-1.5)[c]	8.0 ± 0.6(-2.9)[c]
400+150	36.52	10	1.6640 ± 0.1200(+9.1)	45.6 ± 2.4(+4.0)	0.2850 ± 0.0201(+0.7)	7.8 ± 0.6(-5.2)
			Thymus		Heart	
0+0	34.62	10	0.0385 ± 0.0044(—)	1.1 ± 0.2(—)	0.1490 ± 0.0110(—)	4.4 ± 0.6(—)
100+0	34.93	9	0.0350 ± 0.0046(-9.1)	1.0 ± 0.2(-11.0)	0.1563 ± 0.0130(+4.9)[d]	4.5 ± 0.3(+3.4)[d]
200+0	35.98	10	0.0333 ± 0.0059(-13.5)*	0.9 ± 0.1(-19.0)*	0.1510 ± 0.0166(+1.3)	4.2 ± 0.4(-3.5)
400+0	36.60[c]	10	0.0373 ± 0.0074(-3.1)	1.0 ± 0.2(-7.9)[c]	0.1450 ± 0.0118(-2.7)	4.0 ± 0.2(-9.0)*[c]
0+50	37.36	10	0.0361 ± 0.0061(-6.2)[c]	1.0 ± 0.1(-15.1)*[c]	0.1550 ± 0.0108(+4.0)	4.2 ± 0.2(-4.9)
100+50	38.86*[c]	10	0.0349 ± 0.0053(-9.3)	0.9 ± 0.1(-21.5)*[c]	0.1580 ± 0.0140(+6.0)	4.1 ± 0.5(-5.8)[c]
200+50	37.09	10	0.0395 ± 0.0071(+2.6)	1.1 ± 0.2(-6.4)	0.1510 ± 0.0145(+1.3)	4.1 ± 0.3(-6.7)
400+50	35.49	10	0.0316 ± 0.0048(-18.0)*[c]	0.9 ± 0.1(-20.7)*[c]	0.1490 ± 0.0120(+0.0)	4.2 ± 0.4(-3.4)
0+100	36.38	10	0.0369 ± 0.0043(-4.2)[c]	1.0 ± 0.1(-9.0)[c]	0.1450 ± 0.0127(-2.7)	4.0 ± 0.2(-8.4)*
100+100	35.91	10	0.0361 ± 0.0017(-6.2)	1.0 ± 0.1(-11.3)	0.1500 ± 0.0105(+0.7)	4.2 ± 0.3(-4.2)
200+100	35.15	10	0.0333 ± 0.0047(-13.5)*	1.0 ± 0.1(-16.3)*	0.1480 ± 0.0103(-0.7)	4.2 ± 0.3(-3.3)
400+100	33.80	10	0.0355 ± 0.0074(-7.8)	1.0 ± 0.2(-7.8)	0.1420 ± 0.0140(-4.7)	4.2 ± 0.3(-3.6)
0+150	34.15	10	0.0366 ± 0.0040(-4.9)	1.1 ± 0.2(-4.4)	0.1510 ± 0.0120(+1.3)	4.5 ± 1.8(+2.9)
100+150	35.68	10	0.0342 ± 0.0046(-11.2)	1.0 ± 0.1(-15.7)*	0.1540 ± 0.0151(+3.4)	4.3 ± 0.3(-1.0)
200+150	35.10	10	0.0366 ± 0.0061(-4.9)	1.0 ± 0.2(-7.9)	0.1510 ± 0.0099(+1.3)	4.3 ± 0.3(-1.2)
400+150	36.52	10	0.0360 ± 0.0033(-6.5)	1.0 ± 0.1(-13.0)*	0.1590 ± 0.0145(+6.7)	4.4 ± 0.3(-0.2)

TABLE A2
Summary Organ Weight Data for B6C3F$_1$ Mice from the 13-Week Toxicity Study of AZT and Isoniazid Combinations

Core-Study Males

Dose[a]	Mean Body Weight (g)	n	Organ Weight (g)[b]	Organ to Body Ratio × 1,000[b]	Organ Weight (g)[b]	Organ to Body Ratio × 1,000[b]
			Lungs		Right Testicle	
0+0	34.62	10	0.2150 ± 0.0519(—)	6.3 ± 1.4(—)	0.1116 ± 0.0151(—)[c]	3.2 ± 0.4(—)[c]
100+0	34.93	9	0.2156 ± 0.0388(+0.3)	6.2 ± 1.0(-1.1)	0.1151 ± 0.0072(+3.2)	3.3 ± 0.3(+4.3)
200+0	35.98	10	0.2189 ± 0.0470(+1.8)[c]	6.2 ± 1.4(-1.2)[c]	0.1075 ± 0.0131(-3.6)	3.0 ± 0.4(-5.4)
400+0	36.60[c]	10	0.1989 ± 0.0237(-7.5)[c]	5.5 ± 0.6(-12.4)[d]	0.1130 ± 0.0121(+1.3)	3.1 ± 0.3(-1.4)[c]
0+50	37.36	10	0.2210 ± 0.0479(+2.8)	5.9 ± 1.3(-5.3)	0.1184 ± 0.0099(+6.1)	3.2 ± 0.2(-0.2)
100+50	38.86*[c]	10	0.2156 ± 0.0461(+0.3)[c]	5.6 ± 1.5(-10.2)[c]	0.1215 ± 0.0130(+8.9)*	3.1 ± 0.4(-1.3)[c]
200+50	37.09	10	0.2144 ± 0.0279(-0.3)[c]	5.7 ± 0.7(-8.6)[c]	0.1087 ± 0.0148(-2.6)	2.9 ± 0.3(-7.8)
400+50	35.49	10	0.1850 ± 0.0107(-14.0)[d]	5.4 ± 0.4(-14.0)[d]	0.1092 ± 0.0094(-2.1)[c]	3.1 ± 0.2(-2.8)[c]
0+100	36.38	10	0.2220 ± 0.0413(+3.3)	6.2 ± 1.3(-1.5)	0.1147 ± 0.0047(+2.8)	3.2 ± 0.3(+0.2)
100+100	35.91	10	0.2180 ± 0.0498(+1.4)	6.1 ± 1.4(-2.7)	0.1177 ± 0.0069(+5.5)	3.3 ± 0.2(+3.5)
200+100	35.15	10	0.2020 ± 0.0294(-6.0)	5.8 ± 0.9(-7.8)	0.1133 ± 0.0054(+1.6)	3.2 ± 0.2(+1.9)
400+100	33.80	10	0.2078 ± 0.0549(-3.4)[c]	6.0 ± 1.3(-4.2)[c]	0.1052 ± 0.0120(-5.7)	3.1 ± 0.4(-1.5)
0+150	34.15	10	0.2170 ± 0.0359(+0.9)	6.6 ± 2.1(+5.0)	0.1143 ± 0.0092(+2.5)	3.4 ± 0.5(+6.8)
100+150	35.68	10	0.2144 ± 0.02961(-0.3)[c]	5.9 ± 0.6(-5.2)[c]	0.1152 ± 0.0062(+3.3)[c]	3.2 ± 0.4(+0.8)[c]
200+150	35.10	10	0.2122 ± 0.0342(-1.3)[c]	6.0 ± 0.9(-3.9)[c]	0.1108 ± 0.0136(-0.7)	3.2 ± 0.3(-0.7)
400+150	36.52	10	0.2140 ± 0.0259(-0.5)	5.9 ± 1.0(-5.6)	0.1106 ± 0.0074(-0.9)	3.0 ± 0.2(-4.3)

[a] AZT + isoniazid in mg/kg/day
[b] Mean value ± SD (% difference from control)
[c] n=9
[d] n=8
* $P \leq 0.05$ by Student's *t*-test

TABLE A2
Summary Organ Weight Data for B6C3F$_1$ Mice from the 13-Week Toxicity Study of AZT and Isoniazid Combinations

Core-Study Females

Dose[a]	Mean Body Weight (g)	n	Organ Weight (g)[b]	Organ to Body Ratio × 1,000[b]	Organ Weight (g)[b]	Organ to Body Ratio × 1,000[b]
			Liver		**Right Kidney**	
0+0	28.18	10	1.1756 ± 0.1033(—)[c]	44.0 ± 7.4(—)[c]	0.1750 ± 0.0151(—)	6.3 ± 1.1(—)
100+0	27.39[c]	10	1.1550 ± 0.0987(-1.7)	42.2 ± 1.9(-4.3)[c]	0.1760 ± 0.0107(+0.6)	6.4 ± 0.6(+1.6)[c]
200+0	27.02	10	1.1350 ± 0.0799(-3.4)	42.1 ± 3.2(-4.4)	0.1730 ± 0.0134(-1.0)	6.4 ± 0.3(+1.2)
400+0	27.26[c]	10	1.1322 ± 0.1059(-3.7)[c]	41.6 ± 2.5(-5.6)[c]	0.1720 ± 0.0132(-1.7)	6.3 ± 0.5(+0.0)[c]
0+50	29.39	10	1.2510 ± 0.0936(+6.4)	43.3 ± 7.5(-1.6)	0.1860 ± 0.0143(+6.3)	6.4 ± 1.0(+1.5)
100+50	29.71[d]	9	1.1756 ± 0.0814(+0.0)	40.0 ± 3.8(-9.2)[d]	0.1778 ± 0.0097(+1.6)	6.0 ± 0.8(-4.6)[d]
200+50	29.58[c]	10	1.1890 ± 0.0999(+1.1)	40.3 ± 2.8(-8.6)[c]	0.1730 ± 0.0157(-1.1)	6.0 ± 0.6(-6.0)[c]
400+50	28.94	8	1.1417 ± 0.1329(-2.9)[e]	41.0 ± 3.7(-6.9)[e]	0.1743 ± 0.0199(-0.4)[f]	6.1 ± 0.8(-4.0)[f]
0+100	30.60	10	1.2300 ± 0.1001(+4.6)[c]	41.5 ± 2.4(-5.7)[c]	0.1860 ± 0.0158(+6.3)	6.1 ± 0.7(-3.2)
100+100	27.98	9	1.1633 ± 0.1136(-1.0)	41.7 ± 2.5(-5.3)	0.1789 ± 0.0136(+2.2)	6.4 ± 0.5(+1.5)
200+100	28.50	10	1.1820 ± 0.1324(+0.5)	41.5 ± 4.4(-5.7)	0.1780 ± 0.0162(+1.7)	6.3 ± 0.5(-1.3)
400+100	28.10[d]	9	1.2244 ± 0.1152(+4.2)	43.6 ± 7.8(-0.9)[d]	0.1867 ± 0.0087(+6.7)	6.8 ± 1.2(+7.3)[d]
0+150	26.78[e]	7	1.1817 ± 0.1344(+0.5)[e]	44.0 ± 3.2(+0.0)[e]	0.1814 ± 0.0135(+3.7)	6.7 ± 0.5(+6.2)[e]
100+150	26.87	9	1.1633 ± 0.1183(-1.0)	43.4 ± 3.6(-1.4)	0.1833 ± 0.0173(+4.8)	6.9 ± 0.8(+8.4)
200+150	25.85	10	1.1113 ± 0.0442(-5.5)[d]	41.8 ± 2.1(-5.0)[d]	0.1710 ± 0.0208(-2.3)	6.6 ± 0.5(+4.4)
400+150	27.90	5	1.1740 ± 0.0483(-0.1)	42.1 ± 2.3(-4.4)	0.1840 ± 0.0055(+5.1)	6.6 ± 0.3(+4.2)
			Thymus		**Heart**	
0+0	28.18	10	0.0446 ± 0.0042(—)	1.6 ± 0.3(—)	0.1210 ± 0.0099(—)	4.4 ± 0.7(—)
100+0	27.39[c]	10	0.0382 ± 0.0071(-14.3)*	1.4 ± 0.2(-14.5)[c]	0.1210 ± 0.0099(+0.0)	4.4 ± 0.4(+0.4)[c]
200+0	27.02	10	0.0411 ± 0.0070(-7.8)	1.5 ± 0.3(-5.0)	0.1220 ± 0.0114(+0.8)	4.5 ± 0.2(+3.1)
400+0	27.26[c]	10	0.0418 ± 0.0053(-6.3)	1.5 ± 0.2(-5.6)[c]	0.1240 ± 0.0084(+2.5)	4.6 ± 0.4(+5.7)[c]
0+50	29.39	10	0.0426 ± 0.0067(-4.4)[d]	1.5 ± 0.4(-7.8)[d]	0.1280 ± 0.0114(+5.8)	4.4 ± 0.7(+1.0)
100+50	29.71[d]	9	0.0411 ± 0.0044(-7.8)	1.4 ± 0.3(-12.8)[d]	0.1233 ± 0.0100(+1.9)	4.2 ± 0.6(-4.9)[d]
200+50	29.58[c]	10	0.0400 ± 0.0062(-10.3)[c]	1.3 ± 0.2(-18.2)*[d]	0.1190 ± 0.0166(-1.7)	4.0 ± 0.6(-8.7)[c]
400+50	28.94	8	0.0358 ± 0.0086(-19.8)*	1.3 ± 0.3(-22.1)*	0.1175 ± 0.0139(-2.9)	4.1 ± 0.3(-6.7)
0+100	30.60	10	0.0456 ± 0.0081(+2.2)	1.5 ± 0.3(-6.9)	0.1240 ± 0.0126(+2.5)	4.1 ± 0.6(-6.3)
100+100	27.98	9	0.0424 ± 0.0066(-4.8)	1.5 ± 0.2(-5.9)	0.1256 ± 0.0133(+3.8)	4.5 ± 0.4(+2.8)
200+100	28.50	10	0.0413 ± 0.0089(-7.4)	1.5 ± 0.3(-10.0)	0.1240 ± 0.0097(+2.5)	4.4 ± 0.4(-0.4)
400+100	28.10[d]	9	0.0402 ± 0.0041(-9.8)	1.5 ± 0.3(-7.8)[d]	0.1244 ± 0.0113(+2.8)	4.5 ± 0.6(+2.4)[d]
0+150	26.78[e]	7	0.0407 ± 0.0060(-8.7)	1.5 ± 0.1(-9.8)[e]	0.1186 ± 0.0090(-2.0)	4.5 ± 0.3(+2.5)[e]
100+150	26.87	9	0.0396 ± 0.0036(-11.3)	1.5 ± 0.2(-8.2)	0.1144 ± 0.0053(-5.4)	4.3 ± 0.3(-2.1)
200+150	25.85	10	0.0386 ± 0.0087(-13.5)*	1.5 ± 0.3(-7.0)	0.1122 ± 0.0083(-7.3)[c]	4.4 ± 0.3(+0.0)[c]
400+150	27.90	5	0.0396 ± 0.0061(-11.2)	1.4 ± 0.2(-11.9)	0.1300 ± 0.0100(+7.4)	4.7 ± 0.4(+6.4)

TABLE A2
Summary Organ Weight Data for B6C3F$_1$ Mice from the 13-Week Toxicity Study of AZT and Isoniazid Combinations

Core-Study Females

Dose[a]	Mean Body Weight (g)	n	Organ Weight (g)[b]	Organ to Body Ratio × 1,000[b]
			Lungs	
0+0	28.18	10	0.1850 ± 0.0212(—)	6.6 ± 0.9(—)
100+0	27.39[c]	10	0.1790 ± 0.0223(-3.2)	6.5 ± 0.8(-2.0)[c]
200+0	27.02	10	0.1890 ± 0.0269(+2.2)	7.0 ± 1.0(+5.6)
400+0	27.26[c]	10	0.1790 ± 0.0191(-3.2)	6.5 ± 0.7(-2.3)[c]
0+50	29.39	10	0.1711 ± 0.0154(-7.5)[c]	6.0 ± 1.3(-9.9)[c]
100+50	29.71[d]	9	0.1900 ± 0.0287(+2.7)	6.4 ± 1.4(-3.4)[d]
200+50	29.58[c]	10	0.1850 ± 0.0264(+0.0)	6.2 ± 0.8(-6.7)[c]
400+50	28.94	8	0.1750 ± 0.0193(-5.4)	6.2 ± 1.3(-7.0)
0+100	30.60	10	0.1820 ± 0.0175(-1.6)	6.0 ± 0.7(-9.6)
100+100	27.98	9	0.1700 ± 0.0158(-8.1)	6.1 ± 0.7(-7.8)
200+100	28.50	10	0.1730 ± 0.0250(-6.5)	6.1 ± 0.9(-8.4)
400+100	28.10[d]	9	0.1800 ± 0.0300(-2.7)	6.4 ± 1.2(-3.9)[d]
0+150	26.78[e]	7	0.1643 ± 0.0172(-11.2)	6.2 ± 0.7(-6.1)[e]
100+150	26.87	9	0.1733 ± 0.01941(-6.3)	6.5 ± 0.7(-2.4)
200+150	25.85	10	0.1690 ± 0.0242(-8.6)	6.5 ± 0.6(-1.7)
400+150	27.90	5	0.1760 ± 0.0219(-4.9)	6.3 ± 0.8(-4.9)

