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NTP Technical Report
on Toxicity Studies of

Pesticide/Fertilizer Mixtures

Administered in Drinking Water
to F344/N Rats and B6C3F$_1$ Mice

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This NTP report on the toxicity studies of pesticide/fertilizer mixtures is based primarily on 26-week studies that took place from June 1990 through February 1991.

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ABSTRACT

Pesticide/Fertilizer Mixtures

Toxicity studies were performed with pesticide and fertilizer mixtures representative of groundwater contamination found in California and Iowa. The California mixture was composed of aldicarb, atrazine, 1,2-dibromo-3-chloropropane, 1,2-dichloropropane, ethylene dibromide, simazine, and ammonium nitrate. The Iowa mixture contained alachlor, atrazine, cyanazine, metolachlor, metribuzin, and ammonium nitrate. The mixtures were administered in drinking water (with 512 ppm propylene glycol) to F344/N rats and B6C3F$_1$ mice of each sex at concentrations ranging from 0.1X to 100X, where 1X represented the median concentrations of the individual chemicals found in studies of groundwater contamination from normal agricultural activities. This report focuses primarily on 26-week toxicity studies describing histopathology, clinical pathology, neurobehavior/neuropathology, and reproductive system effects. The genetic toxicity of the mixtures was assessed by determining the frequency of micronuclei in peripheral blood of mice and evaluating micronuclei and sister chromatid exchanges in splenocytes from female mice and male rats. Additional studies with these mixtures that are briefly reviewed in this report include teratology studies with Sprague-Dawley rats and continuous breeding studies with CD-1 Swiss mice.

In 26-week drinking water studies of the California and the Iowa mixtures, all rats (10 per sex and group) survived to the end of the studies, and there were no significant effects on body weight gains. Water consumption was not affected by the pesticide/fertilizer contaminants, and there were no clinical signs of toxicity or neurobehavioral effects as measured by a functional observational battery, motor activity evaluations, thermal sensitivity evaluations, and startle response. There were no clear adverse effects noted in clinical pathology (including serum cholinesterase activity), organ weight, reproductive system, or histopathologic evaluations, although absolute and relative liver weights were marginally increased with increasing exposure concentration in both male and female rats consuming the Iowa mixture.

In 26-week drinking water studies in mice, one male receiving the California mixture at 100X died during the study, and one control female and one female in the 100X group in the Iowa mixture study also died early. It could not be determined if the death of either

of the mice in the 100X groups was related to consumption of the pesticide/fertilizer mixtures. Water consumption and body weight gains were not affected in these studies, and no signs of toxicity were noted in clinical observations or in neurobehavioral assessments. No clear adverse effects were noted in clinical pathology, reproductive system, organ weight, or histopathologic evaluations of exposed mice.

The pesticide/fertilizer mixtures, when tested over a concentration range similar to that used in the 26-week studies, were found to have no effects in teratology studies or in a continuous breeding assay examining reproductive and developmental toxicity.

The California and Iowa pesticide mixtures were tested for induction of micronuclei in peripheral blood erythrocytes of female mice. Results of tests with the California mixture were negative. Significant increases in micronucleated normochromatic erythrocytes were seen at the two highest concentrations (10X and 100X) of the Iowa mixture, but the increases were within the normal range of micronuclei in historical control animals. Splenocytes of male rats and female mice exposed to these mixtures were examined for micronucleus and sister chromatid exchange frequencies. Sister chromatid exchange frequencies were marginally increased in rats and mice receiving the California mixture, but neither species exhibited increased frequencies of micronucleated splenocytes. None of these changes were considered to have biological importance.

In summary, studies of potential toxicity associated with the consumption of mixtures of pesticides and a fertilizer representative of groundwater contamination in agricultural areas of Iowa and California failed to demonstrate any significant adverse effects in rats or mice receiving the mixtures in drinking water at concentrations as high as 100 times the median concentrations of the individual chemicals determined by groundwater surveys.

PEER REVIEW PANEL

The members of the Peer Review Panel who evaluated the draft report on the toxicity studies of pesticide/fertilizer mixtures on December 2, 1992, are listed below. Panel members serve as independent scientists, not as representatives of any institution, company, or governmental agency. In this capacity, panel members act to determine if the design and conditions of the NTP studies are appropriate and to ensure that the toxicity study report presents the experimental results and conclusions fully and clearly.

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SUMMARY OF PEER REVIEW COMMENTS

On December 2, 1992, the Technical Reports Review Subcommittee of the Board of Scientific Counselors for the National Toxicology Program met in Research Triangle Park, NC, to review the draft technical report on toxicity studies of pesticide/fertilizer mixtures.

Dr. John Bucher, NIEHS, introduced the short-term toxicity studies of pesticide/fertilizer mixtures by reviewing the rationale for the study, experimental design, and results.

Dr. Davidson, a principal reviewer, said that this was an interesting set of studies, and the design and maximum doses of groundwater contaminants seemed appropriate. She asked that the report state more clearly whether splenocyte tests were performed on animals evaluated at 13 weeks or on those evaluated at 26 weeks and why 26 weeks was chosen for the study length. Dr. Davidson also asked that a table listing the CAS number, molecular formula, weight, physical state, and water solubility of each of the chemicals in the mixtures be added to the introduction.

Dr. Taylor, a second principal reviewer, thought that the study appeared straightforward and focused. He asked that information concerning the carcinogenicity of the individual chemicals be added to the report and said that he thought the groundwater surveys that formed the basis for dose selection should be more fully cited in the report.

Dr. Bucher responded by agreeing to the suggested additions to the report. He stated that the splenocyte studies were performed on animals evaluated at the 13-week interim and that the 26-week study length was selected to maximize the chances of detecting an adverse response. Dr. Raymond Yang, Colorado State University, stated that the original study design also allowed for cessation of dosing at 13 weeks if significant toxicity was observed. The remaining animals would then have been held for 13 weeks to assess recovery.

After a short discussion of issues concerning the usefulness of performing studies of chemical mixtures, Dr. Klaassen accepted the report on behalf of the peer review panel.

INTRODUCTION

Human exposure to chemicals is rarely limited to a single chemical. People are exposed daily to a variety of chemicals in food, drink, cosmetics or personal hygiene products, and indoor and outdoor pollutants. For this reason, exposure to a single chemical may be considered a higher concentration excursion of a multiple-chemical exposure. In recent years, various environmental problems have led to increased concern about potential toxicity from exposure to multiple chemicals, including those associated with hazardous waste disposal sites and agricultural activities (Yang, 1992).

The National Institute of Environmental Health Sciences (NIEHS) and the NTP, in an interagency agreement with the Agency for Toxic Substances and Disease Registry, has begun studying the long-term effects of exposure to low levels of mixtures of contaminants frequently found in groundwater (Yang and Rauckman, 1987; Yang *et al.*, 1989a,b; NTP, 1990). The initial phase of this program centered around the investigation of a 25-chemical mixture that simulated groundwater contamination from hazardous waste disposal sites on a "worst-case" basis. Although this exact chemical mixture may never actually exist in the environment, the study results provided evidence for measurable adverse biological effects at environmentally relevant contamination concentrations (NTP, 1992). As a continuation of the effort to evaluate complex mixtures, the potential health effects of pesticide and fertilizer contamination of groundwater in farming-intensive states were studied.

Occurrence and Exposure

Pesticides have been an integral part of modern agriculture for decades. However, until very recently, little attention had been given to the potential problem of groundwater contamination by pesticides, particularly from nonpoint sources (*i.e.*, field application). Until the early 1980s, groundwater contamination by pesticides and other agricultural chemicals was considered unlikely because of the volatility and the subsequent dispersion of many of these chemicals into the atmosphere, the immense dilution and filtration processes occurring during and after their application, degradation by sunlight and microorganisms, and adsorption to soil (Holden, 1986; USEPA, 1986; Yang, 1987a,b). However, several major episodes (*e.g.*, episodes involving aldicarb, 1,2-dibromo-3-chloropropane, and ethylene dibromide) of groundwater contamination brought the

problem to national attention (Rothschild *et al.*, 1982; Zaki *et al.*, 1982; California State Water Resources Control Board, 1983; USEPA, 1986, 1988; Green *et al.*, 1987; Ritter, 1990). Further monitoring efforts by state and federal agencies found significant groundwater contamination by pesticides and fertilizers from point and nonpoint sources (California State Water Resources Control Board, 1983; Pye *et al.*, 1983; NRC/NAS, 1984; Hallberg, 1986; Holden, 1986; Kelley *et al.*, 1986; Valiulis, 1986; Fairchild, 1987; Libra *et al.*, 1987; Richards *et al.*, 1987; Urbain, 1987; USEPA, 1986, 1988; USPIRG, 1988; Ritter, 1990). It appears from the data presently available that pesticide and fertilizer contamination of groundwater, though at relatively low concentrations, is a widespread problem, particularly in those areas where intensive farming takes place and where waste disposal sites are located. In California, more than 40 different pesticides have been found in groundwater basins in 23 counties (California State Water Resources Control Board, 1983). The United States Environmental Protection Agency (USEPA, 1988) listed 46 pesticides as confirmed groundwater contaminants in many different states due to normal agricultural use. Because more than half of the U.S. population depends on groundwater for its drinking water needs, the health effects of long-term, low-level intake of a chemical mixture, whether pesticides or other organic and inorganic compounds, is an important area that must be addressed.

Because of the immense number of potential pesticide/fertilizer mixtures in the groundwater, testing even most potential mixtures is unfeasible. To prepare a representative mixture of pesticide and fertilizer contaminants, the NIEHS/NTP conducted a survey on groundwater contamination by pesticides and fertilizers in each state; 39 agencies in 28 states responded. From the results of this survey, a draft protocol for the testing of a mixture of 22 pesticides and a fertilizer, representing a worst-case scenario of groundwater contamination, was developed. Based on suggestions from external reviewers, information from the USEPA, and information about groundwater contamination in California and Iowa, the protocol was changed to focus on studies of two pesticide/fertilizer mixtures (California State Water Resources Control Board, 1983; Holden, 1986; Kelly *et al.*, 1986; USEPA, 1988). These mixtures contained fewer components than the initially recommended mixture of 23 components, but were more representative of localized groundwater contamination due to normal agricultural use of pesticides and fertilizers in two farming-intensive states, California and Iowa (Yang, 1992).

The pesticide/fertilizer mixture representative of actual groundwater contamination in California contained six pesticides and ammonium nitrate, a fertilizer; the Iowa mixture contained five pesticides and ammonium nitrate. Because aldicarb is typically found in groundwater as aldicarb sulfone and aldicarb sulfoxide, the aldicarb used as a component of the California mixture was a 1:1:1 mixture by weight of aldicarb, aldicarb sulfone, and aldicarb sulfoxide. Physical and chemical characteristics of the individual components of the California and Iowa mixtures are provided in Table 1.

TABLE 1 Physical and Chemical Characteristics of Pesticide/Fertilizer Mixture Components

Component	CAS Number	Chemical Formula	Molecular Weight	Physical State	Solubility in Water
Alachlor	15972-60-8	$C_{14}H_{20}ClNO_2$	269.77	white crystals	242 mg/L at 25° C[1]
Aldicarb	116-06-3	$C_7H_{14}N_2O_2S$	190.26	white crystals	6 g/L at 20° C[2]
Aldicarb sulfone	1646-88-4	$C_7H_{14}N_2O_4S$	222.26	clear crystals	not available
Aldicarb sulfoxide	1646-87-3	$C_7H_{14}N_2O_3S$	206.26	white crystals	not available
Ammonium nitrate	6484-52-2	$H_4N_2O_3$	80.04	white crystals	38.0 g/L at 20° C[3]
Atrazine	1912-24-9	$C_8H_{14}ClN_5$	215.68	white powder	30 mg/L at 20° C[1]
Cyanazine	21725-46-2	$C_9H_{13}N_6Cl$	240.69	white powder	171 mg/L at 25° C[1]
1,2-Dibromo-3-chloropropane	96-12-8	$C_3H_5Br_2Cl$	236.33	pale yellow liquid	1.23 g/L at 25° C[4]
1,2-Dichloropropane	78-87-5	$C_3H_6Cl_2$	112.99	clear yellow liquid	2.6 g/L at 20° C[5]
Ethylene dibromide	106-93-4	$C_2H_4Br_2$	187.86	clear liquid	4.04 g/L at 20° C[6]
Metolachlor	51218-45-2	$C_{15}H_{22}ClNO_2$	283.81	yellow-brown liquid	530 mg/L at 20° C[1]
Metribuzin	21087-64-0	$C_8H_{14}N_4OS$	214.28	white powder	122 mg/L at 20° C[1]
Simazine	122-34-9	$C_7H_{12}ClN_5$	201.67	white powder	3.5 mg/L at 20° C[2]

[1] Beste, 1983.
[2] IARC, 1991.
[3] Weast, 1979.
[4] Kenaga and Goring, 1980.
[5] *Hawley's Condensed Chemical Dictionary*, 1987.
[6] *Kirk-Othmer*, 1981.

Study Rationale and Design

Two mixtures of pesticide/fertilizer groundwater contaminants were selected for toxicologic characterization based on potential widespread exposure through groundwater sources resulting from normal agricultural use. The selected amounts of individual components were based on median concentrations found in groundwater in California and Iowa in a USEPA survey (USEPA, 1988; Yang, 1992); drinking water was chosen as the route of administration because this is the primary route of potential human exposure. F344/N rats and B6C3F$_1$ mice were used in the 26-week studies. The studies performed included reproductive system, developmental, clinical pathology, neurobehavioral/neuropathologic,

and histopathologic evaluations. In addition, the genetic toxicity of these mixtures was assessed by determination of micronuclei in the peripheral blood erythrocytes of female mice and in splenocytes of male rats and female mice and by determination of sister chromatid exchanges in splenocytes of male rats and female mice.

MATERIALS AND METHODS

Characterization of Pesticide/Fertilizer Mixtures

Stock solutions of pesticide/fertilizer mixtures were prepared by Midwest Research Institute (MRI; Kansas City, MO). The California mixture stock consisted of eight organic components in propylene glycol, and the Iowa mixture stock consisted of five organic components in propylene glycol. The identity and purity of each lot of the organic components was analyzed using infrared or nuclear magnetic resonance spectroscopy, gas chromatography by two systems, or high-performance liquid chromatography (HPLC); at least one spectroscopic and one chromatographic method was used for each organic component. The purity of all organic components except metolachlor and metribuzin was 99% or greater; metolachlor was approximately 97% pure, and metribuzin was approximately 93% pure. Propylene glycol (USP grade; Lot 989-1009-81759) for use as a vehicle was obtained from Van Waters and Rogers, Incorporated (Kansas City, MO). The boiling point and density of Lot 989-1009-81759 were consistent with literature references (*Merck Index*, 1989); the infrared, ultraviolet/visible, and nuclear magnetic resonance spectra were generally consistent with the structure of propylene glycol, with the spectra of a lot of propylene glycol previously analyzed at MRI, and with literature references (*Sadtler Standard Spectra*). Results of elemental analyses, Karl Fischer water analysis, titration of acidic components, thin-layer chromatography by two solvent systems, and gas chromatography by two systems indicated a purity of greater than 99% for this lot of propylene glycol. During the studies, propylene glycol was stored in glass containers, in the dark, at room temperature.

The organic and inorganic components and the target concentrations of the components in the drinking water solutions are given in Table 2. These concentrations were based on the results of U.S. Environmental Protection Agency surveys of pesticide and fertilizer contaminants in groundwater in California and Iowa (USEPA, 1988; Yang, 1992), toxicity data of individual components, and volatility and physical and chemical interactions of the individual components in an aqueous solution (Yang *et al.*, 1989b).

TABLE 2 Components of Pesticide/Fertilizer Mixtures

Component	Target Concentration (ppb)			
	0.1X	1X	10X	100X
California Mixture				
Aldicarb	0.3	3	30	300
Aldicarb sulfone	0.3	3	30	300
Aldicarb sulfoxide	0.3	3	30	300
Ammonium nitrate (ppm)	1	10	100	1000
Atrazine	0.05	0.5	5.0	50
1,2-Dibromo-3-chloropropane	0.001	0.01	0.1	1
1,2-Dichloropropane	0.45	4.5	45	450
Ethylene dibromide	0.09	0.9	9	90
Simazine	0.03	0.3	3	30
Iowa Mixture				
Alachlor	0.09	0.9	9	90
Ammonium nitrate (ppm)	1	10	100	1000
Atrazine	0.05	0.5	5	50
Cyanazine	0.04	0.4	4	40
Metolachlor	0.04	0.4	4	40
Metribuzin	0.06	0.6	6	60

California Mixture Stock: To prepare the California mixture stock, a prestock was prepared by mixing a portion of the 1,2-dibromo-3-chloropropane with a portion of the propylene glycol using a gastight syringe. Aldicarb, aldicarb sulfone, aldicarb sulfoxide, atrazine, and simazine were weighed and then combined with the remaining propylene glycol. The solution was alternately stirred and sonicated for approximately 3 hours and then stirred overnight to completely dissolve the organic components. 1,2-Dichloropropane, ethylene dibromide, and a portion of the 1,2-dibromo-3-chloropropane prestock were added to the solution using a gastight syringe; the needle was discharged below the surface of the solvent, and the solution was stirred again until all components were dissolved. The stock was analyzed for aldicarb using HPLC by 1 system and for aldicarb sulfone and aldicarb sulfoxide using a second HPLC system. The concentrations of ethylene dibromide, 1,2-dibromo-3-chloropropane, and 1,2-dichloropropane were determined with gas chromatography by one system, and the concentrations of atrazine and simazine were determined by a second gas chromatographic system.

For the first batch of California mixture stock prepared at MRI, all components were present at concentrations within 15% of the target concentrations; four component concentrations were within 5% of the target concentrations. For the second batch, all

components were within 10% of the target concentrations except 1,2-dibromo-3-chloropropane, which was present at 141% of the target concentration.

Iowa Mixture Stock: To prepare the Iowa mixture stock, alachlor, atrazine, cyanazine, and metribuzin were combined with propylene glycol. Metolachlor was added volumetrically. The stock was further diluted with propylene glycol and then alternately sonicated and magnetically stirred for approximately 2.5 hours to ensure that all components were completely dissolved and well mixed. The results of gas chromatographic analysis of the stock showed that all components were within 9% of the target concentrations.

The stability of a drinking water solution containing all of the components present in the California and Iowa mixtures, stored under animal room conditions for up to 7 days or sealed in amber glass bottles with no headspace in the dark at 5° C or room temperature for 7 or 14 days, was tested by MRI. Results of these studies showed that the drinking water solutions were stable, with minor losses of some components and somewhat higher losses of the volatile components, when stored for up to 7 days under animal room conditions or up to 14 days when stored in the dark at room temperature or at 5° C. Most losses occurred immediately after mixing. Because storage at 5° C improved the stability of some components, the California and Iowa mixture stock solutions were stored in glass containers in the dark at 5° C during the 26-week studies.

Dose Formulations

The study laboratory received two shipments of the California mixture stock and one shipment of the Iowa mixture stock prepared by MRI. High-dose (100X) solutions were prepared by adding 10 mL nitrate stock (1 L solution of 129 g ammonium nitrate in reagent-grade deionized water) to 990 mL deionized water while stirring, and then slowly injecting 0.5 mL of the California or Iowa mixture stock into the vortex of the stirred nitrate solution using a gastight syringe. Lower concentrations (0.1X, 1X, and 10X) were prepared by diluting the 100X solutions with deionized water. The vehicle control solutions were prepared by adding propylene glycol (518 ppm) to deionized water. Dose formulations were prepared every 8 days (California mixture) or 9 days (Iowa mixture). The drinking water solutions were stored in amber glass bottles, in the dark, at 5° C.

The study laboratory monitored the drinking water formulations for three marker compounds, ethylene dibromide (California mixture), metribuzin (Iowa mixture), and

ammonium nitrate. The concentrations of ethylene dibromide and metribuzin were monitored using gas chromatography. The concentration of ammonium nitrate was monitored using HPLC. The study laboratory also monitored the propylene glycol concentration (target concentration 518 ppm) in the 100X solution using gas chromatography.

For rats and mice receiving the California mixture, the concentration of ethylene dibromide was within 10% of the target concentration for at least 75% of the 0.1X, 1X, 10X, and 100X formulations except the 0.1X formulation for mice (73%) and for 75% of all animal room samples except the 10X formulation (67% for rats and 63% for mice). The ammonium nitrate concentrations were within 10% of the target concentration for at least 75% of the 1X, 10X, and 100X formulations and for at least 75% of all animal room samples; 64% of the 0.1X formulations for rats and mice were within 10% of the target concentration for ammonium nitrate. The propylene glycol concentration was within 10% of the target concentration for 91% of the dose formulations for rats, 82% of the dose formulations for mice, and 88% of all animal room samples.

For the Iowa mixture, 56% of the 1X dose formulations, 50% of the 1X animal room samples, and 71% of the 100X animal room samples for rats had metribuzin concentrations within 10% of the target concentration. For mice, 73% of the 100X dose formulations, 57% of the 100X animal room samples, and 67% of the 1X animal room samples were within 10% of the target concentrations for metribuzin. At least 75% of all other dose formulations and animal room samples were within 10% of the target concentrations for metribuzin. The ammonium nitrate concentrations were within 10% of the target concentrations for 56% of the 0.1X and 1X formulations for rats, for at least 83% of the 10X and 100X formulations for rats, for at least 75% of all dose formulations for mice, and for at least 83% of all animal room samples for rats and mice. The propylene glycol concentration was within 10% of the target concentration for 60% of the dose formulations for rats, 56% of the dose formulations for mice, and 57% of all animal room samples.

There was a high degree of variation in the concentrations of ethylene dibromide and ammonium nitrate prior to and after dosing. The variability for ethylene dibromide was attributed to loss of ethylene dibromide in the calibration standard material, resulting in

loss of precision. The variability for ammonium nitrate was attributed to technical difficulties in the chromatographic analyses involving degradation of the stationary phase.

Toxicity Study Designs

BASE STUDIES

Male and female F344/N rats and B6C3F$_1$ were obtained from Simonsen Laboratories (Gilroy, CA). Rats and mice were approximately 29 days old at receipt, were quarantined 11 to 12 days, and were approximately 40 to 41 days old when the studies began. Blood samples were collected from five male and five female control rats at the end of each study, from five male and five female control mice in the California mixture study during Week 20 and at the end of the study, and from five male and five female control mice in the Iowa mixture study during Week 17 and at the end of the study. The sera were analyzed for antibody titers to rodent viruses (Boorman *et al.*, 1986; Rao *et al.*, 1989a,b). All results for rats and for mice in the California mixture study were negative; for the Iowa mixture study in mice, sera from five females at Week 17 and four females at the end of the study showed antibodies to mouse hepatitis virus. Additional details concerning the study design are provided in Table 3.

The exposure levels selected for the 26-week studies were based on known human exposure levels for pesticides and fertilizers (based on USEPA survey results for groundwater contamination by pesticides and fertilizers) and on acute toxicity data for each of the components in the mixtures used in these studies. The concentration of each component in the base-level (1X) dose was equivalent to the median concentration reported by the USEPA (USEPA, 1988). The 100X concentration was selected to provide a safety margin for potential risk assessment of toxicologic responses, and the 0.1X concentration was selected to allow evaluation of any synergistic toxicologic interactions. Twenty rats and 20 mice per sex received drinking water containing a mixture of pesticides (eight in the California mixture, five in the Iowa mixture) and ammonium nitrate, a fertilizer. Twenty rats and 20 mice per sex were maintained as vehicle controls for each study, and received drinking water plus the propylene glycol solvent. After 13 weeks of exposure, 10 animals per group were evaluated. The study design allowed for cessation of exposure to dosed water during the second 13 weeks of the study to assess recovery if clinical signs of toxicity were noted during the first 13 weeks. This did not occur and therefore animals were exposed to the pesticide/fertilizer mixtures for 26 weeks.

Rats were housed five per cage and mice were housed individually. NIH-07 Open Formula Diet (Zeigler Brothers, Inc., Gardners, PA) in pellet form was available *ad libitum*. Water consumption was measured twice per week. Animal rooms were maintained at 69° to 75° F and 35% to 65% relative humidity, with 12 hours of fluorescent light per day and at least 10 room air changes per hour.

Complete necropsies and histopathologic examinations were performed on all base-study animals. The heart, right kidney, liver, lungs, right testis, and thymus were weighed. Organs and tissues were examined for gross lesions and fixed in 10% neutral buffered formalin. Tissues to be examined microscopically were trimmed, embedded in paraffin, sectioned, and stained with hematoxylin and eosin. Tissues examined microscopically are listed in Table 3.

Upon completion of the laboratory pathologist's histologic evaluation, the slides, paraffin blocks, and residual wet tissues were sent to the NTP Archives for inventory, slide/block match, and wet tissue audit. The slides, individual animal data records, and pathology tables were sent to an independent pathology laboratory where quality assessment was performed. Results were reviewed and evaluated by the NTP. Details of these review procedures have been described by Maronpot and Boorman (1982) and Boorman *et al.* (1985).

SUPPLEMENTAL EVALUATIONS

Summaries of the teratology and continuous breeding studies are given in Appendices E and F, respectively.

Clinical Pathology

Clinical pathology studies were performed on base-study mice and on rats designated for clinical pathology testing. Ten animals per sex and exposure level were evaluated. For rats, samples were collected on Days 5, 22, and 92 and at the end of the study (Day 183). Urinalysis samples were collected on Days 3, 18, 88, and 179. For mice, blood samples for hematology and clinical chemistry tests were collected on Days 92 and 183. For the hematology and clinical chemistry evaluations, animals were anesthetized with CO_2 and blood samples were drawn from the retroorbital sinus. Samples for hematology analysis were placed in tubes containing EDTA; samples for clinical chemistry evaluations were

placed in tubes devoid of anticoagulant. The latter samples were allowed to clot at room temperature; the samples were then centrifuged and serum was removed. All hematologic and biochemical analyses were performed on the day of sample collection.

Hematology determinations were performed with a Technicon H•1 hematology analyzer (Technicon Corp., Tarrytown, NY). The parameters that were evaluated are listed in Table 3. Differential leukocyte counts and reticulocyte counts were determined by microscopic examination of blood smears using modified Romanowsky and new methylene blue stains, respectively.

Clinical chemistry variables and methemoglobin concentrations were measured with a Roche Cobas Fara chemistry analyzer (Roche Diagnostic Systems, Inc., Montclair, NJ). The parameters that were evaluated are listed in Table 3. Reagents for assay of sorbitol dehydrogenase activity and bile acid concentrations were obtained from Sigma Chemical Company (St. Louis, MO); reagents for the other endpoints were obtained from the analyzer manufacturer.

Urine samples were collected overnight from fasted rats individually housed in metabolism cages (Hoeltge, Inc., Cincinnati, OH). After volume, pH, and specific gravity were measured, the following urinalysis variables were measured using a Roche Cobas Fara chemistry analyzer: urine glucose, protein, alkaline phosphatase, aspartate aminotransferase, creatinine, and *N*-acetyl-β-D-glucosaminidase. Reagents for the *N*-acetyl-β-D-glucosaminidase assay were obtained from Boehringer Mannheim (Indianapolis, IN).

Sperm Morphology and Vaginal Cytology in Rats and Mice

Vaginal cytology and sperm morphology evaluations were performed on base-study rats and mice (10 animals per sex) from the 0, 1X, 10X, and 100X exposure groups at the 13-week interim evaluations. The parameters that were evaluated are listed in Table 3. Methods were those described by Morrissey *et al.* (1988). Briefly, for the 12 days prior to interim or terminal sacrifice, the vaginal vaults of 10 females of each species per dose group were moistened with saline, if necessary, and samples of vaginal fluid were collected and cells were stained. Relative numbers of leukocytes, nucleated epithelial cells, and large squamous epithelial cells were determined and used to ascertain estrous cycle stage (*i.e.*, diestrus, proestrus, estrus, and metestrus).

Sperm motility was evaluated at necropsy in the following manner. The left epididymis was isolated and weighed. The tail of the epididymis (cauda epididymis) was then removed from the epididymal body (corpus epididymis) and weighed. Test yolk (rats) or Tyrode's buffer (mice) was applied to slides and a small incision was made at the distal border of the cauda epididymis. The sperm effluxing from the incision were dispersed in the buffer on the slides and the numbers of motile and nonmotile spermatozoa were counted for five fields per slide.

Following completion of sperm motility estimates, each left cauda epididymis was placed in buffered saline solution. Cauda were teased and the tissue was incubated in the saline solution and then heat fixed at 65° C. Sperm density was then determined microscopically with the aid of a hemacytometer. To quantify spermatogenesis, 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 using a hemacytometer.

Neurobehavior/Neuropathology Studies

Neurobehavioral and neuropathologic evaluations were performed on rats and mice designated for these studies. Ten animals per sex received concentrations of 0 (vehicle control), 0.1X, 1X, 10X, or 100X for 26 weeks. Tests were performed 4 days before the first day of dosing and during Weeks 7, 13, 18 (Iowa mixture studies), 19 (California mixture studies), and 25. The tests that were performed are listed in Table 3. The least interactive evaluations were performed first, and the most manipulative were performed last.

Home cage observations included evaluations of posture, presence or absence of tonic or clonic convulsions, vocalizations, and palpebral closure. Handling behavior evaluations included general observation, ease of removal from cage, ease of handling, lacrimation, palpebral closure, fur appearance, piloerection, and salivation. Physiologic evaluations included body weight and temperature.

Open field behavior of individual animals was measured for 3-minute periods, and parameters evaluated included number of supported and unsupported rears, presence or absence of tonic or clonic convulsions, gait and gait score, mobility score, arousal level, presence or absence of stereotyped behavior, and number of fecal boli or urine pools. Reflex responses included approach response, touch response, click response, tail-pinch

response, presence or absence of vocalizations to tail pinch, pupil response, righting reflex, and landing footsplay. Forelimb and hindlimb grip strength were measured using strain gauges (Chatillion Force Measurement Co., Greensboro, NC).

Motor activity was measured using an Opto-Varimax Mini Activity Monitor (Columbus Instruments International Corp., Columbus, OH) over a 10-minute period. Ambulatory behavior and other behaviors were scored. Thermal sensitivity was evaluated by measuring the time before each animal removed its tail from a 55° C water bath. Startle response to acoustic and air-puff stimuli was measured using a Responder-X Startle Monitor (Columbus Instruments International Corp.). Latency to respond, peak threshold, and time of the peak were recorded.

Neuropathologic evaluations were conducted on five males and five females from the control and high-dose groups of animals in the neurobehavioral evaluations. Perfusion fixation was performed on anesthetized animals at the end of the study. The brain, gasserian ganglion, spinal cord, cervical and lumbosacral dorsal root ganglia with root fibers, sciatic nerves, and lower tibial and sural nerves were collected. Sections of brain, spinal cord, and left and right sciatic nerves were dehydrated, embedded in paraffin, and stained with hematoxylin and eosin.

TABLE 3 Experimental Design and Materials and Methods in the 26-Week Drinking Water Studies of Pesticide/Fertilizer Mixtures

EXPERIMENTAL DESIGN	
Study Laboratory	Southern Research Institute (Birmingham, AL)
Size of Study Groups	Base Studies: 20 males and 20 females per species per exposure group Clinical Pathology Study: 10 male and 10 female rats per exposure group Neurobehavioral/Neuropathology Studies: 10 males and 10 females per species per exposure group
Route of Administration	Drinking water
Doses/Duration of Dosing	Rats and mice: 0 (vehicle control), 0.1X, 1X, 10X, or 100X daily for 13 or 26 weeks
Date of First Dose	*California Mixture:* Rats: 18 June 1990 (males), 19 June 1990 (females) Mice: 23 July 1990 (males), 24 July 1990 (females) *Iowa Mixture:* Rats: 6 August 1990 (males), 7 August 1990 (females) Mice: 13 August 1990 (males), 14 August 1990 (females)
Date of Last Dose	*California Mixture:* 13-Week interim: Rats: 17 September 1990 (males), 18 September 1990 (females) Mice: 22 October 1990 (males), 23 October 1990 (females) Study termination: Rats: 17 December 1990 (males), 18 December 1990 (females) Mice: 21 January 1991 (males), 22 January 1991 (females) *Iowa Mixture:* 13-Week interim: Rats: 5 November 1990 (males), 6 November 1990 (females) Mice: 12 November 1990 (males), 13 November 1990 (females) Study termination: Rats: 4 February 1991 (males), 5 February 1991 (females) Mice: 11 February 1991 (males), 12 February 1991 (females)
Necropsy Dates	*California Mixture:* 13-Week interim: Rats: 17 September 1990 (males), 18 September 1990 (females) Mice: 22 October 1990 (males), 23 October 1990 (females) Study termination: Rats: 17 December 1990 (males), 18 December 1990 (females) Mice: 21 January 1991 (males), 22 January 1991 (females) *Iowa Mixture:* 13-Week interim: Rats: 5 November 1990 (males), 6 November 1990 (females) Mice: 12 November 1990 (males), 13 November 1990 (females) Study termination: Rats: 4 February 1991 (males), 5 February 1991 (females) Mice: 11 February 1991 (males), 12 February 1991 (females)
Type and Frequency of Observation	Animals were observed twice daily. Body weights and clinical observations were recorded at the start of the study, weekly thereafter, and at sacrifice. Feed consumption by cage was measured weekly, and water consumption by cage was measured twice weekly.

TABLE 3 Experimental Design and Materials and Methods in the 26-Week Drinking Water Studies of Pesticide/Fertilizer Mixtures (continued)

Necropsy and Histologic Examinations	Complete necropsies and histopathologic evaluations were performed on all animals in the base studies. The following tissues were examined microscopically: adrenal glands, brain (three sections), clitoral glands, esophagus, eyes (if grossly abnormal), femur and marrow, gallbladder, gross lesions and tissue masses, heart, kidneys, large intestine (cecum, colon, rectum), liver, lungs, lymph nodes (mandibular and mesenteric), mammary gland, nasal cavity and turbinates (three sections), ovaries, pancreas, parathyroid glands, pituitary gland, preputial glands, prostate gland, salivary gland, seminal vesicle, small intestine (duodenum, jejunum, ileum), spinal cord/sciatic nerve (if neurologic signs were present) spleen, stomach (forestomach and glandular stomach), testes (with epididymis), thigh muscle (if neurologic signs were present), thymus, thyroid gland, trachea, urinary bladder, uterus, and vagina (females in vaginal cytology studies only).
Supplemental Evaluations	Clinical Pathology Studies: Blood for hematology and clinical chemistry evaluations was collected from rats designated for the clinical pathology special study on Days 5, 22, 92, and 183. Urinalysis samples were collected from special study rats overnight on Days 3, 18, 88, and 179. Blood for hematology and clinical chemistry evaluations was collected from base-study mice on Days 92 and 183. Hematology parameters included hematocrit (HCT), hemoglobin (HGB) concentration, erythrocyte (RBC) count, reticulocyte count, mean cell volume (MCV), mean cell hemoglobin (MCH), mean cell hemoglobin concentration (MCHC), platelet count, leukocyte (WBC) count and differential, and methemoglobin concentration. Clinical chemistry parameters included urea nitrogen, creatinine, total protein, albumin, alanine aminotransferase (ALT), creatine kinase (CK), sorbitol dehydrogenase (SDH), cholinesterase, and bile acids. Urinalysis parameters included creatinine, glucose, protein, alkaline phosphatase (AP), aspartate aminotransferase (AST), *N*-acetyl-β-D-glucosaminidase, volume, specific gravity, and pH. Sperm Morphology and Vaginal Cytology Evaluations: Sperm morphology and vaginal cytology evaluations were performed on base-study animals at the 13-week interim evaluations. Animals in the 0, 1X, 10X, and 100X groups were evaluated. Male rats and mice were evaluated for necropsy body and reproductive tissue weights, spermatozoal data, and spermatogenesis. Females were evaluated for necropsy body weight, estrous cycle length, and the percent of cycle spent in the various stages. Neurobehavior/Neuropathology Studies: Rats and mice (10 males and 10 females per group) designated for the neurobehavior/neuropathology studies were subjected to a battery of neurobehavioral tests 4 days prior to the first day of dosing and during Weeks 7, 13, 18 (Iowa mixture studies), 19 (California mixture studies), and 25. Rats and mice received 0, 0.1X, 1X, 10X, or 100X concentrations. Four groups of tests were conducted: 1) a functional observational battery that included assessment of home cage behaviors, handling behaviors, physiological measures, open field behavior, reflex responses, and forelimb and hindlimb grip strength; 2) motor activity; 3) thermal sensitivity; and 4) startle responsiveness. After the neurobehavioral evaluations were completed, five rats and five mice of each sex from the control and high-dose groups were used for neuropathologic evaluations. The brain (sagittal), cervical and lumbosacral spinal cord, and left and right sciatic nerve were histopathologically examined.
ANIMALS AND ANIMAL MAINTENANCE	
Strain and Species	F344/N rats B6C3F$_1$ mice
Animal Source	Simonsen Laboratories (Gilroy, CA)
Time Held Before Study	11 days (males), 12 days (females)

TABLE 3 Experimental Design and Materials and Methods in the 26-Week Drinking Water Studies of Pesticide/Fertilizer Mixtures (continued)

Age When Placed on Study	40-41 days
Age When Killed	19 weeks (13-week interim); 32 weeks (26-week termination)
Method of Animal Distribution	Animals were weighed and were randomized using a table of random numbers.
Diet	NIH-07 Open Formula Diet (Zeigler Brothers, Inc., Gardners, PA) in pellet form and deionized, dosed water (City of Birmingham) were available *ad libitum*
Animal Room Environment	Rats were housed five animals per cage and mice were housed individually. The temperature was maintained at 69° to 75° F and relative humidity at 35% to 65%, with at least 10 air changes per hour. Fluorescent light was provided for 12 hours per day.

Genetic Toxicity Studies

PERIPHERAL BLOOD MICRONUCLEUS TEST PROTOCOL

A detailed discussion of this assay can be found in MacGregor *et al.* (1990). Peripheral blood samples were obtained from female B6C3F$_1$ mice at the 13-week interim evaluation of the toxicity study. Smears were immediately prepared and fixed in absolute methanol, stained with Wright-Giemsa, and coded. Slides were scanned to determine the frequency of micronuclei in 2000 normochromatic erythrocytes (NCEs) in each animal per dose group. Eight female mice per dose group were treated with the California mixture and nine female mice per dose group were treated with the Iowa mixture. The vehicle control was propylene glycol. The criteria of Schmid (1976) were used to define micronuclei; the minimum size limit was approximately one twentieth the diameter of the NCE cell.

SPLENOCYTE TEST PROTOCOLS

The micronucleus and sister chromatid exchange (SCE) tests with splenocytes were performed as reported in Erexson and Kligerman (1987) and Erexson *et al.* (1987). Spleens were obtained from female B6C3F$_1$ mice and male F344 rats at the 13-week interim evaluation. There were four animals per dose group in the California mixture studies and five animals per dose group in the Iowa mixture studies. Purified splenocyte suspensions were prepared and incubated at 37° C in a humidified, 5% CO_2 atmosphere. For the SCE determinations, 5 µM 5-bromo-2′-deoxyuridine was added 20 hours after culture initiation. Mouse cell cultures were harvested at 51 hours and rat cell cultures at 71 hours after initiation, after a 3-hour demecolcine treatment. Cells were treated with a hypotonic solution and fixed, and slides were prepared and stained as described in Erexson and Kligerman (1987). The cells to be used for the micronucleus analyses were treated with

3 µg cytochalasin B per mL at 21 (mouse cells) or 28 hours (rat cells) to induce formation of binucleated cells for facilitating the scoring of micronuclei. Cells were harvested 50 (mouse) or 70 hours (rat) after culture initiation and stained with acridine orange (Erexson *et al.*, 1987). All slides were coded prior to scoring. Fifty second-division metaphase cells were scored for SCEs, and 2000 binucleated splenocytes were scored for the presence of micronuclei.

Statistical Methods

ANALYSIS OF CONTINUOUS VARIABLES

Two approaches were employed to assess the significance of pairwise comparisons between dosed and control groups in the analysis of continuous variables. Organ and body weight data, which are approximately normally distributed, were analyzed using the parametric multiple comparisons procedures of Williams (1971, 1972) or Dunnett (1955). Clinical chemistry, hematology, and urinalysis data, which typically have skewed distributions, were analyzed using the nonparametric multiple comparisons methods of Shirley (1977) or Dunn (1964). Jonckheere's test (Jonckheere, 1954) was used to assess the significance of dose-response trends and to determine whether a trend-sensitive test (Williams, Shirley) was more appropriate for pairwise comparisons than a test capable of detecting departures from monotonic dose response (Dunnett, Dunn). If the P-value from Jonckheere's test was greater than or equal to 0.10, Dunn's or Dunnett's test was used rather than Shirley's or Williams' test.

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. The extreme values chosen by the statistical test were subject to approval by NTP personnel. In addition, values indicated by the laboratory report as being inadequate due to technical problems were eliminated from the analysis.

ANALYSIS OF VAGINAL CYTOLOGY DATA

Since the data are proportions (the proportion of the observation period that an animal was in a given estrous state), an arcsine transformation was used to bring the data into closer conformance with normality assumptions. Treatment effects were investigated by

applying a multivariate analysis of variance (Morrison, 1976) to the transformed data to test for simultaneous equality of measurements across dose levels.

