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CHRONIC INHALATION TOXICITY OF HYDRAZINE: ONCOGENIC EFFECTS

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Year-long exposures of animals were conducted to hydrazine in the listed concentrations: 0.05, 0.25, 1.0, 5.0 ppm - rats and hamsters; 0.05, 0.25, 1.0 ppm - mice; and 0.25, 1.0 ppm - dogs.

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20. Abstract

Hamsters were held one year postexposure, rats - 18 months postexposure, mice - 15 months postexposure and dogs - 38 months postexposure. Hamsters exposed to the higher concentration showed pathologic changes characteristic of degenerative disease while rats exhibited changes in respiratory epithelium related to chronic irritation. After exposure to 5.0 ppm hydrazine, hamsters developed a 10% incidence of benign nasal polyps compared to 0.5% in controls. Male and female rats showed dose-dependent incidences of microscopic benign epithelial nasal tumors and small numbers of microscopic malignant epithelial nasal tumors after one year exposure to hydrazine and 18 months postexposure holding.

PREFACE

This is one of a series of technical reports describing results of the experimental laboratory program being conducted in the Toxic Hazards Research Unit. This document constitutes the final report on the Chronic Inhalation Toxicity of Hydrazine: Oncogenic Effects. The research covered in this report began in September 1974 and was completed August 1979 and was performed under Air Force Contract No. F33615-73-C-4059 and F33615-76-C-5005. K. C. Back, Ph.D., Chief of the Toxicology Branch was the technical monitor for the Aerospace Medical Research Laboratory.

J. D. MacEwen, Ph.D., served as the Laboratory Director for the THRU of the University of California, Irvine and as co-principal investigator with T. T. Crocker, M.D., Professor and Chairman, Department of Community and Environmental Medicine. Acknowledgement is made to A. K. Roychowdhury, Ph.D., J. D. Diaz, G. L. Fogle, Maj. R. Amster and J. A. Sizemore for their significant contributions and assistance in the preparation of this report.

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SECTION I

INTRODUCTION

Hydrazine (N_2H_4) is a highly reactive reducing agent which is widely used as an intermediate in organic synthesis and, either singly or in combination with other hydrazines, as a missile propellant. An important and increasing use of hydrazine is that of a boiler feed water additive as an oxygen scavenger. It is a colorless polar liquid, weakly basic, which fumes in air. It has a slightly ammoniacal odor.

Clark et al. (1968) provided a detailed review of the toxicology and pharmacology of propellant hydrazines. Hydrazine is a strong convulsant at high doses but may cause central nervous system depression at lower doses. Animals may die acutely of convulsions, respiratory arrest, or cardiovascular collapse within a few hours of an acute exposure by any route of administration, or may die 2 to 4 days later of liver and kidney toxicity (Weir et al., 1964; Witkin, 1956). Jacobsen et al. (1955) reported the 4-hour LC_{50} value as 252 ppm (330 mg/m^3) for the mouse and 570 ppm (750 mg/m^3) for the rat. House (1964) exposed monkeys, rats, and mice to a hydrazine concentration of 1.0 ppm continuously for 90 days. Though mortality was very high, some animals survived. Ninety-six percent of the rats and 98% of the mice died during the exposure; monkeys proved to be the most resistant species with only a 20% mortality. Comstock et al. (1954) exposed dogs, in separate experiments, to 5 and 14 ppm. Two of 2 dogs survived the repeated 6-hour exposures to 5.0 ppm hydrazine for 6 months, and 2 of 4 dogs lived after 194 6-hour exposures to 14 ppm while two died during the third and fifteenth weeks in a debilitated condition. The dog that died during the fifteenth week had a severe convulsive seizure prior to death. Prior to death, both dogs showed signs of anorexia and general fatigue. Changing diets and forced feedings resulted in the survival of the remaining two dogs.

A 6-month chronic inhalation study of hydrazine, reported by Haun and Kinkead (1973), employed 4 exposure level groups and an unexposed control group. Each group comprised 8 male beagle dogs, 4 female rhesus monkeys, 50 male Sprague-Dawley rats, and 40 female ICR mice. The experimental groups were exposed to vapor of hydrazine at concentrations of 1.0 or 0.2 ppm continuously, or at 5.0 and 1.0 ppm intermittently for 6 months duration. The continuous exposures were designed to approximate the same weekly doses of hydrazine received by the intermittent exposure groups with continuously exposed animals receiving 168 and 33.6 ppm-hours of hydrazine/week and intermittently exposed animals 150 and 30 ppm-hours/week. Dogs exposed at the higher dose levels, either intermittently or continuously, exhibited 10-20% reductions in erythrocyte, hematocrit, and hemoglobin values which continued throughout the 6-month exposure but returned to control values within 2 weeks after the exposure ended. Hematology values for dogs exposed to lower doses remained within the normal limits of the control group.