[a] AZT + isoniazid in mg/kg/day
[b] Mean value ± standard deviation (% difference from control)
[c] n=9
[d] n=8
[e] n=6
[f] n=7
* P≤0.05 by Student's *t*-test

APPENDIX B
CLINICAL PATHOLOGY

List of Abbreviations

WBC	White blood cells
RBC	Red blood cells
HGB	Hemoglobin
HCT	Hematocrit
MCV	Mean corpuscular volume
MCH	Mean corpuscular hemoglobin
MCHC	Mean corpuscular hemoglobin concentration
LUC	Large unstained cells
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
SDH	Sorbitol dehydrogenase
BILA	Total bile acids

TABLE B1
Summary of Hematology Parameters for B6C3F$_1$ Mice from the 13-Week Toxicity Study of AZT and Isoniazid Combinations: Day 4
Males

Test: / Units:	WBC[c] $10^3/\mu L$	RBC $10^6/\mu L$	Hgb g/dL	Hct %	MCV fL	MCH pg	MCHC g/dL	Plt $10^3/\mu L$
Dose[a]: 0 + 0								
Mean[b]	5.92	9.00	14.5	43.4	48.3	16.1	33.4	1,432
SD	1.082	0.298	0.44	1.10	1.12	0.23	0.55	178.9
Dose: 100 + 0								
Mean	5.48	8.89	14.3	42.6	47.9	16.1	33.5	1,448
SD	1.097	0.183	0.28	1.05	1.15	0.27	0.68	158.2
Dose: 200 + 0								
Mean	5.46	8.90	14.4	42.9	48.3	16.2	33.5	1,427
SD	1.377	0.289	0.37	0.83	0.98	0.38	0.57	112.6
Dose: 400 + 0								
Mean	5.26	8.75	14.3	41.9	47.9	16.4	34.2	1,389
SD	1.062	0.246	0.47	1.77	1.11	0.42	1.12	162.7
Dose: 0 + 50								
Mean	5.67	8.86	14.2	42.7	48.2	16.1	33.3	1,392
SD	0.806	0.355	0.49	1.69	0.81	0.42	0.72	117.9
Dose: 100 + 50								
Mean	5.15	8.83	14.3	42.8	48.5	16.2	33.4	1,367
SD	1.152	0.293	0.37	1.11	0.85	0.30	0.60	129.6
Dose: 200 + 50								
Mean	5.45	8.79	14.1	42.2	48.0	16.1	33.6	1,307
SD	1.052	0.152	0.32	1.16	0.93	0.19	0.80	236.2
Dose: 400 + 50								
Mean	5.31	8.57**	13.8**	41.4*	48.3	16.0	33.2	1,215
SD	1.646	0.253	0.39	1.52	0.71	0.34	0.71	169.7

[a] AZT + isoniazid in mg/kg/day
[b] n=10 in all groups, unless noted
[c] WBC corrected for nucleated RBCs≥10/100 WBC
* Significant difference from control P≤0.05 using analysis of variance followed by Dunnett's procedure
** Significant difference from control P≤0.01 using analysis of variance followed by Dunnett's procedure

TABLE B1
Summary of Hematology Parameters for B6C3F$_1$ Mice from the 13-Week Toxicity Study of AZT and Isoniazid Combinations: Day 4
Males

Test: / Units:	Reticulocyte $10^5/\mu L$	Neutrophil $10^3/\mu L$	Lymphocyte $10^3/\mu L$	Monocyte $10^3/\mu L$	Eosinophil $10^3/\mu L$	Basophil $10^3/\mu L$	LUC $10^3/\mu L$
Dose[a]: 0 + 0							
Mean[b]	3.9	0.70	5.00	0.09	0.05	0.04	0.04
SD	0.83	0.140	0.934	0.022	0.038	0.026	0.022
Dose: 100 + 0							
Mean	2.8**	0.67	4.61	0.08	0.04	0.03	0.04
SD	0.27	0.131	0.960	0.030	0.009	0.024	0.020
Dose: 200 + 0							
Mean	2.5**	0.65	4.59	0.07	0.08	0.03	0.04
SD	0.34	0.171	1.175	0.017	0.054	0.023	0.014
Dose: 400 + 0							
Mean	2.2**	0.58	4.48	0.10	0.05	0.02	0.04
SD	0.59	0.154	0.919	0.030	0.047	0.007	0.013
Dose: 0 + 50							
Mean	4.0	0.74	4.72	0.09	0.05	0.03	0.05
SD	0.55	0.217	0.760	0.059	0.038	0.020	0.020
Dose: 100 + 50							
Mean	2.7**	0.60	4.36	0.07	0.05	0.02	0.04
SD	0.33	0.188	0.954	0.034	0.034	0.022	0.013
Dose: 200 + 50							
Mean	2.5**	0.65	4.60	0.08	0.06	0.03	0.04
SD	0.15	0.145	0.905	0.020	0.029	0.021	0.017
Dose: 400 + 50							
Mean	1.7**	0.60	4.52	0.07	0.06	0.02	0.05
SD	0.55	0.193	1.399	0.021	0.031	0.022	0.046

[a] AZT + isoniazid in mg/kg/day
[b] n=10 in all groups, unless noted
[c] WBC corrected for nucleated RBCs≥10/100 WBC
* Significant difference from control P≤0.05 using analysis of variance followed by Dunnett's procedure
** Significant difference from control P≤0.01 using analysis of variance followed by Dunnett's procedure

TABLE B1
Summary of Hematology Parameters for B6C3F$_1$ Mice from the 13-Week Toxicity Study of AZT and Isoniazid Combinations: Day 4

Males

Test: / Units:	WBC[c] 10^3/μL	RBC 10^6/μL	Hgb g/dL	Hct %	MCV fL	MCH pg	MCHC g/dL	Plt 10^3/μL
Dose[a]: 0 + 100								
Mean[b]	5.49	8.95	14.4	42.6	47.5	16.1	33.9	1,344
SD	1.482	0.170	0.26	0.92	0.91	0.23	0.59	150.4
Dose: 100 + 100								
Mean	4.93	8.70	14.1	42.1	48.3	16.2	33.5	1,364
SD	1.138	0.166	0.26	0.74	0.91	0.24	0.71	115.3
Dose: 200 + 100								
Mean	5.02	8.60*	13.9*	41.3**	48.0	16.2	33.8	1,438
SD	1.324	0.224	0.27	1.05	0.69	0.24	0.59	106.7
Dose: 400 + 100								
Mean	4.86	8.68	14.0	41.8	48.1	16.2	33.6	1,461
SD	1.133	0.277	0.42	1.02	1.12	0.37	0.71	150.0
Dose: 0 + 150								
Mean	5.05	8.92	14.3	42.9	48.1	16.0	33.3	1,377
SD	1.414	0.352	0.60	1.80	0.81	0.26	0.52	145.1
Dose: 100 + 150								
Mean	4.97	8.88	14.4	43.1	48.6	16.2	33.3	1,364
SD	1.154	0.297	0.53	1.83	1.17	0.22	0.44	162.3
Dose: 200 + 150								
Mean	5.13	8.67	14.0	41.6*	47.9	16.1	33.6	1,440
SD	1.331	0.318	0.54	1.71	0.67	0.19	0.40	177.6
Dose: 400 + 150[d]								
Mean	4.79	8.32**	13.6**	40.2**	48.3	16.4	34.0	1,352
SD	0.677	0.280	0.39	1.91	1.66	0.42	0.85	92.7

[a] AZT + isoniazid in mg/kg/day
[b] n=10 in all groups, unless noted
[c] WBC corrected for nucleated RBCs≥10/100 WBC
[d] n=9
* Significant difference from control P≤0.05 using analysis of variance followed by Dunnett's procedure
** Significant difference from control P≤0.01 using analysis of variance followed by Dunnett's procedure

TABLE B1
Summary of Hematology Parameters for B6C3F$_1$ Mice from the 13-Week Toxicity Study of AZT and Isoniazid Combinations: Day 4

Males

Test: / Units:	Reticulocyte $10^5/\mu L$	Neutrophil $10^3/\mu L$	Lymphocyte $10^3/\mu L$	Monocyte $10^3/\mu L$	Eosinophil $10^3/\mu L$	Basophil $10^3/\mu L$	LUC $10^3/\mu L$
Dose[a]: 0 + 100							
Mean[b]	3.8	0.67	4.61	0.08	0.06	0.03	0.04
SD	0.55	0.180	1.297	0.022	0.035	0.022	0.020
Dose: 100 + 100							
Mean	2.7**	0.53	4.22	0.07	0.05	0.03	0.03
SD	0.43	0.109	1.001	0.030	0.028	0.016	0.014
Dose: 200 + 100							
Mean	2.3**	0.54	4.28	0.07	0.07	0.02	0.04
SD	0.34	0.188	1.044	0.021	0.054	0.025	0.021
Dose: 400 + 100							
Mean	2.0**	0.57	4.08	0.07	0.09	0.03	0.03
SD	0.36	0.181	0.923	0.016	0.053	0.019	0.015
Dose: 0 + 150							
Mean	3.5	0.66	4.21	0.07	0.06	0.02	0.03
SD	0.40	0.232	1.165	0.021	0.040	0.016	0.017
Dose: 100 + 150							
Mean	2.6**	0.65	4.12	0.07	0.06	0.03	0.04
SD	0.50	0.391	0.772	0.021	0.040	0.015	0.011
Dose: 200 + 150							
Mean	2.4**	0.61	4.31	0.07	0.08	0.03	0.04
SD	0.43	0.211	1.088	0.023	0.071	0.019	0.019
Dose: 400 + 150[d]							
Mean	1.4**	0.61	4.03	0.06	0.04	0.02	0.03
SD	0.15	0.160	0.564	0.021	0.011	0.009	0.010

[a] AZT + isoniazid in mg/kg/day
[b] n=10 in all groups, unless noted
[c] WBC corrected for nucleated RBCs≥10/100 WBC
[d] n=9
* Significant difference from control P≤0.05 using analysis of variance followed by Dunnett's procedure
** Significant difference from control P≤0.01 using analysis of variance followed by Dunnett's procedure

TABLE B1
Summary of Hematology Parameters for B6C3F$_1$ Mice from the 13-Week Toxicity Study of AZT and Isoniazid Combinations: Day 4

Females

Test: / Units:	WBC[c] $10^3/\mu L$	RBC $10^6/\mu L$	Hgb g/dL	Hct %	MCV fL	MCH pg	MCHC g/dL	Plt $10^3/\mu L$
Dose[a]: 0 + 0								
Mean[b]	7.55	9.77	15.2	45.3	46.3	15.6	33.6	1,003
SD	2.015	0.677	1.45	4.23	2.13	0.76	0.39	167.1
Dose: 100 + 0								
Mean	7.24	9.10**	14.5	42.8	47.0	16.1	34.2	977
SD	1.757	0.580	0.76	3.07	1.83	1.68	3.13	180.3
Dose: 200 + 0								
Mean	6.84	9.25*	14.4	43.0	46.5	15.6	33.6	967
SD	1.259	0.272	0.81	2.08	1.48	0.65	0.47	144.6
Dose: 400 + 0								
Mean	7.38	9.23*	14.6	43.1	46.7	15.7	33.7	995
SD	1.960	0.229	0.58	1.68	1.63	0.72	0.65	177.0
Dose: 0 + 50[d]								
Mean	7.09	9.28	14.6	43.2	46.5	15.7	33.8	1,106
SD	1.426	0.228	0.82	1.67	1.34	0.82	0.91	133.3
Dose: 100 + 50[d]								
Mean	6.64	9.30	14.5	42.8	46.1	15.6	33.9	939
SD	1.582	0.215	0.86	1.93	1.44	0.69	0.71	119.8
Dose: 200 + 50								
Mean	6.52	9.24*	14.5	42.9	46.5	15.7	33.7	1,020
SD	1.299	0.247	0.74	1.83	1.55	0.67	0.45	154.1
Dose: 400 + 50								
Mean	6.52	8.80**	13.7	41.2	46.8	15.6	33.2	899
SD	1.669	0.512	1.42	3.86	2.21	0.89	0.61	162.5

[a] AZT + isoniazid in mg/kg/day
[b] n=10 in all groups, unless noted
[c] WBC corrected for nucleated RBCs≥10/100 WBC
[d] n=9
* Significant difference from control P≤0.05 using analysis of variance followed by Dunnett's procedure
** Significant difference from control P≤0.01 using analysis of variance followed by Dunnett's procedure

TABLE B1
Summary of Hematology Parameters for B6C3F$_1$ Mice from the 13-Week Toxicity Study of AZT and Isoniazid Combinations: Day 4

Females

Test: / Units:	Reticulocyte $10^5/\mu L$	Neutrophil $10^3/\mu L$	Lymphocyte $10^3/\mu L$	Monocyte $10^3/\mu L$	Eosinophil $10^3/\mu L$	Basophil $10^3/\mu L$	LUC $10^3/\mu L$
Dose[a]: 0 + 0							
Mean[b]	2.7	1.03	6.01	0.18	0.24	0.05	0.04
SD	0.52	0.855	1.506	0.051	0.091	0.023	0.018
Dose: 100 + 0							
Mean	1.5**	0.71	6.07	0.18	0.21	0.04	0.04
SD	0.31	0.360	1.329	0.079	0.107	0.016	0.021
Dose: 200 + 0							
Mean	1.3**	0.77	5.68	0.15	0.18	0.04	0.03[d]
SD	0.37	0.322	0.952	0.057	0.054	0.016	0.017
Dose: 400 + 0							
Mean	1.3**	0.78	6.16	0.15	0.21	0.05	0.04
SD	0.34	0.385	1.497	0.060	0.102	0.027	0.017
Dose: 0 + 50[d]							
Mean	2.6	0.81	5.87	0.15	0.18	0.04	0.04
SD	0.38	0.352	1.123	0.046	0.062	0.017	0.020
Dose: 100 + 50[d]							
Mean	1.4**	0.61	5.63	0.12	0.19	0.05	0.03
SD	0.24	0.245	1.235	0.048	0.083	0.026	0.016
Dose: 200 + 50							
Mean	1.5**	0.63	5.47	0.12	0.22	0.05	0.03
SD	0.41	0.220	1.054	0.035	0.102	0.020	0.011
Dose: 400 + 50							
Mean	1.0**	0.62	5.54	0.13	0.16	0.04	0.03
SD	0.51	0.206	1.427	0.052	0.069	0.025	0.013

[a] AZT + isoniazid in mg/kg/day
[b] n=10 in all groups, unless noted
[c] WBC corrected for nucleated RBCs≥10/100 WBC
[d] n=9
* Significant difference from control P≤0.05 using analysis of variance followed by Dunnett's procedure
** Significant difference from control P≤0.01 using analysis of variance followed by Dunnett's procedure

TABLE B1
Summary of Hematology Parameters for B6C3F$_1$ Mice from the 13-Week Toxicity Study of AZT and Isoniazid Combinations: Day 4