ANALYSIS OF NEUROBEHAVIORAL DATA

The methods of Haggerty (1989) were used for many procedures. Results of individual animal data were evaluated for an overall treatment-related effect; if no significant effect was indicated, no further analyses were performed. If the P-value for an overall treatment-related effect was less than 0.05, pairwise comparisons of exposed groups and controls were conducted. Home cage and handling behavior data were analyzed by chi-square analyses or Fisher's exact test. Physiologic data and open field activity continuous variables (number of rears, defecation, and urination) were analyzed by analysis of variance (ANOVA) with *post hoc* least squares analysis and protection levels for significant testing. Open field activity categorical variables (mobility, ataxic gait, arousal, gait, and tonic and clonic convulsions) were analyzed by categorical modeling and frequency tabulations using chi-square and Fisher's exact analyses. Reflex data were analyzed by categorical modeling, chi-square, and Fisher's exact analyses.

ANALYSIS OF PERIPHERAL BLOOD MICRONUCLEUS DATA

The data were analyzed using a trend test and test for pairwise comparisons included on a PC software package specific for cytogenetic test data analysis (Integrated Laboratory Systems, Research Triangle Park, NC).

ANALYSIS OF SPLENOCYTE DATA

Micronuclei data were analyzed as described above for the peripheral blood smears. SCE data were analyzed by a one-way analysis of variance.

Quality Assurance

The animal studies of the California and Iowa pesticide/fertilizer mixtures were performed in compliance with U.S. Food and Drug Administration Good Laboratory Practices regulations (21 CFR 58). The Quality Assurance Unit of Southern Research Institute performed audits and inspections of protocols, procedures, data, and reports throughout the course of the studies.

RESULTS

26-Week Drinking Water Studies in F344/N Rats

All rats exposed to the California or the Iowa mixture survived to the end of the studies (Tables 4 through 7). In the California study, the final mean body weights of males in the 0.1X and 1X groups and the weight gain of males in the 1X group were higher than those of the controls at 13 weeks (Table 4). At 26 weeks, the final mean body weights and mean body weight gains of exposed males and females were similar to those of the controls (Table 5 and Figure 1). In the Iowa mixture study, the mean body weights of males in the 0.1X and 1X groups and the mean weight gain of males in 0.1X group were higher than those of the controls at 13 weeks (Table 6); the mean body weights and mean body weight gains of exposed and control rats were similar at 26 weeks (Table 7 and Figure 2). No clinical signs attributed to exposure to the California or the Iowa mixture were noted in male or female rats.

For both the California and Iowa mixture studies, water consumption by exposed rats was similar to that by the controls (Tables 4 through 7). Average compound consumption for each component in the California mixture is shown in Table 8, and average compound consumption for each component in the Iowa mixture is shown in Table 9.

TABLE 4 Survival, Weight Gain, and Water Consumption of F344/N Rats at the 13-Week Interim Evaluation in the 26-Week Drinking Water Study of a California Pesticide/Fertilizer Mixture

Dose	Survival[1]	Mean Body Weight (grams)			Final Weight Relative to Controls (%)[3]	Average Water Consumption (g/day)[4]
		Initial	Final	Change[2]		
MALE						
0	10/10	114	324	210		19.7
0.1X	10/10	118	342	224	106	20.1
1X	10/10	109	350	241	108	21.4
10X	10/10	112	338	226	104	20.6
100X	10/10	108	324	216	100	21.0
FEMALE						
0	10/10	96	188	92		16.4
0.1X	10/10	97	189	92	101	16.0
1X	10/10	96	189	93	100	16.5
10X	10/10	98	195	97	103	16.8
100X	10/10	96	184	88	98	17.0

[1] Number surviving at 13 weeks/number of animals per dose group.
[2] Mean weight change.
[3] (Dose group mean/control group mean) × 100.
[4] Average of mean individual consumption values for Weeks 1-13 for all animals in the base, neurobehavior/neuropathology, and clinical pathology studies.

TABLE 5 Survival, Weight Gain, and Water Consumption of F344/N Rats in the 26-Week Drinking Water Study of a California Pesticide/Fertilizer Mixture

Dose	Survival[1]	Mean Body Weight (grams)			Final Weight Relative to Controls (%)[3]	Average Water Consumption (g/day)[4]
		Initial	Final	Change[2]		
MALE						
0	10/10	113	410	297		19.5
0.1X	10/10	113	410	297	100	20.0
1X	10/10	107	411	304	100	21.0
10X	10/10	105	415	310	101	20.4
100X	10/10	109	409	300	100	20.9
FEMALE						
0	10/10	96	215	119		15.6
0.1X	10/10	98	222	124	103	15.0
1X	10/10	96	217	121	101	16.1
10X	10/10	95	207	112	96	15.8
100X	10/10	98	216	118	100	16.4

[1] Number surviving at 26 weeks/number of animals per dose group.
[2] Mean weight change.
[3] (Dose group mean/control group mean) × 100.
[4] Average of mean individual consumption values for Weeks 1-26 for all animals in the base, neurobehavior/neuropathology, and clinical pathology studies.

TABLE 6 Survival, Weight Gain, and Water Consumption of F344/N Rats at the 13-Week Interim Evaluation in the 26-Week Drinking Water Study of an Iowa Pesticide/Fertilizer Mixture

Dose	Survival[1]	Mean Body Weight (grams)			Final Weight Relative to Controls (%)[3]	Average Water Consumption (g/day)[4]
		Initial	Final	Change[2]		
MALE						
0	10/10	104	320	216		21.5
0.1X	10/10	98	340	241	106	21.1
1X	10/10	107	336	229	105	22.0
10X	10/10	101	312	211	98	21.3
100X	10/10	104	326	222	102	20.8
FEMALE						
0	10/10	97	185	87		16.7
0.1X	10/10	94	181	86	98	15.1
1X	10/10	91	186	95	101	16.7
10X	10/10	92	185	93	101	16.2
100X	10/10	95	183	88	99	17.2

[1] Number surviving at 13 weeks/number of animals per dose group.
[2] Mean weight change.
[3] (Dose group mean/control group mean) × 100.
[4] Average of mean individual consumption values for Weeks 1-13 for all animals in the base, neurobehavior/neuropathology, and clinical pathology studies.

TABLE 7 Survival, Weight Gain, and Water Consumption of F344/N Rats in the 26-Week Drinking Water Study of an Iowa Pesticide/Fertilizer Mixture

Dose	Survival[1]	Mean Body Weight (grams)			Final Weight Relative to Controls (%)[3]	Average Water Consumption (g/day)[4]
		Initial	Final	Change[2]		
MALE						
0	10/10	104	410	306		20.8
0.1X	10/10	107	418	311	102	20.5
1X	10/10	102	406	304	99	21.2
10X	10/10	107	402	295	98	20.9
100X	10/10	104	406	303	99	20.7
FEMALE						
0	10/10	95	216	121		15.9
0.1X	10/10	95	222	127	103	14.7
1X	10/10	92	218	127	101	16.7
10X	10/10	94	214	120	99	15.8
100X	10/10	93	216	123	100	16.9

[1] Number surviving at 26 weeks/number of animals per dose group.
[2] Mean weight change.
[3] (Dose group mean/control group mean) × 100.
[4] Average of mean individual consumption values for Weeks 1-26 for all animals in the base, neurobehavior/neuropathology, and clinical pathology studies.

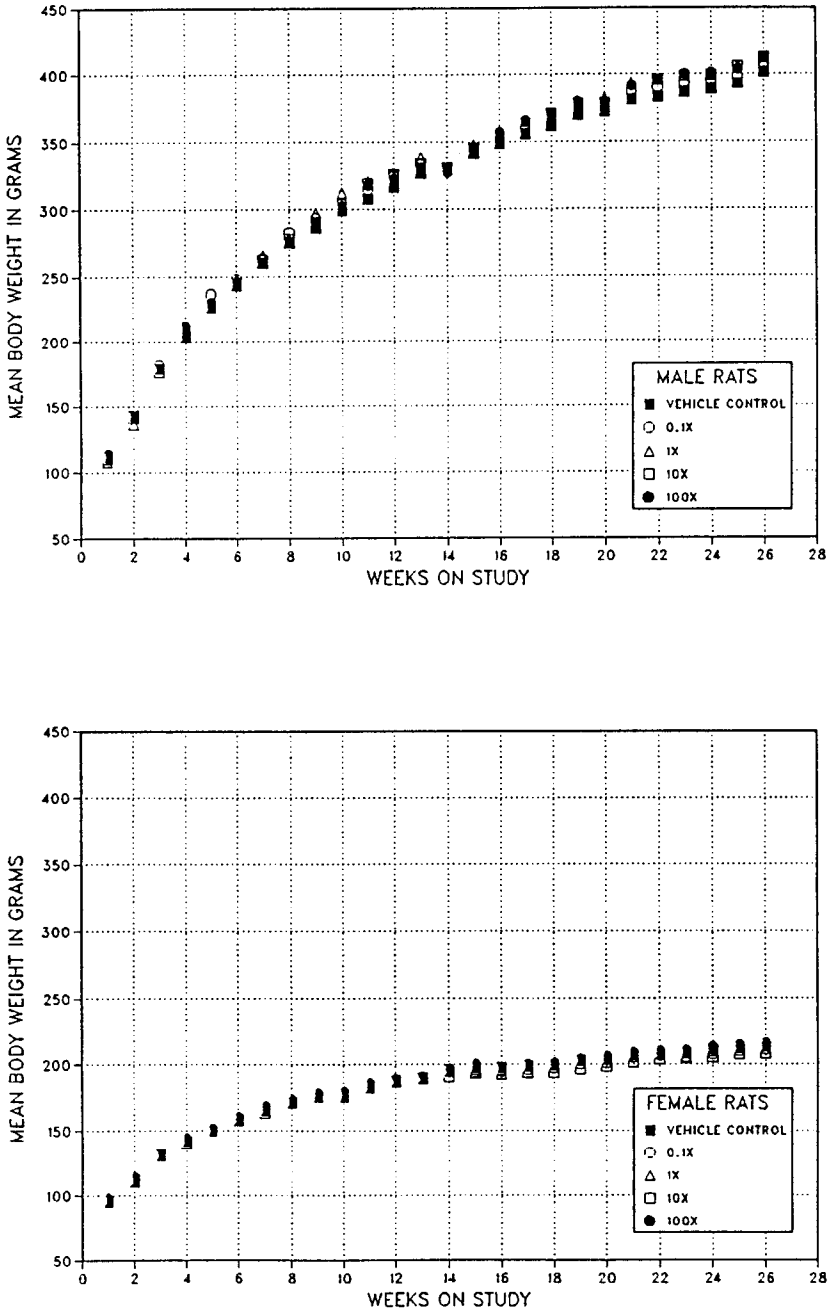

FIGURE 1 Body Weights of F344/N Rats Administered a California Pesticide/Fertilizer Mixture in Drinking Water for 26 Weeks

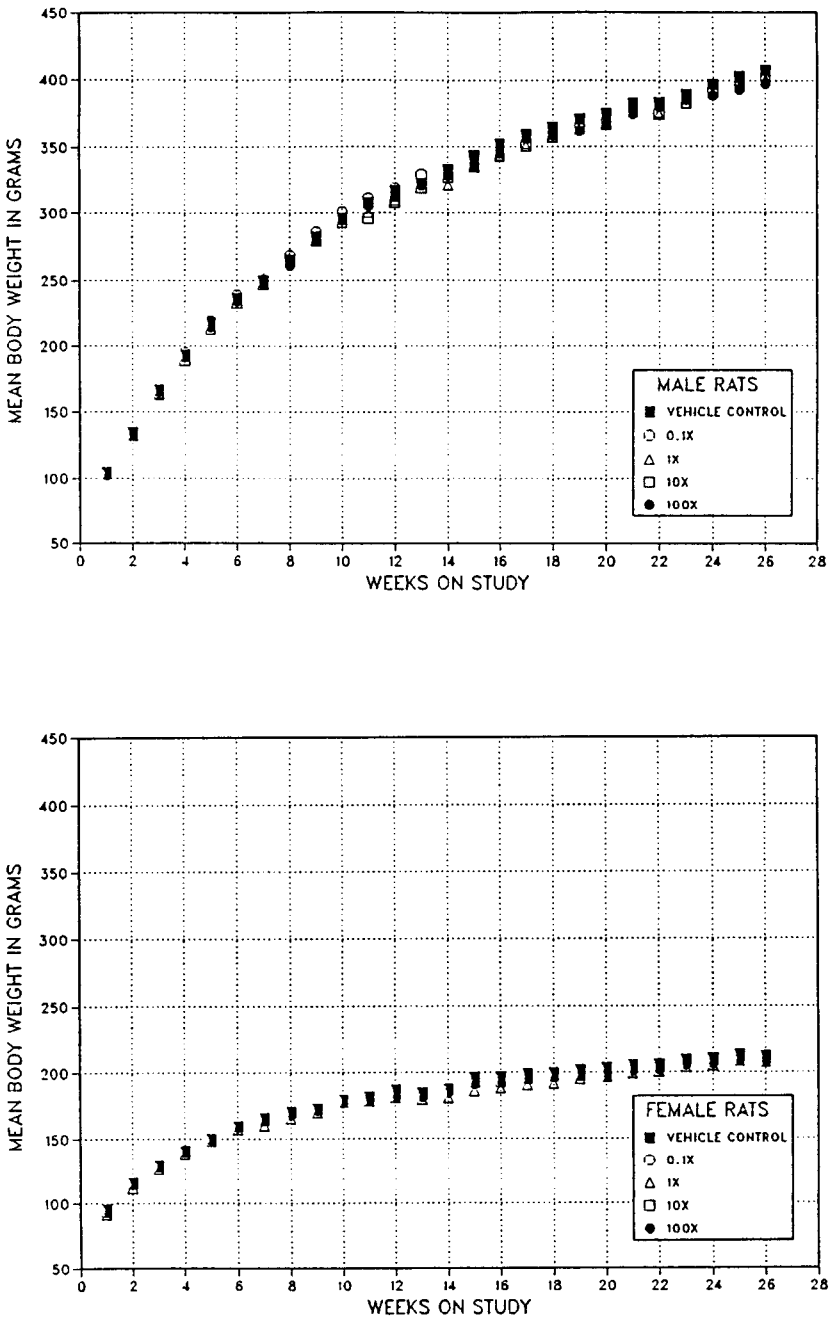

FIGURE 2 Body Weights of F344/N Rats Administered an Iowa Pesticide/Fertilizer Mixture in Drinking Water for 26 Weeks

TABLE 8 Compound Consumption by F344/N Rats in the 26-Week Drinking Water Study of a California Pesticide/Fertilizer Mixture[1]

Compound	Concentration			
	0.1X	1X	10X	100X
MALE				
Aldicarb	20.6	233.1	2237	23,107
Aldicarb sulfone	20.6	233.1	2237	23,107
Aldicarb sulfoxide	20.6	233.1	2237	23,107
Atrazine	3.4	38.9	372.8	3851
1,2-Dibromo-3-chloropropane	0.07	0.8	7.5	77.0
1,2-Dichloropropane	30.8	349.7	3355	34,661
Ethylene dibromide	6.17	69.9	671.0	6932
Simazine	2.1	23.3	223.7	2311
Ammonium nitrate	6.9×10^4	7.8×10^5	7.5×10^6	7.7×10^7
FEMALE				
Aldicarb	25.2	287.3	2889	31,064
Aldicarb sulfone	25.2	287.3	2889	31,064
Aldicarb sulfoxide	25.2	287.3	2889	31,064
Atrazine	4.2	47.9	481.5	5177
1,2-Dibromo-3-chloropropane	0.08	1.0	9.6	103.5
1,2-Dichloropropane	37.8	430.9	4333	46,595
Ethylene dibromide	7.56	86.2	866.6	9319
Simazine	2.5	28.7	288.9	3106
Ammonium nitrate	8.4×10^4	9.6×10^5	9.6×10^6	1.0×10^8

[1] Compound consumption (ng/kg/day) is based on average water consumption data for Weeks 1-26.

TABLE 9 Compound Consumption by F344/N Rats in the 26-Week Drinking Water Study of an Iowa Pesticide/Fertilizer Mixture[1]

Compound	Concentration			
	0.1X	1X	10X	100X
MALE				
Alachlor	6.8	71.1	706.2	6968
Atrazine	3.8	39.5	392.3	3871
Cyanazine	3.0	31.6	313.9	3097
Metolachlor	3.0	31.6	313.9	3097
Metribuzin	4.5	47.4	470.8	4646
Ammonium nitrate	7.5×10^4	7.9×10^5	7.8×10^6	7.7×10^7
FEMALE				
Alachlor	7.9	91.8	830.9	9076
Atrazine	4.4	51.0	461.6	5042
Cyanazine	3.5	40.8	369.3	4034
Metolachlor	3.5	40.8	369.3	4034
Metribuzin	5.3	61.2	553.9	6051
Ammonium nitrate	8.8×10^4	1.0×10^6	9.2×10^6	1.0×10^8

[1] Compound consumption (ng/kg/day) is based on average water consumption data for Weeks 1-26.

California Pesticide/Fertilizer Mixture: Male rats in the 100X group evaluated at 13 weeks had slightly decreased absolute and relative liver weights; the relative liver weights of males in the 0.1X and 1X groups were also marginally decreased at 13 weeks and at 26 weeks (Table C1). There were no differences in the organ weights of exposed and control female rats.

Statistically significant changes in the clinical pathology endpoints occurred at various exposure levels and time points in rats exposed to the California pesticide/fertilizer mixture (Appendix D). In general, these changes were sporadic and minor and did not suggest any treatment-related effects. Increases in hematocrit (HCT), hemoglobin (HGB) concentration, erythrocyte (RBC) count, and serum total protein indicated a mild dehydration in treated male rats at Day 92. Additionally, minimal decreases in HCT, HGB concentration, and RBC count in female rats in the two highest exposure groups at Day 183 may suggest a very mild normocytic normochromic anemia. However, these decreases were only statistically significant at a P-value less than or equal to 0.05; the results were within normal reference values for F344/N rats and would not be considered clinically significant.

No gross lesions or histopathologic findings in rats were attributed to exposure to the California pesticide/fertilizer mixture (Appendix A). There were no significant differences in sperm morphology and vaginal cytology parameters between exposed and control males or females (Appendix E).

Iowa Pesticide/Fertilizer Mixture: The absolute and relative liver weights of males and females evaluated at 26 weeks were generally increased with increasing exposure levels, and the increases were statistically significant for rats in the 1X, 10X, and 100X groups (Table C2). The relative heart and right kidney weights of females in the 10X and 100X groups were also increased.

Statistically significant changes occurred in the clinical pathology endpoints at various exposure levels and time points in rats exposed to the Iowa pesticide/fertilizer mixture (Appendix D). These changes were sporadic and minor and did not suggest any treatment-related effects. Increases in hematocrit (HCT), hemoglobin (HGB) concentration, erythrocyte (RBC) count, and serum total protein indicated a mild dehydration in treated male rats at Day 182.

No gross lesions or histopathologic findings in rats were attributed to exposure to the Iowa pesticide/fertilizer mixture (Appendix A). There were no significant differences in sperm morphology and vaginal cytology parameters between exposed and control males or females (Appendix E).

Teratology Studies in Sprague-Dawley Rats

Teratology studies were conducted in Sprague-Dawley rats administered the California or the Iowa pesticide/fertilizer mixture at concentrations of 0 (vehicle control), 1X, 10X, or 100X concentrations in drinking water on Gestation Days 6 through 20 (Appendix E). Control females received either 512 ppm propylene glycol in drinking water or untreated drinking water. In both the California and the Iowa pesticide/fertilizer mixture studies, there were no significant exposure-related clinical signs or evidence of developmental toxicity. The incidences of fetal/embryo deaths, malformations, and variations did not differ from those in the controls, and fetal weights were normal.

26-Week Drinking Water Studies in B6C3F$_1$ Mice

In the California pesticide/fertilizer mixture study, all mice designated for interim evaluation survived to Week 13 (Table 10); one male in the 100X group of the base study died during Week 3, and one female in the 10X group was accidentally killed during Week 13 (Table 11). In the Iowa mixture study, one control female died during Week 6 (Table 12), and one female in the 100X group died during Week 25 (Table 13). At Week 13, the final mean body weights of all groups of exposed females in the California mixture study were slightly higher than those of the controls, but mean body weights of exposed mice were similar to those of the controls at the end of the study (Table 11 and Figure 3). In the Iowa mixture study, there were no consistent effects on mean body weight gains or on final mean body weights (Tables 12 and 13 and Figure 4). The only clinical sign that may have been associated with exposure to the California mixture was hyperactivity. There were no clinical signs of toxicity in male or female mice exposed to the Iowa mixture.

In both the California and the Iowa mixture studies, water consumption by exposed and control mice was similar (Tables 10 through 13). Average compound consumption for each component in the California mixture is shown in Table 14, and average compound consumption for each component in the Iowa mixture is shown in Table 15.

TABLE 10 Survival, Weight Gain, and Water Consumption of B6C3F$_1$ Mice at the 13-Week Interim Evaluation in the 26-Week Drinking Water Study of a California Pesticide/Fertilizer Mixture

Dose	Survival[1]	Mean Body Weight (grams)			Final Weight Relative to Controls (%)[3]	Average Water Consumption (g/day)[4]
		Initial	Final	Change[2]		
MALE						
0	10/10	23.7	38.2	14.5		5.2
0.1X	10/10	22.9	37.5	14.6	98	5.6
1X	10/10	23.0	38.0	15.0	100	5.3
10X	10/10	22.1	37.8	15.7	99	5.6
100X	10/10	22.7	35.9	13.1	94	5.2
FEMALE						
0	10/10	19.5	27.1	7.7		5.1
0.1X	10/10	19.4	32.0	12.7	118	5.2
1X	10/10	19.0	28.5	9.4	105	5.3
10X	10/10	19.1	29.2	10.1	108	5.5
100X	10/10	19.5	28.5	9.0	105	5.8

[1] Number surviving at 13 weeks/number of animals per dose group.
[2] Mean weight change.
[3] (Dose group mean/control group mean) × 100.
[4] Average of mean individual consumption values for Weeks 1-13 for all animals in the base and neurobehavior/neuropathology studies.

TABLE 11 Survival, Weight Gain, and Water Consumption of B6C3F$_1$ Mice in the 26-Week Drinking Water Study of a California Pesticide/Fertilizer Mixture

Dose	Survival[1]	Mean Body Weight (grams)			Final Weight Relative to Controls (%)[3]	Average Water Consumption (g/day)[4]
		Initial	Final	Change[2]		
MALE						
0	10/10	23.0	47.5	24.5		5.1
0.1X	10/10	22.8	48.4	25.6	102	5.3
1X	10/10	22.7	47.6	24.9	100	5.2
10X	10/10	22.8	48.6	25.8	102	5.5
100X	9/10[5]	23.3	45.7	22.4	96	5.1
FEMALE						
0	10/10	19.4	42.9	23.5		5.0
0.1X	10/10	19.4	46.0	26.6	107	5.1
1X	10/10	19.6	44.1	24.5	103	5.2
10X	9/10[6]	19.4	45.3	25.9	106	5.4
100X	10/10	20.0	43.7	23.7	102	5.5

[1] Number surviving at 26 weeks/number of animals per dose group.
[2] Mean weight change.
[3] (Dose group mean/control group mean) × 100.
[4] Average of mean individual consumption values for Weeks 1-26 for all animals in the base and neurobehavior/neuropathology studies.
[5] Week of death: 3.
[6] Week of death: 13.

TABLE 12 Survival, Weight Gain, and Water Consumption of B6C3F$_1$ Mice at the 13-Week Interim Evaluation in the 26-Week Drinking Water Study of an Iowa Pesticide/Fertilizer Mixture

Dose	Survival[1]	Mean Body Weight (grams)			Final Weight Relative to Controls (%)[3]	Average Water Consumption (g/day)[4]
		Initial	Final	Change[2]		
MALE						
0	10/10	23.1	33.0	9.9		5.6
0.1X	10/10	22.8	34.9	12.0	105	5.3
1X	10/10	23.0	37.0	14.0	112	5.4
10X	10/10	22.6	33.2	10.6	100	5.6
100X	10/10	22.0	33.9	11.9	103	5.2
FEMALE						
0	9/10[5]	20.6	29.7	9.1		5.1
0.1X	10/10	18.4	28.1	9.8	95	5.0
1X	10/10	18.9	27.7	8.8	93	5.4
10X	10/10	18.5	25.8	7.3	87	5.4
100X	10/10	19.1	28.3	9.2	95	4.9

[1] Number surviving at 13 weeks/number of animals per dose group.
[2] Mean weight change.
[3] (Dose group mean/control group mean) × 100.
[4] Average of mean individual consumption values for Weeks 1-13 for all animals from the base and neurobehavior/neuropathology studies.
[5] Week of death: 6.

TABLE 13 Survival, Weight Gain, and Water Consumption of B6C3F$_1$ Mice in the 26-Week Drinking Water Study of an Iowa Pesticide/Fertilizer Mixture

Dose	Survival[1]	Mean Body Weight (grams)			Final Weight Relative to Controls (%)[3]	Average Water Consumption (g/day)[4]
		Initial	Final	Change[2]		
MALE						
0	10/10	22.7	45.4	22.7		5.4
0.1X	10/10	22.7	47.0	24.3	104	5.3
1X	10/10	22.1	45.3	23.2	100	5.3
10X	10/10	23.4	46.9	23.5	103	5.4
100X	10/10	22.7	45.5	22.8	100	5.2
FEMALE						
0	10/10	19.8	40.6	20.8		4.9
0.1X	10/10	18.3	40.7	22.4	100	4.7
1X	10/10	19.2	40.7	21.5	100	5.2
10X	10/10	18.5	39.2	20.7	97	5.2
100X	9/10[5]	18.0	39.3	21.2	97	4.9

[1] Number surviving at 26 weeks/number of animals per dose group.
[2] Mean weight change.
[3] (Dose group mean/control group mean) × 100.
[4] Average of mean individual consumption values for Weeks 1-26 for all animals in the base and neurobehavior/neuropathology studies.
[5] Week of death: 25.

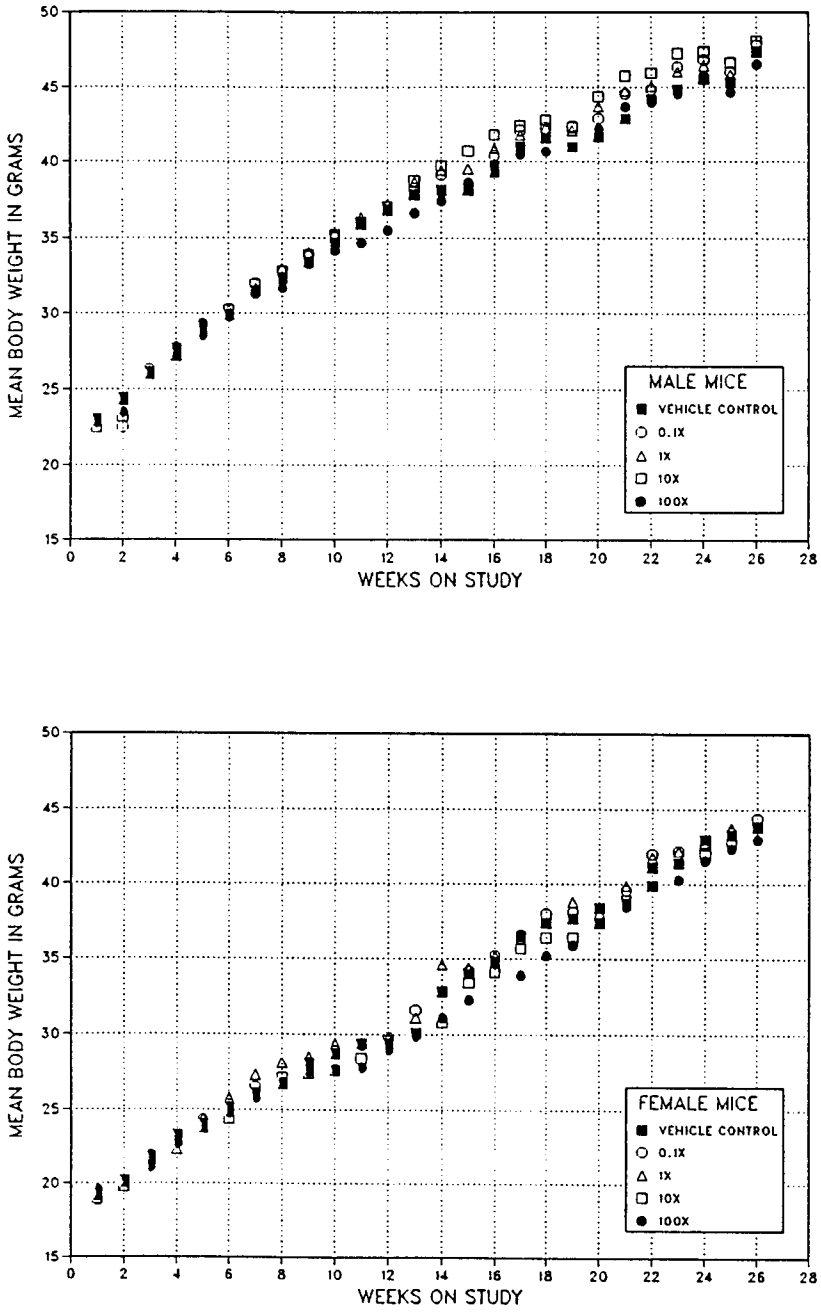

FIGURE 3 Body Weights of B6C3F$_1$ Mice Administered a California Pesticide/Fertilizer Mixture in Drinking Water for 26 Weeks

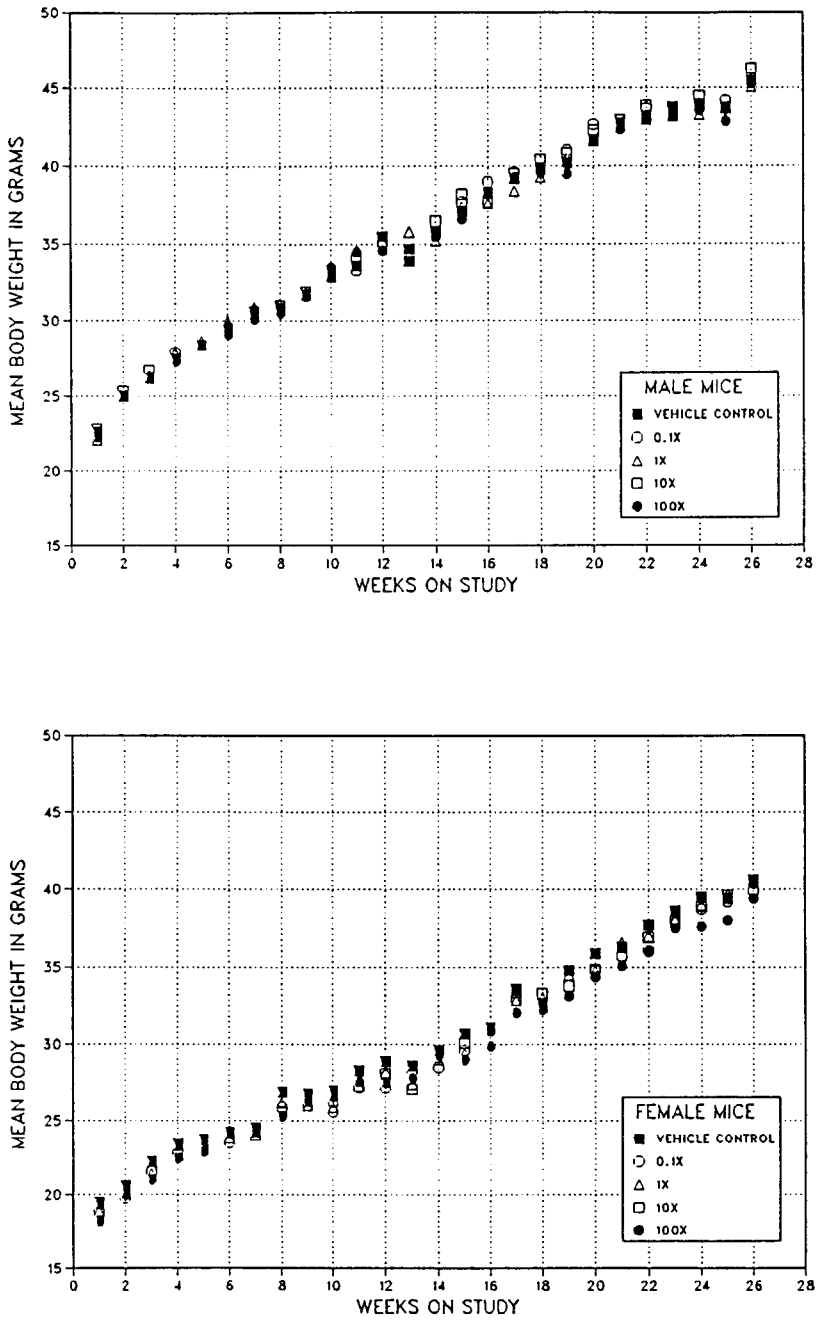

FIGURE 4 **Body Weights of B6C3F$_1$ Mice Administered an Iowa Pesticide/Fertilizer Mixture in Drinking Water for 26 Weeks**

TABLE 14 Compound Consumption by B6C3F$_1$ Mice in the 26-Week Drinking Water Study of a California Pesticide/Fertilizer Mixture[1]

Compound	Concentration			
	0.1X	1X	10X	100X
MALE				
Aldicarb	45.6	450.2	4749	45,024
Aldicarb sulfone	45.6	450.2	4749	45,024
Aldicarb sulfoxide	45.6	450.2	4749	45,024
Atrazine	7.6	75.0	791.5	7504
1,2-Dibromo-3-chloropropane	0.15	1.5	15.8	150.1
1,2-Dichloropropane	68.4	675.2	7123	67,536
Ethylene dibromide	13.7	135.0	1425	13,507
Simazine	4.6	45.0	474.9	4502
Ammonium nitrate	1.5×10^5	1.5×10^6	1.6×10^7	1.5×10^8
FEMALE				
Aldicarb	52.1	522.6	5645	56,805
Aldicarb sulfone	52.1	522.6	5645	56,805
Aldicarb sulfoxide	52.1	522.6	5645	56,805
Atrazine	8.7	87.1	940.8	9468
1,2-Dibromo-3-chloropropane	0.17	1.7	18.8	189.4
1,2-Dichloropropane	78.1	783.9	8467	85,208
Ethylene dibromide	15.6	156.8	1693	17,042
Simazine	5.2	52.3	564.5	5681
Ammonium nitrate	1.7×10^5	1.7×10^6	1.9×10^7	1.9×10^8

[1] Compound consumption (ng/kg/day) is based on average water consumption data for Weeks 1-26.

TABLE 15 Compound Consumption by B6C3F$_1$ Mice in the 26-Week Drinking Water Study of an Iowa Pesticide/Fertilizer Mixture[1]

Compound	Concentration			
	0.1X	1X	10X	100X
MALE				
Alachlor	16.2	175.7	1728	17,248
Atrazine	9.0	97.6	959.8	9582
Cyanazine	7.2	78.1	767.9	7666
Metolachlor	7.2	78.1	767.9	7666
Metribuzin	10.8	117.1	1152	11,499
Ammonium nitrate	1.8×10^5	2.0×10^6	1.9×10^7	1.9×10^8
FEMALE				
Alachlor	15.5	169.3	1676	15,955
Atrazine	8.6	94.1	931.1	8864
Cyanazine	6.9	75.3	744.9	7091
Metolachlor	6.9	75.3	744.9	7091
Metribuzin	10.4	112.9	1117	10,637
Ammonium nitrate	1.7×10^5	1.9×10^6	1.9×10^7	1.8×10^8

[1] Compound consumption (ng/kg/day) is based on average water consumption data for Weeks 1-26.

California Pesticide/Fertilizer Mixture: The absolute liver weight of male mice in the 100X group was significantly decreased at 13 weeks, and the relative right testis weight was significantly increased at 26 weeks (Table C3). The only significant change in female mice exposed to the California mixture was a decrease in relative right kidney weight in the 0.1X group at 13 weeks. These changes were considered within the limits of normal organ weight variation.

Statistically significant changes in the clinical pathology endpoints occurred at various exposure levels and time points in male mice exposed to the California pesticide/fertilizer mixture (Appendix D). In general, these changes were sporadic and minor and did not suggest any treatment-related effects. There were no significant differences in hematology or clinical chemistry parameters between exposed and control female mice.

No gross lesions or histopathologic findings in mice were attributed to exposure to the California pesticide/fertilizer mixture (Appendix B). Left epididymal weights of males exposed to 10X or 100X were significantly less than the epididymal weight of the controls (Appendix E). There were no significant differences in sperm morphology or vaginal cytology parameters between exposed and control mice.

Iowa Pesticide/Fertilizer Mixture: There were no consistent changes in organ weights of exposed male or female mice compared to the controls (Table C4).

Statistically significant changes occurred in a few clinical pathology endpoints at various exposure levels and time points in mice exposed to the Iowa pesticide/fertilizer mixture (Appendix D); however, these changes were sporadic and minor and did not suggest any treatment-related effects.

No gross lesions or histopathologic findings in mice were attributed to exposure to the Iowa pesticide/fertilizer mixture (Appendix B). There were no significant differences in sperm morphology and vaginal cytology parameters between exposed and control males or females (Appendix E).

Continuous Breeding Studies in CD-1 Swiss Mice

Continuous breeding studies were conducted in CD-1 Swiss mice administered the California or the Iowa pesticide/fertilizer mixture at concentrations of 0 (propylene glycol vehicle control), 1X, 10X, or 100X for 7 days prior to breeding and for 98 days while housed in breeding pairs (Appendix F). Second-generation fertility and organ and sperm parameters were also measured. In both the California and the Iowa mixture studies, there were no exposure-related clinical signs of toxicity. Reproductive performance of the F_0 and F_1 mice, reproductive organ weights, sperm parameters, and histologic appearance of the testis/epididymis of the F_1 male mice, and F_1 female estrous cyclicity and ovarian weights were normal.

Genetic Toxicity

Peripheral Blood Micronucleus Study: Peripheral blood smears obtained from the female mice evaluated at the 13-week interim of the toxicity studies were analyzed for frequency of micronucleated erythrocytes. Mice exposed to the Iowa pesticide/fertilizer mixture showed significantly increased incidences of micronucleated normochromatic erythrocytes at the two highest concentrations tested (10X and 100X), but the increased incidences were well within the normal historical control range for this assay and were lower than the concurrent control incidence in the California mixture assay. No increase in the frequency of micronucleated erythrocytes was observed in the peripheral blood of female mice treated

with varying concentrations of the California mixture (Table G1). The positive response noted for the Iowa mixture must be qualified because no confirmatory test was performed.

Splenocyte Studies: Splenocytes obtained from the male rats and female mice treated with the Iowa and the California pesticide mixtures were analyzed for frequencies of micronuclei. No increase in micronucleated splenocytes was observed in rats or mice (Table G2). Sister chromatid exchanges were marginally elevated in male rats treated with the California mixture at all three dose levels tested, although no dose-related response was apparent. In female mice treated with the California mixture, sister chromatid exchanges were significantly increased only at the highest concentration (100X) tested, and the increased incidence was lower than the concurrent control incidence for the Iowa mixture assay (Table G3). No increases in sister chromatid exchanges were observed in female mice treated with the Iowa mixture. Because of the small magnitude and variability of the responses, none of the genetic toxicity findings were considered biologically important.

Neurobehavioral and Neuropathologic Effects

The results of four groups of neurobehavioral tests, including a functional observational battery of assessments of home cage behavior, handling behavior, physiologic measures, open field behavior, reflex responses, and forelimb and hindlimb grip strength; motor activity evaluations; thermal sensitivity evaluations; and startle responsiveness evaluations, did not reveal any changes that could clearly be related to exposure to the pesticide/fertilizer mixtures. The data for individual animals are on file at NIEHS. No neuropathologic effects from exposure to the California or the Iowa pesticide/fertilizer mixture were observed in rats or mice.

DISCUSSION

Both mixtures of agricultural chemicals used in these studies are termed pesticide/fertilizer mixtures, but the California and Iowa mixtures are actually quite different in their chemical makeup and in the major uses of the individual chemicals. The Iowa mixture contains five herbicides. The herbicides for which a mechanism has been established are thought to act in plants as photosynthesis inhibitors or protein synthesis inhibitors (Beste, 1983). The California mixture contains aldicarb, a carbamate insecticide; 1,2-dibromo-3-chloropropane, a fumigant and nematocide; 1,2-dichloropropane, also a fumigant; ethylene dibromide, a fumigant, insecticide, and nematocide; and the triazine herbicides atrazine and simazine.