Rats showed a dose-related growth rate depression and a sustained difference in mean body weights of up to 35 grams throughout the exposure. Weight loss in dogs which occurred only in the high dose group was recovered within 2 weeks postexposure, suggesting that the loss was due to appetite suppression.

Gross and microscopic examination of tissues from these animals taken at termination of the exposure showed fatty liver changes in mice and dogs at the high exposure levels but no exposure related changes in the livers of monkeys and rats.

Ten mice and 10 rats from each of the exposure groups were held for a postexposure period. Most of the rats in the two high exposure dose groups died within 6-8 weeks postexposure from chronic pulmonary disease similar to that seen in other rats from these experimental groups at necropsy after termination of exposures. This infection spread to the other groups housed in the same animal room. Consequently, none of the rats survived long enough to evaluate the carcinogenic potential of inhaled hydrazine for this species.

Approximately half of the mice in each group were alive one year postexposure. Tumorigenic changes in these mice were reported by MacEwen et al. in 1974. Mice exposed to the high doses (continuous exposure to 1.0 ppm hydrazine or intermittent exposure to 5.0 ppm) had increased incidences of alveolargenic carcinomas, lymphosarcomas, and hepatomas. Both lower dose level exposure groups had an increased incidence of alveolargenic carcinomas when compared with unexposed controls. The total tumor incidence appeared to be dose related; approximately 87% tumor incidence occurred at the high dose level; 33% incidence at the low dose level; and 12% in the unexposed control group. Although the group sizes were very small, the findings were important in that they demonstrated tumorigenic response at the current Threshold Limit Value.

Attempts to define the fate of inhaled or injected hydrazine to date have failed to achieve a material balance. McKennis et al. (1959) studied the excretion of hydrazine and its metabolites after injection of lethal or near lethal single doses in anesthetized mongrel dogs. Up to 50% of the injected nitrogen from the hydrazine was recovered in the urine of dogs that survived for 5 days. Dambrauskas and Cornish (1964) reported on the distribution, metabolism, and excretion of hydrazine in rats and mice; it was measured spectrophotometrically following reaction with p-dimethylaminobenzaldehyde. They found that about 48% of the injected dose was excreted unchanged in urine by 48 hours and about 2% of the total injected dose could be found in various body tissues primarily in the kidney. No hydrazine was found in the carcass after 48 hours. Dost (1979) reported on the metabolic fate of injected ^{15}N-hydrazine in rats maintained in a closed system which permitted collection and analysis of expired $^{15}N_2$. He found that about 15% of the injected dose of nitrogen was exhaled as gaseous nitrogen within 30 minutes. Another 10% of the original dose could be found in expired air within 48 hours. Careful analysis of the urinary ammonia collected from these animals failed to show any ^{15}N content as had been speculated by McKennis and Weatherby (1956) when they found increased blood ammonia levels following hydrazine injection. Cumulative recovery of ^{15}N-hydrazine and its derivatives in the urine was slightly more than 50% during 48 hours. Thus, about 75% of the injected doses can now be accounted for. Further investigation with the ^{15}N isotope may reveal the fate of the other 25% of injected doses of hydrazine.

Interest in the oncogenicity of hydrazine was initially aroused by findings that the antitubercular drug isonicotinic acid hydrazide (INH) induced lung adenomas, leukemias and lymphosarcomas in mice after intraperitoneal administration (Juhasz et al., 1957). Feeding INH to mice at a concentration of 0.01 to 0.25% in the diet led to the development of pulmonary tumors with dose-dependent incidences (Mori and Yasuno, 1959; Mori et al., 1960). Similar results were found in various strains of mice by Biancifiori and Ribacchi (1962a,b), Biancifiori et al. (1963), Toth and Shubik (1966a,b), Kelly et al. (1969), Toth and Toth (1970), Yamamoto and Weisburger (1970) and Jones et al. (1971). The subject was reviewed by Biancifiori and Severi (1966).