Females

Test: / Units:	WBC[c] $10^3/\mu L$	RBC $10^6/\mu L$	Hgb g/dL	Hct %	MCV fL	MCH pg	MCHC g/dL	Plt $10^3/\mu L$
Dose[a]: 0 + 100								
Mean[b]	6.70	9.37	14.6	43.5	46.5	15.6	33.6	966
SD	1.041	0.253	0.74	1.77	1.62	0.69	0.72	117.3
Dose: 100 + 100								
Mean	6.26	9.11**	14.1	42.3	46.5	15.5	33.4	1,003
SD	0.995	0.503	0.86	2.68	1.48	0.63	0.76	98.4
Dose: 200 + 100								
Mean	6.98	9.27*	14.5	43.1	46.5	15.6	33.5	977
SD	1.134	0.339	0.82	1.92	1.61	0.77	0.60	183.2
Dose: 400 + 100								
Mean	6.45	9.23*	14.3	42.6	46.1	15.5	33.6	1,046
SD	1.378	0.189	0.72	1.56	1.69	0.71	0.62	187.2
Dose: 0 + 150[d]								
Mean	6.26	9.16**	14.1	42.2	46.1	15.4	33.5	1,002
SD	0.866	0.306	0.65	1.79	1.56	0.75	0.76	87.9
Dose: 100 + 150								
Mean	6.23	9.09**	14.1	42.2	46.5	15.6	33.5	1,017
SD	1.325	0.412	0.46	1.43	1.79	0.84	0.81	150.6
Dose: 200 + 150								
Mean	6.60	9.17**	14.3	42.5	46.3	15.5	33.5	1,056
SD	1.574	0.229	0.70	1.99	1.62	0.64	0.65	202.6
Dose: 400 + 150								
Mean	6.01	8.89**	13.9	41.2	46.4	15.6	33.6	1,006
SD	1.086	0.365	0.75	2.03	1.84	0.79	0.79	117.6

[a] AZT + isoniazid in mg/kg/day
[b] n=10 in all groups, unless noted
[c] WBC corrected for nucleated RBCs≥10/100 WBC
[d] n=9
* Significant difference from control P≤0.05 using analysis of variance followed by Dunnett's procedure
** Significant difference from control P≤0.01 using analysis of variance followed by Dunnett's procedure

TABLE B1
Summary of Hematology Parameters for B6C3F$_1$ Mice from the 13-Week Toxicity Study of AZT and Isoniazid Combinations: Day 4

Females

Test: / Units:	Reticulocyte $10^5/\mu L$	Neutrophil $10^3/\mu L$	Lymphocyte $10^3/\mu L$	Monocyte $10^3/\mu L$	Eosinophil $10^3/\mu L$	Basophil $10^3/\mu L$	LUC $10^3/\mu L$
Dose[a]: 0 + 100							
Mean[b]	2.4	0.75	5.55	0.15	0.18	0.04	0.03
SD	0.25	0.204	0.960	0.040	0.081	0.012	0.008
Dose: 100 + 100							
Mean	1.8**	0.61	5.30	0.14	0.16	0.03	0.02
SD	0.74	0.226	0.830	0.039	0.048	0.013	0.013
Dose: 200 + 100							
Mean	2.4	0. 77	5.80	0.15	0.18	0.04	0.04
SD	0.25	0.218	0.889	0.057	0.089	0.015	0.010
Dose: 400 + 100							
Mean	1.1**	0.70	5.35	0.13	0.19	0.04	0.04
SD	0.37	0.260	1.147	0.030	0.094	0.014	0.012
Dose: 0 + 150[d]							
Mean	2.3	0.81	5.07	0.15	0.16	0.03	0.03
SD	0.55	0.208	0.651	0.044	0.072	0.007	0.008
Dose: 100 + 150							
Mean	1.6**	0.61	5.27	0.11	0.18	0.04	0.03
SD	0.30	0.227	1.104	0.039	0.055	0.008	0.012
Dose: 200 + 150							
Mean	1.0**	0.66	5.57	0.13	0.16	0.04	0.04
SD	0.43	0.219	1.325	0.047	0.068	0.013	0.012
Dose: 400 + 150							
Mean	0.7**	0.49	5.21	0.09	0.16	0.03	0.03[d]
SD	0.16	0.111	1.005	0.032	0.061	0.015	0.018

[a] AZT + isoniazid in mg/kg/day
[b] n=10 in all groups, unless noted
[c] WBC corrected for nucleated RBCs≥10/100 WBC
[d] n=9
* Significant difference from control P≤0.05 using analysis of variance followed by Dunnett's procedure
** Significant difference from control P≤0.01 using analysis of variance followed by Dunnett's procedure

TABLE B1
Summary of Hematology Parameters for B6C3F$_1$ Mice from the 13-Week Toxicity Study of AZT and Isoniazid Combinations: Day 30

Males

Test: / Units:	WBC[c] $10^3/\mu L$	RBC $10^6/\mu L$	Hgb g/dL	Hct %	MCV fL	MCH pg	MCHC g/dL	Plt $10^3/\mu L$
Dose[a]: 0 + 0[d]								
Mean[b]	8.99	9.91	16.2	48.1	48.5	16.3	33.7	1,165
SD	0.761	0.351	0.44	1.52	0.91	0.25	0.30	145.2
Dose: 100 + 0								
Mean	7.78	8.62**	15.3**	45.0**	52.2**	17.7**	33.9	1,180
SD	0.641	0.328	0.50	1.98	0.69	0.33	0.75	186.7
Dose: 200 + 0								
Mean	8.00	8.50**	15.2**	46.1	54.2**	17.9**	33.0*	1,308
SD	0.913	0.328	0.60	2.11	1.12	0.34	0.52	119.6
Dose: 400 + 0[d]								
Mean	8.05	7.80**	14.5**	44.0**	56.5**	18.6**	33.0*	1,326
SD	0.905	0.333	0.76	1.99	1.06	0.30	0.44	202.6
Dose: 0 + 50[d]								
Mean	8.31	9.99	16.1	47.9	47.9	16.1	33.6	1,187
SD	0.804	0.179	0.35	1.20	1.00	0.17	0.55	133.6
Dose: 100 + 50								
Mean	8.56	8.57**	15.1*	45.0**	52.5**	17.6**	33.5	1,222
SD	1.233	0.235	0.52	1.57	0.81	0.25	0.33	157.5
Dose: 200 + 50								
Mean	8.00	8.35**	14.9**	45.2**	54.1**	17.9**	33.1	1,259
SD	1.063	0.225	0.48	1.55	0.90	0.24	0.41	109.5
Dose: 400 + 50[e]								
Mean	8.04	7.67**	14.2**	43.2**	56.4**	18.5**	32.8**	1,266
SD	1.085	0.238	0.40	1.44	1.02	0.21	0.38	149.0

[a] AZT + isoniazid in mg/kg/day
[b] n=10 in all groups, unless noted
[c] WBC corrected for nucleated RBCs≥10/100 WBC
[d] n=9
[e] n=8
* Significant difference from control P≤0.05 using analysis of variance followed by Dunnett's procedure
** Significant difference from control P≤0.01 using analysis of variance followed by Dunnett's procedure

TABLE B1
Summary of Hematology Parameters for B6C3F$_1$ Mice from the 13-Week Toxicity Study of AZT and Isoniazid Combinations: Day 30

Males

Test: / Units:	Reticulocyte $10^5/\mu L$	Neutrophil $10^3/\mu L$	Lymphocyte $10^3/\mu L$	Monocyte $10^3/\mu L$	Eosinophil $10^3/\mu L$	Basophil $10^3/\mu L$	LUC $10^3/\mu L$
Dose[a]: 0 + 0[d]							
Mean[b]	3.0	0.88	7.59	0.20	0.25	0.06	0.03
SD	0.37	0.140	0.764	0.039	0.081	0.024	0.012
Dose: 100 + 0							
Mean	3.4	0.81	6.53	0.18	0.21	0.04	0.03
SD	0.39	0.141	0.633	0.032	0.053	0.016	0.013
Dose: 200 + 0							
Mean	3.6*	0.83	6.68	0.16	0.25	0.04	0.03
SD	0.35	0.155	0.905	0.026	0.055	0.021	0.008
Dose: 400 + 0[d]							
Mean	4.1**	0.75	6.81	0.16	0.26	0.04	0.03
SD	0.35	0.142	0.719	0.032	0.104	0.011	0.012
Dose: 0 + 50[d]							
Mean	2.8	0.79	7.01	0.19	0.24	0.05	0.03
SD	0.25	0.151	0.694	0.032	0.068	0.022	0.012
Dose: 100 + 50							
Mean	3.3	0.89	7.17	0.18	0.24	0.05	0.03
SD	0.34	0.184	1.131	0.041	0.073	0.019	0.008
Dose: 200 + 50							
Mean	3.7*	0.84	6.70	0.17	0.24	0.03	0.02
SD	0.27	0.116	0.927	0.055	0.123	0.015	0.013
Dose: 400 + 50[e]							
Mean	4.3**	0.78	6.78	0.15	0.25	0.05	0.03
SD	0.52	0.124	1.041	0.035	0.075	0.023	0.010

[a] AZT + isoniazid in mg/kg/day
[b] n=10 in all groups, unless noted
[c] WBC corrected for nucleated RBCs≥10/100 WBC
[d] n=9
[e] n=8
* Significant difference from control P≤0.05 using analysis of variance followed by Dunnett's procedure
** Significant difference from control P≤0.01 using analysis of variance followed by Dunnett's procedure

TABLE B1
Summary of Hematology Parameters for B6C3F$_1$ Mice from the 13-Week Toxicity Study of AZT and Isoniazid Combinations: Day 30

Males

Test: / Units:	WBC[c] $10^3/\mu L$	RBC $10^6/\mu L$	Hgb g/dL	Hct %	MCV fL	MCH pg	MCHC g/dL	Plt $10^3/\mu L$
Dose[a]: 0 + 100								
Mean[b]	8.58	9.84	15.9	47.2	48.0	16.2	33.8	1,190
SD	0.949	0.185	0.30	1.34	1.08	0.31	0.73	167.2
Dose: 100 + 100								
Mean	8.59	8.61**	15.0**	45.2**	52.5**	17.5**	33.3	1,296
SD	1.080	0.162	0.39	1.16	0.79	0.33	0.58	161.5
Dose: 200 + 100								
Mean	8.56	8.05**	14.5**	43.9**	54.6**	18.0**	33.0*	1,364
SD	0.976	0.128	0.37	0.69	0.62	0.30	0.58	196.1
Dose: 400 + 100								
Mean	7.57	7.83**	14.4**	43.5**	55.7**	18.3**	33.0*	1,371
SD	0.555	0.317	0.52	1.69	0.81	0.30	0.33	118.6
Dose: 0 + 150								
Mean	8.58	10.04	16.1	47.9	47.7	16.0	33.6	1,230
SD	1.147	0.451	0.59	1.77	0.79	0.29	0.36	176.9
Dose: 100 + 150								
Mean	8.28	8.44**	14.7**	44.1**	52.3**	17.4**	33.3	1,411*
SD	0.948	0.217	0.26	1.11	0.94	0.25	0.37	142.4
Dose: 200 + 150								
Mean	7.89	7.89**	14.3**	43.3**	54.9**	18.1**	33.0*	1,374
SD	1.104	0.324	0.61	1.62	0.54	0.32	0.44	219.6
Dose: 400 + 150[d]								
Mean	7.20	7.02**	12.9**	39.2**	55.9**	18.4**	32.9**	1,664**
SD	0.834	0.529	0.96	2.93	1.15	0.40	0.50	312.7

[a] AZT + isoniazid in mg/kg/day
[b] n=10 in all groups, unless noted
[c] WBC corrected for nucleated RBCs≥10/100 WBC
[d] n=9
* Significant difference from control P≤0.05 using analysis of variance followed by Dunnett's procedure
** Significant difference from control P≤0.01 using analysis of variance followed by Dunnett's procedure

TABLE B1
Summary of Hematology Parameters for B6C3F$_1$ Mice from the 13-Week Toxicity Study of AZT and Isoniazid Combinations: Day 30

Males

Test: / Units:	Reticulocyte $10^5/\mu L$	Neutrophil $10^3/\mu L$	Lymphocyte $10^3/\mu L$	Monocyte $10^3/\mu L$	Eosinophil $10^3/\mu L$	Basophil $10^3/\mu L$	LUC $10^3/\mu L$
Dose[a]: 0 + 100							
Mean[b]	3.0	0.80	7.27	0.18	0.26	0.05	0.03
SD	0.17	0.135	0.908	0.036	0.060	0.022	0.008
Dose: 100 + 100							
Mean	3.5	0.86	7.24	0.20	0.22	0.05	0.03
SD	0.31	0.162	0.943	0.096	0.079	0.018	0.011
Dose: 200 + 100							
Mean	3.7*	0.87	7.23	0.16	0.22	0.04	0.03
SD	0.30	0.162	0.843	0.031	0.046	0.025	0.015
Dose: 400 + 100							
Mean	4.3**	0.73	6.37	0.13	0.27	0.04	0.02
SD	0.43	0.108	0.524	0.030	0.114	0.013	0.009
Dose: 0 + 150							
Mean	3.1	0.92	7.11	0.20	0.27	0.05	0.03
SD	0.24	0.137	1.096	0.050	0.092	0.018	0.011
Dose: 100 + 150							
Mean	3.5	0.85	6.96	0.19	0.21	0.04	0.03
SD	0.38	0.171	0.839	0.036	0.073	0.021	0.009
Dose: 200 + 150							
Mean	4.0**	0.83[d]	6.63[d]	0.15[d]	0.25[d]	0.04[d]	0.03[e]
SD	0.51	0.237	1.124	0.048	0.060	0.025	0.018
Dose: 400 + 150[d]							
Mean	4.7**	0.76	6.03	0.14	0.20	0.04	0.02
SD	1.40	0.351	0.901	0.036	0.070	0.030	0.009

[a] AZT + isoniazid in mg/kg/day
[b] n=10 in all groups, unless noted
[c] WBC corrected for nucleated RBCs≥10/100 WBC
[d] n=9
[e] n=8
* Significant difference from control P≤0.05 using analysis of variance followed by Dunnett's procedure
** Significant difference from control P≤0.01 using analysis of variance followed by Dunnett's procedure

TABLE B1
Summary of Hematology Parameters for B6C3F$_1$ Mice from the 13-Week Toxicity Study of AZT and Isoniazid Combinations: Day 30

Females

Test: / Units:	WBC[c] $10^3/\mu L$	RBC $10^6/\mu L$	Hgb g/dL	Hct %	MCV fL	MCH pg	MCHC g/dL	Plt $10^3/\mu L$
Dose[a]: 0 + 0[d]								
Mean[b]	7.91	9.49	15.6	47.0	49.5	16.5	33.2	1,023
SD	0.827	0.355	0.56	1.54	0.79	0.33	0.72	173.9
Dose: 100 + 0								
Mean	6.90	7.96**	14.4	43.6	54.9**	18.2**	33.1	1,136
SD	1.233	0.398	0.52	2.12	0.65	0.53	0.82	152.7
Dose: 200 + 0								
Mean	6.61	7.63**	14.1	43.2	56.7**	18.5**	32.6	1,195
SD	1.243	0.238	0.42	1.83	0.96	0.41	0.88	111.6
Dose: 400 + 0								
Mean	6.09*	7.15**	13.5*	41.8	58.5**	18.9**	32.2	1,202
SD	0.552	0.256	0.45	1.23	1.42	0.36	0.55	157.3
Dose: 0 + 50[e]								
Mean	8.62	9.91	16.2	48.4	48.9	16.4	33.5	1,015
SD	2.307	0.658	1.11	2.99	0.97	0.19	0.76	124.6
Dose: 100 + 50[d]								
Mean	6.93	7.87**	14.3	42.8	54.4**	18.2**	33.5	1,098
SD	1.334	0.241	0.48	1.56	0.67	0.56	1.25	193.9
Dose: 200 + 50								
Mean	6.76	7.65**	14.0	43.2	56.5**	18.3**	32.3	1,237
SD	0.929	0.228	0.50	1.11	0.91	0.39	0.78	153.7
Dose: 400 + 50[d]								
Mean	6.79	7.01**	13.1**	40.7*	58.0**	18.6**	32.2	1,408*
SD	1.384	0.475	0.98	3.05	1.26	0.35	0.82	501.3

[a] AZT + isoniazid in mg/kg/day
[b] n=10 in all groups, unless noted
[c] WBC corrected for nucleated RBCs≥10/100 WBC
[d] n=9
[e] n=8
* Significant difference from control P≤0.05 using analysis of variance followed by Dunnett's procedure
** Significant difference from control P≤0.01 using analysis of variance followed by Dunnett's procedure