Although many of the individual components of the pesticide/fertilizer mixtures are clearly toxic to mammals and adverse health effects of these chemicals have been widely covered in the literature, no adverse effects were noted in any of the endpoints evaluated in these studies. A number of the endpoints are known targets for the toxic effects of some of the individual chemicals at higher concentrations. For example, aldicarb inhibits cholinesterase activity, but no inhibition of serum cholinesterase activity occurred in these studies in which the maximum aldicarb concentrations were approximately 1 ppm. 1,2-Dibromo-3-chloropropane is known to cause sterility in males exposed occupationally and causes testicular damage in a number of species (Creasy and Foster, 1991; Thomas, 1991), but no effects on fertility were seen in the continuous breeding studies with CD-1 Swiss mice exposed to either the California or the Iowa mixture. The fertilizer component of the mixtures, ammonium nitrate, was the major contaminant on a weight basis and was present at concentrations from 1 ppm to as high as 1000 ppm. In unpublished NTP studies, significant increases in methemoglobin concentrations occurred in rats given drinking water containing 5000 ppm sodium nitrite, but not in rats given lower concentrations, for 13 weeks. Thus, even if all of the nitrate were converted to nitrite *in vivo*, it would still not be expected to cause a measurable increase in methemoglobin in these animals. However, rodents have the capacity to reduce methemoglobin to hemoglobin more rapidly than do humans (Smith, 1991); thus rodent studies may underestimate the risk associated with the consumption of nitrate-contaminated groundwater, especially for newborns (Klaassen and Rozman, 1991).

In these studies, the only effect that was possibly related to chemical administration was the small increase in liver weights in male and female rats receiving the Iowa mixture. This effect was dose related but was not associated with a discernable histopathologic change. The cause of this minor weight increase is not known, and it is doubtful that this change is of any biologic significance.

While the results of these studies do not suggest the potential for overt toxicity from the consumption of pesticide- and fertilizer-contaminated groundwater at concentrations up to 100-fold higher than those currently occurring in agricultural areas, a few precautionary notes may be useful. These studies were performed on healthy young adult animals over a relatively short portion of their 2- to 3-year life span. Human consumption of contaminated groundwater can occur over a lifetime, and the very young and the elderly may be at increased risk. The endpoints evaluated in these studies did not include potential immunosuppression or myelotoxicity, measures that were found to be more sensitive indicators of toxic effects than more traditional histopathologic assessments in studies of a chemical mixture of 25 groundwater contaminants (NTP, 1993). The International Agency for Research on Cancer (IARC) has determined that there is sufficient evidence from animal studies to consider 1,2-dibromo-3-chloropropane and ethylene dibromide carcinogens (IARC, 1987), and there is limited evidence for the carcinogenicity of 1,2-dichloropropane (IARC, 1987) and atrazine (IARC, 1991). The current 26-week studies are not considered adequate for assessment of potential carcinogenicity of the groundwater contaminant mixtures because of insufficient animal numbers and exposure duration. Finally, it should be remembered that these are but two of a vast number of combinations of chemicals contributing to groundwater contamination, and while studies of a few mixtures may provide some sense of the risk posed by groundwater contaminants, this is perhaps too limited a sample on which to base broad conclusions concerning risks to human health.

In summary, studies of potential toxicity associated with the consumption of mixtures of pesticides and a fertilizer representative of groundwater contamination in agricultural areas of Iowa and California failed to demonstrate any significant adverse effects in rats or mice receiving the mixtures in drinking water at concentrations as high as 100 times the median concentrations of the individual components determined by groundwater surveys.

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APPENDIX A

Summary of Nonneoplastic Lesions in Rats

TABLE A1 Summary of the Incidence of Nonneoplastic Lesions in Male F344/N Rats in the 26-Week Drinking Water Study of a California Pesticide/Fertilizer Mixture[1]

	Vehicle Control	0.1X	1X	10X	100X
DISPOSITION SUMMARY					
Animals initially in study	20	20	20	20	20
13-Week interim evaluation	10	10	10	10	10
Survivors					
Terminal sacrifice	10	10	10	10	10
Animals examined microscopically	20	20	20	20	20
13-WEEK INTERIM EVALUATION					
Alimentary System					
Intestine large, rectum	(10)	(10)	(10)	(10)	(10)
Parasite metazoan	1 (10%)	2 (20%)	1 (10%)	2 (20%)	
Liver	(10)	(10)	(10)	(10)	(10)
Fibrosis, focal		1 (10%)		1 (10%)	
Hepatodiaphragmatic nodule		1 (10%)		1 (10%)	1 (10%)
Mesentery	(1)				
Fat, necrosis	1 (100%)				
Pancreas	(10)	(10)	(10)	(10)	(10)
Atrophy, focal	2 (20%)				
Cardiovascular System					
None					
Endocrine System					
Adrenal cortex	(10)	(10)	(10)	(10)	(10)
Accessory adrenal cortical nodule		1 (10%)			
Pituitary gland	(10)	(10)	(10)	(10)	(10)
Cyst					1 (10%)
Pars distalis, focal cellular change				1 (10%)	
Thyroid gland	(10)	(10)	(10)	(10)	(10)
Ultimobranchial cyst	1 (10%)			2 (20%)	1 (10%)
General Body System					
None					
Genital System					
Ductus deferens	(1)				
Inflammation, chronic	1 (100%)				
Preputial gland	(10)	(10)	(10)	(10)	(10)
Inflammation, chronic				2 (20%)	1 (10%)
Prostate	(10)	(10)	(10)	(10)	(10)
Inflammation, suppurative	1 (10%)				3 (30%)

TABLE A1 Summary of the Incidence of Nonneoplastic Lesions in Male F344/N Rats in the 26-Week Drinking Water Study of a California Pesticide/Fertilizer Mixture (continued)

	Vehicle Control	0.1X	1X	10X	100X
13-WEEK INTERIM EVALUATION (continued)					
Hematopoietic System					
Lymph node, mandibular	(10)	(10)	(10)	(10)	(9)
Hyperplasia					1 (11%)
Thymus	(10)	(10)	(10)	(10)	(10)
Hemorrhage	2 (20%)				1 (10%)
Integumentary System					
None					
Musculoskeletal System					
None					
Nervous System					
None					
Respiratory System					
None					
Special Senses System					
None					
Urinary System					
Kidney	(10)	(10)	(10)	(10)	(10)
Renal tubule, dilatation, focal		1 (10%)			
26-WEEK STUDY					
Alimentary System					
Intestine large, colon	(10)	(10)	(10)	(10)	(10)
Parasite metazoan		1 (10%)			
Intestine large, rectum	(10)	(10)	(10)	(10)	(10)
Parasite metazoan		2 (20%)			2 (20%)
Liver	(10)	(10)	(10)	(10)	(10)
Hepatodiaphragmatic nodule	2 (20%)				1 (10%)
Mesentery			(1)		(2)
Inflammation, chronic, focal					1 (50%)
Fat, necrosis			1 (100%)		1 (50%)
Pancreas	(10)	(10)	(10)	(10)	(10)
Atrophy, focal	1 (10%)				

TABLE A1 Summary of the Incidence of Nonneoplastic Lesions in Male F344/N Rats in the 26-Week Drinking Water Study of a California Pesticide/Fertilizer Mixture (continued)

	Vehicle Control	0.1X	1X	10X	100X
26-WEEK STUDY (continued)					
Cardiovascular System					
Heart	(10)	(10)	(10)	(10)	(10)
Artery, inflammation, chronic					2 (20%)
Endocrine System					
Adrenal cortex	(10)	(10)	(10)	(10)	(10)
Accessory adrenal cortical nodule			1 (10%)		
Pituitary gland	(10)	(9)	(10)	(10)	(10)
Cyst	1 (10%)				
Pars distalis, focal cellular change	1 (10%)				
Thyroid gland	(10)	(10)	(10)	(10)	(10)
Ultimobranchial cyst	2 (20%)				1 (10%)
General Body System					
None					
Genital System					
Preputial gland	(10)	(10)	(10)	(10)	(10)
Inflammation, chronic	2 (20%)				1 (10%)
Prostate	(10)	(10)	(10)	(10)	(10)
Inflammation, suppurative		1 (10%)	3 (30%)		
Hematopoietic System					
Lymph node					(1)
Mediastinal, hemorrhage					1 (100%)
Lymph node, mesenteric	(10)	(10)	(10)	(10)	(10)
Hyperplasia, lymphoid	1 (10%)				
Integumentary System					
None					
Musculoskeletal System					
None					
Nervous System					
None					

TABLE A1 Summary of the Incidence of Nonneoplastic Lesions in Male F344/N Rats in the 26-Week Drinking Water Study of a California Pesticide/Fertilizer Mixture (continued)

	Vehicle Control	0.1X	1X	10X	100X
26-WEEK STUDY (continued)					
Respiratory System					
Lung	(10)	(10)	(10)	(10)	(10)
Hemorrhage, focal					1 (10%)
Alveolar epithelium, hyperplasia					1 (10%)
Nose	(10)	(10)	(10)	(10)	(10)
Inflammation, suppurative			1 (10%)		
Special Senses System					
None					
Urinary System					
Urinary bladder	(10)	(10)	(10)	(10)	(10)
Calculus gross observation					1 (10%)

[1] Number of animals examined microscopically at site and number of animals with lesion.

TABLE A2 Summary of the Incidence of Nonneoplastic Lesions in Female F344/N Rats in the 26-Week Drinking Water Study of a California Pesticide/Fertilizer Mixture[1]

	Vehicle Control	0.1X	1X	10X	100X
DISPOSITION SUMMARY					
Animals initially in study	20	20	20	20	20
13-Week interim evaluation	10	10	10	10	10
Survivors					
Terminal sacrifice	10	10	10	10	10
Animals examined microscopically	20	20	20	20	20
13-WEEK INTERIM EVALUATION					
Alimentary System					
Intestine large, colon	(10)	(10)	(10)	(10)	(10)
Parasite metazoan				1 (10%)	
Intestine large, rectum	(10)	(10)	(9)	(10)	(10)
Parasite metazoan	1 (10%)			1 (10%)	2 (20%)
Liver	(10)	(10)	(10)	(10)	(10)
Hepatodiaphragmatic nodule				1 (10%)	
Stomach, forestomach	(10)	(10)	(10)	(10)	(10)
Mucosa, hyperplasia			1 (10%)		
Cardiovascular System					
None					
Endocrine System					
Pituitary gland	(9)	(10)	(10)	(10)	(10)
Cyst			1 (10%)		1 (10%)
Pars distalis, hyperplasia, focal	1 (11%)				
Thyroid gland	(10)	(10)	(10)	(10)	(10)
Ultimobranchial cyst	2 (20%)			1 (10%)	1 (10%)
General Body System					
None					
Genital System					
Ovary	(10)	(10)	(10)	(10)	(10)
Cyst	1 (10%)				
Uterus	(10)	(10)	(10)	(10)	(10)
Hydrometra	4 (40%)	1 (10%)	1 (10%)	4 (40%)	3 (30%)
Inflammation, suppurative	1 (10%)				
Endometrium, hyperplasia, cystic				1 (10%)	1 (10%)
Hematopoietic System					
None					

TABLE A2 Summary of the Incidence of Nonneoplastic Lesions in Female F344/N Rats in the 26-Week Drinking Water Study of a California Pesticide/Fertilizer Mixture (continued)

	Vehicle Control	0.1X	1X	10X	100X
13-WEEK INTERIM EVALUATION (continued)					
Integumentary System					
None					
Musculoskeletal System					
None					
Nervous System					
None					
Respiratory System					
None					
Special Senses System					
None					
Urinary System					
None					
26-WEEK STUDY					
Alimentary System					
Intestine large, rectum	(10)	(10)	(10)	(10)	(10)
Parasite metazoan				1 (10%)	1 (10%)
Liver	(10)	(10)	(10)	(10)	(10)
Hepatodiaphragmatic nodule	1 (10%)		1 (10%)		
Mesentery		(2)		(1)	(1)
Accessory spleen					1 (100%)
Fat, necrosis		2 (100%)		1 (100%)	
Cardiovascular System					
None					
Endocrine System					
Adrenal cortex	(10)	(10)	(10)	(10)	(10)
Accessory adrenal cortical nodule					1 (10%)
Pituitary gland	(10)	(10)	(10)	(10)	(10)
Cyst		1 (10%)			
Thyroid gland	(10)	(10)	(10)	(10)	(10)
Ultimobranchial cyst	2 (20%)		2 (20%)	2 (20%)	

TABLE A2 Summary of the Incidence of Nonneoplastic Lesions in Female F344/N Rats in the 26-Week Drinking Water Study of a California Pesticide/Fertilizer Mixture (continued)

	Vehicle Control	0.1X	1X	10X	100X
26-WEEK STUDY (continued)					
General Body System					
None					
Genital System					
Ovary	(10)	(10)	(10)	(10)	(10)
Cyst					1 (10%)
Uterus	(10)	(10)	(10)	(10)	(10)
Hydrometra		2 (20%)	1 (10%)	1 (10%)	2 (20%)
Hematopoietic System					
None					
Integumentary System					
None					
Musculoskeletal System					
None					
Nervous System					
None					
Respiratory System					
None					
Special Senses System					
None					
Urinary System					
None					

[1] Number of animals examined microscopically at site and number of animals with lesion.

TABLE A3 Summary of the Incidence of Nonneoplastic Lesions in Male F344/N Rats in the 26-Week Drinking Water Study of an Iowa Pesticide/Fertilizer Mixture[1]

	Vehicle Control	0.1X	1X	10X	100X
DISPOSITION SUMMARY					
Animals initially in study	20	20	20	20	20
13-Week interim evaluation	10	10	10	10	10
Survivors					
Terminal sacrifice	10	10	10	10	10
Animals examined microscopically	20	20	20	20	20
13-WEEK INTERIM EVALUATION					
Alimentary System					
Intestine large, rectum	(10)	(10)	(10)	(10)	(10)
Parasite metazoan	1 (10%)		2 (20%)	1 (10%)	
Liver	(10)	(10)	(10)	(10)	(10)
Hepatodiaphragmatic nodule				2 (20%)	1 (10%)
Pancreas	(10)	(10)	(10)	(10)	(10)
Atrophy, focal	1 (10%)				1 (10%)
Cardiovascular System					
Heart	(10)	(10)	(10)	(10)	(10)
Artery, inflammation, chronic	1 (10%)				1 (10%)
Endocrine System					
Adrenal cortex	(10)	(10)	(10)	(10)	(10)
Accessory adrenal cortical nodule		1 (10%)			
Pituitary gland	(10)	(10)	(10)	(10)	(9)
Angiectasis				1 (10%)	
Cyst	2 (20%)				
Thyroid gland	(10)	(10)	(10)	(10)	(10)
Ultimobranchial cyst		1 (10%)	1 (10%)	3 (30%)	
Follicular cell, hyperplasia		1 (10%)			
General Body System					
None					
Genital System					
Preputial gland	(10)	(10)	(10)	(10)	(10)
Inflammation, chronic	2 (20%)	2 (20%)	1 (10%)	1 (10%)	3 (30%)
Prostate	(10)	(10)	(10)	(10)	(10)
Inflammation, suppurative	1 (10%)	2 (20%)	2 (20%)	2 (20%)	1 (10%)

TABLE A3 Summary of the Incidence of Nonneoplastic Lesions in Male F344/N Rats in the 26-Week Drinking Water Study of an Iowa Pesticide/Fertilizer Mixture (continued)

	Vehicle Control	0.1X	1X	10X	100X
13-WEEK INTERIM EVALUATION (continued)					
Hematopoietic System					
Lymph node			(1)		
Mediastinal, hemorrhage			1 (100%)		
Lymph node, mandibular	(10)	(10)	(10)	(10)	(10)
Hyperplasia				1 (10%)	
Thymus	(10)	(10)	(10)	(10)	(10)
Hemorrhage		1 (10%)			
Integumentary System					
None					
Musculoskeletal System					
None					
Nervous System					
None					
Respiratory System					
None					
Special Senses System					
None					
Urinary System					
None					
26-WEEK STUDY					
Alimentary System					
Intestine large, rectum	(10)	(10)	(10)	(10)	(10)
Parasite metazoan	2 (20%)	1 (10%)	1 (10%)		
Liver	(10)	(10)	(10)	(10)	(10)
Hepatodiaphragmatic nodule			1 (10%)		1 (10%)
Mesentery			(1)		
Fat, necrosis			1 (100%)		
Pancreas	(10)	(10)	(10)	(10)	(10)
Atrophy, focal	1 (10%)	2 (20%)			2 (20%)

TABLE A3 Summary of the Incidence of Nonneoplastic Lesions in Male F344/N Rats in the 26-Week Drinking Water Study of an Iowa Pesticide/Fertilizer Mixture (continued)

	Vehicle Control	0.1X	1X	10X	100X
26-WEEK STUDY (continued)					
Cardiovascular System					
Heart	(10)	(10)	(10)	(10)	(10)
Artery, inflammation, chronic					1 (10%)
Endocrine System					
Pituitary gland	(10)	(10)	(10)	(10)	(9)
Cyst	2 (20%)	1 (10%)			
Pars distalis, hyperplasia, focal					2 (22%)
Thyroid gland	(10)	(10)	(10)	(10)	(10)
Ultimobranchial cyst		1 (10%)			1 (10%)
General Body System					
None					
Genital System					
Preputial gland	(10)	(10)	(10)	(10)	(10)
Inflammation, chronic	1 (10%)	1 (10%)			
Prostate	(10)	(10)	(10)	(10)	(10)
Inflammation, suppurative	3 (30%)	3 (30%)	3 (30%)	4 (40%)	2 (20%)
Hematopoietic System					
None					
Integumentary System					
None					
Musculoskeletal System					
None					
Nervous System					
None					
Respiratory System					
Nose	(10)	(10)	(10)	(10)	(10)
Inflammation, suppurative					1 (10%)
Special Senses System					
None					

TABLE A3 Summary of the Incidence of Nonneoplastic Lesions in Male F344/N Rats in the 26-Week Drinking Water Study of an Iowa Pesticide/Fertilizer Mixture (continued)

	Vehicle Control	0.1X	1X	10X	100X
26-WEEK STUDY (continued)					
Urinary System					
None					

[1] Number of animals examined microscopically at site and number of animals with lesion.

TABLE A4 Summary of the Incidence of Nonneoplastic Lesions in Female F344/N Rats in the 26-Week Drinking Water Study of an Iowa Pesticide/Fertilizer Mixture[1]

	Vehicle Control	0.1X	1X	10X	100X
DISPOSITION SUMMARY					
Animals initially in study	20	20	20	20	20
13-Week interim evaluation	10	10	10	10	10
Survivors					
Terminal sacrifice	10	10	10	10	10
Animals examined microscopically	20	20	20	20	20
13-WEEK INTERIM EVALUATION					
Alimentary System					
Intestine large, colon	(10)	(10)	(10)	(10)	(10)
Parasite metazoan			1 (10%)		
Intestine large, rectum	(10)	(10)	(9)	(10)	(10)
Parasite metazoan			2 (22%)		1 (10%)
Liver	(10)	(10)	(10)	(10)	(10)
Fibrosis, focal				1 (10%)	
Hepatodiaphragmatic nodule		1 (10%)	1 (10%)	1 (10%)	1 (10%)
Necrosis, focal					1 (10%)
Cardiovascular System					
None					
Endocrine System					
Adrenal cortex	(10)	(10)	(10)	(10)	(10)
Accessory adrenal cortical nodule	2 (20%)				
Angiectasis					1 (10%)
Adrenal medulla	(10)	(10)	(10)	(10)	(10)
Angiectasis					1 (10%)
Thyroid gland	(10)	(10)	(10)	(10)	(10)
Ultimobranchial cyst	3 (30%)	1 (10%)	1 (10%)		
General Body System					
None					
Genital System					
Ovary	(10)	(10)	(10)	(10)	(10)
Cyst	1 (10%)				
Uterus	(10)	(10)	(10)	(10)	(10)
Hydrometra	1 (10%)	3 (30%)	4 (40%)	1 (10%)	4 (40%)

TABLE A4 Summary of the Incidence of Nonneoplastic Lesions in Female F344/N Rats in the 26-Week Drinking Water Study of an Iowa Pesticide/Fertilizer Mixture (continued)

	Vehicle Control	0.1X	1X	10X	100X
13-WEEK INTERIM EVALUATION (continued)					
Hematopoietic System					
Lymph node, mandibular	(10)	(10)	(10)	(10)	(10)
Hemorrhage					1 (10%)
Spleen	(10)	(10)	(10)	(10)	(10)
Congestion		1 (10%)			
Thymus	(10)	(9)	(10)	(10)	(10)
Hemorrhage	1 (10%)	1 (11%)			
Integumentary System					
Skin	(10)	(10)	(10)	(10)	(10)
Nipple, cyst epithelial inclusion		1 (10%)			
Musculoskeletal System					
None					
Nervous System					
None					
Respiratory System					
None					
Special Senses System					
None					
Urinary System					
Kidney	(10)	(10)	(10)	(10)	(10)
Infiltration cellular, focal, lymphocyte					1 (10%)
26-WEEK STUDY					
Alimentary System					
Intestine large, colon	(10)	(10)	(10)	(10)	(10)
Parasite metazoan				1 (10%)	
Intestine large, rectum	(10)	(10)	(10)	(10)	(10)
Parasite metazoan	2 (20%)	2 (20%)	1 (10%)	2 (20%)	
Intestine small, ileum	(10)	(10)	(10)	(10)	(10)
Lymphoid tissue, inflammation, chronic					1 (10%)

TABLE A4 Summary of the Incidence of Nonneoplastic Lesions in Female F344/N Rats in the 26-Week Drinking Water Study of an Iowa Pesticide/Fertilizer Mixture (continued)

	Vehicle Control	0.1X	1X	10X	100X
26-WEEK STUDY (continued)					
Alimentary System (continued)					
Liver	(10)	(10)	(10)	(10)	(10)
Hepatodiaphragmatic nodule	1 (10%)	2 (20%)		2 (20%)	2 (20%)
Serosa, inflammation, chronic		1 (10%)			
Mesentery				(1)	
Fat, necrosis				1 (100%)	
Cardiovascular System					
None					
Endocrine System					
Adrenal cortex	(10)	(10)	(10)	(10)	(10)
Angiectasis, focal					1 (10%)
Hyperplasia, focal					1 (10%)
Pituitary gland	(10)	(10)	(10)	(10)	(10)
Cyst		1 (10%)	1 (10%)	2 (20%)	
Pars distalis, hyperplasia, focal		1 (10%)			
Thyroid gland	(10)	(10)	(10)	(10)	(10)
Ultimobranchial cyst		1 (10%)	1 (10%)		
General Body System					
None					
Genital System					
Ovary	(10)	(10)	(10)	(10)	(10)
Cyst					1 (10%)
Uterus	(10)	(10)	(10)	(10)	(10)
Hydrometra	3 (30%)	1 (10%)	2 (20%)	3 (30%)	1 (10%)
Hematopoietic System					
Spleen	(10)	(10)	(10)	(10)	(10)
Fibrosis, focal					1 (10%)
Integumentary System					
None					
Musculoskeletal System					
None					

TABLE A4 Summary of the Incidence of Nonneoplastic Lesions in Female F344/N Rats in the 26-Week Drinking Water Study of an Iowa Pesticide/Fertilizer Mixture (continued)

	Vehicle Control	0.1X	1X	10X	100X
26-WEEK STUDY (continued)					
Nervous System					
None					
Respiratory System					
None					
Special Senses System					
None					
Urinary System					
None					

[1] Number of animals examined microscopically at site and number of animals with lesion.

APPENDIX B

Summary of Nonneoplastic Lesions in Mice

TABLE B1 Summary of the Incidence of Nonneoplastic Lesions in Male B6C3F$_1$ Mice in the 26-Week Drinking Water Study of a California Pesticide/Fertilizer Mixture[1]

	Vehicle Control	0.1X	1X	10X	100X
DISPOSITION SUMMARY					
Animals initially in study	20	20	20	20	20
13-Week interim evaluation	10	10	10	10	10
Early deaths					
Natural deaths					1
Survivors					
Terminal sacrifice	10	10	10	10	9
Animals examined microscopically	20	20	20	20	20
13-WEEK INTERIM EVALUATION					
Alimentary System					
Liver	(10)	(10)	(10)	(10)	(10)
Lobules, necrosis		1 (10%)			
Pancreas	(10)	(10)	(10)	(10)	(10)
Cyst		1 (10%)			
Necrosis				1 (10%)	
Cardiovascular System					
None					
Endocrine System					
Adrenal cortex	(10)	(10)	(10)	(10)	(10)
Accessory adrenal cortical nodule		2 (20%)	1 (10%)	2 (20%)	1 (10%)
Parathyroid gland	(9)	(10)	(9)	(9)	(10)
Cyst	1 (11%)	1 (10%)			
General Body System					
None					
Genital System					
None					
Hematopoietic System					
Spleen	(10)	(10)	(10)	(10)	(10)
Pigmentation, hemosiderin			1 (10%)		
Integumentary System					
None					

TABLE B1 Summary of the Incidence of Nonneoplastic Lesions in Male B6C3F$_1$ Mice in the 26-Week Drinking Water Study of a California Pesticide/Fertilizer Mixture (continued)

	Vehicle Control	0.1X	1X	10X	100X
13-WEEK INTERIM EVALUATION (continued)					
Musculoskeletal System					
None					
Nervous System					
None					
Respiratory System					
Lung	(10)	(10)	(10)	(10)	(10)
Hemorrhage				1 (10%)	
Special Senses System					
None					
Urinary System					
Kidney	(10)	(10)	(10)	(10)	(10)
Casts protein		1 (10%)			
Renal tubule, regeneration		1 (10%)	1 (10%)		
26-WEEK STUDY					
Alimentary System					
Stomach, glandular	(10)	(10)	(10)	(10)	(10)
Erosion			1 (10%)	1 (10%)	
Cardiovascular System					
None					
Endocrine System					
Adrenal cortex	(10)	(10)	(10)	(10)	(10)
Accessory adrenal cortical nodule	2 (20%)	1 (10%)			1 (10%)
Hypertrophy, focal	1 (10%)				
Islets, pancreatic	(10)	(10)	(10)	(10)	(10)
Hyperplasia		3 (30%)	1 (10%)	3 (30%)	
Parathyroid gland	(10)	(10)	(8)	(10)	(10)
Cyst					1 (10%)
Thyroid gland	(10)	(10)	(10)	(10)	(10)
Ectopic thymus			1 (10%)		1 (10%)
Follicle, cyst				1 (10%)	

TABLE B1 Summary of the Incidence of Nonneoplastic Lesions in Male B6C3F$_1$ Mice in the 26-Week Drinking Water Study of a California Pesticide/Fertilizer Mixture (continued)

	Vehicle Control	0.1X	1X	10X	100X
26-WEEK STUDY (continued)					
General Body System					
None					
Genital System					
Preputial gland	(10)	(10)	(10)	(10)	(10)
Inflammation, chronic		1 (10%)			
Seminal vesicle	(10)	(10)	(10)	(10)	(10)
Dilatation	1 (10%)				
Hematopoietic System					
Spleen	(10)	(10)	(10)	(10)	(10)
Hematopoietic cell proliferation	1 (10%)				
Integumentary System					
None					
Musculoskeletal System					
None					
Nervous System					
None					
Respiratory System					
Lung	(10)	(10)	(10)	(10)	(10)
Alveolar epithelium, hyperplasia			1 (10%)		
Special Senses System					
None					
Urinary System					
None					

[1] Number of animals examined microscopically at site and number of animals with lesion.

TABLE B2 Summary of the Incidence of Nonneoplastic Lesions in Female B6C3F$_1$ Mice in the 26-Week Drinking Water Study of a California Pesticide/Fertilizer Mixture[1]

	Vehicle Control	0.1X	1X	10X	100X
DISPOSITION SUMMARY					
Animals initially in study	20	20	20	20	20
13-Week interim evaluation	10	10	10	10	10
Early deaths					
Accidently killed				1	
Survivors					
Terminal sacrifice	10	10	10	9	10
Animals examined microscopically	20	20	20	20	20
13-WEEK INTERIM EVALUATION					
Alimentary System					
Liver	(10)	(10)	(10)	(10)	(10)
Inflammation, subacute	1 (10%)	1 (10%)	1 (10%)	1 (10%)	
Cardiovascular System					
None					
Endocrine System					
Adrenal cortex	(10)	(10)	(10)	(10)	(10)
Accessory adrenal cortical nodule	1 (10%)	1 (10%)		2 (20%)	2 (20%)
Parathyroid gland	(10)	(9)	(10)	(10)	(10)
Cyst		1 (11%)			
Thyroid gland	(10)	(10)	(10)	(10)	(10)
Degeneration, cystic	1 (10%)			2 (20%)	
General Body System					
None					
Genital System					
Ovary	(10)	(10)	(10)	(10)	(10)
Angiectasis		1 (10%)			
Hematopoietic System					
None					
Integumentary System					
Skin	(10)	(10)	(10)	(10)	(10)
Inflammation, subacute				1 (10%)	

TABLE B2 Summary of the Incidence of Nonneoplastic Lesions in Female B6C3F$_1$ Mice in the 26-Week Drinking Water Study of a California Pesticide/Fertilizer Mixture (continued)

	Vehicle Control	0.1X	1X	10X	100X
13-WEEK INTERIM EVALUATION (continued)					
Musculoskeletal System					
None					
Nervous System					
None					
Respiratory System					
None					
Special Senses System					
None					
Urinary System					
Kidney	(10)	(10)	(10)	(10)	(10)
Casts protein			1 (10%)	1 (10%)	
26-WEEK STUDY					
Alimentary System					
Liver	(10)	(10)	(10)	(10)	(10)
Inflammation, subacute	1 (10%)		1 (10%)		
Pancreas	(10)	(10)	(10)	(10)	(10)
Cyst		1 (10%)			
Salivary glands	(10)	(10)	(10)	(10)	(10)
Hyperplasia, lymphoid	1 (10%)	1 (10%)	1 (10%)		1 (10%)
Stomach, glandular	(10)	(10)	(10)	(10)	(10)
Erosion				1 (10%)	
Cardiovascular System					
None					
Endocrine System					
Adrenal cortex	(10)	(10)	(10)	(10)	(10)
Accessory adrenal cortical nodule	2 (20%)	1 (10%)	2 (20%)	1 (10%)	1 (10%)
Parathyroid gland	(9)	(10)	(8)	(10)	(10)
Cyst				1 (10%)	
Thyroid gland	(10)	(10)	(10)	(10)	(10)
Degeneration, cystic	1 (10%)	1 (10%)	2 (20%)	1 (10%)	2 (20%)

TABLE B2 Summary of the Incidence of Nonneoplastic Lesions in Female B6C3F$_1$ Mice in the 26-Week Drinking Water Study of a California Pesticide/Fertilizer Mixture (continued)

	Vehicle Control	0.1X	1X	10X	100X
26-WEEK STUDY (continued)					
General Body System					
None					
Genital System					
Uterus	(10)	(10)	(10)	(10)	(10)
Hyperplasia, cystic	4 (40%)	9 (90%)	8 (80%)	9 (90%)	8 (80%)
Hematopoietic System					
Lymph node, mandibular	(9)	(10)	(10)	(10)	(9)
Hemorrhage	1 (11%)		1 (10%)		
Hyperplasia, lymphoid		1 (10%)	1 (10%)		
Spleen	(9)	(10)	(10)	(10)	(10)
Hematopoietic cell proliferation	1 (11%)				1 (10%)
Integumentary System					
None					
Musculoskeletal System					
None					
Nervous System					
None					
Respiratory System					
None					
Special Senses System					
None					
Urinary System					
Kidney	(10)	(10)	(10)	(10)	(10)
Casts protein	1 (10%)	1 (10%)		1 (10%)	

[1] Number of animals examined microscopically at site and number of animals with lesion.

TABLE B3 Summary of the Incidence of Nonneoplastic Lesions in Male B6C3F$_1$ Mice in the 26-Week Drinking Water Study of an Iowa Pesticide/Fertilizer Mixture[1]

	Vehicle Control	0.1X	1X	10X	100X
DISPOSITION SUMMARY					
Animals initially in study	20	20	20	20	20
13-Week interim evaluation	10	10	10	10	10
Survivors					
Terminal sacrifice	10	10	10	10	10
Animals examined microscopically	20	20	20	20	20
13-WEEK INTERIM EVALUATION					
Alimentary System					
Liver	(10)	(10)	(10)	(10)	(10)
Hemorrhage			1 (10%)		
Cardiovascular System					
None					
Endocrine System					
Thyroid gland	(10)	(10)	(10)	(10)	(10)
Degeneration, cystic	1 (10%)				
General Body System					
None					
Genital System					
None					
Hematopoietic System					
None					
Integumentary System					
None					
Musculoskeletal System					
None					
Nervous System					
None					

TABLE B3 Summary of the Incidence of Nonneoplastic Lesions in Male B6C3F$_1$ Mice in the 26-Week Drinking Water Study of an Iowa Pesticide/Fertilizer Mixture (continued)

	Vehicle Control	0.1X	1X	10X	100X
13-WEEK INTERIM EVALUATION (continued)					
Respiratory System					
None					
Special Senses System					
None					
Urinary System					
None					
26-WEEK STUDY					
Alimentary System					
Intestine large, rectum	(10)	(10)	(10)	(10)	(10)
Mucosa, cyst					1 (10%)
Liver	(10)	(10)	(10)	(10)	(10)
Hepatocyte, vacuolization cytoplasmic	6 (60%)				6 (60%)
Pancreas	(10)	(10)	(10)	(10)	(10)
Atrophy, focal				1 (10%)	
Salivary glands	(10)	(10)	(10)	(10)	(10)
Duct, hyperplasia				1 (10%)	
Duct, metaplasia, squamous				1 (10%)	
Cardiovascular System					
None					
Endocrine System					
Adrenal cortex	(10)	(10)	(10)	(10)	(10)
Accessory adrenal cortical nodule					1 (10%)
Parathyroid gland	(9)	(10)	(10)	(10)	(10)
Cyst			2 (20%)	1 (10%)	
General Body System					
None					
Genital System					
Seminal vesicle	(10)	(10)	(10)	(10)	(10)
Developmental malformation					1 (10%)

TABLE B3 Summary of the Incidence of Nonneoplastic Lesions in Male B6C3F$_1$ Mice in the 26-Week Drinking Water Study of an Iowa Pesticide/Fertilizer Mixture (continued)

	Vehicle Control	0.1X	1X	10X	100X
26-WEEK STUDY (continued)					
Hematopoietic System					
Thymus	(9)	(10)	(10)	(10)	(10)
Cyst				1 (10%)	
Integumentary System					
None					
Musculoskeletal System					
None					
Nervous System					
None					
Respiratory System					
None					
Special Senses System					
None					
Urinary System					
Kidney	(10)	(10)	(10)	(10)	(10)
Pelvis, dilatation					1 (10%)
Ureter					(1)
Developmental malformation					1 (100%)

[1] Number of animals examined microscopically at site and number of animals with lesion.

TABLE B4 Summary of the Incidence of Nonneoplastic Lesions in Female B6C3F$_1$ Mice in the 26-Week Drinking Water Study of an Iowa Pesticide/Fertilizer Mixture[1]

	Vehicle Control	0.1X	1X	10X	100X
DISPOSITION SUMMARY					
Animals initially in study	20	20	20	20	20
13-Week interim evaluation	10	10	10	10	10
Early deaths					
Natural deaths					1
Survivors					
Terminal sacrifice	10	10	10	10	9
Animals examined microscopically	20	20	20	20	20
13-WEEK INTERIM EVALUATION					
Alimentary System					
Liver	(10)	(10)	(10)	(10)	(10)
Inflammation, focal			2 (20%)		
Pancreas	(10)	(10)	(10)	(10)	(10)
Accessory spleen					1 (10%)
Cardiovascular System					
None					
Endocrine System					
Parathyroid gland	(10)	(9)	(10)	(10)	(9)
Cyst		1 (11%)			1 (11%)
General Body System					
None					
Genital System					
Ovary	(10)	(10)	(10)	(10)	(10)
Cyst				1 (10%)	
Uterus	(10)	(10)	(10)	(10)	(10)
Endometrium, edema				1 (10%)	1 (10%)
Hematopoietic System					
None					
Integumentary System					
Skin	(10)	(10)	(10)	(10)	(10)
Cyst epithelial inclusion					1 (10%)

TABLE B4 Summary of the Incidence of Nonneoplastic Lesions in Female B6C3F$_1$ Mice in the 26-Week Drinking Water Study of an Iowa Pesticide/Fertilizer Mixture (continued)

	Vehicle Control	0.1X	1X	10X	100X
13-WEEK INTERIM EVALUATION (continued)					
Musculoskeletal System					
None					
Nervous System					
None					
Respiratory System					
None					
Special Senses System					
None					
Urinary System					
None					
26-WEEK STUDY					
Alimentary System					
Pancreas	(10)	(10)	(10)	(10)	(10)
Acinar cell, focal cellular change		1 (10%)			
Cardiovascular System					
None					
Endocrine System					
Adrenal cortex	(10)	(10)	(10)	(10)	(10)
Accessory adrenal cortical nodule			1 (10%)	1 (10%)	
Thyroid gland	(10)	(10)	(10)	(9)	(10)
Degeneration, cystic		2 (20%)	1 (10%)		
General Body System					
None					
Genital System					
Uterus	(10)	(10)	(10)	(10)	(10)
Endometrium, hyperplasia, cystic	10 (100%)	9 (90%)	8 (80%)	10 (100%)	9 (90%)

TABLE B4 Summary of the Incidence of Nonneoplastic Lesions in Female B6C3F$_1$ Mice in the 26-Week Drinking Water Study of an Iowa Pesticide/Fertilizer Mixture (continued)

	Vehicle Control	0.1X	1X	10X	100X
26-WEEK STUDY (continued)					
Hematopoietic System					
None					
Integumentary System					
Skin	(10)	(10)	(10)	(10)	(10)
Inflammation, chronic, focal	1 (10%)	1 (10%)			
Musculoskeletal System					
None					
Nervous System					
None					
Respiratory System					
None					
Special Senses System					
None					
Urinary System					
Kidney	(10)	(10)	(10)	(10)	(10)
Hydronephrosis	1 (10%)			1 (10%)	

[1] Number of animals examined microscopically at site and number of animals with lesion.