In contrast to the findings in mice, little or no oncogenic effects have been noted in rats and hamsters after administration of INH (Loscalzo, 1964; Toth and Toth, 1970; Severi and Biancifiori, 1968; Peacock and Peacock, 1966; Toth and Shubik, 1969). Biancifiori et al. (1964) investigated the induction of pulmonary tumors and hepatomas in mice by INH and its putative metabolites, hydrazine (as the sulfate) and isonicotinic acid. Isonicotinic acid had little or no effect on tumor incidence whereas equimolar concentrations of INH and hydrazine sulfate induced roughly the same incidence of lung tumors. Administration of hydrazine sulfate but not of INH led to an increase in hepatomas. Induction of lung tumors in mice by hydrazine usually, as the sulfate, has been repeatedly shown by a large number of investigators (Roe et al., 1967; Toth, 1969, 1971, 1972b; Biancifiori et al., 1963a,b, 1964; Biancifiori, 1969, 1970a,b,c; Biancifiori and Ribacchi, 1962a,b; Kelly et al., 1969; Yamamoto and Weisburger, 1970). Hepatomas and hepatocarcinomas have been observed in 3 strains of mice treated orally with hydrazine sulfate (Biancifiori, 1970a,b,d, 1971; Biancifiori et al., 1964; Severi and Biancifiori, 1967, 1968). The findings of MacEwen et al. (1974) after 6-months inhalation exposure were consistent with these results.

Severi and Biancifiori (1968) administered daily doses of 18 mg or 12 mg hydrazine sulfate by stomach tube to 14 male and 18 female Cb/Se rats for 68 weeks. Lung tumors (adenomas and adenocarcinomas) were observed in 3/14 males and in 5/18 females in 109 weeks. Of 13 male and 13 female rats, hepatic cell carcinomas or spindle cell sarcomas were observed in 4 male rats. No lung or liver tumors were found in untreated controls (28 males and 22 females) surviving up to 104 weeks.

Biancifiori (1970d) and Toth (1972a) administered hydrazine sulfate orally to Syrian golden hamsters and noted no significant increase in the number of tumors produced in either experiment.

Although workmen have inhaled hydrazine vapor for many years and in larger numbers since World War II, to date there have been no reported cases of hydrazine-induced cancer in humans. The only known epidemiologic study of hydrazine workers reported to date is an ongoing study of a major hydrazine manufacturer (Roe, 1978). This study of 423 workmen traced 272 through 1973 of whom 18 had died, 2 from cancers. Both the numbers of deaths and numbers of cancers found for this group matched the expected ratios for English workmen for that period. Since 1973, 3 of 8 further deaths known to have occurred among the 272 traced workers were from malignant disease. Two of the deaths occurred in medium exposure groups, both cancers of the stomach, one in a man 74 years of age and another in a man 64 years old. The third cancer death was in a 58-year old man from the lowest exposure group who had a tumor of the prostate. Further epidemiologic studies are needed to evaluate the cancer hazard of hydrazine to man.

Since chronic hydrazine inhalation at the Threshold Limit Value increased the incidence of pulmonary tumors in mice, a more comprehensive study of hydrazine effects on multiple species was undertaken and the results reported herewith.

SECTION II

MATERIALS AND METHODS

Animals

The objectives of this study were to evaluate: (a) the chronic effects of inhaled hydrazine on rats, mice, hamsters, and dogs, and; (b) the oncogenic potential of hydrazine in rodents observed for a maximum period of 1-1/2 years after one year of industrial-type inhalation exposure. The animals used in this study were C57BL/6 mice obtained from the Jackson Laboratories, Fischer 344 albino rats from Charles River, Golden Syrian hamsters from Engle Laboratory Animals, Incorporated, and beagle dogs obtained from Ridglan Farms. The rodent strains were selected after consultation with personnel of the National Cancer Institute. The numbers of animals of each species and sex are listed in Table 1 which also shows the chambers used and the exposure concentrations.

TABLE 1. EXPERIMENTAL DESIGN FOR HYDRAZINE INHALATION EXPOSURE CONCENTRATIONS

Hydrazine Concentration, ppm	Animal Numbers, Sex, and Species	Chamber Number
0.05	100♂, 100♀ rats; 400♀ mice	7
0.25	200♂ hamsters; 400♀ mice	5
0.25	100♂, 100♀ rats; 4♂, 4♀ dogs	6
1.0	200♂ hamsters; 400♀ mice	1
1.0	100♂, 100♀ rats; 4♂, 4♀ dogs	4
5.0	100♂, 100♀ rats; 200♂ hamsters	8
Control	150♂, 150♀ rats, 800♀ mice; 200♂ hamsters; 4♂, 4♀ dogs	Vivarium

The animals were placed into the chambers over a 4-month period due to difficulties experienced in the acquisition of large enough groups that passed quality control tests. Three sets of hamsters were received in quarantine before a satisfactory group of healthy hamsters was found. The first group of mice placed in the 1.0 ppm hydrazine exposure group was removed from the experiment after an equipment malfunction caused several deaths. A separate set of unexposed control mice was established for the new C57BL/6 mice exposed to 1.0 ppm hydrazine.