TABLE B1
Summary of Hematology Parameters for B6C3F$_1$ Mice from the 13-Week Toxicity Study of AZT and Isoniazid Combinations: Day 30

Females

Test: / Units:	Reticulocyte $10^5/\mu L$	Neutrophil $10^3/\mu L$	Lymphocyte $10^3/\mu L$	Monocyte $10^3/\mu L$	Eosinophil $10^3/\mu L$	Basophil $10^3/\mu L$	LUC $10^3/\mu L$
Dose[a]: 0 + 0[d]							
Mean[b]	3.0	0.83	6.59	0.21	0.22	0.03	0.03
SD	0.23	0.175	0.764	0.056	0.094	0.011	0.009
Dose: 100 + 0							
Mean	3.5	0.69	5.82	0.16	0.17	0.03	0.03
SD	0.64	0.242	1.028	0.057	0.077	0.009	0.016
Dose: 200 + 0							
Mean	4.6*	0.53	5.71	0.16	0.17	0.02	0.03
SD	0.64	0.140	1.114	0.039	0.082	0.009	0.011
Dose: 400 + 0							
Mean	4.8**	0.52	5.24	0.15*	0.13	0.02	0.03
SD	0.95	0.200	0.424	0.044	0.036	0.013	0.011
Dose: 0 + 50[e]							
Mean	2.6	0.86	7.27	0.21	0.22	0.04	0.04
SD	0.25	0.319	1.941	0.067	0.121	0.017	0.012
Dose: 100 + 50[d]							
Mean	4.0	0.61	5.96	0.16	0.14	0.03	0.02
SD	0.91	0.136	1.144	0.042	0.054	0.013	0.010
Dose: 200 + 50							
Mean	4.5*	0.58	5.82	0.15	0.17	0.02	0.03
SD	1.14	0.191	0.737	0.052	0.046	0.008	0.014
Dose: 400 + 50[d]							
Mean	6.1**	0.62	5.76	0.15	0.21	0.03	0.03
SD	2.35	0.118	1.389	0.030	0.079	0.011	0.012

[a] AZT + isoniazid in mg/kg/day
[b] n=10 in all groups, unless noted
[c] WBC corrected for nucleated RBCs≥10/100 WBC
[d] n=9
[e] n=8
* Significant difference from control P≤0.05 using analysis of variance followed by Dunnett's procedure
** Significant difference from control P≤0.01 using analysis of variance followed by Dunnett's procedure

TABLE B1
Summary of Hematology Parameters for B6C3F$_1$ Mice from the 13-Week Toxicity Study of AZT and Isoniazid Combinations: Day 30

Females

Test: / Units:	WBC[c] $10^3/\mu L$	RBC $10^6/\mu L$	Hgb g/dL	Hct %	MCV fL	MCH pg	MCHC g/dL	Plt $10^3/\mu L$
Dose[a]: 0 + 100								
Mean[b]	8.03	9.39	15.4	45.7	48.6	16.4	33.7	1,013
SD	1.236	0.354	0.55	1.58	0.60	0.44	0.92	220.8
Dose: 100 + 100								
Mean	6.91	7.83**	14.0	42.5	54.2**	17.9**	32.9	1,164
SD	1.420	0.285	0.45	1.31	1.01	0.43	0.84	150.3
Dose: 200 + 100								
Mean	7.25	7.53**	13.8	42.7	56.7**	18.4**	32.5	1,279
SD	0.869	0.207	0.42	1.25	0.88	0.16	0.56	112.1
Dose: 400 + 100[d]								
Mean	6.14	7.21**	13.5*	41.3	57.4**	18.7**	32.6	1,379*
SD	1.323	0.452	0.73	2.27	1.33	0.35	0.75	150.0
Dose: 0 + 150[d]								
Mean	7.72	9.18	14.9	45.0	49.0	16.2	33.1	1,123
SD	2.046	0.232	0.31	1.41	0.58	0.31	0.82	77.9
Dose: 100 + 150								
Mean	7.58	7.71**	13.8	42.6	55.3**	17.9**	32.4	1,230
SD	1.438	0.269	0.66	1.24	1.02	0.39	0.87	109.5
Dose: 200 + 150[e]								
Mean	5.74*	5.86**	10.7**	33.3**	55.7**	17.3	31.0	1,202
SD	2.134	2.582	5.24	15.37	4.01	3.18	5.59	566.6
Dose: 400 + 150[e]								
Mean	4.75**	2.17**	3.7**	11.0**	47.2	16.4	35.0	2,273**
SD	1.197	1.765	3.51	11.41	5.41	1.14	2.14	483.0

[a] AZT + isoniazid in mg/kg/day
[b] n=10 in all groups, unless noted
[c] WBC corrected for nucleated RBCs≥10/100 WBC
[d] n=9
[e] n=8
* Significant difference from control P≤0.05 using analysis of variance followed by Dunnett's procedure
** Significant difference from control P≤0.01 using analysis of variance followed by Dunnett's procedure

TABLE B1
Summary of Hematology Parameters for B6C3F$_1$ Mice from the 13-Week Toxicity Study of AZT and Isoniazid Combinations: Day 30

Females

Test: / Units:	Reticulocyte $10^5/\mu L$	Neutrophil $10^3/\mu L$	Lymphocyte $10^3/\mu L$	Monocyte $10^3/\mu L$	Eosinophil $10^3/\mu L$	Basophil $10^3/\mu L$	LUC $10^3/\mu L$
Dose[a]: 0 + 100							
Mean[b]	3.2	0.79	6.83	0.21	0.13	0.05	0.03
SD	0.37	0.253	1.017	0.055	0.051	0.018	0.012
Dose: 100 + 100							
Mean	3.6	0.62	5.94	0.14*	0.16	0.03	0.03
SD	0.66	0.174	1.283	0.028	0.083	0.012	0.010
Dose: 200 + 100							
Mean	4.8**	0.78	6.07	0.16	0.18	0.03	0.03
SD	0.62	0.193	0.781	0.044	0.068	0.014	0.016
Dose: 400 + 100[d]							
Mean	6.4**	0.63	5.17	0.15	0.14	0.02	0.02
SD	1.25	0.191	1.139	0.032	0.052	0.009	0.010
Dose: 0 + 150[d]							
Mean	3.2	0.81	6.51	0.20	0.14	0.03	0.03
SD	0.40	0.300	1.722	0.046	0.084	0.009	0.012
Dose: 100 + 150[d]							
Mean	4.2	0.81	6.37	0.17	0.17	0.03	0.03
SD	0.83	0.235	1.196	0.044	0.045	0.011	0.012
Dose: 200 + 150[e]							
Mean	4.2	0.59	4.81*	0.13**	0.17	0.02	0.02
SD	2.05	0.386	1.582	0.093	0.126	0.009	0.015
Dose: 400 + 150[e]							
Mean	1.5	0.51	4.08**	0.07**	0.04	0.01**	0.04
SD	2.54	0.108	1.099	0.034	0.028	0.009	0.024

[a] AZT + isoniazid in mg/kg/day
[b] n=10 in all groups, unless noted
[c] WBC corrected for nucleated RBCs≥10/100 WBC
[d] n=9
[e] n=8
* Significant difference from control P≤0.05 using analysis of variance followed by Dunnett's procedure
** Significant difference from control P≤0.01 using analysis of variance followed by Dunnett's procedure

TABLE B1
Summary of Hematology Parameters for B6C3F$_1$ Mice from the 13-Week Toxicity Study of AZT and Isoniazid Combinations: Day 60

Males

Test: / Units:	WBC[c] $10^3/\mu L$	RBC $10^6/\mu L$	Hgb g/dL	Hct %	MCV fL	MCH pg	MCHC g/dL	Plt $10^3/\mu L$
Dose[a]: 0 + 0								
Mean[b]	5.53	10.27	16.6	49.6	48.3	16.2	33.6	1,257
SD	1.921	0.515	0.80	3.01	1.07	0.43	0.85	141.1
Dose: 100 + 0[d]								
Mean	5.28	8.63**	15.3**	46.1**	53.4**	17.7**	33.2	1,348
SD	1.312	0.252	0.39	1.18	1.37	0.53	1.09	172.5
Dose: 200 + 0[d]								
Mean	5.44	8.10**	14.9**	45.4**	56.1**	18.4**	32.8	1,395
SD	1.629	0.367	0.64	2.10	1.60	0.58	0.93	175.8
Dose: 400 + 0								
Mean	4.94	7.46**	14.3**	43.6**	58.5**	19.1**	32.7	1,418
SD	0.842	0.347	0.65	2.25	1.14	0.55	0.77	122.9
Dose: 0 + 50[d]								
Mean	5.42	10.06	16.0	47.7	47.5	15.9	33.6	1,178
SD	1.324	0.403	0.71	1.89	1.21	0.48	0.63	147.2
Dose: 100 + 50								
Mean	5.26	8.33**	14.8**	44.3**	53.3**	17.9**	33.5	1,398
SD	1.248	0.387	0.45	1.83	1.18	0.65	0.85	154.0
Dose: 200 + 50[d]								
Mean	4.63	7.97**	14.6**	44.6**	55.9**	18.4**	32.9	1,455
SD	1.151	0.358	0.69	2.60	1.86	0.39	0.83	180.2
Dose: 400 + 50								
Mean	5.25	7.42**	14.1**	43.2**	58.2**	19.0**	32.5	1,505*
SD	1.455	0.386	0.75	2.29	1.58	0.44	0.67	161.2

[a] AZT + isoniazid in mg/kg/day
[b] n=10 in all groups, unless noted
[c] WBC corrected for nucleated RBCs≥10/100 WBC
[d] n=9
* Significant difference from control P≤0.05 using analysis of variance followed by Dunnett's procedure
** Significant difference from control P≤0.01 using analysis of variance followed by Dunnett's procedure

TABLE B1
Summary of Hematology Parameters for B6C3F$_1$ Mice from the 13-Week Toxicity Study of AZT and Isoniazid Combinations: Day 60

Males

Test: / Units:	Reticulocyte $10^5/\mu L$	Neutrophil $10^3/\mu L$	Lymphocyte $10^3/\mu L$	Monocyte $10^3/\mu L$	Eosinophil $10^3/\mu L$	Basophil $10^3/\mu L$	LUC $10^3/\mu L$
Dose[a]: 0 + 0							
Mean[b]	3.1	0.57	4.63	0.17	0.12	0.03	0.02
SD	0.25	0.215	1.592	0.059	0.076	0.022	0.009
Dose: 100 + 0[d]							
Mean	3.5	0.58	4.47	0.11	0.08	0.02	0.02
SD	0.24	0.128	1.144	0.045	0.030	0.015	0.009
Dose: 200 + 0[d]							
Mean	3.9**	0.64	4.53	0.13	0.10	0.02	0.02
SD	0.25	0.273	1.330	0.062	0.055	0.012	0.010
Dose: 400 + 0							
Mean	4.6**	0.47	4.25	0.10	0.08	0.02	0.02
SD	0.28	0.104	0.742	0.028	0.046	0.008	0.013
Dose: 0 + 50[d]							
Mean	3.2	0.57	4.58	0.12	0.10	0.02	0.02
SD	0.27	0.135	1.148	0.042	0.028	0.019	0.009
Dose: 100 + 50							
Mean	3.5*	0.58	4.45	0.11	0.09	0.03	0.02
SD	0.33	0.175	1.086	0.034	0.032	0.034	0.008
Dose: 200 + 50[d]							
Mean	3.6**	0.50	3.92	0.09	0.10	0.01	0.02
SD	0.37	0.180	0.947	0.023	0.057	0.009	0.005
Dose: 400 + 50							
Mean	4.5**	0.58	4.40	0.11	0.13	0.02	0.02
SD	0.36	0.232	1.191	0.046	0.068	0.012	0.012

[a] AZT + isoniazid in mg/kg/day
[b] n=10 in all groups, unless noted
[c] WBC corrected for nucleated RBCs≥10/100 WBC
[d] n=9
* Significant difference from control P≤0.05 using analysis of variance followed by Dunnett's procedure
** Significant difference from control P≤0.01 using analysis of variance followed by Dunnett's procedure

TABLE B1
Summary of Hematology Parameters for B6C3F$_1$ Mice from the 13-Week Toxicity Study of AZT and Isoniazid Combinations: Day 60

Males

Test: / Units:	WBC[c] $10^3/\mu L$	RBC $10^6/\mu L$	Hgb g/dL	Hct %	MCV fL	MCH pg	MCHC g/dL	Plt $10^3/\mu L$
Dose[a]: 0 + 100								
Mean[b]	5.58	9.93	15.7*	46.6*	47.0	15.8	33.7	1,248
SD	1.488	0.378	0.53	1.92	0.79	0.38	0.94	128.0
Dose: 100 + 100								
Mean	5.79	8.65**	15.1**	45.5**	52.6**	17.5**	33.2	1,492*
SD	1.593	0.432	0.71	2.48	1.10	0.41	0.53	156.2
Dose: 200 + 100								
Mean	5.61	7.96**	14.4**	43.9**	55.1**	18.1**	32.9	1,509**
SD	1.975	0.433	0.73	2.68	1.86	0.39	0.60	220.5
Dose: 400 + 100								
Mean	5.24	7.50**	14.0**	42.8**	57.1**	18.7**	32.7	1,625**
SD	1.745	0.235	0.44	1.49	1.17	0.50	1.13	241.7
Dose: 0 + 150								
Mean	5.40	9.98	15.7**	46.8*	46.9	15.7	33.5	1,292
SD	1.204	0.398	0.66	1.74	0.94	0.31	0.71	139.0
Dose: 100 + 150								
Mean	4.85	8.38**	14.5**	44.1**	52.6**	17.3**	33.0	1,456
SD	1.475	0.283	0.55	2.29	1.35	0.49	1.10	170.7
Dose: 200 + 150[d]								
Mean	5.37	7.62**	13.6**	42.1**	55.3**	17.9**	32.4*	1,666**
SD	1.081	0.282	0.40	1.61	1.25	0.33	0.80	102.6
Dose: 400 + 150								
Mean	4.20	6.81**	12.7**	39.5**	58.0**	18.7**	32.3**	1,822**
SD	0.787	0.370	0.57	1.62	2.83	0.83	0.60	185.2

[a] AZT + isoniazid in mg/kg/day
[b] n=10 in all groups, unless noted
[c] WBC corrected for nucleated RBCs≥10/100 WBC
[d] n=9
* Significant difference from control P≤0.05 using analysis of variance followed by Dunnett's procedure
** Significant difference from control P≤0.01 using analysis of variance followed by Dunnett's procedure

TABLE B1
Summary of Hematology Parameters for B6C3F$_1$ Mice from the 13-Week Toxicity Study of AZT and Isoniazid Combinations: Day 60

Males

Test: / Units:	Reticulocyte $10^5/\mu L$	Neutrophil $10^3/\mu L$	Lymphocyte $10^3/\mu L$	Monocyte $10^3/\mu L$	Eosinophil $10^3/\mu L$	Basophil $10^3/\mu L$	LUC $10^3/\mu L$
Dose[a]: 0 + 100							
Mean[b]	3.2	0.66	4.64	0.14	0.10	0.02	0.01
SD	0.22	0.281	1.196	0.035	0.059	0.012	0.009
Dose: 100 + 100							
Mean	3.4	0.63	4.91	0.10	0.11	0.02	0.02
SD	0.25	0.212	1.359	0.027	0.050	0.011	0.008
Dose: 200 + 100							
Mean	3.9**	0.53	4.84	0.10	0.10	0.02	0.02
SD	0.20	0.228	1.668	0.040	0.062	0.010	0.008
Dose: 400 + 100							
Mean	4.0**	0.54	4.44	0.11	0.12	0.02	0.02
SD	0.22	0.218	1.494	0.048	0.064	0.012	0.008
Dose: 0 + 150							
Mean	3.3	0.61	4.53	0.12	0.09	0.03	0.02
SD	0.34	0.237	0.975	0.031	0.032	0.020	0.008
Dose: 100 + 150							
Mean	4.0**	0.57	4.06	0.12	0.07	0.02	0.02
SD	0.19	0.243	1.203	0.039	0.038	0.017	0.007
Dose: 200 + 150[d]							
Mean	4.1**	0.60	4.54	0.11	0.09	0.02	0.02
SD	0.36	0.145	0.905	0.030	0.043	0.011	0.011
Dose: 400 + 150							
Mean	4.2**	0.47	3.53	0.09	0.08	0.01	0.01[d]
SD	0.56	0.164	0.748	0.062	0.034	0.007	0.005