APPENDIX C

Organ Weights and Organ-Weight-to-Body-Weight Ratios

TABLE C1 Organ Weights and Organ-Weight-to-Body-Weight Ratios for F344/N Rats in the 26-Week Drinking Water Study of a California Pesticide/Fertilizer Mixture[1]

	Vehicle Control	0.1X	1X	10X	100X
MALE					
13-Week Interim Evaluation					
n	10	10	10	10	10
Necropsy body wt	342 ± 6	346 ± 8	351 ± 6	345 ± 5	331 ± 5
Heart					
Absolute	0.942 ± 0.031	0.969 ± 0.020	0.957 ± 0.034	0.947 ± 0.025	0.930 ± 0.023
Relative	2.76 ± 0.08	2.80 ± 0.05	2.72 ± 0.08	2.74 ± 0.04	2.81 ± 0.04
Right kidney					
Absolute	1.243 ± 0.028	1.214 ± 0.023	1.230 ± 0.031	1.248 ± 0.031	1.220 ± 0.032
Relative	3.64 ± 0.09	3.51 ± 0.05	3.50 ± 0.07	3.62 ± 0.08	3.69 ± 0.07
Liver					
Absolute	12.478 ± 0.212	11.812 ± 0.468	11.962 ± 0.493	11.880 ± 0.332	11.029 ± 0.347*
Relative	36.54 ± 0.68	34.06 ± 0.85*	33.95 ± 0.94*	34.41 ± 0.75	33.30 ± 0.80**
Lungs					
Absolute	1.349 ± 0.045	1.361 ± 0.064	1.362 ± 0.033	1.291 ± 0.030	1.274 ± 0.035
Relative	3.94 ± 0.11	3.92 ± 0.13	3.88 ± 0.07	3.74 ± 0.07	3.85 ± 0.07
Right testis					
Absolute	1.421 ± 0.036	1.422 ± 0.024	1.434 ± 0.021	1.432 ± 0.017	1.413 ± 0.018[2]
Relative	4.17 ± 0.12	4.12 ± 0.08	4.09 ± 0.07	4.15 ± 0.05	4.29 ± 0.06[2]
Thymus					
Absolute	0.309 ± 0.012	0.294 ± 0.017	0.308 ± 0.019	0.269 ± 0.017	0.251 ± 0.013*[2]
Relative	0.90 ± 0.03	0.86 ± 0.06	0.88 ± 0.06	0.78 ± 0.05	0.76 ± 0.04[2]
26-Week Study					
n	10	10	10	10	10
Necropsy body wt	421 ± 7	416 ± 11	420 ± 5	425 ± 9	418 ± 11
Heart					
Absolute	1.058 ± 0.029	1.020 ± 0.037	1.062 ± 0.029	1.035 ± 0.055	1.076 ± 0.040
Relative	2.51 ± 0.04	2.45 ± 0.04	2.53 ± 0.06	2.45 ± 0.14	2.57 ± 0.05
Right kidney					
Absolute	1.509 ± 0.036	1.452 ± 0.056	1.449 ± 0.021	1.544 ± 0.035	1.458 ± 0.063
Relative	3.58 ± 0.07	3.49 ± 0.07	3.46 ± 0.07	3.63 ± 0.05	3.48 ± 0.10
Liver					
Absolute	16.137 ± 0.486	14.708 ± 0.592	15.022 ± 0.168	15.892 ± 0.404	16.179 ± 0.601
Relative	38.27 ± 0.83	35.30 ± 0.75*	35.82 ± 0.50*	37.40 ± 0.61	38.65 ± 0.67
Lungs					
Absolute	1.538 ± 0.053	1.528 ± 0.053	1.527 ± 0.036	1.518 ± 0.033	1.508 ± 0.034
Relative	3.65 ± 0.11	3.69 ± 0.12	3.64 ± 0.08	3.57 ± 0.05	3.62 ± 0.08
Right testis					
Absolute	1.497 ± 0.023	1.446 ± 0.036	1.498 ± 0.032[2]	1.484 ± 0.021	1.518 ± 0.036
Relative	3.56 ± 0.06	3.48 ± 0.05	3.56 ± 0.06[2]	3.50 ± 0.07	3.64 ± 0.06
Thymus					
Absolute	0.203 ± 0.010	0.206 ± 0.014	0.235 ± 0.019	0.207 ± 0.023	0.224 ± 0.017
Relative	0.48 ± 0.02	0.50 ± 0.03	0.56 ± 0.04	0.48 ± 0.05	0.54 ± 0.04

TABLE C1 Organ Weights and Organ-Weight-to-Body-Weight Ratios for F344/N Rats in the 26-Week Drinking Water Study of a California Pesticide/Fertilizer Mixture (continued)

	Vehicle Control	0.1X	1X	10X	100X
FEMALE					
13-Week Interim Evaluation					
n	10	10	10	10	10
Necropsy body wt	192 ± 3	194 ± 3	191 ± 3	197 ± 4	189 ± 3
Heart					
Absolute	0.579 ± 0.012	0.585 ± 0.009	0.622 ± 0.047	0.603 ± 0.018	0.575 ± 0.013
Relative	3.03 ± 0.06	3.02 ± 0.05	3.26 ± 0.24	3.06 ± 0.07	3.04 ± 0.05
Right kidney					
Absolute	0.684 ± 0.017	0.708 ± 0.016	0.670 ± 0.017	0.716 ± 0.015	0.694 ± 0.018
Relative	3.57 ± 0.07	3.65 ± 0.07	3.51 ± 0.06	3.64 ± 0.07	3.67 ± 0.07
Liver					
Absolute	6.189 ± 0.185	6.637 ± 0.157	6.234 ± 0.187	6.361 ± 0.158	6.122 ± 0.181
Relative	32.30 ± 0.76	34.25 ± 0.77	32.65 ± 0.82	32.44 ± 1.06	32.39 ± 0.69
Lungs					
Absolute	0.898 ± 0.016	0.894 ± 0.024	0.930 ± 0.029	0.939 ± 0.039	0.935 ± 0.018
Relative	4.69 ± 0.07	4.61 ± 0.11	4.87 ± 0.14	4.78 ± 0.19	4.95 ± 0.07
Thymus					
Absolute	0.217 ± 0.007	0.237 ± 0.013	0.220 ± 0.014	0.216 ± 0.011	0.219 ± 0.009
Relative	1.13 ± 0.03	1.23 ± 0.08	1.15 ± 0.06	1.10 ± 0.05	1.16 ± 0.04
26-Week Study					
n	10	10	10	10	10
Necropsy body wt	218 ± 3	225 ± 4	221 ± 3	211 ± 6	220 ± 4
Heart					
Absolute	0.635 ± 0.015	0.637 ± 0.013	0.649 ± 0.018	0.593 ± 0.015	0.610 ± 0.011
Relative	2.91 ± 0.06	2.83 ± 0.05	2.93 ± 0.06	2.81 ± 0.04	2.78 ± 0.04
Right kidney					
Absolute	0.766 ± 0.020	0.775 ± 0.027	0.773 ± 0.030	0.768 ± 0.021	0.764 ± 0.021
Relative	3.51 ± 0.06	3.44 ± 0.09	3.49 ± 0.11	3.64 ± 0.04	3.48 ± 0.08
Liver					
Absolute	6.993 ± 0.188	6.826 ± 0.226	7.044 ± 0.108	6.895 ± 0.287	7.171 ± 0.240
Relative	32.05 ± 0.56	30.34 ± 0.94	31.90 ± 0.66	32.58 ± 0.75	32.62 ± 0.86
Lungs					
Absolute	1.028 ± 0.018	1.032 ± 0.028	1.007 ± 0.030	1.037 ± 0.025	0.970 ± 0.018
Relative	4.72 ± 0.08	4.59 ± 0.10	4.56 ± 0.15	4.94 ± 0.16	4.42 ± 0.07
Thymus					
Absolute	0.168 ± 0.008	0.172 ± 0.007	0.163 ± 0.007	0.172 ± 0.006[2]	0.161 ± 0.009[2]
Relative	0.77 ± 0.04	0.77 ± 0.03	0.74 ± 0.04	0.82 ± 0.02[2]	0.74 ± 0.04[2]

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

[2] n=9.

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

** Significantly different (P≤0.01) from the control group by Williams' test.

TABLE C2 Organ Weights and Organ-Weight-to-Body-Weight Ratios for F344/N Rats in the 26-Week Drinking Water Study of an Iowa Pesticide/Fertilizer Mixture[1]

	Vehicle Control	0.1X	1X	10X	100X
MALE					
13-Week Interim Evaluation					
n	10	10	10	10	10
Necropsy body wt	334 ± 4	356 ± 4**	351 ± 3*	326 ± 4	343 ± 7
Heart					
Absolute	0.952 ± 0.021	0.967 ± 0.013	0.949 ± 0.019	0.955 ± 0.020	0.938 ± 0.025
Relative	2.85 ± 0.05	2.72 ± 0.04	2.70 ± 0.05	2.93 ± 0.05	2.74 ± 0.07
Right kidney					
Absolute	1.279 ± 0.030[2]	1.319 ± 0.029	1.292 ± 0.032	1.258 ± 0.034	1.260 ± 0.024
Relative	3.83 ± 0.10[2]	3.70 ± 0.07	3.68 ± 0.08	3.86 ± 0.07	3.68 ± 0.09
Liver					
Absolute	13.158 ± 0.468	14.337 ± 0.318	13.724 ± 0.271	12.841 ± 0.305	13.389 ± 0.326
Relative	39.36 ± 1.15	40.19 ± 0.58	39.05 ± 0.62	39.43 ± 0.71	39.01 ± 0.68
Lungs					
Absolute	1.263 ± 0.019	1.331 ± 0.030	1.318 ± 0.038	1.233 ± 0.023	1.297 ± 0.036
Relative	3.78 ± 0.05	3.73 ± 0.06	3.75 ± 0.09	3.79 ± 0.06	3.79 ± 0.13
Right testis					
Absolute	1.410 ± 0.014	1.439 ± 0.010	1.448 ± 0.017	1.401 ± 0.017	1.422 ± 0.020
Relative	4.23 ± 0.06	4.04 ± 0.06	4.12 ± 0.05	4.31 ± 0.05	4.15 ± 0.06
Thymus					
Absolute	0.282 ± 0.016	0.267 ± 0.017	0.278 ± 0.010	0.256 ± 0.006	0.269 ± 0.020
Relative	0.84 ± 0.05	0.75 ± 0.04	0.79 ± 0.03	0.79 ± 0.02	0.78 ± 0.06
26-Week Study					
n	10	10	10	10	10
Necropsy body wt	405 ± 8	422 ± 11	416 ± 6	410 ± 12	410 ± 8
Heart					
Absolute	1.094 ± 0.038	1.086 ± 0.032	1.088 ± 0.027	1.076 ± 0.028	1.072 ± 0.035
Relative	2.70 ± 0.06	2.58 ± 0.04	2.62 ± 0.06	2.63 ± 0.06	2.61 ± 0.05
Right kidney					
Absolute	1.425 ± 0.038	1.397 ± 0.062	1.425 ± 0.033	1.453 ± 0.040[2]	1.480 ± 0.023
Relative	3.52 ± 0.06	3.31 ± 0.10	3.42 ± 0.06	3.55 ± 0.07[2]	3.62 ± 0.05
Liver					
Absolute	13.865 ± 0.248	14.667 ± 0.569	15.390 ± 0.444*	15.830 ± 0.459**	16.283 ± 0.521**
Relative	34.27 ± 0.58	34.75 ± 0.91	36.97 ± 0.79*	38.65 ± 0.71**	39.77 ± 1.14**
Lungs					
Absolute	1.460 ± 0.045	1.544 ± 0.074	1.524 ± 0.047	1.504 ± 0.034	1.487 ± 0.029
Relative	3.60 ± 0.08	3.65 ± 0.10	3.66 ± 0.10	3.68 ± 0.09	3.63 ± 0.07
Right testis					
Absolute	1.520 ± 0.028	1.487 ± 0.025	1.500 ± 0.021	1.523 ± 0.023	1.491 ± 0.020
Relative	3.75 ± 0.05	3.53 ± 0.04	3.61 ± 0.07	3.73 ± 0.09	3.65 ± 0.05
Thymus					
Absolute	0.192 ± 0.012	0.188 ± 0.014	0.183 ± 0.012	0.201 ± 0.014	0.202 ± 0.009
Relative	0.48 ± 0.03	0.45 ± 0.04	0.44 ± 0.02	0.49 ± 0.04	0.49 ± 0.02

TABLE C2 Organ Weights and Organ-Weight-to-Body-Weight Ratios for F344/N Rats in the 26-Week Drinking Water Study of an Iowa Pesticide/Fertilizer Mixture (continued)

	Vehicle Control	0.1X	1X	10X	100X
FEMALE					
13-Week Interim Evaluation					
n	10	10	10	10	10
Necropsy body wt	188 ± 3	186 ± 2	190 ± 3	191 ± 3	189 ± 4
Heart					
Absolute	0.601 ± 0.016	0.620 ± 0.017	0.617 ± 0.013	0.624 ± 0.018	0.597 ± 0.009
Relative	3.20 ± 0.06	3.33 ± 0.09	3.24 ± 0.05	3.28 ± 0.09	3.17 ± 0.07
Right kidney					
Absolute	0.722 ± 0.025	0.716 ± 0.027	0.726 ± 0.021	0.718 ± 0.022	0.728 ± 0.019
Relative	3.84 ± 0.10	3.84 ± 0.13	3.81 ± 0.08	3.78 ± 0.14	3.86 ± 0.08
Liver					
Absolute	6.332 ± 0.152	6.796 ± 0.231	6.176 ± 0.122	6.445 ± 0.221	6.156 ± 0.193
Relative	33.69 ± 0.60	36.51 ± 1.27	32.47 ± 0.51	33.84 ± 1.08	32.59 ± 0.47
Lungs					
Absolute	0.949 ± 0.042[2]	0.979 ± 0.024	0.928 ± 0.030	0.973 ± 0.028[2]	0.983 ± 0.033
Relative	5.05 ± 0.22[2]	5.26 ± 0.14	4.87 ± 0.11	5.10 ± 0.13[2]	5.22 ± 0.18
Thymus					
Absolute	0.215 ± 0.007	0.209 ± 0.010	0.224 ± 0.008	0.235 ± 0.013	0.223 ± 0.010
Relative	1.14 ± 0.03	1.12 ± 0.05	1.18 ± 0.04	1.24 ± 0.07	1.18 ± 0.04
26-Week Study					
n	10	10	10	10	10
Necropsy body wt	220 ± 4	225 ± 4	223 ± 4	216 ± 4	221 ± 5
Heart					
Absolute	0.635 ± 0.007	0.685 ± 0.012	0.655 ± 0.017	0.670 ± 0.013	0.674 ± 0.024
Relative	2.89 ± 0.04	3.04 ± 0.06	2.94 ± 0.04	3.11 ± 0.09*	3.05 ± 0.07*
Right kidney					
Absolute	0.767 ± 0.016	0.803 ± 0.016	0.794 ± 0.020	0.811 ± 0.015	0.830 ± 0.026*
Relative	3.49 ± 0.07	3.57 ± 0.07	3.57 ± 0.09	3.77 ± 0.12*	3.76 ± 0.06*
Liver					
Absolute	6.721 ± 0.148	7.237 ± 0.220	7.364 ± 0.169*	7.598 ± 0.195**	7.547 ± 0.167**
Relative	30.57 ± 0.75	32.08 ± 0.73	33.09 ± 0.60*	35.22 ± 0.96**	34.28 ± 0.77**
Lungs					
Absolute	1.013 ± 0.025	1.086 ± 0.027	1.027 ± 0.027	1.022 ± 0.020	1.039 ± 0.038
Relative	4.60 ± 0.09	4.83 ± 0.15	4.61 ± 0.11	4.74 ± 0.13	4.71 ± 0.13
Thymus					
Absolute	0.172 ± 0.009	0.178 ± 0.008	0.173 ± 0.009	0.149 ± 0.008	0.184 ± 0.014
Relative	0.78 ± 0.04	0.79 ± 0.03	0.77 ± 0.04	0.69 ± 0.03	0.83 ± 0.06

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

[2] *n*=9.

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

** Significantly different (P≤0.01) from the control group by Williams' or Dunnett's test.

TABLE C3 Organ Weights and Organ-Weight-to-Body-Weight Ratios for B6C3F$_1$ Mice in the 26-Week Drinking Water Study of a California Pesticide/Fertilizer Mixture[1]

	Vehicle Control	0.1X	1X	10X	100X
MALE					
13-Week Interim Evaluation					
n	10	10	10	10	10
Necropsy body wt	41.0 ± 0.6	39.2 ± 0.7	40.0 ± 0.6	39.7 ± 0.8	37.5 ± 0.7**
Heart					
Absolute	0.157 ± 0.005	0.154 ± 0.004	0.160 ± 0.005	0.157 ± 0.004	0.149 ± 0.003
Relative	3.83 ± 0.08	3.94 ± 0.09	4.00 ± 0.08	3.96 ± 0.07	4.00 ± 0.15
Right kidney					
Absolute	0.317 ± 0.011	0.314 ± 0.007	0.316 ± 0.010	0.291 ± 0.016	0.299 ± 0.007
Relative	7.73 ± 0.21	8.05 ± 0.27	7.89 ± 0.16	7.37 ± 0.42	8.01 ± 0.26
Liver					
Absolute	1.781 ± 0.068	1.699 ± 0.070	1.739 ± 0.068	1.727 ± 0.068	1.524 ± 0.047**
Relative	43.37 ± 0.95	43.22 ± 0.98	43.42 ± 1.32	43.44 ± 0.99	40.76 ± 1.27
Lungs					
Absolute	0.188 ± 0.008[2]	0.195 ± 0.007	0.194 ± 0.004	0.192 ± 0.004	0.183 ± 0.006
Relative	4.57 ± 0.18[2]	5.00 ± 0.21	4.86 ± 0.09	4.86 ± 0.14	4.92 ± 0.23
Right testis					
Absolute	0.126 ± 0.002	0.124 ± 0.002	0.124 ± 0.002	0.120 ± 0.002	0.120 ± 0.002
Relative	3.08 ± 0.06	3.18 ± 0.07	3.10 ± 0.06	3.04 ± 0.09	3.22 ± 0.08
Thymus					
Absolute	0.038 ± 0.003	0.034 ± 0.002	0.033 ± 0.002	0.036 ± 0.002	0.034 ± 0.002
Relative	0.93 ± 0.06	0.88 ± 0.03	0.82 ± 0.04	0.90 ± 0.05	0.91 ± 0.04
26-Week Study					
n	10	10	10	10	9
Necropsy body wt	47.5 ± 0.5	48.9 ± 0.7	47.5 ± 1.0	48.5 ± 0.8	45.5 ± 0.9
Heart					
Absolute	0.168 ± 0.004	0.175 ± 0.005	0.179 ± 0.005	0.180 ± 0.005	0.173 ± 0.006
Relative	3.54 ± 0.07	3.57 ± 0.08	3.78 ± 0.12	3.72 ± 0.12	3.81 ± 0.08
Right kidney					
Absolute	0.383 ± 0.012	0.389 ± 0.013	0.410 ± 0.013	0.414 ± 0.013	0.377 ± 0.017
Relative	8.06 ± 0.19	7.94 ± 0.18	8.64 ± 0.22	8.53 ± 0.20	8.27 ± 0.27
Liver					
Absolute	2.353 ± 0.148	2.449 ± 0.133	2.555 ± 0.145	2.548 ± 0.134	2.119 ± 0.102
Relative	49.35 ± 2.65	49.86 ± 2.18	53.44 ± 2.11	52.31 ± 2.01	46.48 ± 1.66
Lungs					
Absolute	0.205 ± 0.006	0.206 ± 0.007	0.212 ± 0.011	0.197 ± 0.005	0.208 ± 0.008
Relative	4.32 ± 0.12	4.21 ± 0.12	4.49 ± 0.28	4.07 ± 0.09	4.57 ± 0.17
Right testis					
Absolute	0.117 ± 0.003	0.122 ± 0.002	0.124 ± 0.003	0.124 ± 0.004	0.123 ± 0.003
Relative	2.46 ± 0.06	2.49 ± 0.06	2.60 ± 0.05	2.56 ± 0.07	2.72 ± 0.07**
Thymus					
Absolute	0.053 ± 0.006	0.053 ± 0.005	0.044 ± 0.004	0.048 ± 0.004	0.043 ± 0.004
Relative	1.12 ± 0.13	1.08 ± 0.09	0.93 ± 0.10	0.99 ± 0.09	0.94 ± 0.07

TABLE C3 Organ Weights and Organ-Weight-to-Body-Weight Ratios for B6C3F$_1$ Mice in the 26-Week Drinking Water Study of a California Pesticide/Fertilizer Mixture (continued)

	Vehicle Control	0.1X	1X	10X	100X
FEMALE					
13-Week Interim Evaluation					
n	10	10	10	10	10
Necropsy body wt	28.6 ± 0.5	32.3 ± 0.6**	29.9 ± 0.5	30.5 ± 0.6	29.7 ± 1.1
Heart					
Absolute	0.131 ± 0.004	0.132 ± 0.004	0.129 ± 0.004	0.130 ± 0.003	0.131 ± 0.004
Relative	4.59 ± 0.10	4.12 ± 0.17	4.34 ± 0.17	4.29 ± 0.12	4.48 ± 0.20
Right kidney					
Absolute	0.211 ± 0.008	0.209 ± 0.005	0.203 ± 0.004	0.203 ± 0.006	0.209 ± 0.007
Relative	7.38 ± 0.20	6.51 ± 0.21*	6.82 ± 0.18	6.70 ± 0.27	7.14 ± 0.30
Liver					
Absolute	1.332 ± 0.032	1.404 ± 0.035	1.393 ± 0.041	1.330 ± 0.027	1.296 ± 0.050
Relative	46.72 ± 1.10	43.63 ± 1.13	46.63 ± 0.90	43.88 ± 1.33	44.08 ± 1.36
Lungs					
Absolute	0.191 ± 0.006	0.202 ± 0.013	0.204 ± 0.009	0.187 ± 0.004	0.179 ± 0.005[2]
Relative	6.69 ± 0.17	6.31 ± 0.47	6.88 ± 0.37	6.17 ± 0.21	6.16 ± 0.29[2]
Thymus					
Absolute	0.041 ± 0.003	0.044 ± 0.002	0.045 ± 0.003	0.047 ± 0.002	0.045 ± 0.002
Relative	1.43 ± 0.11	1.37 ± 0.08	1.52 ± 0.10	1.53 ± 0.06	1.54 ± 0.08
26-Week Study					
n	10	10	10	9	10
Necropsy body wt	43.6 ± 2.2	45.8 ± 2.5	44.8 ± 1.7	45.7 ± 1.8	44.4 ± 1.8
Heart					
Absolute	0.135 ± 0.005	0.148 ± 0.003	0.149 ± 0.006	0.157 ± 0.007*	0.143 ± 0.004
Relative	3.14 ± 0.14	3.30 ± 0.16	3.34 ± 0.12	3.45 ± 0.16	3.27 ± 0.17
Right kidney					
Absolute	0.231 ± 0.010	0.256 ± 0.007	0.243 ± 0.007	0.261 ± 0.013	0.249 ± 0.007
Relative	5.33 ± 0.13	5.68 ± 0.20	5.46 ± 0.16	5.71 ± 0.16	5.65 ± 0.17
Liver					
Absolute	1.583 ± 0.081	1.713 ± 0.110	1.659 ± 0.063	1.763 ± 0.103	1.652 ± 0.074
Relative	36.33 ± 0.57	37.44 ± 1.17	37.09 ± 0.70	38.47 ± 1.33	37.24 ± 0.77
Lungs					
Absolute	0.189 ± 0.005	0.212 ± 0.006	0.202 ± 0.008	0.208 ± 0.010	0.199 ± 0.006
Relative	4.43 ± 0.25	4.72 ± 0.23	4.54 ± 0.16	4.56 ± 0.19	4.56 ± 0.25
Thymus					
Absolute	0.039 ± 0.006	0.054 ± 0.007	0.046 ± 0.003	0.058 ± 0.007	0.041 ± 0.004
Relative	0.88 ± 0.11	1.17 ± 0.13	1.04 ± 0.08	1.25 ± 0.11	0.93 ± 0.10

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

[2] n=9.

* Significantly different (P≤0.05) from the control group by Dunnett's test.

** Significantly different (P≤0.01) from the control group by Williams' or Dunnett's test.

TABLE C4 Organ Weights and Organ-Weight-to-Body-Weight Ratios for B6C3F$_1$ Mice in the 26-Week Drinking Water Study of an Iowa Pesticide/Fertilizer Mixture[1]

	Vehicle Control	0.1X	1X	10X	100X
MALE					
13-Week Interim Evaluation					
n	10	10	10	10	10
Necropsy body wt	35.8 ± 1.1	36.4 ± 0.9	38.1 ± 1.0	36.0 ± 0.7	35.3 ± 1.3
Heart					
Absolute	0.148 ± 0.004	0.151 ± 0.007	0.153 ± 0.003	0.146 ± 0.002	0.143 ± 0.005
Relative	4.16 ± 0.16	4.15 ± 0.17	4.03 ± 0.07	4.06 ± 0.08	4.07 ± 0.11
Right kidney					
Absolute	0.308 ± 0.007	0.311 ± 0.007	0.327 ± 0.007	0.318 ± 0.005	0.296 ± 0.011
Relative	8.64 ± 0.21	8.57 ± 0.18	8.62 ± 0.23	8.86 ± 0.25	8.40 ± 0.16
Liver					
Absolute	1.517 ± 0.071	1.688 ± 0.052	1.681 ± 0.064	1.671 ± 0.065	1.518 ± 0.076
Relative	42.26 ± 1.27	46.53 ± 1.54	44.10 ± 0.91	46.42 ± 1.79	42.90 ± 1.01
Lungs					
Absolute	0.196 ± 0.007	0.194 ± 0.011	0.192 ± 0.006	0.181 ± 0.005	0.197 ± 0.012
Relative	5.50 ± 0.20	5.34 ± 0.30	5.06 ± 0.18	5.04 ± 0.15	5.56 ± 0.20
Right testis					
Absolute	0.122 ± 0.002	0.117 ± 0.002	0.120 ± 0.003	0.122 ± 0.001	0.119 ± 0.003
Relative	3.41 ± 0.07	3.24 ± 0.11	3.16 ± 0.10	3.41 ± 0.08	3.39 ± 0.12
Thymus					
Absolute	0.038 ± 0.003	0.038 ± 0.004	0.031 ± 0.001	0.026 ± 0.002[2]	0.036 ± 0.003
Relative	1.05 ± 0.07	1.04 ± 0.10	0.81 ± 0.05	0.72 ± 0.07*[2]	1.01 ± 0.09
26-Week Study					
n	10	10	10	10	10
Necropsy body wt	43.4 ± 1.3	47.2 ± 1.1	45.8 ± 1.1	46.9 ± 1.0	45.8 ± 0.8
Heart					
Absolute	0.178 ± 0.008	0.185 ± 0.005	0.183 ± 0.007	0.181 ± 0.004	0.187 ± 0.007
Relative	4.12 ± 0.20	3.92 ± 0.07	4.01 ± 0.15	3.87 ± 0.11	4.08 ± 0.13
Right kidney					
Absolute	0.376 ± 0.011	0.393 ± 0.014	0.377 ± 0.015	0.383 ± 0.012[2]	0.380 ± 0.012
Relative	8.67 ± 0.13	8.33 ± 0.23	8.22 ± 0.21	8.22 ± 0.23[2]	8.29 ± 0.19
Liver					
Absolute	1.889 ± 0.133	2.225 ± 0.157	2.054 ± 0.110	2.206 ± 0.114	2.012 ± 0.052
Relative	43.13 ± 1.82	46.74 ± 2.21	44.66 ± 1.48	46.80 ± 1.70	43.88 ± 0.53
Lungs					
Absolute	0.193 ± 0.010	0.219 ± 0.012	0.201 ± 0.008	0.215 ± 0.010	0.192 ± 0.009
Relative	4.45 ± 0.19	4.66 ± 0.26	4.40 ± 0.18	4.59 ± 0.19	4.19 ± 0.16
Right testis					
Absolute	0.121 ± 0.003	0.124 ± 0.007	0.115 ± 0.004	0.122 ± 0.002	0.116 ± 0.007
Relative	2.81 ± 0.10	2.64 ± 0.15	2.54 ± 0.13	2.61 ± 0.07	2.55 ± 0.17
Thymus					
Absolute	0.029 ± 0.003	0.047 ± 0.004**	0.038 ± 0.005	0.042 ± 0.004	0.035 ± 0.004
Relative	0.65 ± 0.07	0.99 ± 0.09*	0.83 ± 0.11	0.88 ± 0.08	0.77 ± 0.08

TABLE C4 Organ Weights and Organ-Weight-to-Body-Weight Ratios for B6C3F$_1$ Mice in the 26-Week Drinking Water Study of an Iowa Pesticide/Fertilizer Mixture (continued)

	Vehicle Control	0.1X	1X	10X	100X
FEMALE					
13-Week Interim Evaluation					
n	9	10	10	10	10
Necropsy body wt	31.1 ± 1.1	30.2 ± 1.0	29.3 ± 0.9	27.4 ± 0.7*	28.4 ± 0.8*
Heart					
Absolute	0.132 ± 0.003	0.131 ± 0.004	0.129 ± 0.003	0.129 ± 0.003	0.132 ± 0.004
Relative	4.28 ± 0.14	4.36 ± 0.12	4.43 ± 0.13	4.72 ± 0.10	4.69 ± 0.21
Right kidney					
Absolute	0.210 ± 0.003	0.207 ± 0.005	0.210 ± 0.007	0.203 ± 0.007	0.209 ± 0.004
Relative	6.81 ± 0.21	6.89 ± 0.17	7.19 ± 0.21	7.42 ± 0.23	7.40 ± 0.22
Liver					
Absolute	1.367 ± 0.045	1.399 ± 0.050	1.344 ± 0.050	1.295 ± 0.075	1.248 ± 0.036
Relative	44.04 ± 0.82	46.55 ± 1.48	45.91 ± 1.11	47.09 ± 1.79	44.00 ± 0.71
Lungs					
Absolute	0.209 ± 0.012	0.191 ± 0.010	0.208 ± 0.009	0.184 ± 0.005	0.208 ± 0.007
Relative	6.77 ± 0.46	6.34 ± 0.29	7.13 ± 0.30	6.73 ± 0.15	7.40 ± 0.37
Thymus					
Absolute	0.044 ± 0.003	0.046 ± 0.004	0.043 ± 0.004	0.041 ± 0.003	0.036 ± 0.002
Relative	1.43 ± 0.10	1.52 ± 0.11	1.46 ± 0.11	1.48 ± 0.09	1.28 ± 0.10
26-Week Study					
n	10	10	10	10	9
Necropsy body wt	41.0 ± 1.8	41.7 ± 1.2	41.5 ± 1.4	40.0 ± 1.5	39.6 ± 1.6
Heart					
Absolute	0.139 ± 0.005	0.144 ± 0.006	0.135 ± 0.005	0.142 ± 0.004	0.151 ± 0.009
Relative	3.42 ± 0.11	3.47 ± 0.15	3.29 ± 0.17	3.61 ± 0.22	3.90 ± 0.32
Right kidney					
Absolute	0.246 ± 0.014	0.239 ± 0.007	0.239 ± 0.005	0.237 ± 0.007[2]	0.241 ± 0.010
Relative	5.99 ± 0.14	5.76 ± 0.19	5.79 ± 0.12	5.82 ± 0.25[2]	6.19 ± 0.38
Liver					
Absolute	1.492 ± 0.046	1.561 ± 0.022	1.545 ± 0.046	1.486 ± 0.051	1.440 ± 0.074
Relative	36.65 ± 0.88	37.76 ± 1.42	37.40 ± 1.14	37.26 ± 0.91	36.84 ± 2.25
Lungs					
Absolute	0.193 ± 0.006	0.191 ± 0.006	0.204 ± 0.009	0.181 ± 0.004	0.189 ± 0.009
Relative	4.77 ± 0.19	4.61 ± 0.19	4.95 ± 0.27	4.58 ± 0.20	4.87 ± 0.36
Thymus					
Absolute	0.045 ± 0.005	0.045 ± 0.005	0.047 ± 0.004	0.044 ± 0.003	0.042 ± 0.005
Relative	1.11 ± 0.13	1.08 ± 0.13	1.13 ± 0.09	1.11 ± 0.09	1.06 ± 0.12

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

[2] n=9.

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

** Significantly different (P≤0.01) from the control group by Dunnett's test.

APPENDIX D

Hematology, Clinical Chemistry, and Urinalysis Results

TABLE D1 Hematology, Clinical Chemistry, and Urinalysis Data for F344/N Rats in the 26-Week Drinking Water Study of a California Pesticide/Fertilizer Mixture[1]

	Vehicle Control	0.1X	1X	10X	100X
MALE					
Hematology					
n					
Day 5	9	8	9	9	8
Day 22	10	10	10	10	10
Day 92	9	10	10	10	10
Day 183	10	10	9	9	9
Hematocrit (%)					
Day 5	41.9 ± 0.5	42.8 ± 0.6	42.5 ± 0.7	42.6 ± 0.6	42.7 ± 0.4
Day 22	46.5 ± 0.5	47.1 ± 0.5	46.1 ± 0.5	45.8 ± 0.4	46.3 ± 0.4
Day 92	47.2 ± 0.5	49.2 ± 0.3**	48.0 ± 0.5*	49.5 ± 0.3**	51.0 ± 0.7**
Day 183	46.2 ± 0.5	47.9 ± 0.6	47.9 ± 0.4	46.7 ± 0.6	46.8 ± 0.4
Hemoglobin (g/dL)					
Day 5	13.9 ± 0.1	14.1 ± 0.2	14.0 ± 0.2	14.1 ± 0.2	14.0 ± 0.2
Day 22	15.4 ± 0.2	15.4 ± 0.2	15.2 ± 0.1	15.0 ± 0.1	15.3 ± 0.1
Day 92	16.0 ± 0.2	16.6 ± 0.1*	16.2 ± 0.2	16.7 ± 0.1**	17.2 ± 0.2**
Day 183	15.2 ± 0.2	15.7 ± 0.2	15.7 ± 0.1*	15.4 ± 0.2	15.4 ± 0.1
Erythrocytes (10^6/μL)					
Day 5	7.02 ± 0.08	7.12 ± 0.10	7.10 ± 0.12	7.13 ± 0.12	7.12 ± 0.10
Day 22	7.94 ± 0.11	7.91 ± 0.08	7.82 ± 0.13	7.76 ± 0.09	7.89 ± 0.08
Day 92	9.04 ± 0.11	9.41 ± 0.08*	9.23 ± 0.13	9.54 ± 0.10**	9.81 ± 0.15**
Day 183	9.00 ± 0.09	9.33 ± 0.10*	9.28 ± 0.04	9.19 ± 0.08	9.14 ± 0.08
Reticulocytes (10^6/μL)					
Day 5	0.17 ± 0.01	0.16 ± 0.02	0.17 ± 0.02	0.20 ± 0.02	0.17 ± 0.02
Day 22	0.12 ± 0.01	0.16 ± 0.01*	0.15 ± 0.02	0.14 ± 0.01	0.15 ± 0.01
Day 92	0.09 ± 0.01	0.11 ± 0.01	0.10 ± 0.01	0.09 ± 0.01	0.09 ± 0.01
Day 183	0.20 ± 0.01	0.19 ± 0.01	0.19 ± 0.02	0.18 ± 0.01	0.17 ± 0.01
Nucleated erythrocytes (10^3/μL)					
Day 5	0.03 ± 0.01	0.09 ± 0.03	0.07 ± 0.02	0.06 ± 0.02	0.06 ± 0.02
Day 22	0.03 ± 0.01	0.03 ± 0.02	0.02 ± 0.01	0.02 ± 0.01	0.03 ± 0.01
Day 92	0.07 ± 0.02	0.12 ± 0.05	0.17 ± 0.04	0.06 ± 0.02	0.13 ± 0.03
Day 183	0.06 ± 0.02	0.03 ± 0.03	0.09 ± 0.03	0.03 ± 0.02	0.06 ± 0.02
Mean cell volume (fL)					
Day 5	59.8 ± 0.2	60.0 ± 0.3	59.9 ± 0.5	59.7 ± 0.3	60.0 ± 0.7
Day 22	58.7 ± 0.3	59.5 ± 0.2	59.1 ± 0.6	59.0 ± 0.4	58.7 ± 0.4
Day 92	52.2 ± 0.3	52.4 ± 0.4	52.1 ± 0.3	51.9 ± 0.4	52.0 ± 0.2
Day 183	51.4 ± 0.4	51.3 ± 0.3	51.6 ± 0.4	50.8 ± 0.4	51.2 ± 0.3
Mean cell hemoglobin (pg)					
Day 5	19.7 ± 0.1	19.8 ± 0.1	19.7 ± 0.1	19.8 ± 0.1	19.7 ± 0.2
Day 22	19.4 ± 0.1	19.5 ± 0.1	19.4 ± 0.3	19.3 ± 0.1	19.4 ± 0.1
Day 92	17.7 ± 0.1	17.6 ± 0.1	17.6 ± 0.1	17.5 ± 0.1	17.6 ± 0.1
Day 183	16.9 ± 0.1	16.8 ± 0.1	16.9 ± 0.1	16.7 ± 0.1	16.9 ± 0.1
Mean cell hemoglobin concentration (g/dL)					
Day 5	33.0 ± 0.2	33.1 ± 0.2	32.9 ± 0.2	33.1 ± 0.2	32.8 ± 0.3
Day 22	33.1 ± 0.1	32.7 ± 0.1	32.9 ± 0.3	32.7 ± 0.1	33.0 ± 0.2
Day 92	33.8 ± 0.1	33.6 ± 0.1	33.7 ± 0.1	33.8 ± 0.1	33.8 ± 0.1
Day 183	32.8 ± 0.2	32.8 ± 0.1	32.8 ± 0.1	32.9 ± 0.2	33.0 ± 0.2

TABLE D1 Hematology, Clinical Chemistry, and Urinalysis Data for F344/N Rats in the 26-Week Drinking Water Study of a California Pesticide/Fertilizer Mixture (continued)

	Vehicle Control	0.1X	1X	10X	100X
MALE (continued)					
Hematology (continued)					
Platelets (10^3/μL)					
Day 5	944.9 ± 38.5	1029.9 ± 26.7	974.4 ± 23.5	953.1 ± 38.5	960.3 ± 28.5
Day 22	799.6 ± 17.6	819.4 ± 23.9	811.0 ± 22.9	789.3 ± 12.6	770.4 ± 12.4
Day 92	749.2 ± 19.1	718.9 ± 13.5	781.2 ± 61.4	735.1 ± 15.5	722.3 ± 13.2
Day 183	737.4 ± 33.7	671.9 ± 10.3*	705.3 ± 14.3	726.1 ± 15.2	694.9 ± 12.0
Leukocytes (10^3/μL)					
Day 5	4.78 ± 0.39	5.43 ± 0.53	5.17 ± 0.48	4.59 ± 0.60	5.07 ± 0.55
Day 22	7.64 ± 0.59	7.60 ± 0.68	7.63 ± 0.79	7.01 ± 0.54	7.23 ± 0.71
Day 92	9.96 ± 0.37	10.27 ± 0.58	10.05 ± 0.51	10.78 ± 0.43	10.38 ± 0.61
Day 183	9.06 ± 0.75	9.45 ± 0.65	8.81 ± 0.64	8.76 ± 0.68	7.58 ± 0.28
Segmented neutrophils (10^3/μL)					
Day 5	0.71 ± 0.07	0.95 ± 0.09	0.74 ± 0.06	0.85 ± 0.11	0.71 ± 0.07
Day 22	1.10 ± 0.21	0.98 ± 0.12[2]	1.00 ± 0.13	0.97 ± 0.15	0.90 ± 0.14
Day 92	1.51 ± 0.22	1.48 ± 0.13	1.44 ± 0.19	2.17 ± 0.26	1.42 ± 0.12
Day 183	1.83 ± 0.22	1.74 ± 0.41	1.86 ± 0.24	1.58 ± 0.20	1.40 ± 0.20
Lymphocytes (10^3/μL)					
Day 5	4.00 ± 0.33	4.35 ± 0.44	4.33 ± 0.42	3.64 ± 0.48	4.27 ± 0.49
Day 22	6.21 ± 0.40	6.25 ± 0.60[2]	6.36 ± 0.66	5.89 ± 0.47	5.96 ± 0.57
Day 92	7.94 ± 0.36	8.03 ± 0.47	7.97 ± 0.46	7.95 ± 0.43	8.35 ± 0.55
Day 183	6.87 ± 0.53	7.31 ± 0.31	6.66 ± 0.51	6.78 ± 0.58	5.98 ± 0.31
Monocytes (10^3/μL)					
Day 5	0.06 ± 0.02	0.10 ± 0.05	0.08 ± 0.05	0.08 ± 0.02	0.06 ± 0.02
Day 22	0.26 ± 0.06	0.16 ± 0.03	0.23 ± 0.08	0.14 ± 0.04	0.35 ± 0.09
Day 92	0.38 ± 0.06	0.63 ± 0.07	0.53 ± 0.06	0.49 ± 0.05	0.45 ± 0.08
Day 183	0.22 ± 0.05	0.27 ± 0.09	0.19 ± 0.06	0.29 ± 0.07	0.12 ± 0.03
Eosinophils (10^3/μL)					
Day 5	0.02 ± 0.01	0.03 ± 0.01	0.03 ± 0.01	0.02 ± 0.01	0.03 ± 0.01
Day 22	0.07 ± 0.02	0.02 ± 0.01	0.04 ± 0.02	0.02 ± 0.01	0.03 ± 0.01
Day 92	0.13 ± 0.03	0.13 ± 0.03	0.11 ± 0.03	0.18 ± 0.06	0.16 ± 0.04
Day 183	0.13 ± 0.03	0.12 ± 0.05	0.09 ± 0.03	0.12 ± 0.04	0.08 ± 0.02
Methemoglobin (g/dL)					
Day 5	0.24 ± 0.07[3]	0.22 ± 0.03	0.17 ± 0.03	0.21 ± 0.06	0.32 ± 0.04
Day 22	0.24 ± 0.02[2]	0.26 ± 0.02	0.27 ± 0.03	0.32 ± 0.05	0.32 ± 0.05
Day 92	0.23 ± 0.04	0.24 ± 0.04	0.17 ± 0.02	0.23 ± 0.03	0.16 ± 0.01
Day 183	0.23 ± 0.02	0.25 ± 0.03	0.27 ± 0.03	0.24 ± 0.03	0.22 ± 0.02

TABLE D1 Hematology, Clinical Chemistry, and Urinalysis Data for F344/N Rats in the 26-Week Drinking Water Study of a California Pesticide/Fertilizer Mixture (continued)