Exposure Conditions

The exposure concentrations were selected to span the range from a certainly toxic level to the current OSHA Threshold Limit Value for exposure to hydrazine (1.0 ppm) and the proposed ACGIH Threshold Limit Value of 0.1 ppm. The 5.0 ppm exposure concentration was selected as a maximum tolerable exposure dose which would produce some biologic response without causing death in hamsters and rats. Mice and dogs were not exposed at this concentration because prior studies (Haun and Kinkead, 1973) had shown that repeated daily exposures to 5.0 ppm hydrazine caused death in these species.

The inhalation exposures were conducted on a 6 hour/day, 5 day/week schedule for a one-year period without exposures on weekends and holidays. The animals were exposed in Thomas Dome exposure chambers (Thomas, 1968) at a slightly negative pressure (725 mm Hg) to insure a complete seal and to prevent contamination of the surrounding laboratories and personnel. The air flow, pressure, relative humidity, and temperature were all controlled automatically. Air flow was maintained at 40 ft^3/minute (1.1 m^3/minute), a relative humidity of 50% ± 10%, and a temperature of 22°C ± 2.

Hydrazine Exposures and Monitoring

Anhydrous hydrazine[1], 97% pure, was introduced into the air supply system of the exposure chambers by means of syringe feeders. The syringe feeder metered the liquid N_2H_4 into heated lines where it was volatilized and blended into the air stream. Concentrations were adjusted either by changing the speed of the syringe feeder or by adjusting the air flow or both. The concentration in each dome was monitored using an AutoAnalyzer and a method described by Geiger (1967). A separate analyzer system was operated for each exposure level which resulted in continuous sampling and analysis of the 0.05 ppm and 5.0 ppm exposure chamber concentrations and shared sampling of paired chambers with the same exposure concentrations, 0.25 and 1.0 ppm N_2H_4. In pairs of chambers with the same concentration, an automatic switching valve allowed air samples to be analyzed from alternating chambers at 20-minute intervals.

The rodents were housed in stainless steel cages (25 x 25 x 38 cm) during the exposure. Mice were housed 10 animals per cage, rats 3 per cage and hamsters 5 per cage. Water was provided ad libitum via a closed automatic watering system[2]. No bedding was used. The diet consisted of pelleted feed [3] which was given to the animals after the daily exposure period during routine animal care maintenance. Any remaining food was removed before the start of the next daily exposure to prevent absorption of hydrazine on the food pellets.

Clinical Tests and Observations

All animals were observed hourly during the 12-month hydrazine exposure phase of the study and daily during the postexposure phase. Rats, dogs, and hamsters were weighed individually at biweekly intervals during exposure and monthly during the postexposure period. Mice were weighed in cage groups and group mean weights followed on a monthly schedule throughout the entire study.

Blood samples were drawn from dogs at biweekly intervals during the exposure phase and clinical determinations made for the following battery of tests:

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(1) Matheson, Coleman and Bell, Norwood, Ohio.

(2) Hardco, Inc., Cincinnati, Ohio.

(3) Purina Laboratory Chow, Ralston Purina Company, St. Louis, Missouri.

RBC	Glucose
WBC	Total Protein
HCT	Albumin
HGB	Globulin
Sodium	A/G Ratio
Potassium	SGPT
Calcium	Alkaline Phosphatase

Animals that died or were killed during the study were necropsied following the National Cancer Institute protocol. The necropsy consisted of an external examination, including all body orifices, and the examination and fixation of portions of the following tissues for histopathologic examination:

Gross lesions
Tissue masses
Regional lymph nodes
Mandibular lymph node
Mammary gland
Salivary gland
Larynx
Trachea
Lungs and bronchi
Heart
Thyroids
Parathyroids
Esophagus
Stomach
Duodenum
Jejunum
Ileum
Cecum
Colon
Rectum
Mesenteric lymph node
Liver
Thigh muscle
Sciatic nerve
Sternebrae, vertebrae or femur (plus marrow)
Costochondral junction
Rib
Thymus
Gall bladder
Pancreas
Spleen
Kidneys
Adrenals
Bladder
Seminal vesicles
Prostate
Testes
Ovaries
Uterus
Nasal cavity
Brain
Pituitary
Eyes
Spinal cord

SECTION III

RESULTS

Exposure Measurements

Hydrazine concentrations in the exposure chambers were determined continuously throughout the 12-month exposure phase of the study. The nominal desired concentrations listed in Table 1 were efficiently maintained; monthly mean concentrations with standard deviations are listed in Table 2 for each chamber. Some problems in control of exposure concentration were encountered and corrected during the first few months. Thereafter, the desired concentrations were maintained within 10% with only rare and rapidly corrected excursions.