[a] AZT + isoniazid in mg/kg/day
[b] n=10 in all groups, unless noted
[c] WBC corrected for nucleated RBCs≥10/100 WBC
[d] n=9
* Significant difference from control P≤0.05 using analysis of variance followed by Dunnett's procedure
** Significant difference from control P≤0.01 using analysis of variance followed by Dunnett's procedure

TABLE B1
Summary of Hematology Parameters for B6C3F$_1$ Mice from the 13-Week Toxicity Study of AZT and Isoniazid Combinations: Day 60

Females

Test: / Units:	WBC[c] $10^3/\mu L$	RBC $10^6/\mu L$	Hgb g/dL	Hct %	MCV fL	MCH pg	MCHC g/dL	Plt $10^3/\mu L$
Dose[a]: 0 + 0								
Mean[b]	4.31	9.48	15.2	45.0	47.5	16.0	33.8	1,158
SD	1.807	0.464	0.73	2.05	1.00	0.23	0.74	98.1
Dose: 100 + 0								
Mean	5.10	8.26**	15.0	45.0	54.4**	18.1**	33.3	1,323
SD	1.912	0.570	1.04	3.07	0.44	0.32	0.51	121.0
Dose: 200 + 0								
Mean	4.63	7.45**	14.0	42.3	56.8**	18.8**	33.0	1,360
SD	1.388	0.459	0.89	2.33	1.16	0.21	0.57	244.7
Dose: 400 + 0								
Mean	4.74	7.20**	14.1	42.8	59.4**	19.5**	32.8**	1,461**
SD	2.157	0.363	0.74	2.38	1.38	0.49	0.43	164.7
Dose: 0 + 50[d]								
Mean	6.65	9.79	15.7	46.8	47.8	16.1	33.6	1,277
SD	1.907	0.284	0.51	1.54	1.14	0.25	0.79	148.9
Dose: 100 + 50								
Mean	4.99	7.99**	14.4	43.1	53.9**	18.0**	33.3	1,263
SD	1.053	0.285	0.61	1.46	0.90	0.28	0.72	240.9
Dose: 200 + 50								
Mean	4.92	7.65**	14.2	43.1	56.4**	18.5**	32.8**	1,333
SD	2.032	0.459	0.73	2.36	0.80	0.30	0.59	194.7
Dose: 400 + 50[d]								
Mean	3.45	6.67**	12.9**	39.7*	59.6**	19.4**	32.6**	1,434*
SD	1.337	0.494	0.89	2.81	1.30	0.16	0.59	147.4

[a] AZT + isoniazid in mg/kg/day
[b] n=10 in all groups, unless noted
[c] WBC corrected for nucleated RBCs≥10/100 WBC
[d] n=9
* Significant difference from control P≤0.05 using analysis of variance followed by Dunnett's procedure
** Significant difference from control P≤0.01 using analysis of variance followed by Dunnett's procedure

TABLE B1
Summary of Hematology Parameters for B6C3F$_1$ Mice from the 13-Week Toxicity Study of AZT and Isoniazid Combinations: Day 60

Females

Test: / Units:	Reticulocyte $10^5/\mu L$	Neutrophil $10^3/\mu L$	Lymphocyte $10^3/\mu L$	Monocyte $10^3/\mu L$	Eosinophil $10^3/\mu L$	Basophil $10^3/\mu L$	LUC $10^3/\mu L$
Dose[a]: 0 + 0							
Mean[b]	3.3[d]	0.58	3.48	0.12	0.11	0.02	0.01
SD	0.40	0.320	1.380	0.059	0.070	0.012	0.005
Dose: 100 + 0							
Mean	4.0	0.62	4.18	0.11	0.15	0.02	0.02[d]
SD	0.52	0.324	1.551	0.079	0.086	0.015	0.014
Dose: 200 + 0							
Mean	3.8	0.36	4.05	0.08	0.11	0.02	0.01
SD	0.69	0.125	1.240	0.032	0.054	0.008	0.008
Dose: 400 + 0							
Mean	4.6**	0.77	3.72	0.11	0.11	0.02	0.02
SD	0.60	1.307	1.068	0.081	0.075	0.007	0.012
Dose: 0 + 50[d]							
Mean	3.1	0.75	5.56	0.15	0.16	0.02	0.02
SD	0.50	0.237	1.643	0.042	0.087	0.016	0.012
Dose: 100 + 50							
Mean	3.5[d]	0.51	4.19	0.11	0.14	0.02	0.02[e]
SD	0.86	0.160	0.921	0.042	0.076	0.013	0.011
Dose: 200 + 50							
Mean	3.7	0.55	4.13	0.10	0.11	0.01	0.01
SD	1.03	0.231	1.718	0.052	0.066	0.011	0.012
Dose: 400 + 50[d]							
Mean	4.9**	0.34	2.95	0.07	0.08	0.01	0.01
SD	1.01	0.089	1.243	0.018	0.031	0.006	0.007

[a] AZT + isoniazid in mg/kg/day
[b] n=10 in all groups, unless noted
[c] WBC corrected for nucleated RBCs≥10/100 WBC
[d] n=9
[e] n=8
* Significant difference from control P≤0.05 using analysis of variance followed by Dunnett's procedure
** Significant difference from control P≤0.01 using analysis of variance followed by Dunnett's procedure

TABLE B1
Summary of Hematology Parameters for B6C3F$_1$ Mice from the 13-Week Toxicity Study of AZT and Isoniazid Combinations: Day 60

Females

Test: / Units:	WBC[c] $10^3/\mu L$	RBC $10^6/\mu L$	Hgb g/dL	Hct %	MCV fL	MCH pg	MCHC g/dL	Plt $10^3/\mu L$
Dose[a]: 0 + 100								
Mean[b]	4.40	9.31	15.0	44.2	47.4	16.1	34.0	1,154
SD	0.902	0.215	0.43	1.07	0.48	0.21	0.34	141.0
Dose: 100 + 100								
Mean	4.31	7.85**	14.0	42.0	53.5**	17.8**	33.3	1,342
SD	1.403	0.295	0.47	1.43	1.11	0.29	0.42	98.4
Dose: 200 + 100[d]								
Mean	4.17	7.24**	13.4*	41.0	56.7**	18.6**	32.8**	1,379
SD	1.386	0.396	0.63	1.75	1.39	0.52	0.47	123.2
Dose: 400 + 100[d]								
Mean	3.70	6.46**	12.2**	37.4**	57.1**	18.8**	32.9*	1,525**
SD	1.519	1.985	3.80	11.91	3.75	0.75	1.15	345.5
Dose: 0 + 150								
Mean	4.46	9.41	14.9	44.8	47.7	15.9	33.3	1,215
SD	1.398	0.299	0.33	1.17	0.83	0.23	0.42	109.9
Dose: 100 + 150								
Mean	4.43	7.94**	14.3	43.4	54.7**	18.0**	32.9*	1,286
SD	1.233	0.424	0.89	2.60	1.43	0.42	0.47	153.2
Dose: 200 + 150[d]								
Mean	4.20	6.83**	12.9**	39.1**	57.2**	18.9**	33.1	1,458**
SD	1.371	0.616	1.07	3.39	0.85	0.39	0.71	283.0
Dose: 400 + 150[f]								
Mean	6.81	6.97**	13.5	40.7	58.3**	19.4**	33.2	1,502
SD	—	—	—	—	—	—	—	—

[a] AZT + isoniazid in mg/kg/day
[b] n=10 in all groups, unless noted
[c] WBC corrected for nucleated RBCs≥10/100 WBC
[d] n=9
[f] n=1
* Significant difference from control P≤0.05 using analysis of variance followed by Dunnett's procedure
** Significant difference from control P≤0.01 using analysis of variance followed by Dunnett's procedure

TABLE B1
Summary of Hematology Parameters for B6C3F$_1$ Mice from the 13-Week Toxicity Study of AZT and Isoniazid Combinations: Day 60

Females

Test: / Units:	Reticulocyte $10^5/\mu L$	Neutrophil $10^3/\mu L$	Lymphocyte $10^3/\mu L$	Monocyte $10^3/\mu L$	Eosinophil $10^3/\mu L$	Basophil $10^3/\mu L$	LUC $10^3/\mu L$
Dose[a]: 0 + 100							
Mean[b]	3.2[e]	0.51	3.68	0.10	0.09	0.01	0.01[d]
SD	0.62	0.188	0.783	0.039	0.037	0.006	0.008
Dose: 100 + 100							
Mean	3.4	0.47	3.63	0.08	0.10	0.01	0.01
SD	0.70	0.158	1.207	0.033	0.040	0.007	0.010
Dose: 200 + 100[d]							
Mean	3.9	0.48	3.46	0.10	0.11	0.01	0.01
SD	0.73	0.262	1.095	0.051	0.071	0.006	0.008
Dose: 400 + 100[d]							
Mean	4.0	0.38	3.14	0.08	0.07	0.01	0.01[e]
SD	1.60	0.187	1.282	0.029	0.057	0.009	0.012
Dose: 0 + 150							
Mean	3.8	0.58	3.65	0.11	0.10	0.02	0.01
SD	0.79	0.265	1.066	0.044	0.076	0.008	0.004
Dose: 100 + 150							
Mean	4.1	0.48	3.77	0.08	0.08	0.01	0.01
SD	1.00	0.258	0.935	0.040	0.045	0.005	0.005
Dose: 200 + 150[d]							
Mean	3.7[e]	0.54	3.44	0.09	0.10	0.01	0.01[e]
SD	0.48	0.252	1.135	0.040	0.077	0.010	0.012
Dose: 400 + 150[f]							
Mean	4.3	0.39	6.10	0.10	0.18	0.02	0.02
SD	—	—	—	—	—	—	—

[a] AZT + isoniazid in mg/kg/day
[b] n=10 in all groups, unless noted
[c] WBC corrected for nucleated RBCs≥10/100 WBC
[d] n=9
[e] n=8
[f] n=1
* Significant difference from control P≤0.05 using analysis of variance followed by Dunnett's procedure
** Significant difference from control P≤0.01 using analysis of variance followed by Dunnett's procedure

TABLE B1
Summary of Hematology Parameters for B6C3F$_1$ Mice from the 13-Week Toxicity Study of AZT and Isoniazid Combinations: Days 92 to 95

Males

Test: / Units:	WBC[c] $10^3/\mu L$	RBC $10^6/\mu L$	Hgb g/dL	Hct %	MCV fL	MCH pg	MCHC g/dL	Plt $10^3/\mu L$
Dose[a]: 0 + 0								
Mean[b]	5.49	9.83	15.6	45.9	46.7	15.8	34.0	1,222
SD	1.394	0.491	1.06	3.80	2.05	0.46	0.93	167.0
Dose: 100 + 0[d]								
Mean	4.90	8.54**	15.0	45.0	52.7**	17.5**	33.3	1,301
SD	1.655	0.468	1.05	3.46	2.11	0.55	0.67	137.9
Dose: 200 + 0								
Mean	4.56	7.91**	14.4*	43.6	55.1**	18.3**	33.2	1,393
SD	1.496	0.245	0.73	2.77	2.61	0.60	0.66	208.3
Dose: 400 + 0								
Mean	4.59	7.18**	13.6**	42.0*	58.4**	19.0**	32.5**	1,568**
SD	1.656	0.290	0.70	2.47	2.32	0.51	0.55	242.6
Dose: 0 + 50								
Mean	5.00	9.78	15.4	45.5	46.5	15.8	34.0	1,235
SD	1.567	0.308	0.80	2.43	1.86	0.57	0.63	159.5
Dose: 100 + 50								
Mean	4.23	8.21**	14.4**	43.2	52.6**	17.5**	33.3	1,354
SD	1.553	0.340	0.84	3.30	2.21	0.40	0.96	262.0
Dose: 200 + 50								
Mean	4.12	7.66**	13.9**	41.7**	54.4**	18.1**	33.2	1,497*
SD	1.692	0.312	0.66	3.03	2.98	0.45	1.19	165.9
Dose: 400 + 50[d]								
Mean	3.80	7.36**	13.5**	40.7**	55.2**	18.3**	33.2	1,500*
SD	1.491	0.235	0.78	2.74	2.34	0.53	0.81	176.7

[a] AZT + isoniazid in mg/kg/day
[b] n=10 in all groups, unless noted
[c] WBC corrected for nucleated RBCs≥10/100 WBC
[d] n=9
* Significant difference from control P≤0.05 using analysis of variance followed by Dunnett's procedure
** Significant difference from control P≤0.01 using analysis of variance followed by Dunnett's procedure

TABLE B1
Summary of Hematology Parameters for B6C3F$_1$ Mice from the 13-Week Toxicity Study of AZT and Isoniazid Combinations: Days 92 to 95

Males

Test: / Units:	Reticulocyte $10^5/\mu L$	Neutrophil $10^3/\mu L$	Lymphocyte $10^3/\mu L$	Monocyte $10^3/\mu L$	Eosinophil $10^3/\mu L$	Basophil $10^3/\mu L$	LUC $10^3/\mu L$
Dose[a]: 0 + 0							
Mean[b]	3.7[d]	0.92	4.25	0.16	0.13	0.02	0.02
SD	0.17	0.689	1.400	0.056	0.062	0.013	0.012
Dose: 100 + 0[d]							
Mean	4.0	0.66	3.96	0.11	0.15	0.01	0.02[e]
SD	0.31	0.196	1.446	0.059	0.070	0.010	0.014
Dose: 200 + 0							
Mean	4.8**	0.48	3.83	0.09**	0.13	0.01	0.02
SD	0.41	0.165	1.306	0.032	0.065	0.010	0.010
Dose: 400 + 0							
Mean	5.4**	0.60	3.76	0.10*	0.12	0.01	0.02[e]
SD	0.39	0.162	1.484	0.052	0.070	0.009	0.008
Dose: 0 + 50							
Mean	3.9	0.66	4.03	0.14	0.14	0.01	0.01
SD	0.45	0.143	1.376	0.056	0.085	0.011	0.009
Dose: 100 + 50							
Mean	4.3**	0.50	3.51	0.10*	0.10	0.01	0.01
SD	0.29	0.173	1.329	0.046	0.032	0.011	0.011
Dose: 200 + 50							
Mean	4.9**[d]	0.50	3.40	0.08**	0.12	0.01	0.02[e]
SD	0.27	0.282	1.379	0.057	0.095	0.008	0.012
Dose: 400 + 50[d]							
Mean	5.2**	0.45	3.13	0.07**	0.12	0.01	0.02[e]
SD	0.38	0.122	1.369	0.041	0.101	0.011	0.010

[a] AZT + isoniazid in mg/kg/day
[b] n=10 in all groups, unless noted
[c] WBC corrected for nucleated RBCs≥10/100 WBC
[d] n=9
[e] n=8
* Significant difference from control P≤0.05 using analysis of variance followed by Dunnett's procedure
** Significant difference from control P≤0.01 using analysis of variance followed by Dunnett's procedure

TABLE B1
Summary of Hematology Parameters for B6C3F$_1$ Mice from the 13-Week Toxicity Study of AZT and Isoniazid Combinations: Days 92 to 95