	Vehicle Control	0.1X	1X	10X	100X
MALE (continued)					
Clinical Chemistry					
n					
Day 5	10	10	10	10	9
Day 22	10	10	10	10	10
Day 92	10	10	10	10	10
Day 183	10	10	10	9	10
Urea nitrogen (mg/dL)					
Day 5	22.0 ± 0.6	21.1 ± 0.5	21.7 ± 0.4	20.3 ± 0.7	22.7 ± 0.6
Day 22	22.5 ± 0.6	21.1 ± 0.7	20.5 ± 0.6*	19.2 ± 0.4**	21.0 ± 0.6*
Day 92	22.2 ± 0.8	23.3 ± 0.5	24.2 ± 1.2	24.5 ± 0.7	21.9 ± 0.8
Day 183	21.5 ± 1.1[2]	20.0 ± 1.0	21.0 ± 0.5	21.2 ± 0.5	21.0 ± 0.7
Creatinine (mg/dL)					
Day 5	0.53 ± 0.03[2]	0.53 ± 0.02[4]	0.55 ± 0.03[5]	0.49 ± 0.02[5]	0.53 ± 0.02[5]
Day 22	0.52 ± 0.01	0.55 ± 0.02	0.54 ± 0.01	0.54 ± 0.02	0.54 ± 0.02
Day 92	0.58 ± 0.02	0.64 ± 0.02	0.60 ± 0.02	0.64 ± 0.02	0.54 ± 0.07
Day 183	0.62 ± 0.02[6]	0.63 ± 0.03[6]	0.60 ± 0.02[7]	0.61 ± 0.03[6]	0.64 ± 0.02[6]
Total protein (g/dL)					
Day 5	5.8 ± 0.1[3]	5.9 ± 0.1	5.9 ± 0.1	5.6 ± 0.2	5.9 ± 0.1
Day 22	6.0 ± 0.1	6.0 ± 0.0	5.9 ± 0.1	5.9 ± 0.1	6.0 ± 0.1
Day 92	6.9 ± 0.1	7.3 ± 0.1**	7.4 ± 0.1**	7.3 ± 0.1**	7.3 ± 0.1**
Day 183	7.2 ± 0.1	7.1 ± 0.3	7.4 ± 0.1	7.3 ± 0.1	7.5 ± 0.1
Albumin (g/dL)					
Day 5	3.4 ± 0.1	3.5 ± 0.1	3.5 ± 0.0	3.5 ± 0.1[2]	3.5 ± 0.0[3]
Day 22	3.4 ± 0.1	3.4 ± 0.1	3.5 ± 0.1	3.4 ± 0.1	3.3 ± 0.1
Day 92	3.8 ± 0.1	4.0 ± 0.1	4.0 ± 0.1	3.9 ± 0.1	4.0 ± 0.1
Day 183	4.1 ± 0.1	4.0 ± 0.0[2]	4.0 ± 0.1	4.0 ± 0.1	4.0 ± 0.1
Alanine aminotransferase (IU/L)					
Day 5	57 ± 3	54 ± 2	54 ± 3	54 ± 3[2]	48 ± 2*
Day 22	50 ± 1	49 ± 2	41 ± 1**	47 ± 2*	46 ± 2*
Day 92	47 ± 2	48 ± 2	48 ± 2	53 ± 2*	52 ± 3
Day 183	61 ± 3	55 ± 4	54 ± 2	61 ± 2	55 ± 4
Alkaline phosphatase (IU/L)					
Day 5	663 ± 16	701 ± 13	691 ± 8	703 ± 16	716 ± 23
Day 22	486 ± 9	500 ± 13	494 ± 10	494 ± 17	492 ± 12
Day 92	225 ± 11	200 ± 15	241 ± 7	166 ± 6**	146 ± 6**
Day 183	220 ± 8	225 ± 11[3]	227 ± 7[2]	222 ± 6	220 ± 6
Creatine kinase (IU/L)					
Day 5	287 ± 44	349 ± 37	360 ± 45	318 ± 43	328 ± 28
Day 22	293 ± 34	319 ± 32	462 ± 80	303 ± 34	357 ± 44
Day 92	257 ± 43	291 ± 52	322 ± 48[2]	326 ± 65	277 ± 29
Day 183	213 ± 38	237 ± 50	345 ± 93	270 ± 58	268 ± 46
Sorbitol dehydrogenase (IU/L)					
Day 5	12 ± 1	14 ± 2	11 ± 1	11 ± 1	10 ± 0
Day 22	12 ± 0	13 ± 1	10 ± 0	12 ± 1	11 ± 0
Day 92	10 ± 1	13 ± 1	10 ± 1	11 ± 1	12 ± 1[2]
Day 183	8 ± 1	8 ± 1[2]	7 ± 1	7 ± 1	8 ± 0

TABLE D1 Hematology, Clinical Chemistry, and Urinalysis Data for F344/N Rats in the 26-Week Drinking Water Study of a California Pesticide/Fertilizer Mixture (continued)

	Vehicle Control	0.1X	1X	10X	100X
MALE (continued)					
Clinical Chemistry (continued)					
Cholinesterase (IU/L)					
Day 5	514.0 ± 20.2[2]	561.8 ± 12.7[2]	578.5 ± 19.2[3]	537.3 ± 14.2[3]	546.0 ± 17.6[4]
Day 22	578.8 ± 30.6	563.1 ± 22.3	600.3 ± 16.3	501.5 ± 13.6	570.5 ± 30.1
Day 92	590.7 ± 25.7	612.8 ± 42.5	649.2 ± 19.9	613.4 ± 17.4	648.9 ± 20.7
Day 183	661.8 ± 17.0	624.0 ± 24.9[2]	686.7 ± 18.7	645.4 ± 17.6	661.6 ± 21.4
Bile acids (µmol/L)					
Day 5	44.00 ± 3.76[2]	50.00 ± 5.40[2]	57.56 ± 4.25[2]	46.50 ± 4.49[4]	44.14 ± 6.48[5]
Day 22	28.00 ± 2.40	24.90 ± 2.90	23.30 ± 3.38	23.40 ± 2.42	23.40 ± 4.29
Day 92	26.60 ± 3.61	28.50 ± 3.82	24.20 ± 4.21	30.10 ± 2.45	20.50 ± 3.33
Day 183	32.20 ± 2.92[6]	26.75 ± 4.78[7]	30.50 ± 5.45[7]	39.20 ± 4.32[6]	37.60 ± 4.57[6]
Urinalysis					
n					
Day 3	10	10	10	10	10
Day 18	10	10	10	10	10
Day 88	10	10	9	10	10
Day 179	10	10	10	9	10
Creatinine (mg/dL)					
Day 3	41.80 ± 6.65	45.20 ± 8.45	46.85 ± 5.36	40.95 ± 4.72	33.90 ± 4.04
Day 18	49.55 ± 8.51	64.70 ± 7.40	52.80 ± 6.23	47.90 ± 6.51	47.00 ± 5.64
Day 88	105.75 ± 11.01	98.45 ± 10.53	139.28 ± 18.90	86.60 ± 7.19	103.60 ± 10.55
Day 179	228.4 ± 22.1	166.9 ± 9.2	181.8 ± 14.3	198.2 ± 25.3	196.5 ± 20.9
Glucose (mg/dL)					
Day 3	9 ± 1	11 ± 2	14 ± 2*	11 ± 1	10 ± 1
Day 18	10 ± 2	13 ± 2	11 ± 1	10 ± 2	10 ± 1
Day 88	20 ± 2	20 ± 2	24 ± 3	18 ± 1	20 ± 2
Day 179	27 ± 3	20 ± 1	23 ± 2	24 ± 3	23 ± 2
Glucose/creatinine ratio					
Day 3	0.21 ± 0.02	0.27 ± 0.03	0.32 ± 0.05	0.30 ± 0.02**	0.28 ± 0.03*[2]
Day 18	0.20 ± 0.01	0.20 ± 0.01	0.20 ± 0.01	0.20 ± 0.01	0.22 ± 0.02
Day 88	0.20 ± 0.01	0.21 ± 0.01	0.16 ± 0.01[3]	0.21 ± 0.01	0.20 ± 0.01
Day 179	0.11 ± 0.01	0.12 ± 0.00	0.13 ± 0.01	0.13 ± 0.01	0.11 ± 0.00
Protein (mg/dL)					
Day 3	10 ± 1	15 ± 3	17 ± 3	12 ± 1	12 ± 3
Day 18	74 ± 13	97 ± 8	73 ± 11	77 ± 12	72 ± 8
Day 88	119 ± 10	109 ± 13	116 ± 17	99 ± 8	117 ± 14
Day 179	160 ± 8[3]	167 ± 9	153 ± 12	147 ± 18	170 ± 15
Protein/creatinine ratio					
Day 3	0.26 ± 0.03	0.35 ± 0.05	0.37 ± 0.05	0.30 ± 0.02	0.35 ± 0.07[2]
Day 18	1.46 ± 0.12	1.56 ± 0.11	1.33 ± 0.08	1.57 ± 0.06	1.59 ± 0.18
Day 88	1.16 ± 0.07	1.13 ± 0.06	0.97 ± 0.20	1.17 ± 0.08	1.11 ± 0.06
Day 179	0.83 ± 0.06[2]	1.01 ± 0.04	0.85 ± 0.04	0.80 ± 0.11	0.89 ± 0.06

TABLE D1 Hematology, Clinical Chemistry, and Urinalysis Data for F344/N Rats in the 26-Week Drinking Water Study of a California Pesticide/Fertilizer Mixture (continued)

	Vehicle Control	0.1X	1X	10X	100X
MALE (continued)					
Urinalysis (continued)					
Alkaline phosphatase (IU/L)					
Day 3	115 ± 9	124 ± 14	152 ± 19	113 ± 10	111 ± 11
Day 18	208 ± 28	341 ± 26*	271 ± 31	216 ± 23	220 ± 18
Day 38	263 ± 19	236 ± 28	227 ± 17	200 ± 20	211 ± 21
Day 179	253 ± 17	244 ± 13	228 ± 27	269 ± 31	273 ± 24
Alkaline phosphatase (IU/g creatinine)					
Day 3	305 ± 29	316 ± 39	341 ± 39	295 ± 26	296 ± 22[2]
Day 18	489 ± 48	544 ± 27	520 ± 28	468 ± 22	496 ± 42
Day 38	266 ± 26	253 ± 24	186 ± 23	236 ± 19	211 ± 22*
Day 179	112 ± 7	147 ± 7*	125 ± 13	142 ± 12	143 ± 10
Aspartate aminotransferase (IU/L)					
Day 3	10 ± 1	14 ± 3	13 ± 1	13 ± 2	8 ± 1
Day 18	14 ± 3	14 ± 3	15 ± 4	16 ± 5	23 ± 4
Day 38	36 ± 2	33 ± 2	43 ± 5	32 ± 3	36 ± 3
Day 179	48 ± 4	44 ± 4	43 ± 3	47 ± 5	44 ± 4
Aspartate aminotransferase (IU/g creatinine)					
Day 3	25 ± 2	31 ± 3	28 ± 3	32 ± 4	23 ± 1[2]
Day 18	33 ± 7	24 ± 6	28 ± 6	37 ± 12	52 ± 11
Day 38	36 ± 3	38 ± 5	35 ± 6	38 ± 2	35 ± 1
Day 179	21 ± 1	26 ± 2*	24 ± 1	25 ± 2	23 ± 0
N-acetyl-β-D-glucosaminidase (IU/L)					
Day 3	7.6 ± 0.8	9.5 ± 1.7	10.5 ± 1.0	9.0 ± 1.2	7.2 ± 0.8
Day 18	7.1 ± 1.1	8.7 ± 0.7	7.1 ± 0.9	7.6 ± 1.2	7.3 ± 0.9
Day 38	11.1 ± 0.9	11.1 ± 0.9	10.7 ± 0.9	9.7 ± 0.7	10.6 ± 0.8
Day 179	12.6 ± 1.0	10.8 ± 0.6	11.9 ± 1.1	12.3 ± 1.1	11.3 ± 0.8
N-acetyl-β-D-glucosaminidase (IU/g creatinine)					
Day 3	19.5 ± 1.9	22.1 ± 2.5	23.9 ± 2.4	23.1 ± 2.9	19.4 ± 1.9[2]
Day 18	14.0 ± 1.3	13.9 ± 0.6	13.4 ± 0.8	15.5 ± 1.0	16.2 ± 1.4
Day 38	11.1 ± 1.0	12.0 ± 0.8	8.7 ± 1.1	11.6 ± 0.9	10.8 ± 0.8
Day 179	5.5 ± 0.2	6.7 ± 0.3*	6.6 ± 0.2*	6.4 ± 0.6	5.9 ± 0.4
Volume (mL/16 hr)					
Day 3	6.0 ± 0.7	4.3 ± 0.8	3.5 ± 0.4*	3.7 ± 0.3*	4.7 ± 0.4
Day 18	9.7 ± 2.6	4.9 ± 0.6	6.4 ± 1.2	8.6 ± 1.3	8.2 ± 0.8
Day 38	3.9 ± 0.6[2]	4.2 ± 0.8	3.9 ± 0.9	3.5 ± 0.8	4.6 ± 1.0
Day 179	3.3 ± 0.5	4.4 ± 0.5	4.1 ± 0.6	4.1 ± 0.7	3.5 ± 0.6
Specific gravity					
Day 3	1.020 ± 0.002	1.028 ± 0.005	1.027 ± 0.002	1.024 ± 0.002	1.021 ± 0.001
Day 18	1.019 ± 0.003	1.024 ± 0.002	1.021 ± 0.002	1.019 ± 0.002	1.020 ± 0.002
Day 38	1.030 ± 0.003[2]	1.032 ± 0.003	1.037 ± 0.004	1.027 ± 0.002	1.037 ± 0.003
Day 179	1.028 ± 0.002	1.029 ± 0.001	1.028 ± 0.002	1.027 ± 0.001	1.026 ± 0.001
pH					
Day 3	6.40 ± 0.07	6.40 ± 0.07	6.35 ± 0.08	6.50 ± 0.07	6.45 ± 0.05
Day 18	6.55 ± 0.05	6.45 ± 0.05	6.70 ± 0.08	6.50 ± 0.00	6.50 ± 0.00
Day 38	6.94 ± 0.10[2]	6.95 ± 0.09	6.78 ± 0.09	6.90 ± 0.07	6.55 ± 0.05**
Day 179	6.70 ± 0.11	7.05 ± 0.05	6.80 ± 0.08	6.78 ± 0.09	7.00 ± 0.07

TABLE D1 Hematology, Clinical Chemistry, and Urinalysis Data for F344/N Rats in the 26-Week Drinking Water Study of a California Pesticide/Fertilizer Mixture (continued)

	Vehicle Control	0.1X	1X	10X	100X
FEMALE					
Hematology					
n					
Day 5	9	9	9	10	10
Day 22	8	10	10	10	10
Day 92	10	10	10	10	10
Day 183	9	9	10	9	9
Hematocrit (%)					
Day 5	43.2 ± 0.5	41.8 ± 0.5	41.7 ± 0.5	43.1 ± 0.5	43.2 ± 0.5
Day 22	46.4 ± 0.6	45.7 ± 0.4	45.1 ± 0.6	46.2 ± 0.5	46.1 ± 0.6
Day 92	45.7 ± 0.4	45.4 ± 0.4	44.4 ± 0.4	45.3 ± 0.5	45.3 ± 0.5
Day 183	46.5 ± 0.4	45.8 ± 0.4	45.4 ± 0.5	44.8 ± 0.4**	45.2 ± 0.4*
Hemoglobin (g/dL)					
Day 5	14.3 ± 0.2	13.8 ± 0.2	13.8 ± 0.2	14.2 ± 0.2	14.2 ± 0.2
Day 22	15.7 ± 0.2	15.4 ± 0.1	15.2 ± 0.2	15.7 ± 0.1	15.6 ± 0.2
Day 92	15.2 ± 0.1	15.2 ± 0.1	14.9 ± 0.2	15.0 ± 0.2	15.0 ± 0.1
Day 183	15.3 ± 0.1	15.3 ± 0.1	15.1 ± 0.1	14.9 ± 0.1*	15.0 ± 0.1*
Erythrocytes (10^6/μL)					
Day 5	7.38 ± 0.11	7.07 ± 0.07	7.10 ± 0.11	7.32 ± 0.10	7.27 ± 0.11
Day 22	7.96 ± 0.13	7.90 ± 0.08	7.63 ± 0.13	7.92 ± 0.07	7.85 ± 0.12
Day 92	8.44 ± 0.08	8.44 ± 0.07	8.25 ± 0.07*	8.36 ± 0.07	8.30 ± 0.07
Day 183	8.50 ± 0.09	8.56 ± 0.07	8.44 ± 0.07	8.19 ± 0.07*	8.37 ± 0.09
Reticulocytes (10^6/μL)					
Day 5	0.15 ± 0.01	0.13 ± 0.01	0.12 ± 0.01	0.11 ± 0.01[2]	0.14 ± 0.01
Day 22	0.13 ± 0.01	0.14 ± 0.01	0.14 ± 0.01	0.15 ± 0.01	0.14 ± 0.01[2]
Day 92	0.20 ± 0.02	0.16 ± 0.01	0.17 ± 0.02	0.18 ± 0.02	0.18 ± 0.02
Day 183	0.10 ± 0.01	0.10 ± 0.00	0.10 ± 0.01	0.09 ± 0.01	0.09 ± 0.01
Nucleated erythrocytes (10^3/μL)					
Day 5	0.02 ± 0.01	0.03 ± 0.01	0.02 ± 0.01	0.05 ± 0.02	0.06 ± 0.02
Day 22	0.00 ± 0.00	0.00 ± 0.00	0.01 ± 0.01	0.01 ± 0.01	0.00 ± 0.00
Day 92	0.10 ± 0.02	0.05 ± 0.01	0.06 ± 0.02	0.07 ± 0.03	0.09 ± 0.02
Day 183	0.06 ± 0.02	0.05 ± 0.02	0.04 ± 0.01	0.03 ± 0.01	0.07 ± 0.02
Mean cell volume (fL)					
Day 5	58.6 ± 0.4	59.0 ± 0.5	58.8 ± 0.4	58.9 ± 0.4	59.5 ± 0.4
Day 22	58.2 ± 0.5	58.0 ± 0.4	59.1 ± 0.4	58.3 ± 0.4	58.7 ± 0.3
Day 92	54.2 ± 0.2	53.8 ± 0.2	53.8 ± 0.3	54.2 ± 0.3	54.6 ± 0.2
Day 183	54.7 ± 0.4	53.5 ± 0.4	53.8 ± 0.4	54.6 ± 0.4	54.1 ± 0.3
Mean cell hemoglobin (pg)					
Day 5	19.3 ± 0.1	19.5 ± 0.1	19.4 ± 0.1	19.4 ± 0.1	19.5 ± 0.1
Day 22	19.7 ± 0.1	19.5 ± 0.2	19.9 ± 0.1	19.8 ± 0.1	19.8 ± 0.1
Day 92	18.0 ± 0.1	18.0 ± 0.1	18.1 ± 0.0	18.0 ± 0.1	18.1 ± 0.1
Day 183	18.0 ± 0.1	17.9 ± 0.1	17.9 ± 0.1	18.2 ± 0.1	17.9 ± 0.2
Mean cell hemoglobin concentration (g/dL)					
Day 5	33.0 ± 0.2	33.0 ± 0.2	33.0 ± 0.1	32.9 ± 0.1	32.9 ± 0.1
Day 22	33.8 ± 0.1	33.7 ± 0.1	33.7 ± 0.2	33.9 ± 0.2	33.7 ± 0.1
Day 92	33.2 ± 0.2	33.5 ± 0.1	33.6 ± 0.2	33.2 ± 0.1	33.1 ± 0.2
Day 183	32.9 ± 0.2	33.4 ± 0.1	33.3 ± 0.1	33.3 ± 0.1	33.1 ± 0.1

TABLE D1 Hematology, Clinical Chemistry, and Urinalysis Data for F344/N Rats in the 26-Week Drinking Water Study of a California Pesticide/Fertilizer Mixture (continued)

	Vehicle Control	0.1X	1X	10X	100X
FEMALE (continued)					
Hematology (continued)					
Platelets (10^3/μL)					
Day 5	832.6 ± 39.1	878.0 ± 18.1	904.4 ± 21.7	849.8 ± 16.9	860.0 ± 44.4
Day 22	807.3 ± 28.3	761.2 ± 17.4	742.2 ± 11.0	762.9 ± 20.7	758.2 ± 16.4
Day 92	824.0 ± 10.0	820.0 ± 7.8	798.9 ± 14.6	760.2 ± 17.0*	820.4 ± 16.2
Day 183	751.4 ± 12.0	741.8 ± 18.2	705.2 ± 13.5	714.0 ± 16.1	743.7 ± 20.7
Leukocytes (10^3/μL)					
Day 5	4.62 ± 0.42	4.21 ± 0.46	4.25 ± 0.45	5.55 ± 0.37	5.03 ± 0.51
Day 22	6.26 ± 0.55	7.06 ± 0.65	5.72 ± 0.63	6.51 ± 0.59	6.20 ± 0.68
Day 92	6.59 ± 0.53	7.41 ± 0.52	5.81 ± 0.48	7.01 ± 0.52	7.49 ± 0.41
Day 183	6.14 ± 0.75	5.57 ± 0.46	5.15 ± 0.49	5.22 ± 0.59	5.78 ± 0.37
Segmented neutrophils (10^3/μL)					
Day 5	0.63 ± 0.07	0.55 ± 0.07	0.55 ± 0.07	0.71 ± 0.07	0.62 ± 0.12
Day 22	0.85 ± 0.13	0.70 ± 0.10	0.64 ± 0.11	0.77 ± 0.09	0.84 ± 0.11
Day 92	0.93 ± 0.07	1.16 ± 0.10	0.98 ± 0.13	1.30 ± 0.22	1.13 ± 0.14
Day 183	0.94 ± 0.12	1.27 ± 0.36	0.80 ± 0.07	0.92 ± 0.12	1.05 ± 0.13
Lymphocytes (10^3/μL)					
Day 5	3.82 ± 0.37	3.52 ± 0.37	3.53 ± 0.39	4.64 ± 0.32	4.24 ± 0.40
Day 22	5.35 ± 0.44	6.26 ± 0.56	5.00 ± 0.57	5.62 ± 0.50	5.25 ± 0.57
Day 92	5.52 ± 0.50	6.08 ± 0.45	4.69 ± 0.35	5.60 ± 0.34	6.21 ± 0.37
Day 183	4.96 ± 0.60	4.18 ± 0.26	4.24 ± 0.45	4.17 ± 0.49	4.57 ± 0.32
Monocytes (10^3/μL)					
Day 5	0.14 ± 0.04	0.11 ± 0.03	0.13 ± 0.02	0.18 ± 0.04	0.14 ± 0.05
Day 22	0.06 ± 0.01	0.06 ± 0.04	0.03 ± 0.01	0.10 ± 0.02	0.09 ± 0.03
Day 92	0.08 ± 0.03	0.10 ± 0.04	0.06 ± 0.02	0.08 ± 0.03	0.09 ± 0.03
Day 183	0.194 ± 0.040	0.068 ± 0.015	0.070 ± 0.017*	0.077 ± 0.016	0.103 ± 0.032
Eosinophils (10^3/μL)					
Day 5	0.03 ± 0.01	0.03 ± 0.01	0.04 ± 0.02	0.03 ± 0.01	0.03 ± 0.01
Day 22	0.01 ± 0.01	0.04 ± 0.01	0.05 ± 0.02	0.02 ± 0.01	0.02 ± 0.01
Day 92	0.06 ± 0.01	0.06 ± 0.02	0.08 ± 0.03	0.03 ± 0.02	0.06 ± 0.02
Day 183	0.05 ± 0.02	0.05 ± 0.03	0.05 ± 0.01	0.05 ± 0.02	0.06 ± 0.02
Methemoglobin (g/dL)					
Day 5	0.28 ± 0.05	0.24 ± 0.02[3]	0.32 ± 0.11	0.24 ± 0.03	0.26 ± 0.03
Day 22	0.26 ± 0.01	0.29 ± 0.03	0.22 ± 0.02	0.32 ± 0.03	0.29 ± 0.03
Day 92	0.23 ± 0.04[2]	0.21 ± 0.03	0.23 ± 0.02	0.23 ± 0.02	0.24 ± 0.04
Day 183	0.31 ± 0.02	0.36 ± 0.03	0.31 ± 0.03	0.28 ± 0.02	0.38 ± 0.06

TABLE D1 Hematology, Clinical Chemistry, and Urinalysis Data for F344/N Rats in the 26-Week Drinking Water Study of a California Pesticide/Fertilizer Mixture (continued)

	Vehicle Control	0.1X	1X	10X	100X
FEMALE (continued)					
Clinical Chemistry					
n	10	10	10	10	10
Urea nitrogen (mg/dL)					
Day 5	23.3 ± 0.6	21.0 ± 0.8	20.0 ± 0.8*	21.3 ± 0.8	21.8 ± 0.7
Day 22	20.2 ± 0.8	20.1 ± 0.5	20.5 ± 0.5	20.9 ± 0.6	20.8 ± 0.4
Day 92	21.4 ± 0.4	19.7 ± 0.6	21.8 ± 0.4	21.4 ± 0.7	22.5 ± 0.6
Day 183	20.5 ± 0.6	21.8 ± 0.9	21.2 ± 0.8	20.9 ± 0.9	22.1 ± 0.8
Creatinine (mg/dL)					
Day 5	0.50 ± 0.04[7]	0.54 ± 0.03[6]	0.49 ± 0.01[7]	0.53 ± 0.01[6]	0.48 ± 0.02[6]
Day 22	0.51 ± 0.01	0.50 ± 0.02[2]	0.50 ± 0.02[2]	0.49 ± 0.02	0.51 ± 0.02
Day 92	0.54 ± 0.03	0.51 ± 0.02	0.55 ± 0.01	0.54 ± 0.02	0.55 ± 0.04
Day 183	0.60 ± 0.02[3]	0.56 ± 0.02[3]	0.60 ± 0.02[3]	0.56 ± 0.02[5]	0.58 ± 0.02[3]
Total protein (g/dL)					
Day 5	5.8 ± 0.1	5.9 ± 0.1	5.8 ± 0.1	6.0 ± 0.1	6.0 ± 0.1
Day 22	5.8 ± 0.1	6.0 ± 0.1	6.1 ± 0.1*	6.0 ± 0.1	6.0 ± 0.1
Day 92	6.7 ± 0.1	6.9 ± 0.1	6.9 ± 0.1	6.6 ± 0.1	6.8 ± 0.1
Day 183	7.3 ± 0.1	7.3 ± 0.1	7.7 ± 0.1	7.2 ± 0.1	7.4 ± 0.1
Albumin (g/dL)					
Day 5	3.4 ± 0.1	3.5 ± 0.1	3.5 ± 0.0	3.5 ± 0.1	3.5 ± 0.1
Day 22	3.5 ± 0.1	3.6 ± 0.1	3.6 ± 0.1	3.6 ± 0.1	3.5 ± 0.0
Day 92	3.9 ± 0.1	4.0 ± 0.1	4.0 ± 0.1	3.9 ± 0.1	4.1 ± 0.1
Day 183	4.0 ± 0.1	4.1 ± 0.1[2]	4.3 ± 0.1	4.0 ± 0.1	4.1 ± 0.1
Alanine aminotransferase (IU/L)					
Day 5	50 ± 3	47 ± 2	50 ± 4	53 ± 4	52 ± 3
Day 22	43 ± 2	49 ± 3	43 ± 2	47 ± 2	41 ± 1
Day 92	38 ± 1[2]	36 ± 1	35 ± 1	40 ± 1	40 ± 1
Day 183	49 ± 2	51 ± 3	45 ± 2	51 ± 5	50 ± 2
Alkaline phosphatase (IU/L)					
Day 5	578 ± 10	598 ± 20	584 ± 6	593 ± 13	598 ± 8
Day 22	402 ± 13	408 ± 17	403 ± 12	423 ± 10	407 ± 9
Day 92	249 ± 9	208 ± 9*	228 ± 10	238 ± 7	243 ± 9
Day 183	218 ± 5	198 ± 7	199 ± 5	197 ± 7	204 ± 4
Creatine kinase (IU/L)					
Day 5	248 ± 36	268 ± 26	273 ± 29	228 ± 17[2]	287 ± 21
Day 22	405 ± 42	380 ± 40	313 ± 42	393 ± 84	288 ± 28
Day 92	241 ± 52	218 ± 20	256 ± 46	254 ± 38	284 ± 54
Day 183	139 ± 14	196 ± 29[2]	127 ± 14	136 ± 29	195 ± 41
Sorbitol dehydrogenase (IU/L)					
Day 5	11 ± 0	12 ± 1	12 ± 1	12 ± 1	11 ± 0
Day 22	10 ± 1	11 ± 1	10 ± 1	11 ± 1	10 ± 0
Day 92	8 ± 0	8 ± 0	8 ± 0	8 ± 0	8 ± 0
Day 183	7 ± 0	7 ± 0	6 ± 0	7 ± 0[2]	6 ± 0
Cholinesterase (IU/L)					
Day 5	865.3 ± 41.7[3]	863.4 ± 46.2[2]	832.4 ± 33.8[2]	851.4 ± 43.6[2]	913.8 ± 30.7
Day 22	1636 ± 66	1803 ± 97	1715 ± 76	1636 ± 65	1692 ± 89
Day 92	2830 ± 133	3038 ± 126	3089 ± 132	2916 ± 111	3093 ± 121
Day 183	3079 ± 82	3112 ± 99	3418 ± 133	3422 ± 125	3099 ± 147

TABLE D1 Hematology, Clinical Chemistry, and Urinalysis Data for F344/N Rats in the 26-Week Drinking Water Study of a California Pesticide/Fertilizer Mixture (continued)

	Vehicle Control	0.1X	1X	10X	100X
FEMALE (continued)					
Clinical Chemistry (continued)					
Bile acids (μmol/L)					
Day 5	38.40 ± 2.18[6]	43.80 ± 7.86[6]	39.63 ± 5.36[3]	28.33 ± 4.14[4]	39.40 ± 5.57[6]
Day 22	24.60 ± 4.07	27.80 ± 3.00	28.10 ± 3.56	26.40 ± 1.81	32.00 ± 2.64
Day 92	37.30 ± 3.74	32.50 ± 3.87	30.80 ± 3.38	27.40 ± 4.13	34.50 ± 4.02
Day 183	52.75 ± 4.06[3]	44.43 ± 4.08[5]	43.86 ± 5.58[5]	36.00 ± 2.60*[5]	51.75 ± 3.43[3]
Urinalysis					
n					
Day 3	10	9	9	10	10
Day 18	10	10	10	10	10
Day 88	10	10	10	9	10
Day 179	9	10	10	10	10
Creatinine (mg/dL)					
Day 3	36.65 ± 4.81	32.67 ± 3.65	30.28 ± 5.39	35.45 ± 5.94	32.25 ± 6.69
Day 18	41.50 ± 4.97	33.90 ± 4.09	33.80 ± 6.71	25.40 ± 1.89*	27.95 ± 3.12*
Day 88	54.75 ± 12.05	54.15 ± 7.11	44.40 ± 5.00	56.61 ± 7.58	41.56 ± 6.68[2]
Day 179	67.39 ± 4.21	89.85 ± 10.44	72.70 ± 5.78	86.00 ± 2.92	65.10 ± 8.60
Glucose (mg/dL)					
Day 3	7 ± 0[2]	7 ± 1[3]	6 ± 1	7 ± 1	9 ± 1
Day 18	6 ± 0[2]	6 ± 1	6 ± 1	4 ± 0*	4 ± 1*
Day 88	8 ± 1	5 ± 1	6 ± 1	8 ± 1	6 ± 1[2]
Day 179	7 ± 1[8]	10 ± 2	7 ± 1	8 ± 1	6 ± 1
Glucose/creatinine ratio					
Day 3	0.22 ± 0.01	0.21 ± 0.02[3]	0.22 ± 0.03	0.22 ± 0.02	0.27 ± 0.03[2]
Day 18	0.16 ± 0.01	0.19 ± 0.03	0.21 ± 0.03	0.17 ± 0.01	0.16 ± 0.01
Day 88	0.17 ± 0.02	0.09 ± 0.02	0.13 ± 0.02	0.14 ± 0.02	0.13 ± 0.01[3]
Day 179	0.10 ± 0.01	0.10 ± 0.01	0.09 ± 0.01	0.09 ± 0.01	0.09 ± 0.01[2]
Protein (mg/dL)					
Day 3	5 ± 0[2]	5 ± 1	4 ± 1	5 ± 1	6 ± 1
Day 18	4 ± 1	3 ± 0	4 ± 1	3 ± 0	3 ± 0
Day 88	5.2 ± 0.9	4.8 ± 0.6	3.1 ± 0.3	3.4 ± 0.6	2.8 ± 0.4*[2]
Day 179	2 ± 0	4 ± 1	2 ± 0	3 ± 1	3 ± 1
Protein/creatinine ratio					
Day 3	0.16 ± 0.01	0.16 ± 0.02	0.14 ± 0.02	0.14 ± 0.01	0.18 ± 0.03[2]
Day 18	0.09 ± 0.00	0.11 ± 0.02	0.14 ± 0.02*	0.12 ± 0.01*	0.12 ± 0.01*
Day 88	0.12 ± 0.02	0.09 ± 0.01	0.08 ± 0.01*	0.06 ± 0.01**	0.06 ± 0.01**[3]
Day 179	0.03 ± 0.01	0.03 ± 0.01	0.03 ± 0.01	0.03 ± 0.01	0.04 ± 0.01
Alkaline phosphatase (IU/L)					
Day 3	118 ± 14	91 ± 11	78 ± 14	77 ± 11	103 ± 17
Day 18	97 ± 14	72 ± 12	73 ± 17	53 ± 7*	58 ± 8*
Day 88	59 ± 13	55 ± 7	48 ± 4	63 ± 10	53 ± 12
Day 179	46 ± 6	81 ± 11*	61 ± 7	71 ± 8	56 ± 10

TABLE D1 Hematology, Clinical Chemistry, and Urinalysis Data for F344/N Rats in the 26-Week Drinking Water Study of a California Pesticide/Fertilizer Mixture (continued)

	Vehicle Control	0.1X	1X	10X	100X
FEMALE (continued)					
Urinalysis (continued)					
Alkaline phosphatase (IU/g creatinine)					
Day 3	326 ± 25	290 ± 27	276 ± 37	238 ± 24*	316 ± 73[2]
Day 18	237 ± 26	237 ± 56	217 ± 17	201 ± 18	207 ± 15
Day 88	117 ± 13	107 ± 8	119 ± 15	116 ± 13	101 ± 11[3]
Day 179	68 ± 7	91 ± 5	84 ± 6	81 ± 8	83 ± 4
Aspartate aminotransferase (IU/L)					
Day 3	10 ± 2[2]	14 ± 5	6 ± 1	19 ± 9	11 ± 1
Day 18	3 ± 0	4 ± 1	4 ± 1	7 ± 2	4 ± 1[2]
Day 88	4 ± 1[2]	10 ± 4	4 ± 1	11 ± 6	10 ± 4
Day 179	4 ± 0[8]	7 ± 1*	5 ± 0	5 ± 0	6 ± 2
Aspartate aminotransferase (IU/g creatinine)					
Day 3	26 ± 2[2]	50 ± 20	20 ± 1	64 ± 28	34 ± 5[2]
Day 18	8 ± 1	15 ± 5	14 ± 5	28 ± 11	16 ± 5[2]
Day 88	12 ± 4	24 ± 8	9 ± 2	19 ± 9	27 ± 13[3]
Day 179	6 ± 0	8 ± 1	7 ± 1	6 ± 1	10 ± 3
N-acetyl-β-D-glucosaminidase (IU/L)					
Day 3	5.2 ± 0.8	4.4 ± 0.7	3.0 ± 0.5	4.2 ± 0.9	4.7 ± 0.8
Day 18	3.1 ± 0.6	2.8 ± 0.4	2.7 ± 0.6	2.0 ± 0.2	2.5 ± 0.3
Day 88	4.1 ± 1.0	3.6 ± 0.5	2.6 ± 0.3	3.9 ± 0.6	3.5 ± 0.6
Day 179	3.6 ± 0.4	5.7 ± 0.9	3.9 ± 0.5	4.8 ± 0.4	4.0 ± 0.6
N-acetyl-β-D-glucosaminidase (IU/g creatinine)					
Day 3	14.5 ± 1.4	14.0 ± 2.4	10.7 ± 1.3	12.4 ± 2.0	14.6 ± 2.5[2]
Day 18	7.1 ± 0.6	8.8 ± 1.5	8.3 ± 0.6	7.9 ± 0.6	8.9 ± 0.9
Day 88	7.5 ± 0.8	6.6 ± 0.5	6.0 ± 0.4	6.8 ± 0.6	6.8 ± 0.3[3]
Day 179	5.4 ± 0.4	6.1 ± 0.4	5.3 ± 0.4	5.5 ± 0.4	6.1 ± 0.3
Volume (mL/16 hr)					
Day 3	4.9 ± 0.6	6.3 ± 1.0	6.2 ± 1.0[8]	6.7 ± 1.5	5.6 ± 0.9
Day 18	6.2 ± 0.8	5.9 ± 1.0	9.1 ± 2.2	10.6 ± 1.2*	9.7 ± 0.9*
Day 88	9.0 ± 2.1	8.4 ± 1.0	9.9 ± 0.8	8.1 ± 1.3	9.6 ± 1.2
Day 179	6.6 ± 0.9[8]	4.7 ± 0.7	6.2 ± 0.7	5.4 ± 0.8	6.5 ± 1.2
Specific gravity					
Day 3	1.019 ± 0.002	1.017 ± 0.002	1.014 ± 0.002	1.018 ± 0.003	1.019 ± 0.002
Day 18	1.016 ± 0.002	1.014 ± 0.001	1.014 ± 0.003	1.010 ± 0.001*	1.012 ± 0.002
Day 88	1.016 ± 0.003	1.014 ± 0.002	1.012 ± 0.001	1.015 ± 0.002	1.016 ± 0.003
Day 179	1.014 ± 0.001	1.019 ± 0.003	1.015 ± 0.001	1.016 ± 0.001	1.014 ± 0.002
pH					
Day 3	6.50 ± 0.07	6.61 ± 0.11	6.65 ± 0.21[8]	6.50 ± 0.07	6.30 ± 0.08
Day 18	6.85 ± 0.11	6.80 ± 0.08	6.80 ± 0.08	6.80 ± 0.08	6.60 ± 0.07
Day 88	6.95 ± 0.16	6.90 ± 0.10	6.70 ± 0.08	7.00 ± 0.12	7.00 ± 0.13
Day 179	7.11 ± 0.07	7.15 ± 0.11	7.00 ± 0.00	6.95 ± 0.09	6.90 ± 0.07

[1] Data are given as mean ± standard error.
[2] n=9.
[3] n=8.
[4] n=6.
[5] n=7.
[6] n=5.
[7] n=4.
[8] n=10.
* Significantly different (P≤0.05) from the control group by Dunn's or Shirley's test.
** Significantly different (P≤0.01) from the control group by Shirley's test.