TABLE 2. MEASURED MONTHLY MEAN CONCENTRATIONS OF HYDRAZINE IN THE ANIMAL EXPOSURE CHAMBERS

Month	Chamber 7 ppm	Chamber 5* ppm	Chamber 6 ppm	Chamber 1 ppm	Chamber 4 ppm	Chamber 8* ppm
1	.060	.18	.26	1.02	0.96	4.10
2	.039	.29	.24	1.00	0.93	4.70
3	.051	.27	.21	1.00	1.07	4.85
4	.051	.25	.25	1.00	1.00	4.59
5	.052	.25	.26	1.00	1.01	4.72
6	.052	.25	.25	1.00	1.00	5.20
7	.051	.26	.25	1.02	1.00	5.02
8	.055	.26	.26	1.01	1.00	5.12
9	.045	.25	.26	1.01	0.99	5.05
10	.051	.26	.26	0.99	1.01	5.13
11	.047	.25	.26	0.99	1.02	4.85
12	.046	.25	.23	1.01	1.02	4.78
13	.053	.25	.27	1.01	1.03	5.35
14		.24				5.15
15		.25				5.08
16		.25				5.33
17		.26				5.31
Overall Mean	.050	.25	.25	1.00	1.00	4.96
Standard Deviation	.005	.02	.02	0.01	0.03	0.32

*Chambers 5 and 8 operated longer to complete exposures of hamsters which started later than those for other animal species.

Growth

The average body weights of the groups of male and female rats are shown in Figures 1 and 2, respectively, for the entire study. Although not dose dependent, growth was reduced in all hydrazine-exposed rats during exposure but the effect was most significant in the male rats exposed to the 5.0 ppm concentration. The differences between exposed and control animals were maintained at relatively constant levels during the first 12 months postexposure but became less significant during months 25 to 30 of the study as the weight decline of the aging animals was observed.

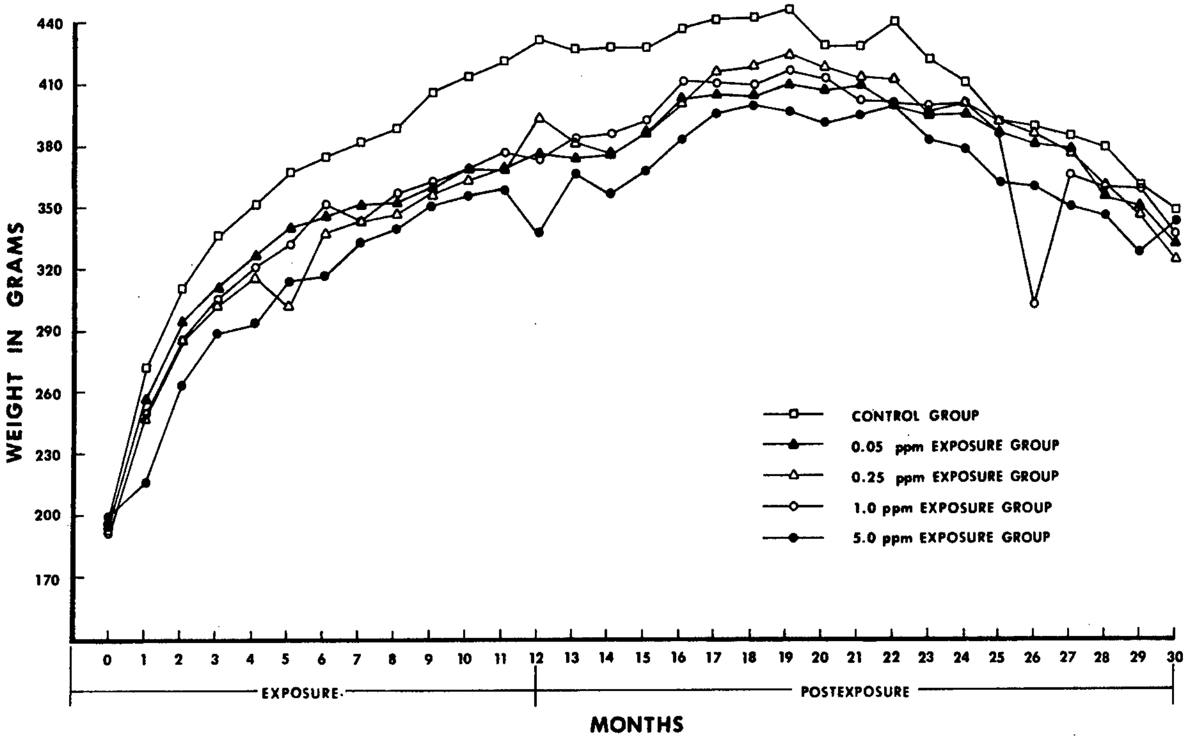

Figure 1. The effect of chronic inhalation exposure to hydrazine on the growth of male Fischer 344 rats.