Males

Test: / Units:	WBC[c] $10^3/\mu L$	RBC $10^6/\mu L$	Hgb g/dL	Hct %	MCV fL	MCH pg	MCHC g/dL	Plt $10^3/\mu L$
Dose[a]: 0 + 100								
Mean[b]	4.83	9.88	15.2	45.3	45.9	15.4	33.5	1,256
SD	1.498	0.384	0.75	2.70	2.11	0.50	0.61	135.6
Dose: 100 + 100								
Mean	4.68	8.10**	14.2**	42.4	52.3**	17.5**	33.4	1,321
SD	1.564	0.458	0.99	3.17	1.53	0.42	0.46	259.9
Dose: 200 + 100								
Mean	4.08	7.34**	13.4**	40.3**	54.9**	18.2**	33.1	1,555**
SD	1.423	0.164	0.50	2.27	2.32	0.44	0.91	136.9
Dose: 400 + 100								
Mean	4.47	6.81**	13.0**	39.7**	58.2**	19.1**	32.8*	1,636**
SD	1.710	0.281	0.57	2.57	2.75	0.52	0.96	182.5
Dose: 0 + 150								
Mean	5.68	9.79	14.9	43.9	44.8	15.2*	33.9	1,275
SD	2.156	0.427	0.75	2.44	1.83	0.33	0.86	204.4
Dose: 100 + 150								
Mean	4.98	7.70**	13.4**	41.1**	53.4**	17.5**	32.8*	1,442
SD	2.244	0.389	0.76	2.77	2.38	0.53	0.75	148.0
Dose: 200 + 150								
Mean	4.47	7.19**	13.1**	39.7**	55.1**	18.1**	32.9	1,456*
SD	1.854	0.310	0.83	3.12	2.51	0.52	0.78	127.9
Dose: 400 + 150								
Mean	3.75	6.59**	12.5**	38.8**	58.8**	18.9**	32.2**	1,518**
SD	1.442	0.377	0.68	2.64	2.59	0.46	0.86	142.7

[a] AZT + isoniazid in mg/kg/day
[b] n=10 in all groups, unless noted
[c] WBC corrected for nucleated RBCs≥10/100 WBC
* Significant difference from control P≤0.05 using analysis of variance followed by Dunnett's procedure
** Significant difference from control P≤0.01 using analysis of variance followed by Dunnett's procedure

TABLE B1
Summary of Hematology Parameters for B6C3F$_1$ Mice from the 13-Week Toxicity Study of AZT and Isoniazid Combinations: Days 92 to 95

Males

Test: / Units:	Reticulocyte $10^5/\mu L$	Neutrophil $10^3/\mu L$	Lymphocyte $10^3/\mu L$	Monocyte $10^3/\mu L$	Eosinophil $10^3/\mu L$	Basophil $10^3/\mu L$	LUC $10^3/\mu L$
Dose[a]: 0 + 100							
Mean[b]	4.0	0.58	3.99	0.11	0.12	0.02	0.01
SD	0.33	0.139	1.317	0.018	0.073	0.012	0.008
Dose: 100 + 100							
Mean	4.8**[d]	0.59	3.80	0.11	0.16	0.01	0.01[d]
SD	0.50	0.188	1.391	0.043	0.108	0.010	0.005
Dose: 200 + 100							
Mean	5.2**	0.52	3.30	0.08**	0.16	0.01	0.01
SD	0.52	0.164	1.215	0.028	0.092	0.006	0.009
Dose: 400 + 100							
Mean	5.8**	0.45	3.81	0.09*	0.10	0.01	0.02[d]
SD	0.42	0.141	1.502	0.043	0.046	0.009	0.015
Dose: 0 + 150							
Mean	4.2*	0.65	4.75	0.14	0.12	0.01	0.02
SD	0.36	0.295	1.834	0.065	0.047	0.014	0.008
Dose: 100 + 150							
Mean	5.0**[d]	0.64	4.09	0.12	0.11	0.01	0.02
SD	0.27	0.330	1.827	0.064	0.080	0.009	0.014
Dose: 200 + 150							
Mean	5.4**	0.51	3.69	0.09**	0.15	0.01	0.02[d]
SD	0.46	0.196	1.590	0.029	0.128	0.009	0.009
Dose: 400 + 150							
Mean	5.5**	0.40	3.16	0.07**	0.11	0.01	0.01
SD	0.27	0.122	1.294	0.034	0.100	0.005	0.006

[a] AZT + isoniazid in mg/kg/day
[b] n=10 in all groups, unless noted
[c] WBC corrected for nucleated RBCs≥10/100 WBC
[d] n=9
* Significant difference from control P≤0.05 using analysis of variance followed by Dunnett's procedure
** Significant difference from control P≤0.01 using analysis of variance followed by Dunnett's procedure

TABLE B1
Summary of Hematology Parameters for B6C3F$_1$ Mice from the 13-Week Toxicity Study of AZT and Isoniazid Combinations: Days 92 to 95

Females

Test: / Units:	WBC[c] $10^3/\mu L$	RBC $10^6/\mu L$	Hgb g/dL	Hct %	MCV fL	MCH pg	MCHC g/dL	Plt $10^3/\mu L$
Dose[a]: 0 + 0[d]								
Mean[b]	4.35	9.63	15.3	45.0	46.8	15.9	34.0	1,214
SD	0.936	0.302	0.32	1.54	1.86	0.41	1.10	95.7
Dose: 100 + 0								
Mean	4.01	7.73**	14.1**	42.1	54.6**	18.3**	33.4	1,404
SD	0.581	0.295	0.51	1.19	2.45	0.51	0.95	218.1
Dose: 200 + 0[d]								
Mean	3.84	7.35**	13.7**	41.5**	56.4**	18.6**	33.1	1,425
SD	0.708	0.353	0.70	2.81	2.38	0.40	0.89	238.5
Dose: 400 + 0[e]								
Mean	3.24	6.84**	13.2**	40.3**	58.9**	19.3**	32.7*	1,517**
SD	0.982	0.421	0.82	2.51	2.16	0.40	0.87	161.6
Dose: 0 + 50								
Mean	4.67	9.49	14.9	43.7	46.1	15.7	34.2	1,212
SD	1.315	0.395	0.82	2.45	2.07	0.50	1.00	189.2
Dose: 100 + 50[d]								
Mean	4.12	7.70**	13.8**	41.7*	54.3**	17.9**	33.0	1,370
SD	1.599	0.478	0.63	2.23	2.63	0.50	1.13	152.5
Dose: 200 + 50								
Mean	3.15	7.23**	13.3**	40.2**	55.6**	18.4**	33.1	1,371
SD	0.975	0.287	0.66	2.25	1.85	0.43	0.57	144.4
Dose: 400 + 50[g]								
Mean	3.83	6.47**	12.5**	38.7**	59.9**	19.3**	32.3**	1,547**
SD	0.310	0.234	0.37	1.40	2.73	0.62	0.98	172.7

[a] AZT + isoniazid in mg/kg/day
[b] n=10 in all groups, unless noted
[c] WBC corrected for nucleated RBCs≥10/100 WBC
[d] n=9
[e] n=8
[g] n=7
* Significant difference from control P≤0.05 using analysis of variance followed by Dunnett's procedure
** Significant difference from control P≤0.01 using analysis of variance followed by Dunnett's procedure

TABLE B1
Summary of Hematology Parameters for B6C3F$_1$ Mice from the 13-Week Toxicity Study of AZT and Isoniazid Combinations: Days 92 to 95

Females

Test: / Units:	Reticulocyte $10^5/\mu L$	Neutrophil $10^3/\mu L$	Lymphocyte $10^3/\mu L$	Monocyte $10^3/\mu L$	Eosinophil $10^3/\mu L$	Basophil $10^3/\mu L$	LUC $10^3/\mu L$
Dose[a]: 0 + 0[d]							
Mean[b]	3.3	0.50	3.63	0.10	0.09	0.01	0.01
SD	0.62	0.141	0.801	0.026	0.025	0.009	0.008
Dose: 100 + 0							
Mean	3.9	0.47	3.31	0.09	0.12	0.01	0.01
SD	0.56	0.076	0.489	0.028	0.070	0.006	0.009
Dose: 200 + 0[d]							
Mean	4.9*	0.38	3.18	0.99	0.17	0.01	0.01
SD	1.30	0.140	0.520	0.040	0.082	0.006	0.009
Dose: 400 + 0[e]							
Mean	6.2**	0.37	2.65	0.08	0.13	0.01	0.01
SD	1.59	0.223	0.736	0.036	0.070	0.004	0.009
Dose: 0 + 50							
Mean	3.3	0.64	3.73	0.14	0.14	0.01	0.02
SD	0.73	0.171	1.125	0.043	0.096	0.007	0.007
Dose: 100 + 50[d]							
Mean	4.1	0.37	3.53	0.09	0.12	0.01	0.02
SD	0.97	0.180	1.309	0.040	0.092	0.004	0.013
Dose: 200 + 50							
Mean	4.5	0.29*	2.68	0.08	0.10	0.01	0.01
SD	1.31	0.107	0.839	0.026	0.034	0.007	0.003
Dose: 400 + 50[g]							
Mean	5.7**	0.44	3.12	0.10	0.14	0.01	0.01
SD	0.66	0.086	0.293	0.033	0.057	0.000	0.008

[a] AZT + isoniazid in mg/kg/day
[b] n=10 in all groups, unless noted
[c] WBC corrected for nucleated RBCs≥10/100 WBC
[d] n=9
[e] n=8
[g] n=7
* Significant difference from control $P \leq 0.05$ using analysis of variance followed by Dunnett's procedure
** Significant difference from control $P \leq 0.01$ using analysis of variance followed by Dunnett's procedure

TABLE B1
Summary of Hematology Parameters for B6C3F$_1$ Mice from the 13-Week Toxicity Study of AZT and Isoniazid Combinations: Days 92 to 95

Females

Test: / Units:	WBC[c] $10^3/\mu L$	RBC $10^6/\mu L$	Hgb g/dL	Hct %	MCV fL	MCH pg	MCHC g/dL	Plt $10^3/\mu L$
Dose[a]: 0 + 100								
Mean[b]	4.10	9.36	14.8	43.8	46.8	15.8	33.8	1,287
SD	0.950	0.401	0.68	2.34	1.50	0.27	0.71	192.7
Dose: 100 + 100								
Mean	3.96	7.78**	13.7**	41.6*	53.5**	17.7**	33.0	1,379
SD	1.282	0.270	0.53	1.78	2.27	0.36	0.85	183.1
Dose: 200 + 100								
Mean	3.22	7.15**	13.1**	39.6**	55.3**	18.3**	33.0	1,348
SD	1.058	0.172	0.38	1.90	2.25	0.30	0.86	154.4
Dose: 400 + 100								
Mean	3.05	6.39**	12.3**	37.9**	59.4**	19.3**	32.5**	1,543**
SD	0.859	0.311	0.62	2.23	2.26	0.53	0.66	133.3
Dose: 0 + 150								
Mean	4.66	9.55	14.9	43.9	45.9	15.6	34.1	1,310
SD	1.119	0.238	0.62	2.10	1.38	0.33	0.79	26.1
Dose: 100 + 150								
Mean	3.47	7.40**	13.2**	40.5**	54.8**	17.8**	32.6**	1,362
SD	0.905	0.215	0.26	1.25	2.29	0.40	0.85	77.2
Dose: 200 + 150								
Mean	3.81	7.07**	13.0**	39.8**	56.3**	18.4**	32.7*	1,369
SD	0.763	0.550	0.81	2.77	1.95	0.53	0.54	147.8
Dose: 400 + 150								
Mean	3.95	6.26**	12.1**	38.1**	60.8**	19.3**	31.8**	1,628**
SD	1.332	0.585	1.16	4.43	2.73	0.34	1.15	115.6

[a] AZT + isoniazid in mg/kg/day
[b] n=10 in all groups, unless noted
[c] WBC corrected for nucleated RBCs≥10/100 WBC
* Significant difference from control P≤0.05 using analysis of variance followed by Dunnett's procedure
** Significant difference from control P≤0.01 using analysis of variance followed by Dunnett's procedure

TABLE B1
Summary of Hematology Parameters for B6C3F$_1$ Mice from the 13-Week Toxicity Study of AZT and Isoniazid Combinations: Days 92 to 95

Females

Test: / Units:	Reticulocyte $10^5/\mu L$	Neutrophil $10^3/\mu L$	Lymphocyte $10^3/\mu L$	Monocyte $10^3/\mu L$	Eosinophil $10^3/\mu L$	Basophil $10^3/\mu L$	LUC $10^3/\mu L$
Dose[a]: 0 + 100							
Mean[b]	3.7	0.50	3.36	0.12	0.09	0.01	0.01
SD	1.01	0.191	0.814	0.048	0.061	0.007	0.006
Dose: 100 + 100							
Mean	4.2	0.41	3.34	0.08	0.11	0.01	0.01
SD	1.21	0.088	1.151	0.038	0.067	0.003	0.004
Dose: 200 + 100							
Mean	4.7	0.30*	2.77	0.06	0.07	0.01	0.01
SD	1.34	0.111	0.912	0.034	0.059	0.007	0.004
Dose: 400 + 100							
Mean	5.2**	0.26**	2.64	0.06	0.08	0.01	0.01
SD	1.43	0.089	0.720	0.030	0.052	0.003	0.005
Dose: 0 + 150							
Mean	4.1	0.54	3.87	0.12	0.10	0.01	0.01
SD	0.79	0.044	1.058	0.017	0.043	0.007	0.008
Dose: 100 + 150							
Mean	4.2	0.37	2.94	0.08	0.05	0.01	0.01
SD	1.02	0.151	0.740	0.036	0.024	0.005	0.007
Dose: 200 + 150							
Mean	4.9*	0.39	3.22	0.07	0.11	0.01	0.01
SD	0.60	0.174	0.679	0.016	0.052	0.008	0.005
Dose: 400 + 150							
Mean	7.1**	0.43	3.34	0.09	0.07	0.01	0.01
SD	1.22	0.167	1.215	0.025	0.033	0.004	0.005

[a] AZT + isoniazid in mg/kg/day
[b] n=10 in all groups, unless noted
[c] WBC corrected for nucleated RBCs≥10/100 WBC
* Significant difference from control P≤0.05 using analysis of variance followed by Dunnett's procedure
** Significant difference from control P≤0.01 using analysis of variance followed by Dunnett's procedure

TABLE B2
Summary of Clinical Chemistry Parameters for B6C3F$_1$ Mice from the 13-Week Toxicity Study of AZT and Isoniazid Combinations: Day 4

Males

Test:	ALP	ALT	AST	SDH	BILA
Units:	U/L	U/L	U/L	U/L	µmol/L
Dose[a]: 0 + 0					
Mean	156	38	89	NA	26
SD	17.4	22.6	25.5	NA	NA
n	8	8	4	0	1
Dose: 100 + 0					
Mean	162	61	64	NA	20
SD	19.8	99.6	13.4	NA	7.2
n	9	9	7	0	3
Dose: 200 + 0					
Mean	156	34	88	NA	21
SD	20.0	6.2	28.5	NA	5.2
n	10	9	8	0	3
Dose: 400 + 0					
Mean	152	41	79	NA	28
SD	15.5	16.3	13.8	NA	6.2
n	10	10	9	0	4
Dose: 0 + 50					
Mean	154	35	78	NA	22
SD	12.3	13.6	21.4	NA	NA
n	10	10	6	0	1
Dose: 100 + 50					
Mean	160	39	94	NA	20
SD	12.1	15.7	30.3	NA	2.0
n	10	10	7	0	3
Dose: 200 + 50					
Mean	163	32	71	NA	16
SD	12.8	10.0	20.7	NA	6.8
n	10	10	5	0	3
Dose: 400 + 50					
Mean	152	53	84	NA	17
SD	21.1	32.9	33.6	NA	NA
n	10	10	8	0	1

[a] AZT + isoniazid in mg/kg/day
NA Not applicable
* Significant difference from control P≤0.05 using analysis of variance followed by Dunnett's procedure
** Significant difference from control P≤0.01 using analysis of variance followed by Dunnett's procedure

TABLE B2
Summary of Clinical Chemistry Parameters for B6C3F$_1$ Mice from the 13-Week Toxicity Study of AZT and Isoniazid Combinations: Day 4

Males

Test:	ALP	ALT	AST	SDH	BILA
Units:	U/L	U/L	U/L	U/L	µmol/L
Dose[a]: 0 + 100					
Mean	151	43	61	NA	18
SD	14.2	26.1	12.3	NA	3.2
n	10	9	6	0	4
Dose: 100 + 100					
Mean	158	44	78	NA	45
SD	12.9	27.5	13.3	NA	37.6
n	10	9	8	0	3
Dose: 200 + 100					
Mean	158	40	76	NA	21
SD	20.3	30.4	24.2	NA	4.2
n	10	10	8	0	3
Dose: 400 + 100					
Mean	157	35	76	NA	21
SD	11.8	13.7	19.2	NA	1.0
n	9	9	7	0	3
Dose: 0 + 150					
Mean	149	45	98	NA	NA
SD	9.5	37.8	23.6	NA	NA
n	10	10	6	0	0
Dose: 100 + 150					
Mean	152	81	105	NA	19
SD	16.4	86.6	23.6	NA	0.7
n	10	9	6	0	2
Dose: 200 + 150					
Mean	151	33	71	NA	24
SD	15.3	7.4	16.7	NA	6.1
n	9	9	6	0	3
Dose: 400 + 150					
Mean	152	34	78	NA	23
SD	8.5	9.0	23.0	NA	3.4
n	10	9	8	0	5