TABLE D2 Hematology, Clinical Chemistry, and Urinalysis Data for F344/N Rats in the 26-Week Drinking Water Study of an Iowa Pesticide/Fertilizer Mixture[1]

	Vehicle Control	0.1X	1X	10X	100X
MALE					
Hematology					
n					
Day 5	9	10	10	10	10
Day 22	10	10	10	10	10
Day 92	9	9	9	10	9
Day 183	8	10	9	9	10
Hematocrit (%)					
Day 5	43.1 ± 0.5	42.8 ± 0.6	42.6 ± 0.5	43.6 ± 0.5	42.7 ± 0.5
Day 22	46.0 ± 0.4	46.0 ± 0.3	46.2 ± 0.5	46.0 ± 0.8	47.1 ± 0.4
Day 92	46.1 ± 0.7	45.9 ± 0.4	45.6 ± 0.3	46.1 ± 0.6	46.6 ± 0.3
Day 183	46.5 ± 0.3	47.2 ± 0.5	47.8 ± 0.5*	48.1 ± 0.4*	49.1 ± 0.4**
Hemoglobin (g/dL)					
Day 5	14.1 ± 0.2	14.0 ± 0.2	14.0 ± 0.2	14.4 ± 0.2	14.0 ± 0.1
Day 22	15.5 ± 0.1	15.5 ± 0.1	15.6 ± 0.1	15.6 ± 0.3	15.9 ± 0.1*
Day 92	15.5 ± 0.2	15.3 ± 0.2	15.4 ± 0.1	15.6 ± 0.2	15.6 ± 0.2
Day 183	15.4 ± 0.2	15.6 ± 0.2	15.9 ± 0.2	16.1 ± 0.1**	16.3 ± 0.1**
Erythrocytes (10^6/μL)					
Day 5	7.08 ± 0.11	7.08 ± 0.10	7.04 ± 0.09	7.25 ± 0.09	7.05 ± 0.07
Day 22	7.66 ± 0.07	7.67 ± 0.06	7.70 ± 0.09	7.70 ± 0.16	7.84 ± 0.07
Day 92	9.16 ± 0.11	9.01 ± 0.08	9.02 ± 0.05	9.13 ± 0.10	9.19 ± 0.08
Day 183	9.15 ± 0.11	9.31 ± 0.10	9.36 ± 0.08	9.48 ± 0.06*	9.54 ± 0.08**
Reticulocytes (10^6/μL)					
Day 5	0.38 ± 0.03	0.33 ± 0.04[2]	0.36 ± 0.02	0.32 ± 0.04	0.35 ± 0.03
Day 22	0.16 ± 0.02	0.18 ± 0.03	0.16 ± 0.02	0.17 ± 0.02	0.19 ± 0.02
Day 92	0.21 ± 0.02[3]	0.18 ± 0.02	0.20 ± 0.03	0.21 ± 0.02	0.23 ± 0.05
Day 183	0.19 ± 0.02	0.19 ± 0.02	0.17 ± 0.02	0.19 ± 0.02	0.20 ± 0.02
Nucleated erythrocytes (10^3/μL)					
Day 5	3.89 ± 1.07	4.10 ± 0.60	2.00 ± 0.58	2.90 ± 0.72	3.00 ± 0.73
Day 22	2.00 ± 0.42	2.40 ± 0.56	1.20 ± 0.33	1.60 ± 0.54	2.00 ± 0.37
Day 92	1.00 ± 0.38[3]	0.78 ± 0.22	0.89 ± 0.48	0.40 ± 0.16	1.89 ± 0.66
Day 183	0.25 ± 0.16	0.70 ± 0.40	0.44 ± 0.24	0.56 ± 0.18	0.40 ± 0.16
Mean cell volume (fL)					
Day 5	61.0 ± 0.4	60.4 ± 0.5	60.6 ± 0.6	60.2 ± 0.4	60.5 ± 0.3
Day 22	60.1 ± 0.3	60.0 ± 0.3	60.1 ± 0.3	59.8 ± 0.3	60.0 ± 0.3
Day 92	50.3 ± 0.3	51.0 ± 0.2	50.6 ± 0.3	50.5 ± 0.2	50.7 ± 0.2
Day 183	50.9 ± 0.5	50.7 ± 0.2	51.1 ± 0.3	50.8 ± 0.2	51.5 ± 0.3
Mean cell hemoglobin (pg)					
Day 5	20.0 ± 0.2	19.9 ± 0.1	19.8 ± 0.1	19.9 ± 0.1	19.9 ± 0.1
Day 22	20.2 ± 0.1	20.3 ± 0.1	20.2 ± 0.1	20.3 ± 0.1	20.3 ± 0.1
Day 92	16.9 ± 0.1	17.0 ± 0.1	17.0 ± 0.1	17.0 ± 0.1	17.0 ± 0.1
Day 183	16.8 ± 0.1	16.8 ± 0.1	17.0 ± 0.1	17.0 ± 0.1	17.1 ± 0.1
Mean cell hemoglobin concentration (g/dL)					
Day 5	32.8 ± 0.2	32.8 ± 0.2	32.7 ± 0.2	33.1 ± 0.1	32.9 ± 0.1
Day 22	33.7 ± 0.2	33.8 ± 0.2	33.7 ± 0.2	33.9 ± 0.1	33.9 ± 0.1
Day 92	33.6 ± 0.1	33.4 ± 0.1	33.7 ± 0.1	33.7 ± 0.1	33.5 ± 0.1
Day 183	33.1 ± 0.2	33.1 ± 0.1	33.2 ± 0.1	33.4 ± 0.1	33.2 ± 0.2

TABLE D2 Hematology, Clinical Chemistry, and Urinalysis Data for F344/N Rats in the 26-Week Drinking Water Study of an Iowa Pesticide/Fertilizer Mixture (continued)

	Vehicle Control	0.1X	1X	10X	100X
MALE (continued)					
Hematology (continued)					
Platelets ($10^3/\mu L$)					
Day 5	1017.1 ± 25.3	997.6 ± 23.6	1004.7 ± 15.8	997.7 ± 22.5	949.8 ± 15.8*
Day 22	755.8 ± 44.1	821.6 ± 25.5	851.7 ± 20.9	781.0 ± 21.6	823.0 ± 30.4
Day 92	737.1 ± 12.6	764.4 ± 10.6	783.3 ± 21.5	754.0 ± 22.5	767.7 ± 20.3
Day 183	712.9 ± 19.9	761.2 ± 37.9	776.8 ± 44.3	750.3 ± 23.5	721.9 ± 21.9
Leukocytes ($10^3/\mu L$)					
Day 5	4.25 ± 0.51	5.48 ± 0.66	4.52 ± 0.65	5.62 ± 0.80	4.93 ± 0.67
Day 22	6.76 ± 0.62	7.17 ± 0.39	7.04 ± 0.62	6.82 ± 0.64	7.30 ± 0.59
Day 92	10.06 ± 0.33	10.43 ± 0.42	9.54 ± 0.54	9.74 ± 0.51	9.94 ± 0.50
Day 183	9.11 ± 0.99	9.73 ± 0.44	10.67 ± 1.08	9.73 ± 0.79	8.20 ± 0.51
Segmented neutrophils ($10^3/\mu L$)					
Day 5	0.66 ± 0.09	0.93 ± 0.14	0.74 ± 0.14	0.89 ± 0.14	0.79 ± 0.14
Day 22	1.16 ± 0.11	0.89 ± 0.11	0.90 ± 0.14	0.88 ± 0.10	0.88 ± 0.12
Day 92	1.41 ± 0.12[3]	1.34 ± 0.14	1.13 ± 0.17	1.63 ± 0.16	1.66 ± 0.38
Day 183	1.99 ± 0.41	1.83 ± 0.17	2.72 ± 0.79	2.49 ± 0.61	1.67 ± 0.17
Lymphocytes ($10^3/\mu L$)					
Day 5	3.51 ± 0.42	4.38 ± 0.52	3.67 ± 0.49	4.64 ± 0.67	4.07 ± 0.54
Day 22	5.51 ± 0.52	6.19 ± 0.35	6.03 ± 0.60	5.89 ± 0.57	6.31 ± 0.52
Day 92	8.04 ± 0.27[3]	8.76 ± 0.39	8.05 ± 0.48	7.63 ± 0.37	7.88 ± 0.15
Day 183	6.76 ± 0.60	7.61 ± 0.35	7.60 ± 0.49	6.94 ± 0.61	6.29 ± 0.46
Monocytes ($10^3/\mu L$)					
Day 5	0.06 ± 0.02	0.13 ± 0.07	0.09 ± 0.04	0.08 ± 0.02	0.06 ± 0.05
Day 22	0.05 ± 0.02	0.05 ± 0.02	0.05 ± 0.03	0.02 ± 0.02	0.04 ± 0.01
Day 92	0.26 ± 0.07[3]	0.19 ± 0.04	0.24 ± 0.09	0.38 ± 0.09	0.31 ± 0.11
Day 183	0.23 ± 0.06	0.18 ± 0.04	0.21 ± 0.06	0.21 ± 0.05	0.17 ± 0.02
Eosinophils ($10^3/\mu L$)					
Day 5	0.03 ± 0.02	0.04 ± 0.01	0.02 ± 0.01	0.00 ± 0.00	0.02 ± 0.01
Day 22	0.04 ± 0.02	0.03 ± 0.01	0.07 ± 0.02	0.03 ± 0.01	0.08 ± 0.03
Day 92	0.09 ± 0.03[3]	0.14 ± 0.03	0.11 ± 0.02	0.10 ± 0.02	0.08 ± 0.03
Day 183	0.13 ± 0.02	0.12 ± 0.03	0.14 ± 0.03	0.09 ± 0.02	0.07 ± 0.02*
Methemoglobin (g/dL)					
Day 5	0.24 ± 0.04	0.21 ± 0.03	0.19 ± 0.03	0.19 ± 0.04	0.16 ± 0.02
Day 22	0.21 ± 0.04	0.22 ± 0.05	0.22 ± 0.05	0.17 ± 0.02	0.18 ± 0.02
Day 92	0.36 ± 0.05	0.34 ± 0.04	0.34 ± 0.04	0.39 ± 0.04	0.30 ± 0.03
Day 183	0.38 ± 0.06	0.33 ± 0.04	0.44 ± 0.11	0.30 ± 0.02	0.40 ± 0.04

TABLE D2 Hematology, Clinical Chemistry, and Urinalysis Data for F344/N Rats in the 26-Week Drinking Water Study of an Iowa Pesticide/Fertilizer Mixture (continued)

	Vehicle Control	0.1X	1X	10X	100X
MALE (continued)					
Clinical Chemistry					
n					
Day 5	10	10	10	10	10
Day 22	10	9	10	10	10
Day 92	9	10	10	10	10
Day 183	9	10	10	10	10
Urea nitrogen (mg/dL)					
Day 5	23.4 ± 0.7	23.3 ± 0.8[2]	24.2 ± 0.5	23.9 ± 0.6	23.8 ± 0.5
Day 22	19.3 ± 0.9	22.1 ± 0.6*	21.7 ± 0.3*	23.6 ± 0.7**	21.6 ± 0.4**
Day 92	23.5 ± 0.8	23.8 ± 0.6	23.8 ± 0.5	24.0 ± 0.7	22.6 ± 0.7
Day 183	22.8 ± 0.6	22.4 ± 0.5	22.4 ± 0.4	21.8 ± 0.7	23.9 ± 0.5[2]
Creatinine (mg/dL)					
Day 5	0.62 ± 0.01	0.57 ± 0.02	0.60 ± 0.01[2]	0.63 ± 0.02[2]	0.62 ± 0.02[2]
Day 22	0.47 ± 0.01[2]	0.53 ± 0.01**	0.50 ± 0.02*	0.50 ± 0.03	0.53 ± 0.02*
Day 92	0.51 ± 0.02[4]	0.56 ± 0.04[5]	0.55 ± 0.03[3]	0.56 ± 0.04[6]	0.59 ± 0.03[5]
Day 183	0.61 ± 0.03	0.58 ± 0.02	0.58 ± 0.01	0.55 ± 0.02	0.56 ± 0.02
Total protein (g/dL)					
Day 5	6.0 ± 0.1	5.9 ± 0.2	6.1 ± 0.1	5.9 ± 0.1	6.0 ± 0.1
Day 22	6.4 ± 0.2	6.1 ± 0.1	6.3 ± 0.1	6.4 ± 0.1	6.4 ± 0.1
Day 92	7.3 ± 0.1[3]	7.1 ± 0.1	7.3 ± 0.1	7.1 ± 0.1	7.3 ± 0.1
Day 183	7.3 ± 0.1	7.4 ± 0.1	7.1 ± 0.2[2]	7.1 ± 0.3	7.2 ± 0.2[2]
Albumin (g/dL)					
Day 5	3.3 ± 0.0	3.4 ± 0.1	3.5 ± 0.0	3.4 ± 0.1	3.4 ± 0.1
Day 22	3.6 ± 0.1	3.4 ± 0.1	3.5 ± 0.0	3.6 ± 0.1	3.6 ± 0.1
Day 92	4.1 ± 0.1[3]	4.0 ± 0.1	4.1 ± 0.0	4.1 ± 0.1	4.1 ± 0.1
Day 183	3.6 ± 0.2	3.8 ± 0.1	3.5 ± 0.2[2]	3.4 ± 0.2	3.7 ± 0.1
Alanine aminotransferase (IU/L)					
Day 5	56 ± 1	62 ± 4	55 ± 2	53 ± 2	55 ± 2
Day 22	63 ± 8	46 ± 1	53 ± 4	51 ± 3	55 ± 3
Day 92	54 ± 5	46 ± 2[2]	49 ± 3	49 ± 2	48 ± 2
Day 183	62 ± 4	59 ± 3	47 ± 4*	52 ± 3	54 ± 4
Alkaline phosphatase (IU/L)					
Day 5	777 ± 19	776 ± 11	773 ± 20	770 ± 15	777 ± 11
Day 22	520 ± 13	545 ± 12[7]	549 ± 10	572 ± 13*	585 ± 13**
Day 92	260 ± 14	259 ± 10[2]	263 ± 6	256 ± 6	279 ± 18
Day 183	209 ± 9	217 ± 4	207 ± 15	227 ± 6[2]	208 ± 12
Creatine kinase (IU/L)					
Day 5	433 ± 56	378 ± 45	329 ± 22	340 ± 37	325 ± 24
Day 22	324 ± 19[2]	381 ± 34	349 ± 53	347 ± 47[2]	395 ± 40
Day 92	224 ± 44	270 ± 36	282 ± 46	226 ± 39	368 ± 58
Day 183	159 ± 17[3]	156 ± 42	139 ± 14[3]	180 ± 37	146 ± 28[2]
Sorbitol dehydrogenase (IU/L)					
Day 5	12 ± 1	12 ± 1	12 ± 0	11 ± 0	11 ± 0
Day 22	19 ± 4	9 ± 0*	14 ± 3	12 ± 1	14 ± 2
Day 92[8]					
Day 183	8 ± 1[3]	7 ± 1[2]	6 ± 1	7 ± 0	7 ± 1[2]

TABLE D2 Hematology, Clinical Chemistry, and Urinalysis Data for F344/N Rats in the 26-Week Drinking Water Study of an Iowa Pesticide/Fertilizer Mixture (continued)

	Vehicle Control	0.1X	1X	10X	100X
MALE (continued)					
Clinical Chemistry (continued)					
Cholinesterase (IU/L)					
Day 5	701.6 ± 20.0	701.3 ± 22.1	692.3 ± 18.0	715.9 ± 23.0	682.0 ± 23.3
Day 22	583.0 ± 39.2	570.7 ± 32.8	563.7 ± 19.3	632.5 ± 34.8	598.0 ± 44.9
Day 92	650.9 ± 28.3[3]	655.8 ± 25.5	659.8 ± 22.7	647.6 ± 20.4	684.4 ± 42.5
Day 183	638.7 ± 22.9	636.5 ± 23.6	588.9 ± 39.5	669.8 ± 25.1[2]	658.9 ± 47.6
Bile acids (µmol/L)					
Day 5	36.30 ± 4.20	35.80 ± 4.99	34.40 ± 5.12	37.00 ± 4.26	40.60 ± 2.86
Day 22	24.40 ± 3.23	27.00 ± 2.13	22.80 ± 3.70	22.90 ± 3.47	24.20 ± 4.58
Day 92	21.00 ± 3.83	22.50 ± 3.92	21.00 ± 2.69[2]	18.22 ± 2.89[2]	26.80 ± 6.45
Day 183	30.22 ± 3.60	29.00 ± 3.11[2]	29.10 ± 3.18	30.20 ± 3.58	27.90 ± 5.10
Urinalysis					
n					
Day 3	9	10	10	10	9
Day 18	9	10	10	10	10
Day 88	9	10	10	10	10
Day 179	9	10	10	10	8
Creatinine (mg/dL)					
Day 3	53.94 ± 5.52	35.70 ± 4.59	39.90 ± 3.69	36.10 ± 3.45	46.67 ± 5.04
Day 18	33.22 ± 4.99	45.60 ± 5.25	40.40 ± 4.25	49.65 ± 5.55*	52.80 ± 7.53*
Day 88	120.7 ± 25.0	154.0 ± 18.6[2]	157.4 ± 23.7	106.5 ± 17.4	126.6 ± 12.3
Day 179	140.9 ± 21.6	149.6 ± 17.1	124.6 ± 10.3	145.2 ± 30.2	179.3 ± 22.0
Glucose (mg/dL)					
Day 3	11 ± 1	7 ± 1	5 ± 1**	7 ± 1	7 ± 1
Day 18	8 ± 1	10 ± 1	8 ± 1	11 ± 2	8 ± 1
Day 88	16 ± 3	19 ± 3	17 ± 2	15 ± 2	16 ± 2
Day 179	18 ± 2	19 ± 2	14 ± 1	18 ± 3	22 ± 2
Glucose/creatinine ratio					
Day 3	0.20 ± 0.01	0.19 ± 0.02	0.12 ± 0.02**	0.21 ± 0.02*	0.15 ± 0.01**
Day 18	0.24 ± 0.02	0.22 ± 0.01	0.19 ± 0.01*	0.22 ± 0.01	0.16 ± 0.02**
Day 88	0.14 ± 0.01	0.11 ± 0.01	0.11 ± 0.01	0.14 ± 0.01	0.12 ± 0.01
Day 179	0.14 ± 0.02	0.13 ± 0.01	0.12 ± 0.00	0.13 ± 0.01	0.12 ± 0.01
Protein (mg/dL)					
Day 3	10 ± 1[3]	7 ± 1	7 ± 1	8 ± 1	9 ± 2
Day 18	57 ± 12	68 ± 9	64 ± 10	72 ± 12	66 ± 10
Day 88	127 ± 39	144 ± 23	137 ± 22	123 ± 27	115 ± 18
Day 179	105 ± 15	123 ± 20	104 ± 16	97 ± 20	117 ± 13
Protein/creatinine ratio					
Day 3	0.18 ± 0.01[3]	0.21 ± 0.03	0.18 ± 0.02	0.23 ± 0.03	0.18 ± 0.02
Day 18	1.79 ± 0.29	1.58 ± 0.16	1.57 ± 0.16	1.47 ± 0.19	1.38 ± 0.17
Day 88	0.93 ± 0.12	0.82 ± 0.09	0.86 ± 0.06	1.10 ± 0.07	0.87 ± 0.10
Day 179	0.80 ± 0.09	0.88 ± 0.14	0.80 ± 0.08	0.67 ± 0.08	0.69 ± 0.07

TABLE D2 Hematology, Clinical Chemistry, and Urinalysis Data for F344/N Rats in the 26-Week Drinking Water Study of an Iowa Pesticide/Fertilizer Mixture (continued)

	Vehicle Control	0.1X	1X	10X	100X
MALE (continued)					
Urinalysis (continued)					
Alkaline phosphatase (IU/L)					
Day 3	117 ± 12	97 ± 10	102 ± 14	132 ± 12	135 ± 23
Day 18	189 ± 23	216 ± 21	225 ± 18	263 ± 24*	235 ± 23
Day 88	203 ± 34	197 ± 21	271 ± 29	207 ± 29	200 ± 30
Day 179	197 ± 22	208 ± 24	201 ± 17	183 ± 30	267 ± 36
Alkaline phosphatase (IU/g creatinine)					
Day 3	217 ± 14	292 ± 29*	249 ± 17	402 ± 69**	286 ± 36**
Day 18	621 ± 78	495 ± 33	595 ± 59	549 ± 36	500 ± 54
Day 88	181 ± 16	123 ± 14	188 ± 23	208 ± 24	155 ± 15
Day 179	155 ± 18	153 ± 20	162 ± 7	143 ± 13	150 ± 9
Aspartate aminotransferase (IU/L)					
Day 3	15 ± 3	7 ± 1	8 ± 1	24 ± 8	14 ± 4
Day 18	17 ± 3	15 ± 3	16 ± 3	32 ± 9	19 ± 4[2]
Day 88	30 ± 5	41 ± 9	41 ± 6	27 ± 3	29 ± 4
Day 179	39 ± 5	42 ± 5	34 ± 3	36 ± 8	43 ± 5
Aspartate aminotransferase (IU/g creatinine)					
Day 3	29 ± 6	23 ± 3	22 ± 5	48 ± 14[2]	30 ± 7
Day 18	63 ± 18	38 ± 9	44 ± 8	48 ± 11[2]	58 ± 17
Day 88	27 ± 3	25 ± 7	30 ± 6	26 ± 2	23 ± 2
Day 179	30 ± 4	29 ± 2	28 ± 2	25 ± 1	24 ± 1
N-acetyl-β-D-glucosaminidase (IU/L)					
Day 3	7.0 ± 0.8	4.9 ± 0.6	5.0 ± 0.5	6.4 ± 0.5	6.3 ± 1.0
Day 18	5.8 ± 0.7	7.0 ± 0.6	6.2 ± 0.6	8.3 ± 0.9	8.1 ± 1.2
Day 88	8.2 ± 1.4	9.3 ± 1.0	9.6 ± 1.1	8.6 ± 1.0	8.5 ± 0.9
Day 179	10.2 ± 1.2	11.2 ± 1.3	9.3 ± 0.8	9.5 ± 1.8	13.0 ± 1.4
N-acetyl-β-D-glucosaminidase (IU/g creatinine)					
Day 3	13.2 ± 0.6	14.8 ± 1.8	12.6 ± 0.7	19.3 ± 2.9	13.2 ± 0.8
Day 18	19.2 ± 2.1	16.0 ± 0.8	15.7 ± 0.8	17.2 ± 1.3	16.4 ± 1.6
Day 88	7.2 ± 0.4	5.7 ± 0.7	6.8 ± 0.9	8.6 ± 0.6	6.7 ± 0.4
Day 179	7.9 ± 0.9	8.0 ± 0.8	7.8 ± 0.4	6.8 ± 0.3	7.3 ± 0.4
Volume (mL/16 hr)					
Day 3	2.7 ± 0.8[7]	4.3 ± 1.1	3.9 ± 0.6	5.1 ± 1.2*	4.2 ± 0.7*[7]
Day 18	9.7 ± 1.5	6.8 ± 1.5	7.9 ± 1.1	5.5 ± 1.2	7.7 ± 1.0
Day 88	5.0 ± 1.5	4.6 ± 1.3	4.1 ± 0.9	3.7 ± 0.9	4.5 ± 0.9
Day 179	7.3 ± 1.3	5.1 ± 1.2	6.8 ± 0.9	8.1 ± 1.7	4.3 ± 0.9[2]
Specific gravity					
Day 3	1.024 ± 0.003	1.017 ± 0.002	1.017 ± 0.002	1.017 ± 0.002	1.020 ± 0.002[7]
Day 18	1.014 ± 0.002	1.020 ± 0.002	1.016 ± 0.002	1.021 ± 0.002	1.018 ± 0.002
Day 88	1.030 ± 0.007	1.029 ± 0.004	1.027 ± 0.004	1.028 ± 0.005	1.026 ± 0.002
Day 179	1.025 ± 0.003	1.031 ± 0.004	1.022 ± 0.002	1.026 ± 0.005	1.032 ± 0.004
pH					
Day 3	6.45 ± 0.05[7]	6.50 ± 0.00	6.60 ± 0.12	7.05 ± 0.09**	6.85 ± 0.08**[7]
Day 18	6.44 ± 0.06	6.35 ± 0.08	6.05 ± 0.05**	6.30 ± 0.08*	6.00 ± 0.00**
Day 88	7.00 ± 0.08	7.10 ± 0.12	7.45 ± 0.05**	7.25 ± 0.08*	7.30 ± 0.08*
Day 179	6.89 ± 0.07	6.60 ± 0.07	7.05 ± 0.05	6.75 ± 0.08	6.94 ± 0.10[2]

TABLE D2 Hematology, Clinical Chemistry, and Urinalysis Data for F344/N Rats in the 26-Week Drinking Water Study of an Iowa Pesticide/Fertilizer Mixture (continued)

	Vehicle Control	0.1X	1X	10X	100X
FEMALE					
Hematology					
n					
Day 5	9	10	10	10	10
Day 22	9	7	9	10	6
Day 92	9	10	9	10	10
Day 183	10	10	10	10	10
Hematocrit (%)					
Day 5	43.6 ± 0.4	44.0 ± 0.7	44.2 ± 0.6	43.2 ± 0.3	43.6 ± 0.3
Day 22	46.5 ± 0.6	47.5 ± 0.8	48.0 ± 0.6	47.2 ± 0.5	46.8 ± 0.7
Day 92	46.1 ± 0.7	44.9 ± 0.4	45.1 ± 0.5	44.4 ± 0.4	45.0 ± 0.6
Day 183	47.3 ± 0.4	46.9 ± 0.7	47.0 ± 0.5	46.8 ± 0.6	47.6 ± 0.6
Hemoglobin (g/dL)					
Day 5	14.5 ± 0.1	14.6 ± 0.2	14.8 ± 0.2	14.4 ± 0.1	14.5 ± 0.1
Day 22	15.8 ± 0.2	16.3 ± 0.3	16.3 ± 0.2	16.1 ± 0.2	16.0 ± 0.3
Day 92	15.5 ± 0.3	15.1 ± 0.2	15.2 ± 0.2	14.9 ± 0.1	15.1 ± 0.2
Day 183	15.5 ± 0.2	15.4 ± 0.2	15.6 ± 0.1	15.5 ± 0.2	15.6 ± 0.2
Erythrocytes (10^6/μL)					
Day 5	7.25 ± 0.09	7.29 ± 0.13	7.41 ± 0.10	7.20 ± 0.07	7.30 ± 0.07
Day 22	7.84 ± 0.10	8.08 ± 0.12	8.16 ± 0.12	8.01 ± 0.08	8.00 ± 0.15
Day 92	8.61 ± 0.13	8.36 ± 0.08	8.43 ± 0.13	8.25 ± 0.07*	8.35 ± 0.12
Day 183	8.65 ± 0.11	8.59 ± 0.13	8.65 ± 0.08	8.60 ± 0.08	8.69 ± 0.09
Reticulocytes (10^6/μL)					
Day 5	0.24 ± 0.02	0.23 ± 0.02	0.24 ± 0.02	0.22 ± 0.03	0.22 ± 0.03
Day 22	0.12 ± 0.01	0.11 ± 0.01	0.12 ± 0.01	0.13 ± 0.01	0.11 ± 0.02
Day 92	0.17 ± 0.01	0.16 ± 0.02	0.17 ± 0.01	0.15 ± 0.01	0.20 ± 0.02
Day 183	0.16 ± 0.04	0.14 ± 0.01	0.16 ± 0.02	0.14 ± 0.01[2]	0.14 ± 0.01
Nucleated erythrocytes (10^3/μL)					
Day 5	2.22 ± 0.36	2.10 ± 0.72	1.50 ± 0.34	1.20 ± 0.29	1.70 ± 0.47
Day 22	0.33 ± 0.24	0.14 ± 0.14	0.89 ± 0.39	0.40 ± 0.22	1.00 ± 0.37
Day 92	0.22 ± 0.15	0.30 ± 0.21	0.56 ± 0.38	1.20 ± 0.57	0.40 ± 0.40
Day 183	0.80 ± 0.33	0.40 ± 0.31	0.30 ± 0.15	0.67 ± 0.17[2]	1.00 ± 0.39
Mean cell volume (fL)					
Day 5	60.2 ± 0.4	60.4 ± 0.3	59.6 ± 0.3	60.1 ± 0.4	59.7 ± 0.4
Day 22	59.3 ± 0.2	58.8 ± 0.2	58.8 ± 0.3	59.0 ± 0.3	58.6 ± 0.4
Day 92	53.6 ± 0.2	53.7 ± 0.3	53.5 ± 0.3	53.8 ± 0.2	54.0 ± 0.2
Day 183	54.7 ± 0.4	54.6 ± 0.2	54.3 ± 0.2	54.4 ± 0.2	54.7 ± 0.2
Mean cell hemoglobin (pg)					
Day 5	20.0 ± 0.1	20.0 ± 0.1	20.0 ± 0.0	20.0 ± 0.1	19.9 ± 0.1
Day 22	20.2 ± 0.1	20.2 ± 0.1	19.9 ± 0.1	20.2 ± 0.1	20.1 ± 0.1
Day 92	18.0 ± 0.1	18.0 ± 0.0	18.1 ± 0.1	18.0 ± 0.0	18.1 ± 0.0
Day 183	18.0 ± 0.1	18.0 ± 0.1	18.0 ± 0.1	18.0 ± 0.1	18.0 ± 0.0
Mean cell hemoglobin concentration (g/dL)					
Day 5	33.2 ± 0.2	33.1 ± 0.2	33.5 ± 0.2	33.2 ± 0.1	33.3 ± 0.2
Day 22	34.1 ± 0.1	34.3 ± 0.1	34.0 ± 0.1	34.1 ± 0.1	34.3 ± 0.1
Day 92	33.6 ± 0.2	33.5 ± 0.2	33.7 ± 0.2	33.5 ± 0.1	33.5 ± 0.1
Day 183	32.9 ± 0.2	32.9 ± 0.2	33.2 ± 0.1	33.2 ± 0.3	32.9 ± 0.1

TABLE D2 Hematology, Clinical Chemistry, and Urinalysis Data for F344/N Rats in the 26-Week Drinking Water Study of an Iowa Pesticide/Fertilizer Mixture (continued)

	Vehicle Control	0.1X	1X	10X	100X
FEMALE (continued)					
Hematology (continued)					
Platelets ($10^3/\mu L$)					
Day 5	933.0 ± 42.5	889.4 ± 15.3	898.1 ± 25.2	886.9 ± 29.9	862.1 ± 21.0
Day 22	807.4 ± 13.7	729.4 ± 41.0	840.2 ± 24.7	765.5 ± 22.6	771.0 ± 17.8
Day 92	840.4 ± 40.7	739.6 ± 44.8	798.8 ± 25.9	806.5 ± 15.4	808.6 ± 19.4
Day 183	868.9 ± 56.3	810.1 ± 59.7	752.3 ± 10.5*	746.2 ± 12.4*	761.0 ± 22.6*
Leukocytes ($10^3/\mu L$)					
Day 5	4.22 ± 0.42	4.14 ± 0.35	4.82 ± 0.47	5.05 ± 0.51	4.19 ± 0.37
Day 22	6.96 ± 0.72	7.56 ± 0.90	6.05 ± 0.67	7.95 ± 0.93	6.83 ± 1.05
Day 92	7.26 ± 1.23	7.57 ± 1.11	6.59 ± 1.18	6.80 ± 0.76	5.96 ± 0.84
Day 183	9.18 ± 0.90	8.50 ± 0.70	7.57 ± 0.38	6.93 ± 0.46	7.74 ± 0.40
Segmented neutrophils ($10^3/\mu L$)					
Day 5	0.61 ± 0.06	0.53 ± 0.06	0.65 ± 0.09	0.66 ± 0.12	0.44 ± 0.05
Day 22	0.67 ± 0.14	0.85 ± 0.13	0.81 ± 0.18	1.04 ± 0.15	0.91 ± 0.14
Day 92	1.63 ± 0.61	1.60 ± 0.75	1.00 ± 0.21	0.92 ± 0.08	2.03 ± 0.89
Day 183	2.51 ± 0.70	1.93 ± 0.27	1.46 ± 0.23	1.37 ± 0.14[2]	1.46 ± 0.25
Lymphocytes ($10^3/\mu L$)					
Day 5	3.53 ± 0.37	3.51 ± 0.29	4.10 ± 0.41	4.29 ± 0.41	3.65 ± 0.33
Day 22	5.97 ± 0.63	6.45 ± 0.78	5.05 ± 0.48	6.50 ± 0.72	5.70 ± 0.89
Day 92	5.28 ± 0.88	5.66 ± 1.02	5.29 ± 0.98	5.66 ± 0.68	3.67 ± 0.57
Day 183	6.18 ± 0.23	5.97 ± 0.45	5.65 ± 0.29	5.40 ± 0.38[2]	5.92 ± 0.36
Monocytes ($10^3/\mu L$)					
Day 5	0.04 ± 0.01	0.06 ± 0.02	0.05 ± 0.01	0.06 ± 0.02	0.05 ± 0.01
Day 22	0.24 ± 0.04	0.18 ± 0.05	0.13 ± 0.03	0.32 ± 0.07	0.19 ± 0.05
Day 92	0.28 ± 0.06	0.24 ± 0.06	0.25 ± 0.09	0.15 ± 0.04	0.21 ± 0.06
Day 183	0.38 ± 0.07	0.54 ± 0.10	0.35 ± 0.08	0.37 ± 0.09[2]	0.29 ± 0.06
Eosinophils ($10^3/\mu L$)					
Day 5	0.04 ± 0.02	0.05 ± 0.01	0.02 ± 0.01	0.04 ± 0.01	0.05 ± 0.01
Day 22	0.08 ± 0.03	0.09 ± 0.03	0.06 ± 0.02	0.10 ± 0.03	0.03 ± 0.02
Day 92	0.07 ± 0.02	0.06 ± 0.03	0.05 ± 0.02	0.07 ± 0.02	0.04 ± 0.02
Day 183	0.09 ± 0.03	0.06 ± 0.03	0.11 ± 0.03	0.08 ± 0.02[2]	0.09 ± 0.03
Methemoglobin (g/dL)					
Day 5	0.22 ± 0.02	0.16 ± 0.02	0.20 ± 0.02	0.23 ± 0.03	0.22 ± 0.04
Day 22	0.32 ± 0.04	0.28 ± 0.03	0.28 ± 0.02	0.39 ± 0.04	0.31 ± 0.04
Day 92	0.41 ± 0.06[3]	0.36 ± 0.05	0.41 ± 0.07	0.33 ± 0.02	0.36 ± 0.03
Day 183	0.29 ± 0.02	0.35 ± 0.06	0.22 ± 0.02	0.32 ± 0.05	0.27 ± 0.02

TABLE D2 Hematology, Clinical Chemistry, and Urinalysis Data for F344/N Rats in the 26-Week Drinking Water Study of an Iowa Pesticide/Fertilizer Mixture (continued)

	Vehicle Control	0.1X	1X	10X	100X
FEMALE (continued)					
Clinical Chemistry					
n					
Day 5	10	10	10	10	10
Day 22	10	10	10	10	10
Day 92	9	10	10	10	10
Day 183	10	10	10	10	10
Urea nitrogen (mg/dL)					
Day 5	23.6 ± 0.7	23.6 ± 1.0	24.5 ± 0.6	23.3 ± 0.7	24.6 ± 0.6
Day 22	24.1 ± 1.1	24.6 ± 0.9[2]	23.7 ± 1.0	21.5 ± 0.8*	22.3 ± 0.9
Day 92	20.6 ± 0.8	19.8 ± 0.5	21.8 ± 0.6	18.8 ± 0.7	20.6 ± 0.6
Day 183	20.7 ± 1.0	21.8 ± 0.4	23.2 ± 0.8*	22.1 ± 0.6	24.4 ± 0.7**
Creatinine (mg/dL)					
Day 5	0.58 ± 0.01	0.60 ± 0.01	0.60 ± 0.01	0.57 ± 0.01	0.57 ± 0.02
Day 22	0.50 ± 0.01[3]	0.49 ± 0.05[4]	0.51 ± 0.03[9]	0.50 ± 0.01[2]	0.49 ± 0.02[3]
Day 92	0.57 ± 0.02[4]	0.58 ± 0.04[6]	0.57 ± 0.01[6]	0.52 ± 0.05[6]	0.55 ± 0.06[4]
Day 183	0.48 ± 0.02[2]	0.47 ± 0.01	0.47 ± 0.01	0.46 ± 0.01	0.47 ± 0.01
Total protein (g/dL)					
Day 5	5.6 ± 0.1	5.7 ± 0.1	5.7 ± 0.1	5.6 ± 0.1	5.6 ± 0.1
Day 22	6.3 ± 0.1[2]	6.4 ± 0.1[3]	6.4 ± 0.1[2]	6.4 ± 0.1[2]	6.3 ± 0.1
Day 92	6.9 ± 0.1	6.8 ± 0.1	6.8 ± 0.2	6.9 ± 0.1	6.8 ± 0.1[2]
Day 183	6.6 ± 0.3	7.0 ± 0.1	6.9 ± 0.1	7.1 ± 0.1	6.9 ± 0.1
Albumin (g/dL)					
Day 5	3.4 ± 0.1	3.5 ± 0.1	3.6 ± 0.1	3.4 ± 0.1	3.5 ± 0.0
Day 22	3.7 ± 0.1[2]	3.7 ± 0.1[3]	3.7 ± 0.1[2]	3.7 ± 0.1	3.7 ± 0.1
Day 92	4.1 ± 0.0[3]	4.0 ± 0.0[2]	4.0 ± 0.1	4.0 ± 0.1[3]	4.0 ± 0.1
Day 183	3.8 ± 0.2	4.0 ± 0.1	4.0 ± 0.1	4.1 ± 0.1	3.9 ± 0.1[2]
Alanine aminotransferase (IU/L)					
Day 5	49 ± 2	54 ± 2	51 ± 2	52 ± 2	53 ± 2
Day 22	52 ± 1	52 ± 2[2]	59 ± 5	66 ± 5*	60 ± 5
Day 92	38 ± 0[10]	34 ± 2[5]	38 ± 1[5]	36 ± 1[4]	39 ± 1[4]
Day 183	46 ± 4	45 ± 2	48 ± 2	48 ± 2	43 ± 1[2]
Alkaline phosphatase (IU/L)					
Day 5	693 ± 17	684 ± 17	650 ± 16	641 ± 10*	670 ± 17
Day 22	480 ± 8	480 ± 13	473 ± 15	470 ± 14	459 ± 10
Day 92	236 ± 7	238 ± 6	234 ± 8[2]	220 ± 7	243 ± 8
Day 183	181 ± 12	195 ± 10	207 ± 8	193 ± 6	182 ± 12
Creatine kinase (IU/L)					
Day 5	354 ± 39	293 ± 17	333 ± 33	374 ± 66	321 ± 25
Day 22	364 ± 42	420 ± 80	386 ± 30	384 ± 41	534 ± 125
Day 92	221 ± 17[7]	275 ± 38[3]	216 ± 30	211 ± 24	210 ± 21
Day 183	253 ± 41	240 ± 43	361 ± 46	216 ± 34	211 ± 36
Sorbitol dehydrogenase (IU/L)					
Day 5	10 ± 0	10 ± 1	11 ± 0	10 ± 0	11 ± 0
Day 22	9 ± 1[2]	10 ± 1	9 ± 1	13 ± 2	10 ± 1
Day 92	4 ± 0	5 ± 0[2]	6 ± 1	4 ± 0[2]	5 ± 0[3]
Day 183	6 ± 0[2]	6 ± 0	6 ± 0	5 ± 0	6 ± 0

TABLE D2 Hematology, Clinical Chemistry, and Urinalysis Data for F344/N Rats in the 26-Week Drinking Water Study of an Iowa Pesticide/Fertilizer Mixture (continued)

	Vehicle Control	0.1X	1X	10X	100X
FEMALE (continued)					
Clinical Chemistry (continued)					
Cholinesterase (IU/L)					
Day 5	1065 ± 52	1136 ± 43	1051 ± 54	1025 ± 24	998 ± 33
Day 22	1563 ± 105	1807 ± 132[3]	1648 ± 101	1671 ± 63	1578 ± 77
Day 92	2798 ± 141	2625 ± 112	2492 ± 113	3047 ± 119	2397 ± 195
Day 183	2726 ± 158[2]	2727 ± 205	2902 ± 130	3078 ± 83	2778 ± 119[2]
Bile acids (μmol/L)					
Day 5	34.90 ± 3.75	32.10 ± 2.80	32.90 ± 4.31	33.40 ± 3.16	28.10 ± 2.36
Day 22	28.50 ± 3.01[3]	25.00 ± 3.46[9]	30.70 ± 5.17	24.90 ± 3.23	31.63 ± 5.90[3]
Day 92	34.25 ± 7.72[4]	35.14 ± 3.22[9]	42.17 ± 4.03[5]	38.67 ± 4.01[5]	38.50 ± 6.20[4]
Day 183	30.30 ± 4.17	26.50 ± 3.06	26.70 ± 4.56	35.80 ± 3.76	34.00 ± 2.97
Urinalysis					
n					
Day 3	10	8	10	9	10
Day 18	10	10	9	10	10
Day 88	9	10	10	10	10
Day 179	10	10	9	10	10
Creatinine (mg/dL)					
Day 3	41.40 ± 5.76	42.88 ± 7.07	41.80 ± 4.85	44.94 ± 6.63	36.15 ± 3.55
Day 18	24.11 ± 3.51[2]	38.95 ± 3.41*	31.22 ± 3.94	37.10 ± 3.94*	45.95 ± 4.10**
Day 88	61.25 ± 8.35[3]	82.00 ± 16.97	57.80 ± 8.74	54.30 ± 7.86	71.75 ± 10.80
Day 179	69.65 ± 8.01	85.00 ± 9.26	75.67 ± 6.89	70.15 ± 9.50	80.65 ± 11.64
Glucose (mg/dL)					
Day 3	7 ± 1	7 ± 1	9 ± 1	8 ± 1	6 ± 1
Day 18	5 ± 1	6 ± 1	4 ± 1[7]	6 ± 1	7 ± 1
Day 88	8 ± 1	10 ± 2	6 ± 1	6 ± 1	7 ± 1
Day 179	9 ± 1	11 ± 1[2]	8 ± 1	9 ± 1	10 ± 1
Glucose/creatinine ratio					
Day 3	0.17 ± 0.01	0.17 ± 0.02	0.22 ± 0.05	0.16 ± 0.01	0.15 ± 0.01
Day 18	0.21 ± 0.03[2]	0.17 ± 0.01*[2]	0.13 ± 0.02**	0.16 ± 0.01**[2]	0.14 ± 0.01**
Day 88	0.14 ± 0.01[3]	0.12 ± 0.00**	0.10 ± 0.01**	0.10 ± 0.01**	0.09 ± 0.01**
Day 179	0.13 ± 0.01	0.13 ± 0.01[2]	0.11 ± 0.01	0.14 ± 0.01	0.13 ± 0.01
Protein (mg/dL)					
Day 3	5 ± 1	4 ± 1	5 ± 1	6 ± 1	4 ± 1
Day 18	4 ± 1	4 ± 0	3 ± 0[7]	3 ± 0	4 ± 0
Day 88	3 ± 1	5 ± 2	3 ± 1	4 ± 1	5 ± 1*
Day 179	3 ± 0	3 ± 1	3 ± 1	4 ± 1	3 ± 1
Protein/creatinine ratio					
Day 3	0.11 ± 0.01	0.10 ± 0.02	0.12 ± 0.02	0.12 ± 0.01	0.10 ± 0.01
Day 18	0.17 ± 0.02[2]	0.10 ± 0.01**	0.09 ± 0.01**	0.10 ± 0.01**	0.10 ± 0.01**
Day 88	0.04 ± 0.01[3]	0.06 ± 0.01	0.05 ± 0.01	0.09 ± 0.01**	0.08 ± 0.01**
Day 179	0.04 ± 0.01	0.04 ± 0.01	0.04 ± 0.01	0.06 ± 0.01	0.04 ± 0.01

TABLE D2 Hematology, Clinical Chemistry, and Urinalysis Data for F344/N Rats in the 26-Week Drinking Water Study of an Iowa Pesticide/Fertilizer Mixture (continued)

	Vehicle Control	0.1X	1X	10X	100X
FEMALE (continued)					
Urinalysis (continued)					
Alkaline phosphatase (IU/L)					
Day 3	98 ± 17	98 ± 18	102 ± 14	102 ± 22	89 ± 13
Day 18	78 ± 10	110 ± 10	78 ± 15	93 ± 12	124 ± 13*
Day 88	86 ± 12	101 ± 14	85 ± 13	63 ± 9	88 ± 12
Day 179	61 ± 7	85 ± 8	65 ± 9	65 ± 8	79 ± 11
Alkaline phosphatase (IU/g creatinine)					
Day 3	206 ± 16[2]	229 ± 20	222 ± 25[2]	224 ± 34	245 ± 21
Day 18	328 ± 55[2]	287 ± 18	242 ± 21	253 ± 34	279 ± 28
Day 88	150 ± 8[3]	133 ± 12	148 ± 9	116 ± 6*	127 ± 7
Day 179	89 ± 5	106 ± 11	83 ± 7	96 ± 7	104 ± 7
Aspartate aminotransferase (IU/L)					
Day 3	15 ± 4	8 ± 1[9]	9 ± 1	18 ± 7	12 ± 5
Day 18	21 ± 9	4 ± 1	5 ± 2	3 ± 0	12 ± 7
Day 88	5 ± 1	7 ± 2[2]	5 ± 1[2]	5 ± 1	5 ± 1
Day 179	13 ± 4	6 ± 1	5 ± 1	5 ± 1	7 ± 1
Aspartate aminotransferase (IU/g creatinine)					
Day 3	39 ± 10	19 ± 1[9]	23 ± 4	35 ± 10	30 ± 9
Day 18	92 ± 38[2]	11 ± 2	21 ± 8	10 ± 2	29 ± 17
Day 88	8 ± 1[3]	10 ± 3[2]	8 ± 1[2]	6 ± 1[2]	8 ± 2
Day 179	22.7 ± 8.3	6.8 ± 0.5*	6.6 ± 0.2*	7.2 ± 0.4	6.1 ± 0.2**[2]
N-acetyl-β-D-glucosaminidase (IU/L)					
Day 3	4.3 ± 0.8	4.7 ± 1.2	4.2 ± 0.5	4.6 ± 1.1	4.4 ± 1.1
Day 18	3.4 ± 0.6	3.7 ± 0.4	2.4 ± 0.5	3.2 ± 0.4	4.5 ± 0.5
Day 88	3.3 ± 0.6	5.0 ± 1.3	3.0 ± 0.5	2.9 ± 0.5	3.9 ± 0.7
Day 179	5.7 ± 0.6	6.1 ± 0.7	4.8 ± 0.6	4.8 ± 0.6	5.8 ± 0.8
N-acetyl-β-D-glucosaminidase (IU/g creatinine)					
Day 3	10.0 ± 0.9	10.4 ± 2.0	11.0 ± 1.8	9.6 ± 0.9	11.3 ± 1.9
Day 18	13.2 ± 2.0[2]	9.4 ± 0.5	7.0 ± 0.8*	8.6 ± 0.8	10.0 ± 0.9
Day 88	5.3 ± 0.5[3]	5.8 ± 0.4	4.9 ± 0.3	5.4 ± 0.3	5.4 ± 0.4
Day 179	8.3 ± 0.7	7.2 ± 0.4	6.0 ± 0.3**	7.1 ± 0.5	7.6 ± 0.4
Volume (mL/16 hr)					
Day 3	4.4 ± 0.9	4.0 ± 0.6	4.3 ± 0.7	4.0 ± 0.7[7]	5.2 ± 1.0
Day 18	9.8 ± 1.5	6.4 ± 0.6	10.5 ± 1.5[7]	7.2 ± 1.2	5.3 ± 0.9*
Day 88	5.8 ± 1.3[7]	5.5 ± 1.5	6.9 ± 1.1	8.8 ± 1.3	6.3 ± 1.4
Day 179	6.7 ± 1.2	4.6 ± 0.5	5.1 ± 0.6	7.1 ± 1.0	6.5 ± 1.5
Specific gravity					
Day 3	1.017 ± 0.002	1.017 ± 0.003	1.018 ± 0.002	1.018 ± 0.002[7]	1.015 ± 0.002
Day 18	1.013 ± 0.002	1.015 ± 0.001	1.010 ± 0.002[7]	1.014 ± 0.001	1.016 ± 0.001
Day 88	1.016 ± 0.002	1.019 ± 0.004	1.012 ± 0.001	1.011 ± 0.002	1.016 ± 0.002
Day 179	1.018 ± 0.002	1.020 ± 0.002	1.017 ± 0.002	1.017 ± 0.002	1.019 ± 0.002
pH					
Day 3	6.55 ± 0.09	6.38 ± 0.08	6.80 ± 0.08	6.80 ± 0.11[7]	6.75 ± 0.08
Day 18	6.35 ± 0.08	6.45 ± 0.09	6.35 ± 0.08[7]	6.20 ± 0.08	6.20 ± 0.08
Day 88	7.35 ± 0.11[7]	7.35 ± 0.08	7.05 ± 0.12*	6.90 ± 0.07**	7.15 ± 0.17*
Day 179	6.90 ± 0.07	6.95 ± 0.09	7.17 ± 0.19	7.10 ± 0.07	6.90 ± 0.07

TABLE D2 Hematology, Clinical Chemistry, and Urinalysis Data for F344/N Rats in the 26-Week Drinking Water Study of an Iowa Pesticide/Fertilizer Mixture (continued)

[1] Data are given as mean ± standard error.
[2] n=9.
[3] n=8.
[4] n=4.
[5] n=6.
[6] n=5.
[7] n=10.
[8] The amount of serum from control rats was insufficient for analysis.
[9] n=7.
[10] n=2.
* Significantly different (P≤0.05) from the control group by Dunn's or Shirley's test.
** Significantly different (P≤0.01) from the control group by Dunn's or Shirley's test.