The effect of depressed growth in female rats was not as pronounced as in males during the exposure phase but was significant and became more noticeable during the postexposure observation period. Mean body weights of rats and hamsters are presented in Tables 17 through 33 in the appendix to this report.

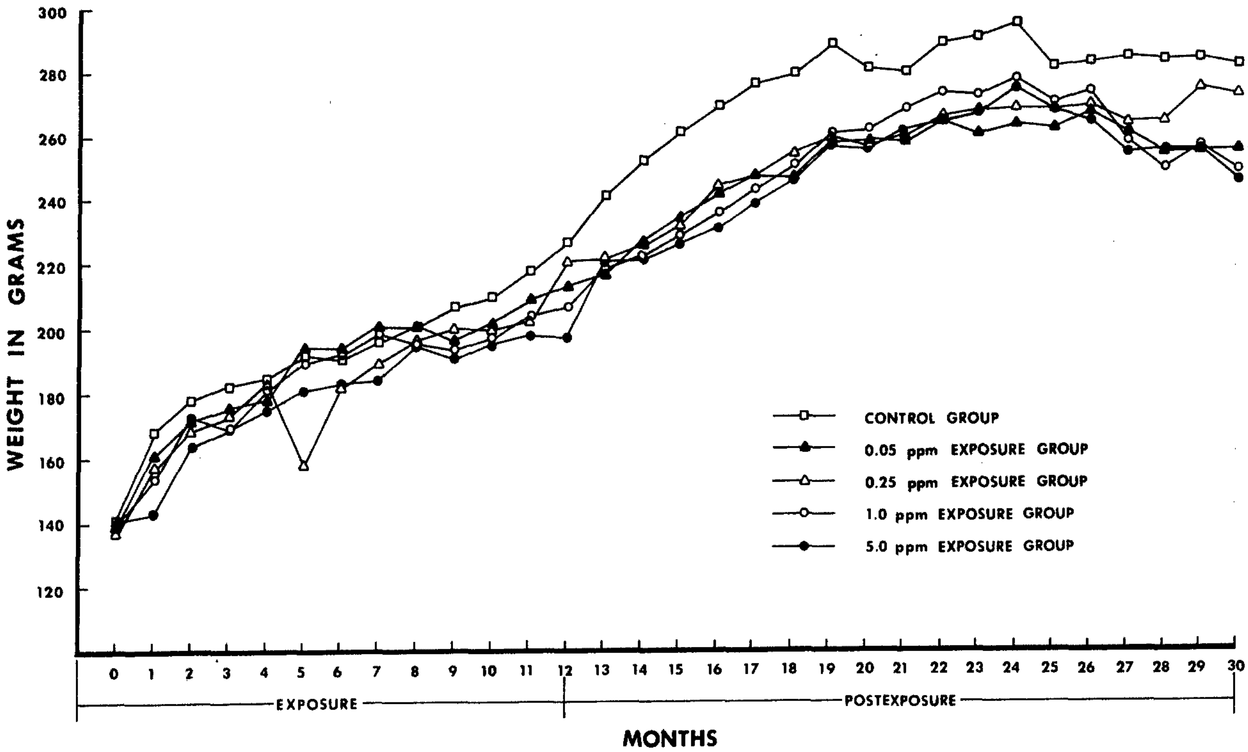

Figure 2. The effect of chronic inhalation exposure to hydrazine on growth of female Fischer 344 rats.

Hamster body weights shown in Figure 3 were depressed for all exposed groups but also exhibited an inexplicable cyclic phenomenon common to all exposed groups as well as unexposed and relatively severe in all groups. In the final months only the 5.0 ppm hydrazine-exposed group continued to show a significant weight difference from controls.