[a] AZT + isoniazid in mg/kg/day
NA Not applicable
* Significant difference from control P≤0.05 using analysis of variance followed by Dunnett's procedure
** Significant difference from control P≤0.01 using analysis of variance followed by Dunnett's procedure

TABLE B2
Summary of Clinical Chemistry Parameters for B6C3F$_1$ Mice from the 13-Week Toxicity Study of AZT and Isoniazid Combinations: Day 30

Males

Test:	ALP	ALT	AST	SDH	BILA
Units:	U/L	U/L	U/L	U/L	µmol/L
Dose[a]: 0 + 0					
Mean	93	34	67	NA	NA
SD	9.9	12.3	22.7	NA	NA
n	9	10	7	0	0
Dose: 100 + 0					
Mean	95	35	82	NA	NA
SD	8.0	9.8	38.8	NA	NA
n	8	9	5	0	0
Dose: 200 + 0					
Mean	91	37	78	NA	NA
SD	6.4	18.0	22.3	NA	NA
n	7	10	6	0	0
Dose: 400 + 0					
Mean	91	32	70	NA	NA
SD	5.8	6.7	9.9	NA	NA
n	8	9	5	0	0
Dose: 0 + 50					
Mean	94	43	92	NA	NA
SD	9.1	24.7	32.5	NA	NA
n	9	10	5	0	0
Dose: 100 + 50					
Mean	90	27	70	NA	NA
SD	11.9	6.4	8.6	NA	NA
n	10	10	7	0	0
Dose: 200 + 50					
Mean	97	29	75	NA	NA
SD	11.1	7.5	16.0	NA	NA
n	7	10	6	0	0
Dose: 400 + 50					
Mean	99	31	70	NA	NA
SD	12.3	11.9	7.4	NA	NA
n	9	9	4	0	0

[a] AZT + isoniazid in mg/kg/day
NA Not applicable
* Significant difference from control P≤0.05 using analysis of variance followed by Dunnett's procedure
** Significant difference from control P≤0.01 using analysis of variance followed by Dunnett's procedure

TABLE B2
Summary of Clinical Chemistry Parameters for B6C3$_{F1}$ Mice from the 13-Week Toxicity Study of AZT and Isoniazid Combinations: Day 30

Males

Test:	ALP	ALT	AST	SDH	BILA
Units:	U/L	U/L	U/L	U/L	µmol/L
Dose[a]: 0 + 100					
Mean	93	31	76	NA	NA
SD	8.9	8.7	14.6	NA	NA
n	8	10	6	0	0
Dose: 100 + 100					
Mean	95	29	69	NA	NA
SD	11.9	8.4	16.7	NA	NA
n	9	10	7	0	0
Dose: 200 + 100					
Mean	95	30	83	NA	NA
SD	10.7	9.0	16.2	NA	NA
n	10	10	8	0	0
Dose: 400 + 100					
Mean	91	33	73	NA	NA
SD	9.9	9.2	9.8	NA	NA
n	10	10	5	0	0
Dose: 0 + 150					
Mean	91	29	79	NA	NA
SD	14.9	7.0	30.8	NA	NA
n	6	10	8	0	0
Dose: 100 + 150					
Mean	89	27	71	NA	NA
SD	7.2	6.6	17.2	NA	NA
n	7	8	5	0	0
Dose: 200 + 150					
Mean	93	31	63	NA	NA
SD	9.0	10.7	1.4	NA	NA
n	5	8	2	0	0
Dose: 400 + 150					
Mean	91	26	74	NA	NA
SD	9.6	8.1	12.6	NA	NA
n	9	10	7	0	0

[a] AZT + isoniazid in mg/kg/day
NA Not applicable
* Significant difference from control P≤0.05 using analysis of variance followed by Dunnett's procedure
** Significant difference from control P≤0.01 using analysis of variance followed by Dunnett's procedure

TABLE B2
Summary of Clinical Chemistry Parameters for B6C3F$_1$ Mice from the 13-Week Toxicity Study of AZT and Isoniazid Combinations: Day 60

Males

Test:	ALP	ALT	AST	SDH	BILA
Units:	U/L	U/L	U/L	U/L	µmol/L
Dose[a]: 0 + 0					
Mean	72	33	75	33	27
SD	23.1	3.1	23.4	8.0	14.7
n	9	10	7	3	4
Dose: 100 + 0					
Mean	82	32	70	28	33
SD	7.9	4.8	11.3	2.8	9.9
n	10	10	7	2	2
Dose: 200 + 0					
Mean	77	33	83	25	43
SD	16.0	7.8	39.1	9.2	27.0
n	8	9	8	2	3
Dose: 400 + 0					
Mean	78	33	86	35	28
SD	7.4	7.7	28.0	8.7	7.9
n	10	10	10	3	4
Dose: 0 + 50					
Mean	74	32	70	25	22
SD	18.8	4.7	19.0	4.7	3.0
n	9	9	9	3	3
Dose: 100 + 50					
Mean	69	38	88	30	29
SD	23.1	14.1	34.9	4.2	5.4
n	9	10	10	4	4
Dose: 200 + 50					
Mean	81	34	91	27	23
SD	10.1	6.7	29.3	5.7	4.0
n	10	10	10	2	4
Dose: 400 + 50					
Mean	77	35	88	33	23
SD	10.4	4.7	14.3	4.9	11.6
n	10	10	9	2	4

[a] AZT + isoniazid in mg/kg/day
NA Not applicable
* Significant difference from control P≤0.05 using analysis of variance followed by Dunnett's procedure
** Significant difference from control P≤0.01 using analysis of variance followed by Dunnett's procedure

TABLE B2
Summary of Clinical Chemistry Parameters for B6C3F$_1$ Mice from the 13-Week Toxicity Study of AZT and Isoniazid Combinations: Day 60

Males

Test:	ALP	ALT	AST	SDH	BILA
Units:	U/L	U/L	U/L	U/L	µmol/L
Dose[a]: 0 + 100					
Mean	81	35	79	24	26
SD	9.8	6.2	28.2	2.1	1.2
n	10	10	9	2	3
Dose: 100 + 100					
Mean	80	33	84	37	32
SD	8.6	7.2	23.6	3.5	10.0
n	8	9	9	2	4
Dose: 200 + 100					
Mean	84	37	89	32	23
SD	6.3	10.3	23.7	11.4	3.2
n	10	10	10	3	5
Dose: 400 + 100					
Mean	77	33	82	35	17
SD	7.1	6.8	16.0	11.3	10.4
n	10	10	10	3	7
Dose: 0 + 150					
Mean	81	34	87	35	24
SD	7.9	6.3	30.4	NA	16.3
n	10	10	7	1	2
Dose: 100 + 150					
Mean	82	35	81	31	22
SD	8.5	6.8	18.0	6.6	3.8
n	10	10	9	3	3
Dose: 200 + 150					
Mean	74	36	108	27	22
SD	8.2	7.9	48.3	4.2	3.6
n	10	10	10	2	4
Dose: 400 + 150					
Mean	78	33	86	32	27
SD	7.3	4.6	25.4	2.8	3.7
n	10	10	10	2	4

[a] AZT + isoniazid in mg/kg/day
NA Not applicable
* Significant difference from control P≤0.05 using analysis of variance followed by Dunnett's procedure
** Significant difference from control P≤0.01 using analysis of variance followed by Dunnett's procedure

TABLE B2
Summary of Clinical Chemistry Parameters for B6C3F$_1$ Mice from the 13-Week Toxicity Study of AZT and Isoniazid Combinations: Days 92 to 95

Males

Test: / Units:	ALP U/L	ALT U/L	AST U/L	SDH U/L	BILA µmol/L
Dose[a]: 0 + 0					
Mean	65	34	72	25	32
SD	5.3	8.1	16.5	5.7	15.6
n	9	10	8	2	2
Dose: 100 + 0					
Mean	67	32	68	32	18
SD	6.5	9.7	15.8	24.7	6.4
n	9	9	8	2	2
Dose: 200 + 0					
Mean	67	31	80	29	19
SD	6.3	8.9	14.9	NA	NA
n	9	10	7	1	1
Dose: 400 + 0					
Mean	67	29	75	26	21
SD	5.0	5.7	17.6	11.3	7.2
n	10	10	8	2	3
Dose: 0 + 50					
Mean	63	41	97	24	26
SD	7.4	29.9	30.2	2.8	13.4
n	9	10	8	2	2
Dose: 100 + 50					
Mean	66	31	83	30	32
SD	4.2	9.7	21.1	8.5	19.6
n	9	9	7	2	3
Dose: 200 + 50					
Mean	64	36	90	16	21
SD	7.5	20.3	25.9	1.4	3.1
n	10	10	8	2	3
Dose: 400 + 50					
Mean	65	29	84	33	19
SD	8.4	12.1	23.2	13.4	2.1
n	9	10	9	2	3

[a] AZT + isoniazid in mg/kg/day
NA Not applicable
* Significant difference from control P≤0.05 using analysis of variance followed by Dunnett's procedure
** Significant difference from control P≤0.01 using analysis of variance followed by Dunnett's procedure

TABLE B2
Summary of Clinical Chemistry Parameters for B6C3F$_1$ Mice from the 13-Week Toxicity Study of AZT and Isoniazid Combinations: Days 92 to 95

Males

Test:	ALP	ALT	AST	SDH	BILA
Units:	U/L	U/L	U/L	U/L	µmol/L
Dose[a]: 0 + 100					
Mean	68	29	93	34	20
SD	12.6	9.2	23.7	9.7	3.8
n	10	10	9	3	4
Dose: 100 + 100					
Mean	67	29	83	24	23
SD	6.9	8.8	17.8	14.1	3.5
n	9	10	8	2	2
Dose: 200 + 100					
Mean	64	30	85	37	20
SD	5.7	12.4	19.0	10.6	2.8
n	10	10	9	2	2
Dose: 400 + 100					
Mean	61	30	88	19	19
SD	6.5	14.1	19.8	1.4	5.2
n	10	10	8	2	4
Dose: 0 + 150					
Mean	63	29	101	39	40
SD	6.2	7.0	26.5	5.1	18.1
n	10	10	9	3	3
Dose: 100 + 150					
Mean	65	27	89	23	27
SD	7.9	9.7	19.5	12.1	6.5
n	10	10	9	4	4
Dose: 200 + 150					
Mean	60	32	83	27	32
SD	13.0	15.3	16.7	9.7	17.6
n	9	9	7	3	3
Dose: 400 + 150					
Mean	67	29	88	31	28
SD	11.2	11.8	11.2	9.5	12.1
n	10	10	9	3	3

[a] AZT + isoniazid in mg/kg/day
NA Not applicable
* Significant difference from control P≤0.05 using analysis of variance followed by Dunnett's procedure
** Significant difference from control P≤0.01 using analysis of variance followed by Dunnett's procedure

TABLE B2
Summary of Clinical Chemistry Parameters for B6C3F$_1$ Mice from the 13-Week Toxicity Study of AZT and Isoniazid Combinations: Day 4

Females

Test:	ALP	ALT	AST	SDH	BILA
Units:	U/L	U/L	U/L	U/L	µmol/L
Dose[a]: 0 + 0					
Mean	226	37	111	NA	22
SD	24.7	33.3	96.9	NA	NA
n	10	9	3	0	1
Dose: 100 + 0					
Mean	231	25	59	NA	17
SD	30.8	1.9	11.6	NA	1.4
n	10	9	7	0	2
Dose: 200 + 0					
Mean	225	24	66	NA	18
SD	24.0	3.8	8.8	NA	7.1
n	10	9	5	0	2
Dose: 400 + 0					
Mean	230	24	60	NA	14
SD	29.4	2.3	6.1	Na	0.7
n	10	10	7	0	2
Dose: 0 + 50					
Mean	232	25	65	NA	19
SD	27.7	1.9	15.2	NA	6.2
n	9	9	4	0	3
Dose: 100 + 50					
Mean	226	29	60	NA	22
SD	25.0	13.4	8.2	NA	3.5
n	10	9	4	0	2
Dose: 200 + 50					
Mean	222	25	51	NA	22
SD	45.6	2.0	18.4	NA	6.0
n	10	10	7	0	3
Dose: 400 + 50					
Mean	196	28	54	NA	12
SD	35.2	12.7	12.4	NA	4.7
n	8	9	7	0	3

[a] AZT + isoniazid in mg/kg/day
NA Not applicable
* Significant difference from control P≤0.05 using analysis of variance followed by Dunnett's procedure
** Significant difference from control P≤0.01 using analysis of variance followed by Dunnett's procedure

TABLE B2
Summary of Clinical Chemistry Parameters for B6C3F$_1$ Mice from the 13-Week Toxicity Study of AZT and Isoniazid Combinations: Day 4

Females

Test: / Units:	ALP U/L	ALT U/L	AST U/L	SDH U/L	BILA µmol/L
Dose[a]: 0 + 100					
Mean	222	25	54	NA	15
SD	22.0	3.2	7.4	NA	2.8
n	10	8	5	0	2
Dose: 100 + 100					
Mean	223	24	57	NA	16
SD	19.7	3.0	12.0	NA	2.1
n	9	8	7	0	2
Dose: 200 + 100					
Mean	223	25	59	NA	14
SD	7.8	2.1	12.8	NA	4.9
n	9	7	6	0	2
Dose: 400 + 100					
Mean	230	25	57	NA	23
SD	23.1	3.7	9.5	NA	0.7
n	10	10	9	0	2
Dose: 0 + 150					
Mean	206	37	76	NA	14
SD	21.3	20.2	23.3	NA	NA
n	10	10	6	0	1
Dose: 100 + 150					
Mean	232	23	58	NA	20
SD	18.3	3.6	6.5	NA	4.7
n	9	9	3	0	3
Dose: 200 + 150					
Mean	219	26	68	NA	16
SD	15.0	2.2	9.1	NA	4.2
n	9	9	5	0	2
Dose: 400 + 150					
Mean	219	25	57	NA	15
SD	14.0	3.3	11.7	NA	3.9
n	9	9	7	0	5

[a] AZT + isoniazid in mg/kg/day
NA Not applicable
* Significant difference from control P≤0.05 using analysis of variance followed by Dunnett's procedure
** Significant difference from control P≤0.01 using analysis of variance followed by Dunnett's procedure

TABLE B2
Summary of Clinical Chemistry Parameters for B6C3F$_1$ Mice from the 13-Week Toxicity Study of AZT and Isoniazid Combinations: Day 30

Females

Test:	ALP	ALT	AST	SDH	BILA
Units:	U/L	U/L	U/L	U/L	µmol/L
Dose[a]: 0 + 0					
Mean	138	28	108	NA	NA
SD	29.1	9.1	40.9	NA	NA
n	8	7	7	0	0
Dose: 100 + 0					
Mean	153	26	70	NA	23
SD	17.1	5.3	18.3	NA	NA
n	8	7	7	0	1
Dose: 200 + 0					
Mean	154	28	89	NA	NA
SD	26.2	2.8	30.2	NA	NA
n	7	4	5	0	0
Dose: 400 + 0					
Mean	147	26	68*	NA	NA
SD	20.1	3.2	20.7	NA	NA
n	9	8	8	0	0
Dose: 0 + 50					
Mean	154	21	53**	22	1
SD	44.5	7.1	33.0	17.0	0.7
n	9	7	7	2	2
Dose: 100 + 50					
Mean	137	28	69	NA	10
SD	34.1	10.8	15.9	NA	NA
n	8	6	5	0	1
Dose: 200 + 50					
Mean	154	25	74	28	NA
SD	26.7	5.2	25.6	NA	NA
n	10	9	8	1	0
Dose: 400 + 50					
Mean	152	29	74	NA	NA
SD	26.9	11.4	17.2	NA	NA
n	8	6	8	0	0