TABLE D3 Hematology and Clinical Chemistry Data for B6C3F$_1$ Mice in the 26-Week Drinking Water Study of a California Pesticide/Fertilizer Mixture[1]

	Vehicle Control	0.1X	1X	10X	100X
MALE					
Hematology					
n					
Day 92	10	9	10	9	10
Day 183	10	10	10	10	9
Hematocrit (%)					
Day 92	45.0 ± 0.7	44.6 ± 0.7	44.3 ± 0.6	45.6 ± 0.6	44.9 ± 0.6
Day 183	46.4 ± 0.4	45.9 ± 0.5	46.2 ± 0.3	46.6 ± 0.4	45.8 ± 0.4
Hemoglobin (g/dL)					
Day 92	14.9 ± 0.2	14.8 ± 0.1	14.8 ± 0.1	15.1 ± 0.1	14.9 ± 0.1
Day 183	15.5 ± 0.1	15.2 ± 0.2	15.3 ± 0.1	15.4 ± 0.1	15.3 ± 0.1
Erythrocytes (10^6/μL)					
Day 92	10.15 ± 0.09	10.08 ± 0.08	10.07 ± 0.08	10.19 ± 0.09	10.17 ± 0.09
Day 183	10.24 ± 0.06	10.12 ± 0.08	10.11 ± 0.05	10.22 ± 0.07	10.11 ± 0.11
Reticulocytes (10^6/μL)					
Day 92	0.20 ± 0.02[2]	0.21 ± 0.02[2]	0.21 ± 0.02[3]	0.22 ± 0.02	0.18 ± 0.02[3]
Day 183	0.18 ± 0.01	0.22 ± 0.02	0.20 ± 0.03[2]	0.20 ± 0.03[2]	0.22 ± 0.03
Nucleated erythrocytes (10^3/μL)					
Day 92	0.01 ± 0.01[2]	0.00 ± 0.00[2]	0.01 ± 0.01[3]	0.01 ± 0.01	0.00 ± 0.00[3]
Day 183	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00
Mean cell volume (fL)					
Day 92	44.3 ± 0.5	44.2 ± 0.5	44.0 ± 0.4	44.7 ± 0.4	44.1 ± 0.4
Day 183	45.3 ± 0.3	45.4 ± 0.2	45.7 ± 0.2	45.6 ± 0.3	45.3 ± 0.3
Mean cell hemoglobin (pg)					
Day 92	14.6 ± 0.1	14.7 ± 0.1	14.7 ± 0.1	14.8 ± 0.1	14.7 ± 0.1
Day 183	15.1 ± 0.1	15.0 ± 0.1	15.2 ± 0.1	15.1 ± 0.1	15.2 ± 0.1
Mean cell hemoglobin concentration (g/dL)					
Day 92	33.0 ± 0.3	33.2 ± 0.4	33.3 ± 0.3	33.1 ± 0.4	33.3 ± 0.3
Day 183	33.3 ± 0.1	33.1 ± 0.2	33.2 ± 0.1	33.1 ± 0.1	33.5 ± 0.2
Platelets (10^3/μL)					
Day 92	1395 ± 33	1477 ± 22	1401 ± 33	1345 ± 46	1366 ± 46
Day 183	1317 ± 29	1372 ± 51	1321 ± 45	1311 ± 45	1246 ± 34
Leukocytes (10^3/μL)					
Day 92	6.86 ± 0.40	6.03 ± 0.86	7.30 ± 0.62	6.37 ± 0.40	6.27 ± 0.68
Day 183	6.59 ± 0.55	6.62 ± 0.42	7.37 ± 0.41	7.22 ± 0.38	8.43 ± 0.33**
Segmented neutrophils (10^3/μL)					
Day 92	0.75 ± 0.07[2]	0.97 ± 0.19[2]	1.10 ± 0.11[3]	0.89 ± 0.09	0.81 ± 0.10[3]
Day 183	1.31 ± 0.16	1.60 ± 0.17	1.58 ± 0.15	1.90 ± 0.45	1.88 ± 0.17*
Lymphocytes (10^3/μL)					
Day 92	5.77 ± 0.30[2]	4.99 ± 0.81[2]	6.30 ± 0.62[3]	5.36 ± 0.35	4.95 ± 0.53[3]
Day 183	4.94 ± 0.40	4.68 ± 0.33	5.41 ± 0.32	4.98 ± 0.48	6.13 ± 0.22*
Monocytes (10^3/μL)					
Day 92	0.04 ± 0.02[2]	0.01 ± 0.01[2]	0.02 ± 0.02[3]	0.02 ± 0.01	0.02 ± 0.01[3]
Day 183	0.13 ± 0.03	0.16 ± 0.05	0.14 ± 0.05	0.17 ± 0.04	0.14 ± 0.03
Eosinophils (10^3/μL)					
Day 92	0.15 ± 0.05[2]	0.09 ± 0.02[2]	0.09 ± 0.02[3]	0.09 ± 0.03	0.11 ± 0.03[3]
Day 183	0.22 ± 0.06	0.18 ± 0.05	0.24 ± 0.07	0.17 ± 0.05	0.28 ± 0.08
Methemoglobin (g/dL)					
Day 92	0.22 ± 0.09[3]	0.29 ± 0.07[4]	0.30 ± 0.09[3]	0.20 ± 0.09[4]	0.17 ± 0.03[2]
Day 183	0.18 ± 0.02[3]	0.19 ± 0.02	0.22 ± 0.03	0.32 ± 0.07	0.22 ± 0.03

TABLE D3 Hematology and Clinical Chemistry Data for B6C3F$_1$ Mice in the 26-Week Drinking Water Study of a California Pesticide/Fertilizer Mixture (continued)

	Vehicle Control	0.1X	1X	10X	100X
MALE (continued)					
Clinical Chemistry					
n					
Day 92	9	7	3	5	7
Day 183	9	10	9	9	7
Urea nitrogen (mg/dL)					
Day 92	32.8 ± 2.7[5]	37.3[6]	37.7 ± 2.5	—[7]	38.9 ± 1.8[5]
Day 183	28.6 ± 1.9[2]	27.1 ± 1.3[8]	25.8 ± 1.1[9]	26.5 ± 0.9[9]	28.7 ± 1.4
Creatinine (mg/dL)					
Day 183	0.49 ± 0.02	0.54 ± 0.02[2]	0.52 ± 0.02[2]	0.51 ± 0.02[8]	0.47 ± 0.03
Total protein (g/dL)					
Day 92	5.6 ± 0.2[5]	5.8[6]	5.4 ± 0.1	—	5.4 ± 0.5[5]
Day 183	5.9 ± 0.1[9]	6.0 ± 0.1[8]	5.8 ± 0.0[9]	5.9 ± 0.1[2]	5.7 ± 0.1
Albumin (g/dL)					
Day 92	3.1 ± 0.0[8]	3.1 ± 0.0[10]	3.1 ± 0.1[10]	3.2 ± 0.0	3.0 ± 0.1[11]
Day 183	3.0 ± 0.1[2]	3.1 ± 0.0	3.0 ± 0.0[9]	3.0 ± 0.1	2.9 ± 0.0
Alkaline phosphatase (IU/L)					
Day 92	68 ± 4[11]	62 ± 2[12]	62 ± 5[11]	61 ± 3[5]	63 ± 7[12]
Day 183	67 ± 5	68 ± 4	73 ± 4	73 ± 4	63 ± 3
Alanine aminotransferase (IU/L)					
Day 92	50 ± 9[10]	45 ± 4[12]	31 ± 2	37 ± 6[12]	31 ± 2[10]
Day 183	57 ± 6[4]	53 ± 3	52 ± 5	56 ± 4	49 ± 5[3]
Creatine kinase (IU/L)					
Day 92	138 ± 32[2]	111 ± 25	77 ± 7[8]	98 ± 20	102 ± 24
Day 183	57 ± 8	57 ± 5[2]	54 ± 8	63 ± 8[2]	70 ± 14[2]
Cholinesterase (IU/L)					
Day 92	6020 ± 178	5934 ± 159	5931 ± 110[3]	6033 ± 110[8]	5943 ± 146
Day 183	6353 ± 182[4]	6445 ± 137	6516 ± 170[4]	6495 ± 212[4]	5943 ± 135[3]
Bile acids (μmol/L)					
Day 183	9.00 ± 0.32[10]	8.50 ± 0.50[5]	8.50 ± 0.50[11]	8.83 ± 0.65[9]	7.00 ± 0.58**[12]
FEMALE					
Hematology					
n					
Day 92	10	10	10	10	10
Day 183	10	10	10	9	10
Hematocrit (%)					
Day 92	45.3 ± 0.5	45.8 ± 0.6	45.9 ± 0.6	45.2 ± 0.6	45.9 ± 0.4
Day 183	45.8 ± 0.4	45.7 ± 0.5	45.5 ± 0.3	45.5 ± 0.5	45.3 ± 0.5
Hemoglobin (g/dL)					
Day 92	15.1 ± 0.1	15.1 ± 0.1	15.2 ± 0.1	15.0 ± 0.1	15.3 ± 0.1
Day 183	15.3 ± 0.1	15.1 ± 0.2	15.3 ± 0.1	15.2 ± 0.2	15.1 ± 0.2
Erythrocytes (10^6/μL)					
Day 92	9.81 ± 0.10	9.90 ± 0.08	9.99 ± 0.11	9.90 ± 0.09	10.03 ± 0.08
Day 183	10.24 ± 0.13	10.09 ± 0.11	10.07 ± 0.06	10.00 ± 0.10	10.03 ± 0.08

TABLE D3 Hematology and Clinical Chemistry Data for B6C3F$_1$ Mice in the 26-Week Drinking Water Study of a California Pesticide/Fertilizer Mixture (continued)

	Vehicle Control	0.1X	1X	10X	100X
FEMALE (continued)					
Reticulocytes (10^6/μL)					
Day 92	0.20 ± 0.01	0.20 ± 0.02[3]	0.28 ± 0.05[3]	0.17 ± 0.02	0.24 ± 0.01
Day 183	0.25 ± 0.03[3]	0.24 ± 0.03	0.24 ± 0.03[3]	0.22 ± 0.03[2]	0.25 ± 0.02
Nucleated erythrocytes (10^3/μL)					
Day 92	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.01 ± 0.01
Day 183	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00
Mean cell volume (fL)					
Day 92	46.2 ± 0.2	46.3 ± 0.2	45.9 ± 0.3	45.7 ± 0.2	45.8 ± 0.2
Day 183	44.8 ± 0.4	45.3 ± 0.3	45.1 ± 0.3	45.5 ± 0.2	45.2 ± 0.3
Mean cell hemoglobin (pg)					
Day 92	15.3 ± 0.1	15.3 ± 0.1	15.2 ± 0.1	15.2 ± 0.1	15.2 ± 0.1
Day 183	14.9 ± 0.1	15.0 ± 0.1	15.2 ± 0.1	15.2 ± 0.0	15.1 ± 0.1
Mean cell hemoglobin concentration (g/dL)					
Day 92	33.2 ± 0.2	33.0 ± 0.2	33.2 ± 0.2	33.2 ± 0.2	33.3 ± 0.2
Day 183	33.3 ± 0.1	33.1 ± 0.1	33.8 ± 0.2	33.4 ± 0.2	33.4 ± 0.2
Platelets (10^3/μL)					
Day 92	1191 ± 45	1232 ± 52	1200 ± 59	1195 ± 28	1217 ± 29
Day 183	1109 ± 41	1217 ± 35	1150 ± 38	1224 ± 28	1134 ± 35
Leukocytes (10^3/μL)					
Day 92	4.56 ± 0.30	5.71 ± 0.40	4.69 ± 0.39	5.42 ± 0.55	5.37 ± 0.42
Day 183	5.68 ± 0.36	6.12 ± 0.56	6.58 ± 0.45	6.03 ± 0.34	5.27 ± 0.27
Segmented neutrophils (10^3/μL)					
Day 92	0.50 ± 0.08	0.73 ± 0.10	0.54 ± 0.08	0.83 ± 0.18	0.75 ± 0.10
Day 183	1.06 ± 0.14	1.00 ± 0.09	1.06 ± 0.11	1.00 ± 0.09	0.83 ± 0.09
Lymphocytes (10^3/μL)					
Day 92	3.95 ± 0.24	4.84 ± 0.35	4.01 ± 0.31	4.49 ± 0.39	4.48 ± 0.36
Day 183	4.44 ± 0.33	4.92 ± 0.53	5.35 ± 0.37	4.79 ± 0.29	4.31 ± 0.23
Monocytes (10^3/μL)					
Day 92	0.01 ± 0.01	0.05 ± 0.01	0.06 ± 0.02	0.03 ± 0.01	0.03 ± 0.01
Day 183	0.08 ± 0.03	0.11 ± 0.04	0.06 ± 0.02	0.12 ± 0.04	0.05 ± 0.02
Eosinophils (10^3/μL)					
Day 92	0.09 ± 0.03	0.10 ± 0.03	0.08 ± 0.02	0.07 ± 0.02	0.11 ± 0.05
Day 183	0.10 ± 0.03	0.10 ± 0.02	0.12 ± 0.03	0.11 ± 0.03	0.08 ± 0.03
Methemoglobin (g/dL)					
Day 92	0.29 ± 0.06	0.31 ± 0.10	0.16 ± 0.02	0.20 ± 0.04	0.21 ± 0.02
Day 183	0.20 ± 0.02	0.14 ± 0.02	0.20 ± 0.05	0.20 ± 0.02	0.16 ± 0.02
Clinical Chemistry					
n					
Day 92	7	9	10	10	8
Day 183	10	10	10	9	7
Alanine aminotransferase (IU/L)					
Day 183	27 ± 3[11]	34 ± 3[3]	33 ± 3[8]	35 ± 4[11]	28 ± 1
Creatine kinase (IU/L)					
Day 183	51 ± 8[12]	52 ± 5[8]	43 ± 7[10]	37 ± 4[12]	43 ± 5
Cholinesterase (IU/L)					
Day 92	7095 ± 299	6858 ± 689	7752 ± 140	7271 ± 234	7600 ± 262
Day 183	8899 ± 274	9190 ± 215	9368 ± 302	9039 ± 230	9493 ± 217[4]

TABLE D3 Hematology and Clinical Chemistry Data for B6C3F$_1$ Mice in the 26-Week Drinking Water Study of a California Pesticide/Fertilizer Mixture (continued)

1 Data are given as mean ± standard error.
2 n=8.
3 n=9.
4 n=10.
5 n=2.
6 n=1; no standard error calculated due to small number of samples.
7 Not measured for this exposure group.
8 n=7.
9 n=6.
10 n=5.
11 n=4.
12 n=3.
* Significantly different (P≤0.05) from the control group by Shirley's test.
** Significantly different (P≤0.01) from the control group by Shirley's test.

TABLE D4 Hematology and Clinical Chemistry Data for B6C3F$_1$ Mice in the 26-Week Drinking Water Study of an Iowa Pesticide/Fertilizer Mixture[1]

	Vehicle Control	0.1X	1X	10X	100X
MALE					
Hematology					
n	10	10	10	10	10
Hematocrit (%)					
Day 92	47.0 ± 0.9	45.1 ± 0.4	45.3 ± 0.2	45.6 ± 0.5	45.5 ± 0.6
Day 183	46.6 ± 0.6	45.3 ± 0.3	45.0 ± 0.4	45.8 ± 0.4	45.0 ± 0.3
Hemoglobin (g/dL)					
Day 92	15.6 ± 0.3	15.1 ± 0.1	15.0 ± 0.1	15.1 ± 0.1	15.2 ± 0.2
Day 183	15.5 ± 0.2	14.8 ± 0.1	14.9 ± 0.2	15.0 ± 0.1	14.9 ± 0.1
Erythrocytes (10^6/μL)					
Day 92	10.47 ± 0.19	10.06 ± 0.08*	10.04 ± 0.06*	10.12 ± 0.09*	10.11 ± 0.12*
Day 183	10.64 ± 0.16	10.16 ± 0.08*	10.12 ± 0.06**	10.22 ± 0.09**	10.08 ± 0.07**
Reticulocytes (10^6/μL)					
Day 92	0.23 ± 0.03[2]	0.22 ± 0.02[3]	0.20 ± 0.02[3]	0.20 ± 0.03	0.20 ± 0.01
Day 183	0.25 ± 0.02[3]	0.23 ± 0.02	0.25 ± 0.02	0.24 ± 0.02	0.27 ± 0.02
Nucleated erythrocytes/100 leukocytes					
Day 92	0.11 ± 0.11[3]	0.00 ± 0.00	0.22 ± 0.15[3]	0.20 ± 0.20	0.20 ± 0.13
Day 183	0.10 ± 0.10	0.00 ± 0.00	0.10 ± 0.10	0.00 ± 0.00	0.00 ± 0.00
Mean cell volume (fL)					
Day 92	44.9 ± 0.2	44.9 ± 0.2	45.1 ± 0.2	45.1 ± 0.3	45.0 ± 0.3
Day 183	43.9 ± 0.2	44.6 ± 0.2*	44.4 ± 0.3	44.8 ± 0.2**	44.6 ± 0.2*
Mean cell hemoglobin (pg)					
Day 92	14.9 ± 0.1	14.9 ± 0.1	15.0 ± 0.1	15.0 ± 0.1	15.0 ± 0.1
Day 183	14.6 ± 0.1	14.6 ± 0.1	14.7 ± 0.1	14.7 ± 0.1	14.8 ± 0.1*
Mean cell hemoglobin concentration (g/dL)					
Day 92	33.2 ± 0.2	33.3 ± 0.2	33.2 ± 0.1	33.2 ± 0.2	33.3 ± 0.1
Day 183	33.3 ± 0.1	32.7 ± 0.1*	33.1 ± 0.2	32.7 ± 0.1*	33.2 ± 0.2
Platelets (10^3/μL)					
Day 92	1562 ± 52	1423 ± 31	1432 ± 38	1425 ± 30	1420 ± 29
Day 183	1436 ± 18	1478 ± 23	1448 ± 33	1462 ± 31	1422 ± 29
Leukocytes (10^3/μL)					
Day 92	6.46 ± 0.41	6.85 ± 0.37	6.47 ± 0.60	7.03 ± 0.31	6.97 ± 0.27
Day 183	7.60 ± 0.34	8.18 ± 0.26	7.27 ± 0.44	7.61 ± 0.18	7.93 ± 0.23
Segmented neutrophils (10^3/μL)					
Day 92	1.18 ± 0.12[3]	1.19 ± 0.15	1.06 ± 0.09[3]	1.02 ± 0.11	1.07 ± 0.08
Day 183	1.35 ± 0.07	1.46 ± 0.11	1.28 ± 0.09	1.37 ± 0.12	1.37 ± 0.09
Lymphocytes (10^3/μL)					
Day 92	5.31 ± 0.31[3]	5.45 ± 0.36	5.48 ± 0.53[3]	5.82 ± 0.32	5.69 ± 0.22
Day 183	6.05 ± 0.34	6.33 ± 0.24	5.75 ± 0.35	5.97 ± 0.19	6.25 ± 0.22
Monocytes (10^3/μL)					
Day 92	0.09 ± 0.03[3]	0.07 ± 0.02	0.01 ± 0.01*[3]	0.08 ± 0.03	0.03 ± 0.02
Day 183	0.12 ± 0.03	0.25 ± 0.02**	0.13 ± 0.02	0.21 ± 0.03	0.19 ± 0.04
Eosinophils (10^3/μL)					
Day 92	0.13 ± 0.03[3]	0.15 ± 0.04	0.16 ± 0.04[3]	0.13 ± 0.03	0.18 ± 0.04
Day 183	0.08 ± 0.02	0.14 ± 0.03	0.10 ± 0.02	0.06 ± 0.02	0.13 ± 0.02
Methemoglobin (g/dL)					
Day 92	0.16 ± 0.01	0.15 ± 0.02	0.27 ± 0.07	0.13 ± 0.02	0.22 ± 0.06
Day 183	0.24 ± 0.07	0.21 ± 0.06	0.16 ± 0.04	0.13 ± 0.02	0.11 ± 0.02

TABLE D4 Hematology and Clinical Chemistry Data for B6C3F$_1$ Mice in the 26-Week Drinking Water Study of an Iowa Pesticide/Fertilizer Mixture (continued)

	Vehicle Control	0.1X	1X	10X	100X
MALE (continued)					
Clinical Chemistry					
n					
Day 92	2	7	3	3	4
Day 183	4	9	6	5	9
Total protein (g/dL)					
Day 183	5.6 ± 0.1[4]	5.7 ± 0.1[4]	5.8 ± 0.1[5]	5.6[6]	5.8 ± 0.0[4]
Albumin (g/dL)					
Day 92	3.2 ± 0.2	3.3[6]	3.3 ± 0.1	3.2 ± 0.0	3.2 ± 0.0[7]
Day 183	3.0 ± 0.1[8]	3.0 ± 0.1	3.0 ± 0.1[2]	3.1 ± 0.1[5]	3.0 ± 0.0[7]
Alanine aminotransferase (IU/L)					
Day 92	25 ± 7	39 ± 4[4]	34 ± 2	64 ± 8**	52 ± 11*
Day 183	44 ± 6	48 ± 6	39 ± 5	55 ± 6	56 ± 4[2]
Alkaline phosphatase (IU/L)					
Day 183	61 ± 6	65 ± 5[2]	58 ± 2	61 ± 2[5]	62 ± 2
Creatine kinase (IU/L)					
Day 92	100 ± 26[5]	90 ± 23[5]	78 ± 15[5]	84 ± 22	97 ± 21
Day 183	163 ± 27	143 ± 15[2]	138 ± 16[9]	143 ± 37	136 ± 18[2]
Cholinesterase (IU/L)					
Day 92	5866 ± 126[9]	5397 ± 170	5714 ± 89[2]	5440 ± 74*[8]	5468 ± 134*[2]
Day 183	6477 ± 274[2]	6283 ± 165[10]	5973 ± 158[3]	6263 ± 121[3]	6131 ± 123
FEMALE					
Hematology					
n					
Day 92	9	10	10	10	10
Day 183	10	10	10	10	9
Hematocrit (%)					
Day 92	45.6 ± 0.7	45.2 ± 0.3	44.8 ± 0.5	45.6 ± 0.4	45.4 ± 0.4
Day 183	44.2 ± 0.3	44.6 ± 0.3	44.4 ± 0.4	44.9 ± 0.3	44.5 ± 0.4
Hemoglobin (g/dL)					
Day 92	15.2 ± 0.2	15.1 ± 0.1	14.9 ± 0.2	15.2 ± 0.1	15.2 ± 0.1
Day 183	14.6 ± 0.1	14.7 ± 0.1	14.6 ± 0.1	14.8 ± 0.1	14.6 ± 0.1
Erythrocytes (10^6/μL)					
Day 92	10.04 ± 0.15	9.87 ± 0.08	9.89 ± 0.12	9.99 ± 0.11	9.98 ± 0.08
Day 183	9.87 ± 0.07	9.84 ± 0.07	9.79 ± 0.08	9.95 ± 0.08	9.91 ± 0.08
Reticulocytes (10^6/μL)					
Day 92	0.22 ± 0.02[2]	0.19 ± 0.02[3]	0.18 ± 0.02	0.19 ± 0.02[3]	0.21 ± 0.01
Day 183	0.25 ± 0.03[3]	0.23 ± 0.02	0.21 ± 0.03	0.21 ± 0.04[3]	0.24 ± 0.03
Nucleated erythrocytes/100 leukocytes					
Day 92	0.22 ± 0.15	0.30 ± 0.15	0.20 ± 0.13	0.20 ± 0.13	0.00 ± 0.00
Day 183	0.22 ± 0.22[3]	0.00 ± 0.00	0.10 ± 0.10	0.10 ± 0.10	0.22 ± 0.15
Mean cell volume (fL)					
Day 92	45.4 ± 0.3	45.8 ± 0.3	45.3 ± 0.1	45.7 ± 0.3	45.6 ± 0.3
Day 183	44.8 ± 0.3	45.3 ± 0.2	45.4 ± 0.2	45.2 ± 0.2	44.9 ± 0.2

TABLE D4 Hematology and Clinical Chemistry Data for B6C3F$_1$ Mice in the 26-Week Drinking Water Study of an Iowa Pesticide/Fertilizer Mixture (continued)

	Vehicle Control	0.1X	1X	10X	100X
FEMALE (continued)					
Hematology (continued)					
Mean cell hemoglobin (pg)					
Day 92	15.1 ± 0.1	15.3 ± 0.1	15.1 ± 0.1	15.2 ± 0.1	15.3 ± 0.1
Day 183	14.8 ± 0.1	14.9 ± 0.1	14.9 ± 0.1	14.9 ± 0.1	14.8 ± 0.1
Mean cell hemoglobin concentration (g/dL)					
Day 92	33.3 ± 0.2	33.4 ± 0.1	33.4 ± 0.1	33.3 ± 0.1	33.5 ± 0.2
Day 183	33.0 ± 0.1	33.0 ± 0.1	32.9 ± 0.1	32.9 ± 0.1	32.9 ± 0.1
Platelets (10^3/μL)					
Day 92	1161 ± 67	1236 ± 41	1175 ± 39	1137 ± 49	1158 ± 43
Day 183	1259 ± 26	1205 ± 55	1123 ± 57	1275 ± 18	1253 ± 21
Leukocytes (10^3/μL)					
Day 92	5.05 ± 0.34	4.53 ± 0.31	5.46 ± 0.52	5.66 ± 0.47	5.89 ± 0.49
Day 183	5.47 ± 0.36	5.67 ± 0.33	4.95 ± 0.41	5.03 ± 0.30	4.52 ± 0.24
Segmented neutrophils (10^3/μL)					
Day 92	0.57 ± 0.08	0.61 ± 0.13	1.04 ± 0.10*	0.85 ± 0.11*	0.89 ± 0.08*
Day 183	1.03 ± 0.12[3]	1.05 ± 0.15	0.82 ± 0.11	0.70 ± 0.12	0.73 ± 0.11
Lymphocytes (10^3/μL)					
Day 92	4.23 ± 0.28	3.69 ± 0.24	4.20 ± 0.46	4.58 ± 0.43	4.79 ± 0.44
Day 183	4.25 ± 0.37[3]	4.45 ± 0.39	3.91 ± 0.33	4.18 ± 0.27	3.61 ± 0.20
Monocytes (10^3/μL)					
Day 92	0.09 ± 0.02	0.09 ± 0.03	0.07 ± 0.02	0.12 ± 0.03	0.10 ± 0.03
Day 183	0.07 ± 0.03[3]	0.11 ± 0.03	0.07 ± 0.02	0.05 ± 0.02	0.05 ± 0.02
Eosinophils (10^3/μL)					
Day 92	0.16 ± 0.04	0.12 ± 0.03	0.16 ± 0.04	0.11 ± 0.02	0.11 ± 0.02
Day 183	0.12 ± 0.03[3]	0.06 ± 0.02	0.15 ± 0.03	0.10 ± 0.04	0.14 ± 0.02
Methemoglobin (g/dL)					
Day 92	0.17 ± 0.03[2]	0.22 ± 0.03[3]	0.17 ± 0.02	0.16 ± 0.02	0.14 ± 0.02[3]
Day 183	0.20 ± 0.03	0.21 ± 0.05	0.18 ± 0.02	0.14 ± 0.02	0.26 ± 0.09
Clinical Chemistry					
n					
Day 92	2	3	4	5	2
Day 183	2	4	3	10	2
Urea nitrogen (mg/dL)					
Day 92	24.9 ± 4.0	30.4 ± 0.6	30.0 ± 1.5[11]	24.2 ± 2.2	27.8 ± 6.2
Day 183	32.1 ± 0.4	30.4 ± 2.4[4]	33.1 ± 4.0	33.8[6]	26.6 ± 4.6
Total protein (g/dL)					
Day 92	5.7 ± 0.2	5.4[6]	5.1[6]	5.2 ± 0.1[11]	4.9[6]
Day 183	5.8 ± 0.0	5.8 ± 0.2	5.4 ± 0.0	5.6[6]	5.8 ± 0.2
Albumin (g/dL)					
Day 92	3.5 ± 0.0[4]	3.4 ± 0.0	3.3 ± 0.1[4]	3.5 ± 0.0[8]	3.3 ± 0.1[4]
Day 183	3.2 ± 0.0	3.3 ± 0.0	3.0 ± 0.1	3.3 ± 0.0[4]	3.3 ± 0.1[4]
Alanine aminotransferase (IU/L)					
Day 92	23 ± 4	32[6]	31[6]	27 ± 3[11]	—[12]
Alkaline phosphatase (IU/L)					
Day 92	100 ± 2	98[6]	104 ± 6	99 ± 4[5]	105 ± 4

TABLE D4 Hematology and Clinical Chemistry Data for B6C3F1 Mice in the 26-Week Drinking Water Study of an Iowa Pesticide/Fertilizer Mixture (continued)

	Vehicle Control	0.1X	1X	10X	100X
FEMALE (continued)					
Clinical Chemistry (continued)					
Creatine kinase (IU/L)					
Day 92	153 ± 43[5]	78 ± 18	160 ± 72	84 ± 15	119 ± 8[5]
Cholinesterase (IU/L)					
Day 92	8447 ± 336[3]	7811 ± 315[10]	7699 ± 180[10]	8179 ± 207[3]	8131 ± 122[10]
Day 183	8440 ± 192[10]	8400 ± 192[10]	8461 ± 172[2]	8702 ± 234	8509 ± 213[2]

[1] Data are given as mean ± standard error.
[2] n=8.
[3] n=9.
[4] n=3.
[5] n=4.
[6] n=1; no standard error calculated due to small number of samples.
[7] n=5.
[8] n=6.
[9] n=7.
[10] n=10.
[11] n=2.
[12] Not measured for this exposure group.
* Significantly different (P≤0.05) from the control group by Dunn's or Shirley's test.
** Significantly different (P≤0.01) from the control group by Dunn's or Shirley's test.

APPENDIX E

Reproductive Tissue Evaluations, Estrous Cycle Characterization, and Teratology Studies

TABLE E1 Summary of Reproductive Tissue Evaluations in Male F344/N Rats at the 13-Week Interim Evaluation in the 26-Week Drinking Water Study of a California Pesticide/Fertilizer Mixture[1]

Study Parameters	Vehicle Control	1X	10X	100X
n	10	10	10	10
Weights (g)				
Necropsy body weight	342 ± 6	351 ± 6	345 ± 5	331 ± 5
Left epididymis	0.434 ± 0.006	0.448 ± 0.008	0.445 ± 0.004	0.438 ± 0.006
Left cauda epididymis	0.192 ± 0.004	0.204 ± 0.004	0.200 ± 0.003	0.202 ± 0.004
Left testis	1.49 ± 0.02	1.50 ± 0.02	1.51 ± 0.02	1.46 ± 0.04
Spermatid measurements				
Spermatid heads (10^7/g testis)	10.98 ± 0.28	10.74 ± 0.60	9.90 ± 0.30	10.47 ± 0.44
Spermatid heads (10^7/testis)	16.35 ± 0.46	16.06 ± 0.88	14.87 ± 0.33	15.17 ± 0.56
Spermatid count (mean/10^{-4} mL suspension)	81.75 ± 2.31	80.28 ± 4.39	74.35 ± 1.65	75.83 ± 2.81
Spermatozoal measurements				
Motility (%)	90.06 ± 0.45	89.23 ± 1.04	88.55 ± 0.46	90.74 ± 0.68
Concentration (10^3/g cauda epididymal tissue)	453 ± 34	469 ± 24	532 ± 25	507 ± 31

[1] Data are presented as mean ± standard error. Differences from the control group for necropsy body weights are not significant by Dunnett's test; differences from the control group for epididymal, cauda epididymal, and testis weights and spermatid and spermatozoal measurements are not significant by Dunn's test.

TABLE E2 Summary of Estrous Cycle Characterization in Female F344/N Rats at the 13-Week Interim Evaluation in the 26-Week Drinking Water Study of a California Pesticide/Fertilizer Mixture[1]

Study Parameters	Vehicle Control	1X	10X	100X
n	10	10	10	10
Necropsy body weight (g)	192 ± 3	191 ± 3	197 ± 4	189 ± 3
Estrous cycle length (days)	5.20 ± 0.20	4.85 ± 0.11	5.00 ± 0.00	5.00 ± 0.00
Estrous stages (% of cycle)				
Diestrus	39.2	39.2	44.2	39.2
Proestrus	17.5	9.2	15.8	16.7
Estrus	20.8	29.2	21.7	24.2
Metestrus	21.7	20.0	18.3	20.0
Uncertain diagnoses	0.8	2.5	0.0	0.0

[1] Necropsy body weight and estrous cycle length data are presented as mean ± standard error. Differences from the control group for necropsy body weights are not significant by Dunnett's test; differences from the control group for estrous cycle lengths are not significant by Dunn's test. By multivariate analysis of variance, exposed groups do not differ significantly from the control group in the relative length of time spent in the estrous stages.

TABLE E3 Summary of Reproductive Tissue Evaluations in Male F344/N Rats at the 13-Week Interim Evaluation in the 26-Week Drinking Water Study of an Iowa Pesticide/Fertilizer Mixture[1]

Study Parameters	Vehicle Control	1X	10X	100X
n	10	10	10	10
Weights (g)				
Necropsy body weight	334 ± 4	351 ± 3*	326 ± 4	343 ± 7
Left epididymis	0.453 ± 0.008	0.442 ± 0.005	0.425 ± 0.008*	0.428 ± 0.009*
Left cauda epididymis	0.213 ± 0.007	0.212 ± 0.004	0.204 ± 0.006	0.204 ± 0.006
Left testis	1.50 ± 0.01	1.54 ± 0.02	1.47 ± 0.02	1.46 ± 0.02
Spermatid measurements				
Spermatid heads (10^7/g testis)	10.12 ± 0.41	9.70 ± 0.39	10.68 ± 0.28	9.90 ± 0.39
Spermatid heads (10^7/testis)	15.15 ± 0.62	14.95 ± 0.64	15.76 ± 0.53	14.51 ± 0.65
Spermatid count (mean/10^{-4} mL suspension)	75.73 ± 3.11	74.75 ± 3.21	78.78 ± 2.67	72.53 ± 3.23
Spermatozoal measurements				
Motility (%)	92.68 ± 0.37	92.88 ± 0.38	93.04 ± 0.22	92.43 ± 0.30
Concentration (10^6/g cauda epididymal tissue)	478 ± 19	491 ± 20	506 ± 17	524 ± 23

[1] Data are presented as mean ± standard error. Differences from the control group for cauda epididymal and testis weights and spermatid and spermatozoal measurements are not significant by Dunn's or Shirley's test.

* Significantly different ($P \leq 0.05$) from the control group by Dunnett's test (necropsy body weight) or Shirley's test (epididymal weight).

TABLE E4 Summary of Estrous Cycle Characterization in Female F344/N Rats at the 13-Week Interim Evaluation in the 26-Week Drinking Water Study of an Iowa Pesticide/Fertilizer Mixture[1]

Study Parameters	Vehicle Control	1X	10X	100X
n	10	10	10	10
Necropsy body weight (g)	188 ± 3	190 ± 3	191 ± 3	189 ± 4
Estrous cycle length (days)	5.10 ± 0.12	5.05 ± 0.05	5.00 ± 0.07	5.00 ± 0.11
Estrous stages (% of cycle)				
Diestrus	40.8	45.0	34.2	37.5
Proestrus	15.0	14.2	15.8	13.3
Estrus	24.2	21.7	28.3	27.5
Metestrus	20.0	18.3	21.7	21.7
Uncertain diagnoses	0.0	0.8	0.0	0.0

[1] Necropsy body weight and estrous cycle length data are presented as mean ± standard error. Differences from the control group for necropsy body weights are not significant by Dunnett's test; differences from the control group for estrous cycle lengths are not significant by Dunn's test. By multivariate analysis of variance, exposed groups do not differ significantly from the control group in the relative length of time spent in the estrous stages.