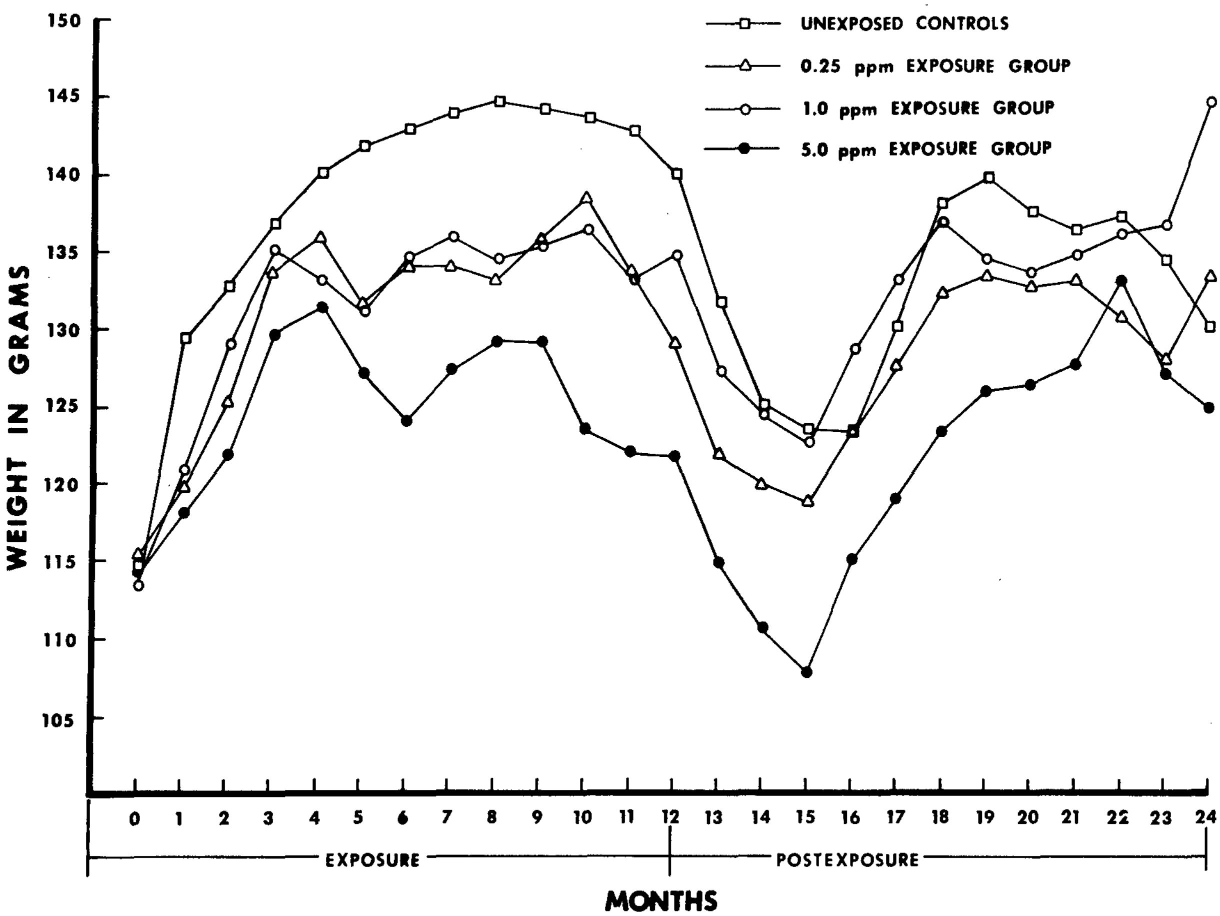

Figure 3. The effect of chronic inhalation exposure to hydrazine on the growth of male Golden Syrian hamsters.

Mean body weights of mice are shown in Table 3. The body weights were unaffected by hydrazine exposure, but there were no mice exposed to the 5.0 ppm atmosphere.