[a] AZT + isoniazid in mg/kg/day
NA Not applicable
* Significant difference from control P≤0.05 using analysis of variance followed by Dunnett's procedure
** Significant difference from control P≤0.01 using analysis of variance followed by Dunnett's procedure

TABLE B2
Summary of Clinical Chemistry Parameters for B6C3F$_1$ Mice from the 13-Week Toxicity Study of AZT and Isoniazid Combinations: Day 30

Females

Test:	ALP	ALT	AST	SDH	BILA
Units:	U/L	U/L	U/L	U/L	µmol/L
Dose[a]: 0 + 100					
Mean	133	22	86	NA	NA
SD	27.8	1.9	21.5	NA	NA
n	10	7	6	0	0
Dose: 100 + 100					
Mean	140	26	78	NA	NA
SD	27.2	2.6	20.7	NA	NA
n	10	7	7	0	0
Dose: 200 + 100					
Mean	152	24	83	NA	NA
SD	34.0	8.9	23.5	NA	NA
n	9	9	7	0	0
Dose: 400 + 100					
Mean	149	27	87	NA	NA
SD	25.0	6.0	24.5	NA	NA
n	9	6	6	0	0
Dose: 0 + 150					
Mean	150	26	70	NA	NA
SD	24.0	7.6	15.9	NA	NA
n	8	6	5	0	0
Dose: 100 + 150					
Mean	145	29	79	NA	NA
SD	21.9	8.1	32.0	NA	NA
n	9	6	7	0	0
Dose: 200 + 150					
Mean	132	29	76	23	28
SD	21.9	12.6	29.6	2.1	NA
n	9	6	9	2	1
Dose: 400 + 150					
Mean	118	21	65	42	32
SD	22.7	3.9	10.5	7.7	16.5
n	10	9	8	4	6

[a] AZT + isoniazid in mg/kg/day
NA Not applicable
* Significant difference from control P≤0.05 using analysis of variance followed by Dunnett's procedure
** Significant difference from control P≤0.01 using analysis of variance followed by Dunnett's procedure

TABLE B2
Summary of Clinical Chemistry Parameters for B6C3F$_1$ Mice from the 13-Week Toxicity Study of AZT and Isoniazid Combinations: Day 60

Females

Test:	ALP	ALT	AST	SDH	BILA
Units:	U/L	U/L	U/L	U/L	µmol/L
Dose[a]: 0 + 0					
Mean	114	30	95	18	17
SD	10.2	6.5	29.8	1.4	3.5
n	10	10	10	2	6
Dose: 100 + 0					
Mean	103	30	90	17	19
SD	15.6	4.9	29.0	2.5	8.8
n	10	10	10	4	8
Dose: 200 + 0					
Mean	110	28	85	19	19
SD	10.1	4.5	17.2	4.2	6.0
n	10	10	10	3	9
Dose: 400 + 0					
Mean	104	31	88	20	19
SD	14.6	4.1	19.2	4.9	4.5
n	10	10	10	3	7
Dose: 0 + 50					
Mean	109	28	94	20	19
SD	12.2	4.8	25.1	1.4	5.5
n	10	10	10	2	8
Dose: 100 + 50					
Mean	99	33	83	32	19
SD	19.9	12.5	20.8	NA	4.6
n	10	10	10	1	6
Dose: 200 + 50					
Mean	109	30	112	25	22
SD	11.9	6.1	38.7	3.5	6.6
n	10	10	10	3	7
Dose: 400 + 50					
Mean	115	29	94	26	18
SD	22.9	5.1	21.7	11.0	6.2
n	9	9	9	3	8

[a] AZT + isoniazid in mg/kg/day
NA Not applicable
* Significant difference from control P≤0.05 using analysis of variance followed by Dunnett's procedure
** Significant difference from control P≤0.01 using analysis of variance followed by Dunnett's procedure

TABLE B2
Summary of Clinical Chemistry Parameters for B6C3F$_1$ Mice from the 13-Week Toxicity Study of AZT and Isoniazid Combinations: Day 60

Females

Test:	ALP	ALT	AST	SDH	BILA
Units:	U/L	U/L	U/L	U/L	µmol/L
Dose[a]: 0 + 100					
Mean	101	29	95	21	20
SD	18.9	6.6	26.6	4.3	11.6
n	10	10	9	4	8
Dose: 100 + 100					
Mean	115	28	94	22	18
SD	10.7	1.4	15.7	3.1	3.6
n	9	9	9	4	9
Dose: 200 + 100					
Mean	104	35	108	26	19
SD	17.8	14.5	38.3	7.8	4.4
n	10	10	10	2	6
Dose: 400 + 100					
Mean	118	29	88	23	24
SD	14.5	6.2	19.8	9.4	11.5
n	10	10	10	5	8
Dose: 0 + 150					
Mean	95	35	121	26	19
SD	17.5	13.0	19.4	5.7	7.9
n	10	10	10	5	9
Dose: 100 + 150					
Mean	106	34	112	23	19
SD	15.1	7.4	27.4	NA	6.0
n	10	10	10	1	7
Dose: 200 + 150					
Mean	109	33	98	26	18
SD	11.0	8.5	18.5	5.6	4.8
n	9	9	9	4	8
Dose: 400 + 150					
Mean	95	25	75	NA	NA
SD	NA	NA	NA	NA	NA
n	1	1	1	0	0

[a] AZT + isoniazid in mg/kg/day
NA Not applicable
* Significant difference from control P≤0.05 using analysis of variance followed by Dunnett's procedure
** Significant difference from control P≤0.01 using analysis of variance followed by Dunnett's procedure

TABLE B2
Summary of Clinical Chemistry Parameters for B6C3F$_1$ Mice from the 13-Week Toxicity Study of AZT and Isoniazid Combinations: Days 92 to 95

Females

Test:	ALP	ALT	AST	SDH	BILA
Units:	U/L	U/L	U/L	U/L	µmol/L
Dose[a]: 0 + 0					
Mean	105	26	75	16	17
SD	10.0	4.5	27.4	6.7	3.8
n	10	10	10	4	4
Dose: 100 + 0					
Mean	112	25	63	19	19
SD	10.7	4.2	7.6	7.5	5.2
n	8	8	6	3	3
Dose: 200 + 0					
Mean	105	28	77	17	20
SD	15.0	11.6	16.6	2.1	4.0
n	10	10	9	2	3
Dose: 400 + 0					
Mean	114	26	90	20	20
SD	12.7	3.3	27.7	0.6	3.1
n	9	10	8	3	4
Dose: 0 + 50					
Mean	101	25	79	20	21
SD	7.6	9.6	18.4	10.3	3.4
n	9	10	8	3	4
Dose: 100 + 50					
Mean	105	22	87	17	24
SD	7.0	4.3	26.6	3.5	5.9
n	8	9	9	2	3
Dose: 200 + 50					
Mean	99	24	96	25	23
SD	8.1	6.6	34.6	10.2	13.1
n	9	10	10	3	6
Dose: 400 + 50					
Mean	99	21	83	17	20
SD	8.6	2.1	12.5	4.2	9.4
n	8	8	8	2	4

[a] AZT + isoniazid in mg/kg/day
NA Not applicable
* Significant difference from control P≤0.05 using analysis of variance followed by Dunnett's procedure
** Significant difference from control P≤0.01 using analysis of variance followed by Dunnett's procedure

TABLE B2
Summary of Clinical Chemistry Parameters for B6C3F$_1$ Mice from the 13-Week Toxicity Study of AZT and Isoniazid Combinations: Days 92 to 95

Females

Test:	ALP	ALT	AST	SDH	BILA
Units:	U/L	U/L	U/L	U/L	µmol/L
Dose[a]: 0 + 100					
Mean	92	22	90	17	15
SD	19.2	5.0	22.1	NA	NA
n	10	10	9	1	1
Dose: 100 + 100					
Mean	95	22	89	23	16
SD	10.0	4.8	12.6	3.5	9.9
n	9	9	9	2	2
Dose: 200 + 100					
Mean	106	23	90	21	22
SD	12.5	7.1	19.9	9.2	9.0
n	10	10	10	2	4
Dose: 400 + 100					
Mean	99	22	87	22	20
SD	14.0	7.7	28.0	7.4	13.4
n	9	9	9	4	5
Dose: 0 + 150					
Mean	105	19	83	15	23
SD	17.7	2.6	10.6	NA	3.5
n	7	7	7	1	2
Dose: 100 + 150					
Mean	103	21	87	17	19
SD	9.9	4.3	23.4	4.0	10.4
n	8	9	8	3	4
Dose: 200 + 150					
Mean	113	19	85	NA	16
SD	7.4	3.2	13.5	NA	10.6
n	8	9	9	0	2
Dose: 400 + 150					
Mean	98	24	105	39	17
SD	13.1	6.0	27.6	5.8	10.0
n	5	5	5	3	3

[a] AZT + isoniazid in mg/kg/day
NA Not applicable
* Significant difference from control P≤0.05 using analysis of variance followed by Dunnett's procedure
** Significant difference from control P≤0.01 using analysis of variance followed by Dunnett's procedure

APPENDIX C
REPRODUCTIVE TISSUE EVALUATIONS AND ESTROUS CYCLE CHARACTERIZATION

TABLE C1
Summary of Reproductive Tissue Evaluations for Male B6C3F$_1$ Mice from the 13-Week Toxicity Study of AZT and Isoniazid Combinations

Dose[a]	Left Caudal Weight (g)	Left Epididymal Weight (g)	Left Testicular Weight (g)
0 + 0	0.0165 ± 0.0008	0.0422 ± 0.0018	0.1074 ± 0.0053
100 + 0	0.0182 ± 0.0026 (9)	0.0477 ± 0.0022 (9)	0.1150 ± 0.0033 (9)
200 + 0	0.0189 ± 0.0009	0.0445 ± 0.0013	0.1054 ± 0.0047
400 + 0	0.0189 ± 0.0008	0.0460 ± 0.0009	0.1118 ± 0.0031
0 + 50	0.0195 ± 0.0027	0.0459 ± 0.0028	0.1161 ± 0.0037
0 + 100	0.0194 ± 0.0018	0.0463 ± 0.0023	0.1134 ± 0.0018
0 + 150	0.0171 ± 0.0005	0.0439 ± 0.0006	0.1114 ± 0.0023
100 + 50	0.0184 ± 0.0016	0.0475 ± 0.0014	0.1174 ± 0.0034
100 + 100	0.0190 ± 0.0008	0.0463 ± 0.0007	0.1158 ± 0.0017
100 + 150	0.0178 ± 0.0006	0.0442 ± 0.0012	0.1081 ± 0.0053
200 + 50	0.0190 ± 0.0006	0.0464 ± 0.0013	0.1078 ± 0.0052
200 + 100	0.0192 ± 0.0007	0.0463 ± 0.0011	0.1123 ± 0.0021
200 + 150	0.0181 ± 0.0009	0.0441 ± 0.0015	0.1100 ± 0.0041
400 + 50	0.0183 ± 0.0008	0.0445 ± 0.0012	0.1048 ± 0.0050
400 + 100	0.0165 ± 0.0014	0.0425 ± 0.0022	0.0998 ± 0.0034 (9)[b]
400 + 150	0.0191 ± 0.0024	0.0498 ± 0.0046	0.1077 ± 0.0019

Dose[a]	Epididymal Sperm Motility (%)	Epididymal Sperm Density (×10^6)	Spermatid Heads Per Gram of Testis (×10^7)
0 + 0	81.47 ± 1.92	1197.49 ± 110.27	20.49 ± 0.72
100 + 0	83.47 ± 0.75 (9)	1505.20 ± 260.31 (9)	19.44 ± 0.43 (9)
200 + 0	74.50 ± 7.75	1136.56 ± 92.27	21.39 ± 0.93
400 + 0	73.79 ± 8.22	1238.60 ± 85.11	19.55 ± 0.31
0 + 50	80.80 ± 1.31	1243.27 ± 149.66	19.68 ± 0.73
0 + 100	78.43 ± 2.33	1484.79 ± 93.67	21.23 ± 0.44
0 + 150	81.05 ± 1.00	1640.72 ± 104.39	20.90 ± 0.58
100 + 50	74.46 ± 8.29	1369.02 ± 261.22	19.88 ± 0.28
100 + 100	58.88 ± 9.62	1193.77 ± 140.75	19.38 ± 0.31
100 + 150	62.61 ± 10.51	1225.16 ± 91.11	19.67 ± 0.28
200 + 50	67.67 ± 7.65	1087.72 ± 98.26	21.20 ± 0.93
200 + 100	67.63 ± 7.80	1290.82 ± 43.99	20.71 ± 0.42
200 + 150	60.34 ± 10.69	1433.99 ± 97.03	20.46 ± 0.50
400 + 50	60.62 ± 8.72	1257.66 ± 153.83	19.99 ± 0.43
400 + 100	74.72 ± 3.96	1337.21 ± 87.85 (9)[b]	22.86 ± 0.49 (9)[b]
400 + 150	74.76 ± 7.46	1254.19 ± 183.83	21.33 ± 0.91

Note: All findings presented as mean value ± standard error; n=10 unless noted in parentheses.
[a] AZT + isoniazid in mg/kg/day
[b] Data for one animal excluded based on the outlier test of Dixon and Massey to detect extreme values.

TABLE C2
Summary of Estrous Cycle Evaluations for Female B6C3F$_1$ Mice from the 13-Week Toxicity Study of AZT and Isoniazid Combinations

			Relative Frequency of Estrous Stages (%)			
Dose[a]	n	Estrous Cycle Length (days)[b]	Proestrus	Estrus[c]	Metestrus	Diestrus
0+0	9	4.11 ± 0.07	21.7	27.5	17.5	33.3
100+0	9	4.61 ± 0.55	18.3	20.8	20.0	40.8
200+0	8	4.19 ± 0.13	19.2	22.5	20.0	38.3
400+0	10	4.70 ± 0.49	19.2	23.3	15.0	42.5
0+50	10	4.10 ± 0.10	18.3	24.2	21.7	35.8
0+100	7	4.71 ± 0.47	18.3	23.3	15.0	43.3
0+150	7	4.50 ± 0.19	19.0	28.6	14.3	38.1
100+0	9	4.39 ± 0.14	18.5	21.3	19.4	40.7
100+100	7	4.00 ± 0.00	20.4	27.8	19.4	32.4
100+150	9	4.61 ± 0.58	19.4	28.7	16.7	35.2
200+50	8	4.13 ± 0.08	17.5	22.5	19.2	40.8
200+100	8	4.25 ± 0.13	16.7	26.7	19.2	37.5
200+150	10	4.35 ± 0.15	16.7	30.8	22.5	30.0
400+50	8	4.88 ± 0.60	18.8	21.9	19.8	39.6
400+100	9	4.22 ± 0.21	18.5	25.0	23.1	33.3
400+150	5	4.30 ± 0.20	16.7	33.3	20.0	30.0

[a] AZT + isoniazid in mg/kg/day
[b] Group mean ± standard error
[c] Results of a two-way analysis of variance indicated a significant isoniazid effect ($P \leq 0.0025$) with respect to the duration of estrus.

Other NIEHS Reports and Publications on the Toxicology of AIDS Therapeutics:

National Institute of Environmental Health Sciences (NIEHS) (1997). Reproductive, Developmental, and General Toxicity Studies of Pyrazinamide Administered by Gavage to Swiss (CD-1®) Mice. NIEHS AIDS Therapeutics Toxicity Report No. 1. NIH Publication No. 97-3938. U.S. Department of Health and Human Services, Public Health Service, National Institutes of Health. Research Triangle Park, NC.

National Institute of Environmental Health Sciences (NIEHS) (1998). Reproductive, Developmental, and General Toxicity Studies of 3′-Azido-3′-deoxythymidine (AZT), Trimethoprim (TMP)/Sulfamethoxazole (SMX), and Folinic Acid Combinations Administered by Gavage to Swiss (CD-1®) Mice. NIEHS AIDS Therapeutics Toxicity Report No. 2. NIH Publication No. 99-3940. U.S. Department of Health and Human Services, Public Health Service, National Institutes of Health. Research Triangle Park, NC.

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http://ntp-server.niehs.nih.gov/Main_Pages/AIDS/AIDSpage.html