TABLE E5 Summary of Reproductive Tissue Evaluations in Male B6C3F$_1$ Mice at the 13-Week Interim Evaluation in the 26-Week Drinking Water Study of a California Pesticide/Fertilizer Mixture[1]

Study Parameters	Vehicle Control	1X	10X	100X
n	10	10	10	10
Weights (g)				
Necropsy body weight	41.0 ± 0.6	40.0 ± 0.6	39.7 ± 0.8	37.5 ± 0.7**
Left epididymis	0.052 ± 0.001	0.054 ± 0.001	0.053 ± 0.001	0.053 ± 0.001
Left cauda epididymis	0.023 ± 0.001	0.023 ± 0.001	0.023 ± 0.001	0.023 ± 0.001
Left testis	0.121 ± 0.001	0.124 ± 0.002	0.123 ± 0.002	0.120 ± 0.001
Spermatid measurements				
Spermatid heads (10^7/g testis)	15.96 ± 0.53	17.67 ± 0.88	16.96 ± 0.82	15.99 ± 0.87
Spermatid heads (10^7/testis)	1.93 ± 0.06	2.18 ± 0.11	2.08 ± 0.11	1.92 ± 0.10
Spermatid count (mean/10^{-4} mL suspension)	60.35 ± 1.88	68.25 ± 3.30	65.08 ± 3.49	60.05 ± 3.15
Spermatozoal measurements				
Motility (%)	93.11 ± 0.33	93.23 ± 0.27	93.36 ± 0.46	89.39 ± 3.95
Concentration (10^6/g cauda epididymal tissue)	940 ± 77	1047 ± 79	1064 ± 50	1077 ± 101

[1] Data are presented as mean ± standard error. Differences from the control group for epididymal, cauda epididymal, and testis weights and spermatid and spermatozoal measurements are not significant by Dunn's test.
** Significantly different (P≤0.01) from the control group by Williams' test.

TABLE E6 Summary of Estrous Cycle Characterization in Female B6C3F$_1$ Mice at the 13-Week Interim Evaluation in the 26-Week Drinking Water Study of a California Pesticide/Fertilizer Mixture[1]

Study Parameters	Vehicle Control	1X	10X	100X
n	10	10	10	10
Necropsy body weight (g)	28.6 ± 0.5	29.9 ± 0.5	30.5 ± 0.6	29.7 ± 1.1
Estrous cycle length (days)	4.10 ± 0.07	4.10 ± 0.12	4.00 ± 0.00	4.10 ± 0.07
Estrous stages (% of cycle)				
Diestrus	26.7	31.7	27.5	26.7
Proestrus	20.0	17.5	21.7	20.0
Estrus	31.7	31.7	27.5	29.2
Metestrus	21.7	19.2	22.5	23.3
Uncertain diagnoses (%)	0.0	0.0	0.8	0.8

[1] Necropsy body weight and estrous cycle length data are presented as mean ± standard error. Differences from the control group for necropsy body weights are not significant by Dunnett's test; differences from the control group for estrous cycle lengths are not significant by Dunn's test. By multivariate analysis of variance, exposed groups do not differ significantly from the control group in the relative length of time spent in the estrous stages.

TABLE E7 Summary of Reproductive Tissue Evaluations in Male B6C3F$_1$ Mice at the 13-Week Interim Evaluation in the 26-Week Drinking Water Study of an Iowa Pesticide/Fertilizer Mixture[1]

Study Parameters	Vehicle Control	1X	10X	100X
n	10	10	9	10
Weights (g)				
Necropsy body weight	35.8 ± 1.1	38.1 ± 1.0	36.0 ± 0.7[2]	35.3 ± 1.3
Left epididymis	0.048 ± 0.001	0.050 ± 0.001	0.051 ± 0.001	0.049 ± 0.001
Left cauda epididymis	0.021 ± 0.001	0.022 ± 0.001	0.022 ± 0.001	0.021 ± 0.001
Left testis	0.122 ± 0.005	0.117 ± 0.002	0.119 ± 0.002	0.119 ± 0.002
Spermatid measurements				
Spermatid heads (10^7/g testis)	16.89 ± 0.74	18.77 ± 0.57	18.12 ± 0.92	16.90 ± 0.61
Spermatid heads (10^7/testis)	2.05 ± 0.07	2.20 ± 0.09	2.15 ± 0.11	1.99 ± 0.05
Spermatid count (mean/10^{-4} mL suspension)	63.95 ± 2.31	68.58 ± 2.67	67.31 ± 3.42	62.38 ± 1.58
Spermatozoal measurements				
Motility (%)	91.68 ± 0.19	91.63 ± 0.46	92.03 ± 0.62	91.21 ± 0.50
Concentration (10^6/g cauda epididymal tissue)	874 ± 66	899 ± 49	1018 ± 98	1067 ± 82

[1] Data are presented as mean ± standard error. Differences from the control group for necropsy body weights are not significant by Dunnett's test; differences from the control group for epididymal, cauda epididymal, and testis weights and spermatid and spermatozoal measurements are not significant by Dunn's or Shirley's test.

[2] n=10.

TABLE E8 Summary of Estrous Cycle Characterization in Female B6C3F$_1$ Mice at the 13-Week Interim Evaluation in the 26-Week Drinking Water Study of an Iowa Pesticide/Fertilizer Mixture[1]

Study Parameters	Vehicle Control	1X	10X	100X
n	9	10	10	10
Necropsy body weight (g)	31.1 ± 1.1	29.3 ± 0.9	27.4 ± 0.7*	28.4 ± 0.8*
Estrous cycle length (days)	4.00 ± 0.00	4.15 ± 0.08	4.00 ± 0.00	4.10 ± 0.10
Estrous stages (% of cycle)				
Diestrus	30.6	27.5	32.5	32.5
Proestrus	23.1	23.3	22.5	21.7
Estrus	23.1	28.3	25.8	23.3
Metestrus	23.1	20.8	18.3	22.5
Uncertain diagnoses (%)	0.0	0.0	0.8	0.0

[1] Necropsy body weight and estrous cycle length data are presented as mean ± standard error. Differences from the control group for estrous cycle lengths are not significant by Dunn's test. By multivariate analysis of variance, dosed groups do not differ significantly from the control group in the relative length of time spent in the estrous stages.

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

TERATOLOGY STUDIES

Materials and Methods

TERATOLOGY STUDIES

To determine the effects of pesticide/fertilizer contamination of groundwater on reproduction, teratology studies were performed in Sprague-Dawley rats (Heindel *et al.*, 1993a). Male and female Sprague-Dawley Crl:CD® BR VAF/Plus outbred albino rats used in the teratology studies were obtained from Charles River Breeding Laboratories (Raleigh, NC) and were 9 weeks old at receipt. All rats were quarantined for 7 days before the start of the studies. Individual breeding pairs were cohoused overnight; the first day of vaginal sperm detection was designated Gestation Day 0.

On Gestation Day 0, 23 to 29 females were assigned to each dose group by weight and were individually housed. The study was conducted over two 3- to 6-day periods, with less than 45 days between the two periods. From Gestation Days 6 to 20, pregnant females received 0, 1X, 10X, or 100X concentrations of either the California mixture or the Iowa mixture in drinking water. The pregnant control females received 512 ppm propylene glycol (the pesticide solvent) in drinking water or untreated drinking water. Purina Certified Rodent Chow (#5002; Ralston Purina Co., St. Louis, MO) was available *ad libitum*. Clinical findings, body weights, and feed and water consumption were recorded every 3 days and at the end of the study (Gestation Day 20). The liver and uterus were weighed, and the corpora lutea, implantation sites, resorptions, and live and dead fetuses were counted. Uteri with no visible implantation sites were stained with ammonium sulfide to detect very early resorptions (Salewski, 1964).

Live fetuses were anesthetized on ice and were weighed, examined for external morphological abnormalities, and dissected. Half of the fetuses were decapitated; heads were fixed in Bouin's solution and examined by free-hand sectioning (Wilson, 1965). All carcasses were stained with Alcian Blue/ Alizarin Red S and examined for skeletal malformations (Marr *et al.*, 1988).

STATISTICAL METHODS

An arcsine-square root transformation was conducted on data for litters to normalize the means (Snedecor and Cochran, 1967), and Bartlett's test for homogeneity of variance (Winer, 1962) and an analysis of variance (ANOVA) were performed on the vehicle control and dosed groups. Williams' or Dunnett's Multiple Comparison Test (Dunnett, 1955, 1964; Williams, 1971, 1972) was used to compare dosed groups to the controls when a significant dose effect was identified by ANOVA. Pairwise comparisons of

data other than organ and body weights were analyzed using a one-tailed test. Data showing significant dose × replicate interactions were analyzed separately for dose effects within each replicate of the study and all replicates combined. Nominal scale measures were analyzed using a chi-square test and a test for linear trend on proportions; a one-tailed Fisher's exact test was used for pairwise comparisons between control and dosed groups showing significant differences by a chi-square test. Water and vehicle control groups were compared by ANOVA.

Results

CALIFORNIA MIXTURE

No deaths occurred in the California pesticide/fertilizer mixture study, and there were no clinical signs of toxicity. In each group, 21 to 23 rats were confirmed pregnant (Table 1). Maternal body weights and were not affected by exposure (Table 1); however, water consumption by females in the 100X group was significantly increased throughout the study. The average daily exposure to the individual chemicals is given in Table 2. No differences in embryo/fetal parameters including fetal weights, mortality, and malformations were noted between the control and vehicle control rats or between vehicle control and exposed groups (Tables 3 and 4).

IOWA MIXTURE

No deaths occurred in the Iowa pesticide/fertilizer mixture study, and there were no clinical signs of toxicity. In each group, 21 to 23 rats were confirmed pregnant (Table 5). Maternal body weights of control and exposed rats were similar throughout the study. Absolute and relative liver weights of vehicle control dams were significantly increased compared to the untreated control group, but the absolute and relative liver weights of vehicle control and exposed dams were similar. The average daily exposure to the individual chemicals is given in Table 6; water consumption was not affected by exposure. The number of implantation sites, percent preimplantation loss, percent resorptions, and percent late fetal deaths per litter and percent nonlive implants were similar for vehicle control and exposed groups (Table 7). No differences in embryo/fetal parameters including fetal weights, mortality, and malformations were noted between the control and vehicle control rats or between vehicle control and exposed groups (Tables 7 and 8). There were no significant differences in embryo/fetal parameters including resorptions per litter, live litter size, sex ratios, live fetal weights, percent fetuses with malformations, percent litters with malformed fetuses, or in the incidence of anatomical variations.

TABLE 1 Maternal Toxicity in Sprague-Dawley Rats Exposed to a California Pesticide/Fertilizer Mixture in Drinking Water on Gestation Day 6 to Day 20

	Untreated Control	Vehicle Control	1X	10X	100X
Subject (Dams)					
Total treated	23	27	23	23	24
Number removed or dead	0	0	0	1	0
Number pregnant at sacrifice	22 (96%)	23 (85%)	21 (95%)	21 (95%)	22 (92%)
Maternal body weight[1] (g)					
Gestation Day 0	244 ± 4	244 ± 4	244 ± 4	242 ± 4	246 ± 4
Gestation Day 20	407 ± 5	406 ± 4	424 ± 6*	408 ± 5	408 ± 6
Maternal weight change[1] (g)					
Treatment period (gestation Days 6-20)	126 ± 4	125 ± 3	143 ± 3*	129 ± 3	129 ± 4
Gestation period (gestation Days 0-20)	156 ± 4	153 ± 4	172 ± 4*	159 ± 5	156 ± 4
Corrected gestation weight gain[2]	68 ± 3	74 ± 4	78 ± 3	73 ± 4	70 ± 4
Gravid uterine weight (g)	88 ± 4	80 ± 3	94 ± 2*	86 ± 3	87 ± 3
Maternal liver weight[1]					
Absolute (g)	17.3 ± 0.3	17.8 ± 0.3	18.7 ± 0.3	18.0 ± 0.3	18.4 ± 0.3
Relative (% body weight)	4.3 ± 0.1	4.5 ± 0.1	4.5 ± 0.1	4.5 ± 0.1	4.6 ± 0.1

[1] Includes all dams pregnant at sacrifice; mean ± standard error.
[2] Gestation weight gain minus gravid uterine weight.
* Significantly different ($P<0.05$) from the control group by pairwise comparison.

TABLE 2 Average Daily Exposure of Sprague-Dawley Rats to Individual Components of a California Pesticide/Fertilizer Mixture in Drinking Water on Gestation Day 6 to Day 20[1]

Compound	Vehicle Control	1X	10X	100X
Aldicarb	—	0.4	3.8	42.1
Aldicarb sulfone	—	0.35	3.7	41.2
Aldicarb sulfoxide	—	0.35	3.7	41.1
Atrazine	—	0.06	0.6	6.8
1,2-Dibromo-3-chloropropane	—	0.001	0.01	0.1
1,2-Dichloropropane	—	0.5	5.6	62.7
Ethylene dibromide	—	0.1	1.1	11.1
Simazine	—	0.03	0.4	4.0
Ammonium nitrate (mg/kg/day)	—	1.2	12.8	142.5
Propylene glycol (mg/kg/day)	61.5	59.8	62.3	69.5

[1] Data are based on mean relative water consumption during the treatment period for each group (μg/kg/day unless otherwise specified). A 90% estimate of target concentrations was used based on the mean of the marker compounds; for marker compounds, actual concentration values (ethylene dibromide, 85.1%; ammonium nitrate, 94.5%) were used.

TABLE 3 Developmental Toxicity in Sprague-Dawley Rats Following Maternal Exposure to a California Pesticide/Fertilizer Mixture on Gestation Day 6 to Day 20

	Untreated Control	Vehicle Control	1X	10X	100X
All litters[1]					
Implantation sites per dam	22	23	22	21	22
Implantation sites per litter[2]	15.6 ± 0.6	14.2 ± 0.6	16.6 ± 0.3	15.2 ± 0.6	14.8 ± 0.7
Preimplantation loss per dam[2] (%)	10.1 ± 2.4	6.3 ± 2.5	3.8 ± 0.9	5.1 ± 2.5	7.5 ± 2.2
Resorptions per litter[2] (%)	3.8 ± 1.1	5.1 ± 1.1	3.9 ± 1.1	4.9 ± 1.6	4.1 ± 1.9
Litters with one or more resorptions (%)	45	57	45	38	32
Number of litters totally resorbed	0	0	0	0	0
Late fetal deaths per litter[2] (%)	0.0 ± 0.0	0.3 ± 0.3	0.0 ± 0.0	0.3 ± 0.3	0.0 ± 0.0
Litters with one or more late fetal deaths (%)	0	1	0	1	0
Litters with one or more nonlive implants (%)	45	61	45	38	32
Live litters[3]					
Live fetuses per dam	22	23	22	21	22
Live fetuses per litter[2]	15.0 ± 0.7	13.5 ± 0.6	15.9 ± 0.4	14.3 ± 0.5	14.4 ± 0.7
Average fetal body weight per litter[2] (g)					
Male fetuses	3.88 ± 0.06	3.84 ± 0.06	3.87 ± 0.06	3.83 ± 0.07	3.90 ± 0.05
Female fetuses	3.72 ± 0.06	3.69 ± 0.06	3.69 ± 0.06	3.68 ± 0.06	3.74 ± 0.05
Male fetuses per litter (%)	53 ± 3	51 ± 3	53 ± 2	48 ± 3	51 ± 3
Malformations[4]					
Fetuses malformed per litter[2] (%)	3.2 ± 1.3	3.5 ± 1.6	3.7 ± 1.4	2.0 ± 1.1	3.7 ± 1.1
Litters with malformed fetuses (%)					
All malformations	36	22	32	19	36
External malformations	5	0	5	0	5
Visceral malformations	32	22	27	19	36
Skeletal malformations	0	0	9	0	0
Variations[4]					
Fetuses with variations per litter[2] (%)	9.8 ± 2.0	8.9 ± 2.4	8.3 ± 2.2	7.1 ± 2.5	7.5 ± 2.0
Litters with variations (%)	73	52	59	43	59

[1] Includes all dams pregnant at sacrifice.
[2] Mean ± standard error.
[3] Includes only dams with live fetuses.
[4] Only live fetuses were examined.

TABLE 4 Morphologic Abnormalities Observed in Sprague-Dawley Rat Fetuses Following Maternal Exposure to a California Pesticide/Fertilizer Mixture on Gestation Day 6 to Day 20

	Untreated Control	Vehicle Control	1X	10X	100X
Total live fetuses examined	314	284	306	302	299
Total litters examined[1]	23	22	22	21	21
External malformations					
Fetuses with external malformations[2]	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Litters with external malformations[3]	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Skeletal malformations					
Fetuses with skeletal malformations	0 (0.0%)	0 (0.0%)	1 (0.3%)	0 (0.0%)	0[4] (0.0%)
Litters with skeletal malformations	0 (0.0%)	0 (0.0%)	1 (4.5%)	0 (0.0%)	0 (0.0%)
Visceral malformations					
Fetuses with visceral malformations	3 (1.0%)	0 (0.0%)	4 (1.3%)	6 (2.0%)	1 (0.3%)
Litters with visceral malformations	3 (13.0%)	0 (0.0%)	4 (18.2%)	4 (19.0%)	1 (4.8%)
Any variations					
Fetuses with any variations	16 (5.1%)	10 (3.5%)	9 (2.9%)	24 (7.9%)	17 (5.7%)
Litters with any variations	11 (47.8%)	6 (27.3%)	9 (40.9%)	10 (47.6%)	9 (42.9%)

[1] Includes only litters with live fetuses.
[2] Number of fetuses with one or more malformations/variations.
[3] Number of litters with one or more malformed/variant fetuses.
[4] Number of fetuses examined = 298.

TABLE 5 Maternal Toxicity in Sprague-Dawley Rats Exposed to an Iowa Pesticide/Fertilizer Mixture in Drinking Water on Gestation Day 6 to Day 20

	Untreated Control	Vehicle Control	1X	10X	100X
Subject (Dams)					
Total treated	28	27	28	29	26
Number removed or dead	2	1	0	1	2
Number pregnant at sacrifice	23 (88%)	22 (85%)	22 (79%)	21 (75%)	21 (88%)
Maternal body weight[1] (g)					
Gestation Day 0	243 ± 3	246 ± 3	250 ± 2	248 ± 3	248 ± 3
Gestation Day 20	410 ± 5	413 ± 7	424 ± 7	423 ± 7	426 ± 6
Maternal weight change[1] (g)					
Treatment period (gestation Days 6-20)	127 ± 3	126 ± 5	133 ± 6	130 ± 5	138 ± 4
Gestation period (gestation Days 0-20)	160 ± 4	159 ± 5	166 ± 6	169 ± 5	171 ± 4
Corrected gestation weight gain[2]	78 ± 3	83 ± 2	83 ± 3	84 ± 4	85 ± 3
Gravid uterine weight (g)	82 ± 4	77 ± 6	84 ± 5	85 ± 4	87 ± 5
Maternal liver weight[1]					
Absolute (g)	17.7 ± 0.3**	18.6 ± 0.3	19.0 ± 0.5	20.0 ± 0.4	19.2 ± 0.3
Relative (% body weight)	4.4 ± 0.1**	4.6 ± 0.1	4.6 ± 0.1	4.7 ± 0.1	4.6 ± 0.1

[1] Includes all dams pregnant at sacrifice (mean ± standard error).
[2] Gestational weight gain minus gravid uterine weight.
** Significant ($P<0.05$) linear trend.

TABLE 6 Average Daily Exposure of Sprague-Dawley Rats to Individual Components of an Iowa Pesticide/Fertilizer Mixture in Drinking Water on Gestation Day 6 to Day 20[1]

Compound	Vehicle Control	1X	10X	100X
Alachlor	—	0.1	1.1	11.6
Atrazine	—	0.06	0.6	6.4
Cyanazine	—	0.05	0.5	5.1
Metolachlor	—	0.05	0.5	5.1
Metribuzin	—	0.07	0.7	7.4
Ammonium nitrate (mg/kg/day)	—	1.3	13.1	132.6
Propylene glycol (mg/kg/day)	70.6	65.6	65.2	65.9

[1] Data are based on mean relative water consumption per group (µg/kg/day unless otherwise specified). A 99% estimate of target concentrations was used based on the mean of the marker compounds; for marker compounds, actual concentration values (metribuzin, 96%; ammonium nitrate, 102%) were used.

TABLE 7 Developmental Toxicity in Sprague-Dawley Rats Following Maternal Exposure to an Iowa Pesticide/Fertilizer Mixture on Gestation Day 6 to Day 20

	Untreated Control	Vehicle Control	1X	10X	100X
All litters[1]					
Implantation sites per dam	23	22	22	21	21
Implantation sites per litter[2]	14.3 ± 0.7	13.7 ± 1.0	14.5 ± 0.9	14.7 ± 0.8	15.0 ± 0.7
Preimplantation loss per dam[2] (%)	7.7 ± 3.5	9.3 ± 4.4	7.3 ± 3.9	6.6 ± 2.7	6.7 ± 2.4
Resorptions per litter[2] (%)	4.8 ± 1.6	7.1 ± 2.9	4.6 ± 1.8	2.4 ± 1.1	5.9 ± 2.6
Litters with one or more resorptions (%)	35	41	32	24	38
Number of litters totally resorbed	0	0	0	0	0
Late fetal deaths per litter[2] (%)	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.3 ± 0.3
Litters with one or more late fetal deaths (%)	0	0	0	0	5
Litters with one or more nonlive implants (%)	35	41	32	24	38
Live litters[3]					
Live fetuses per dam	23	22	22	21	21
Live fetuses per litter[2]	13.7 ± 0.8	12.9 ± 1.1	13.9 ± 0.9	14.4 ± 0.8	14.2 ± 0.8
Average fetal body weight per litter[2] (g)					
Male fetuses	3.99 ± 0.11	3.96 ± 0.13	4.0 ± 0.09	3.93 ± 0.06	3.93 ± 0.07
Female fetuses	3.82 ± 0.12	3.71 ± 0.08	3.80 ± 0.11	3.67 ± 0.06	3.80 ± 0.05
Male fetuses per litter (%)	41 ± 3	50 ± 4	60 ± 3	47 ± 3	52 ± 3
Malformations[4]					
Fetuses malformed per litter[2] (%)	1.0 ± 0.6	0.0 ± 0.0	3.5 ± 2.3	1.7 ± 0.9	0.3 ± 0.3
Litters with malformed fetuses (%)					
All malformations	13	0	23	19	5
External malformations	0	0	0	0	0
Visceral malformations	13	0	18	19	5
Skeletal malformations	0	0	5	0	0
Variations[4]					
Fetuses with variations per litter[2] (%)	6.5 ± 1.9	3.0 ± 1.3	6.9 ± 4.5	8.9 ± 2.7	5.2 ± 2.0
Litters with variations (%)	48	27	41	48	43

[1] Includes all dams pregnant at sacrifice.
[2] Mean ± standard error.
[3] Includes only dams with live fetuses.
[4] Only live fetuses were examined.

TABLE 8 Morphologic Abnormalities Observed in Sprague-Dawley Rat Fetuses Following Maternal Exposure to an Iowa Pesticide/Fertilizer Mixture on Gestation Day 6 to Day 20

	Untreated Control	Vehicle Control	1X	10X	100X
Total live fetuses examined	330	310	350	301	316
Total litters examined[1]	22	23	22	21	22
External malformations					
Fetuses with external malformations[2]	1 (0.3%)	0 (0.0%)	1 (0.3%)	0 (0.0%)	1 (0.3%)
Litters with external malformations[3]	1 (4.5%)	0 (0.0%)	1 (4.5%)	0 (0.0%)	1 (4.5%)
Skeletal malformations					
Fetuses with skeletal malformations	0 (0.0%)	0 (0.0%)	2 (0.6%)	0 (0.0%)	0 (0.0%)
Litters with skeletal malformations	0 (0.0%)	0 (0.0%)	2 (9.1%)	0 (0.0%)	0 (0.0%)
Visceral malformations					
Fetuses with visceral malformations	10 (3.0%)	11 (3.5%)	11 (3.1%)	6 (2.0%)	12 (3.8%)
Litters with visceral malformations	7 (31.8%)	5 (21.7%)	6 (27.3%)	4 (19.0%)	8 (36.4%)
Any variations					
Fetuses with variations	33 (10.0%)	26 (8.4%)	28 (8.0%)	22 (7.3%)	26 (8.2%)
Litters with variations	16 (72.7%)	12 (52.2%)	13 (59.1%)	9 (42.9%)	13 (59.1%)

[1] Includes only litters with live fetuses.
[2] Number of fetuses with one or more malformations/variations.
[3] Number of litters with one or more malformed/variant fetuses.

APPENDIX F

Continuous Breeding Studies

CONTINUOUS BREEDING STUDIES

Materials and Methods

CONTINUOUS BREEDING STUDIES

To determine the effects of pesticide/fertilizer contamination of groundwater on reproduction, continuous breeding studies were performed in CD-1 Swiss mice (Heindel *et al.*, 1993b). Male and female COBS Crl:CD-1 (ICR)BR VAF/PLUS™ outbred albino mice used in the continuous breeding studies were obtained from Charles River Breeding Laboratories (Raleigh, NC for Iowa mixture study and Portage, MI for California mixture study) and were 9 weeks old at receipt. All mice were quarantined for 2 weeks before the start of the studies. Blood samples were collected from two male and two female mice and were analyzed for antibody titers to rodent viruses; all results were negative.

For the continuous breeding studies, groups of 20 breeding pairs received 1X, 10X, or 100X concentrations of either the California mixture or the Iowa mixture in drinking water. For each study, 40 control breeding pairs received 512 ppm propylene glycol (the pesticide solvent) in drinking water. The mice were housed separately for 7 days, then housed in breeding pairs for 98 days, while receiving dosed drinking water; NIH-07 Open Formula Diet (Zeigler Brothers, Inc., Gardners, PA) in pellet form was available *ad libitum*. Clinical findings, body weights, fertility, number of litters per pair, number of live pups per litter, proportion of pups born alive, sex ratio of live pups, pup body weights within 24 hours of birth, and feed and water consumption were recorded.

The final litter of pups born to each breeding pair in the control and 100X groups after the continuous breeding period of the F_0 mice was reared. Siblings were housed three per cage by sex and received the same doses as the F_0 mice. At 74 ± 10 days of age, 20 nonsibling F_1 mice of each sex were cohoused in breeding pairs for up to 7 days and then housed singly through delivery of pups. Body weights, fertility, number of litters per pair, number of live pups per litter, proportion of pups born alive, sex ratio of live pups, pup body weights within 24 hours of birth, and feed and water consumption were recorded. At the end of the study, F_1 mice were necropsied. Selected organs were weighed and fixed in 10% neutral buffered formalin (ovaries were fixed in Bouin's fixative) and embedded in paraffin, and sections were stained with hematoxylin and eosin. Male reproductive tissues were embedded in glycol methacrylate treated with periodic acid Schiff's reagent and counterstained with hematoxylin. Sperm number, motility, and percent abnormal sperm were determined.

STATISTICAL METHODS

For fertility data, which are expressed as proportions, the Cochran-Armitage test (Armitage, 1971) was used to test for dose-related trends. Each dose group was compared to the control group with Fisher's exact test. The number of litters and the number of live pups per litter were determined per fertile pair and then treatment group means were determined. The proportion of live pups was defined as the number of pups born alive divided by the total number of pups produced by each pair. The sex ratio was expressed as the number of male pups born alive divided by the total number of live pups born to each fertile pair. Dose group means were analyzed for overall differences using the Kruskal-Wallis test (Kruskal and Wallis, 1952). Pairwise comparisons were made with the Wilcoxon-Mann-Whitney U test (Mann and Whitney, 1947).

An analysis of covariance (Neter and Wasserman, 1974) was performed to correct for the potential effect of number of live and dead pups per litter on average pup weight. Least-squares were tested for overall equality using an F test and for pairwise equality using a *t*-test. For organ weights, analysis of covariance was also used to adjust for body weight; unadjusted weights were analyzed using the Kruskal-Wallis and Wilcoxon-Mann-Whitney U tests. Possible dose-related trends were tested by Jonckheere's test (Jonckheere, 1954).

Results

CALIFORNIA MIXTURE

One control female, three females in the 1X group, one male in the 10X group, and one female in the 100X group died before the end of the study; however, these deaths were not attributed to exposure to the California pesticide/fertilizer mixture. No clinical signs of toxicity, mean body weight changes, or fertility effects in F_0 mice were attributed to exposure. Additionally, the number of litters per pair, live pups per litter, proportion of pups born alive, sex ratio, pup weight, and interval between births were not affected (Table F1). Feed and water consumption by exposed F_0 mice was similar to that of the controls. The average daily exposure to the individual chemicals for F_0 male mice is shown in Table F2.

For the final litter of F_1 pups, postnatal survival, feed and water consumption, and reproductive performance were not affected by exposure; however, average days to litter was slightly decreased in the 100X group (Table F3). Body weights, spermatid and spermatozoal data, and estrous cycles of exposed mice were similar to those of the controls (Table F4). The seminal vesicle weight of males in the 100X group was lower than that of the controls, and the ovary weight of exposed females was greater than that

of the controls. No treatment-related lesions were observed. The average daily exposure to the individual chemicals for F_1 male mice is shown in Table F2.

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No clinical signs of toxicity, mean body weight changes, or fertility effects were noted in F_0 mice exposed to the Iowa pesticide/fertilizer mixture. Additionally, the number of litters per pair, live pups per litter, proportion of pups born alive, sex ratio, pup weight, and interval between births were not affected (Table F5). Feed and water consumption by exposed F_0 mice was similar to that of the controls. The average daily exposure to the individual chemicals for F_0 male mice is shown in Table F6.

For the final litter of F_1 pups, postnatal survival, feed and water consumption, and reproductive performance were not affected by exposure (Table F7). Organ and body weights, spermatid and spermatozoal data, and estrous cycles of exposed mice were similar to those of the controls (Table F8). No treatment-related lesions were observed. The average daily exposure to the individual chemicals for F_1 male mice is shown in Table F6.

TABLE F1 Fertility and Reproductive Performance Data for F_0 CD-1 Swiss Mice in the Continuous Breeding Study of a California Pesticide/Fertilizer Mixture[1]

Study Parameters	Vehicle Control	1X	10X	100X
Fertile pairs/cohabiting pairs	30/40	17/20	20/20	19/20
Litters/pair	4.7 ± 0.1	4.9 ± 0.1	4.9 ± 0.1	4.8 ± 0.1
Live pups/litter	12.1 ± 0.4	11.3 ± 0.7	11.2 ± 0.7	11.7 ± 0.9
Males/total pups	0.50 ± 0.01	0.52 ± 0.02	0.50 ± 0.02	0.50 ± 0.02
Proportion of pups born alive	0.93 ± 0.03	0.91 ± 0.05	0.87 ± 0.04	0.91 ± 0.04
Combined live pup weight (g)	1.57 ± 0.02	1.55 ± 0.02	1.56 ± 0.02	1.57 ± 0.04

[1] Except for fertile pairs/cohabiting pairs, values are mean ± standard error. Pairs producing one or more litters were considered fertile. Differences from the control group are not significant.

TABLE F2 Compound Consumption by Male CD-1 Swiss Mice in the Continuous Breeding Study of a California Pesticide/Fertilizer Mixture[1]

Compound	F_0 Concentration			F_1 Concentration
	1X	10X	100X	100X
Aldicarb[2]	1.8	18.1	184.2	176.0
Atrazine	0.1	1.0	10.2	9.8
1,2-Dibromo-3-chloropropane	0.002	0.02	0.20	0.20
1,2-Dichloropropane	0.90	9.0	92.0	88.0
Ethylene dibromide	0.182	1.82	18.2	17.6
Simazine	0.061	0.61	6.1	5.9
Ammonium nitrate (mg/kg/day)	2.0	20.1	204.8	195.6

[1] Data are given as µg/kg/day unless otherwise specified.
[2] Includes total consumption data for aldicarb, aldicarb sulfone, and aldicarb sulfoxide (1:1:1 ratio).

TABLE F3 Fertility and Reproductive Performance Data for F_1 CD-1 Swiss Mice in the Continuous Breeding Study of a California Pesticide/Fertilizer Mixture

Study Parameters	Vehicle Control	100X
Females with copulatory plugs/cohabiting pairs	19/20	18/19
Mating index (%)	95	95
Fertile pairs/females with copulatory plugs	19/19	17/18
Fertility index (%)	100	94
Live pups/litter[1]	10.8 ± 0.7	11.8 ± 0.5
Proportion of pups born alive[1]	0.94 ± 0.05	0.99 ± 0.01
Males/total pups[1]	0.56 ± 0.03	0.49 ± 0.03
Live pup weight[1] (g)	1.60 ± 0.02	1.55 ± 0.03
Adjusted live pup weight (g)	1.60 ± 0.02	1.55 ± 0.02
Average days to litter[1]	19.5 ± 0.3	18.8 ± 0.1*

[1] Values are mean ± standard error.
* Significantly different ($P<0.05$) from the control group.

TABLE F4 Organ Weights and Sperm Parameters for F_1 CD-1 Swiss Mice in the Continuous Breeding Study of a California Pesticide/Fertilizer Mixture[1]

Study Parameters	Vehicle Control	100X
MALE		
Necropsy body wt (g)	34.6 ± 0.6	34.7 ± 0.6
Seminal vesicle wt (mg)	413 ± 14	369 ± 12*
Testis wt (mg)	129 ± 4.4	129 ± 4.0
Epididymis wt (mg)	52 ± 1.8	50 ± 1.6
Prostate wt (mg)	28 ± 2.0	31 ± 2.1
Sperm concentration (10^6/g cauda epididymal tissue)	1007 ± 65	1203 ± 62
Sperm motility (%)	77 ± 2.0	77 ± 1.4
Abnormal sperm (%)	3 ± 0.2	4 ± 0.9
FEMALE		
Necropsy body wt (g)	30.0 ± 0.5	31.2 ± 0.4
Ovary wt (mg)	10 ± 0.7	12 ± 0.8*

[1] Values are mean ± standard error; n=20 for all groups.
* Significantly different (P<0.05) from the control group.

TABLE F5 Fertility and Reproductive Performance Data for F_0 CD-1 Swiss Mice in the Continuous Breeding Study of an Iowa Pesticide/Fertilizer Mixture[1]

Study Parameters	Vehicle Control	1X	10X	100X
Fertile pairs/cohabiting pairs	40/40	20/20	20/20	19/20
Litters/pair	4.8 ± 0.1	5.0 ± 0.1	5.0 ± 0.1	4.9 ± 0.1
Live pups/litter	13.0 ± 0.3	12.9 ± 0.5	13.2 ± 0.5	12.7 ± 0.4
Males/total pups	0.48 ± 0.01	0.48 ± 0.01	0.48 ± 0.01	0.47 ± 0.01
Proportion of pups born alive	0.99 ± 0.01	0.97 ± 0.01	0.98 ± 0.01	0.98 ± 0.02
Combined live pup weight (g)	1.58 ± 0.02	1.59 ± 0.02	1.57 ± 0.02	1.62 ± 0.02

[1] Except for fertile pairs/cohabiting pairs, values are mean ± standard error. Pairs producing one or more litters were considered fertile. Differences from the control group are not significant.

TABLE F6 Compound Consumption by Male CD-1 Swiss Mice in the Continuous Breeding Study of an Iowa Pesticide/Fertilizer Mixture[1]

Compound	F_0 Concentration			F_1 Concentration
	1X	10X	100X	100X
Alachlor	0.17	1.76	17.2	22.1
Atrazine	0.09	0.98	9.5	12.3
Cyanazine	0.07	0.78	7.6	9.8
Metolachlor	0.07	0.78	7.6	9.8
Metribuzin	0.12	1.37	12.4	15.8
Ammonium nitrate (mg/kg/day)	1.7	18.2	177.5	227.5

[1] Data are given as µg/kg/day unless otherwise specified.

TABLE F7 Fertility and Reproductive Performance Data for F_1 CD-1 Swiss Mice in the Continuous Breeding Study of an Iowa Pesticide/Fertilizer Mixture

Study Parameters	Vehicle Control	100X
Females with copulatory plugs/cohabiting pairs	17/20	8/20
Mating index (%)	85	90
Fertile pairs/females with copulatory plugs	19/17	20/18
Fertility index (%)	112	111
Live pups/litter[1]	11.6 ± 0.5	12.5 ± 0.6
Proportion of pups born alive[1]	0.99 ± 0.005	1.00 ± 0.00
Males/total pups[1]	0.44 ± 0.05	0.52 ± 0.03
Live pup weight[1] (g)	1.58 ± 0.03	1.61 ± 0.03
Adjusted live pup weight (g)	1.57 ± 0.03	1.63 ± 0.03
Average days to litter[1]	20.6 ± 0.3	21.3 ± 0.4

[1] Values are mean ± standard error. Differences from the control group are not significant.

TABLE F8 Organ Weights and Sperm Parameters for F_1 CD-1 Swiss Mice in the Continuous Breeding Study of an Iowa Pesticide/Fertilizer Mixture

Study Parameters	Vehicle Control	100X
MALE		
Necropsy body wt (g)	36.9 ± 0.8	36.6 ± 1.8
Liver wt (g)	1.9 ± 0.05	2.2 ± 0.14
Kidney/adrenal gland wt (mg)	766 ± 22	751 ± 32
Seminal vesicle wt (mg)	408 ± 16	415 ± 21
Testis wt (mg)	132 ± 3	125 ± 7
Epididymis wt (mg)	33 ± 1.0	34 ± 1.8
Prostate wt (mg)	28 ± 1.5	28 ± 0.2
Sperm concentration (10^6/g cauda epididymal tissue)	1179 ± 60	1135 ± 43
Sperm motility (%)	62 ± 3	68 ± 4
Abnormal sperm (%)	5.0 ± 0.4	5.4 ± 1.3
Spermatid head count (10^7/g testis)	11.1 ± 0.4	11.1 ± 0.84
FEMALE		
Body wt (g)	30.7 ± 0.7	32.5 ± 0.9
Ovary wt (mg)	13 ± 10	14 ± 1.0

[1] Values are mean ± standard error; n=20 for all groups. Differences from the control group are not significant. F_1 mice were necropsied at 117 days of age.

APPENDIX G

Genetic Toxicology

TABLE G1 Frequency of Micronuclei in Peripheral Blood Erythrocytes of Female Mice Following Treatment with California and Iowa Pesticide/Fertilizer Mixtures[1]

		Micronucleated NCEs/1000 NCEs[2]	
	Dose	California Mixture	Iowa Mixture
	0	4.00 ± 0.34	1.54 ± 0.12
	1X	3.81 ± 0.74	2.39 ± 0.49
	10X	3.88 ± 0.49	3.33 ± 0.22*
	100X	3.44 ± 0.72	2.72 ± 0.42*

[1] NCEs = normochromatic erythrocytes. Data are presented as mean ± standard error.
[2] Two thousand normochromatic erythrocytes were scored per animal.
* Significantly different (P<0.01) from the control group by Student's *t*-test.

TABLE G2 Frequency of Micronuclei in Splenocytes of Male Rats and Female Mice Following Treatment with California and Iowa Pesticide/Fertilizer Mixtures[1]

		Micronucleated Splenocytes/1000 Binucleated Splenocytes[2]	
	Dose	California Mixture	Iowa Mixture
MALE RATS	0	12.1 ± 2.7	
	1X	12.8 ± 4.3	
	10X	12.3 ± 2.0	
	100X	10.8 ± 1.0	
FEMALE MICE	0	6.3 ± 3.9[3]	5.6 ± 3.0
	1X	6.3 ± 3.0	3.9 ± 0.7
	10X	4.5 ± 1.3	3.1 ± 1.0
	100X	5.3 ± 1.7	3.4 ± 1.3

[1] Data are presented as mean ± standard deviation.
[2] Two thousand binucleated splenocytes were scored per animal.
[3] n=2.

TABLE G3 Induction of Sister Chromatid Exchanges in Splenocytes of Male Rats and Female Mice Treated with California and Iowa Pesticide/Fertilizer Mixtures[1]

		SCEs/Metaphase[2]	
	Dose	California Mixture	Iowa Mixture
MALE RATS	0	15.2 ± 0.7	
	1X	17.0 ± 0.7*	
	10X	19.5 ± 1.1*	
	100X	18.7 ± 1.1*	
FEMALE MICE	0	9.1 ± 0.6	14.6 ± 0.5
	1X	8.5 ± 0.3	15.6 ± 1.2
	10X	9.4 ± 0.3	15.1 ± 1.0
	100X	10.3 ± 0.4*	15.8 ± 0.9

[1] Data are presented as mean ± standard deviation.
[2] Fifty metaphases were scored per animal.
* Significantly different ($P<0.05$) from the control group by a one-way analysis of variance.

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