TABLE 3. MEAN WEIGHTS OF MICE EXPOSED TO HYDRAZINE FOR ONE YEAR

Time in Study (Months)	Set 1 Unexposed Controls	Set 1 0.05 ppm Exposed	Set 1 0.25 ppm Exposed	Set 2 Unexposed Controls	Set 2 1.0 ppm Exposed
Exposure	16.2	18.0	16.4	17.0	16.9
1	20.0	21.5	20.5	19.3	20.2
2	21.6	22.2	22.0	20.7	22.0
3	22.3	23.2	22.6	21.1	22.7
4	22.5	23.6	23.4	22.0	23.4
5	22.5	24.1	24.0	22.3	24.1
6	23.1	24.2	24.5	22.5	24.5
7	23.6	24.2	25.1	23.6	25.4
8	24.0	25.3	25.5	25.6	26.0
9	23.8	25.3	26.5	25.3	26.1
10	24.1	25.6	25.9	24.9	25.9
11	24.6	26.9	27.0	25.2	27.2
12	25.1	27.0	27.6	---*	26.8
Postexposure					
13	26.5	26.4	26.5	25.2	26.0
14	27.5	26.9	27.5	25.5	26.6
15	27.4	27.0	27.2	26.6	27.4
16	27.2	26.6	26.8	26.4	26.8
17	27.0	26.2	27.0	27.5	27.8
18	27.6	26.0	26.1	27.6	27.3
19	28.7	26.7	27.1	28.1	27.7
20	28.4	27.0	27.2	29.1	27.7
21	29.1	27.8	27.7	29.5	28.3
22	29.0	27.3	27.7	---*	---*
23	28.9	28.0	27.8	28.7	27.5
24	28.8	27.8	27.7	27.3	26.7
25	29.4	28.1	27.5	27.1	26.3
26	26.2	---*	26.1	26.1	25.1
27	27.0	27.5	27.3	27.3	25.9

* Not all animals weighed.

Clinical Laboratory Measurements

Blood samples were drawn biweekly from control dogs and from dogs exposed to 1.0 ppm and 0.25 ppm hydrazine during the course of the exposure and at 2, 5, 9, 14, 33, 83, 96, 121, and 152 weeks postexposure. The routine battery of hematology and clinical chemistry determinations listed in the methods section of this report were made on each set of samples. There was no biologically significant difference between the hydrazine-exposed dogs and their controls either during exposure or throughout the postexposure phase. When occasional differences occurred between exposed and unexposed groups of dogs, it usually arose from a change in the control animals. The results of these tests are tabulated in the appendix to this report.

Mortality

The cumulative mortality experience of the hamsters used in this study is listed in Table 4. The incidence of natural deaths was almost identical among the three exposed groups during the 12-month treatment period while the control death rate was lower. After termination of exposure the mortality rate decreased slightly and remained relatively constant during the next year of postexposure observation. During this period the unexposed hamsters died at a slightly increased rate and total mortality was approximately the same in all groups of hamsters by the 16th month on study. The causes of death for those animals that died during exposure were similar to those in the control group and no specific difference was identified.

TABLE 4. CUMULATIVE MORTALITY IN HYDRAZINE EXPOSED MALE GOLDEN SYRIAN HAMSTERS (N = 200)

Month on Study	Unexposed Controls	0.25 ppm Exposed	1.0 ppm Exposed	5.0 ppm Exposed
1	1%	0%	0%	1%
2	1	2	1	4
3	2	4	2	4
4	2	5	3	5
5	3	5	4	6
6	5	8	8	8
7	6	11	9	11
8	9	17	14	13
9	11	20	21	18
10	13	25	24	23
11	15	28	26	26
12	19	32	33	32
13	22	37	37	40
14	31	46	43	42
15	39	51	47	45
16	47	53	52	48
17	52	58	56	55
18	57	60	64	60
19	64	63	69	65
20	67	69	72	66
21	70	74	79	71
22	78	80	82	75
23	82	84	87	78
24	87	88	91	82

A few deaths occurred in Fischer 344 rats exposed to hydrazine during exposure which appeared to be dose related but were small in number and were not statistically significant. Postexposure deaths as shown in Tables 5 and 6 were similar in all groups.

TABLE 5. CUMULATIVE MORTALITY IN HYDRAZINE EXPOSED FISCHER 344 MALE RATS

Month on Study	Unexposed Controls N = 150	0.05 ppm Exposed N = 100	0.25 ppm Exposed N = 100	1.0 ppm Exposed N = 100	5.0 ppm Exposed N = 100
1	0%	0%	0%	1%	0%
2	0	0	0	1	0
3	0	0	0	1	0
4	0	0	0	1	0
5	0	0	0	1	0
6	0	0	1	1	0
7	0	0	1	1	0
8	0	0	1	1	1
9	0	0	1	1	1
10	0	0	2	2	2
11	1	0	2	3	2
12	1	0	2	3	2
13	1	0	2	3	2
14	1	0	4	3	3
15	1	0	7	3	3
16	2	1	10	3	3
17	3	1	10	4	5
18	4	2	10	4	6
19	6	3	12	5	7
20	8	4	13	5	8
21	13	6	14	6	11
22	20	14	19	10	18
23	27	26	28	18	23
24	33	29	38	22	30
25	37	39	42	30	36
26	57	61	60	46	51
27	68	68	66	53	63
28	78	75	69	63	65
29	84	81	71	75	74
30	91	82	80	81	81

TABLE 6. CUMULATIVE MORTALITY IN HYDRAZINE EXPOSED FISCHER 344 FEMALE RATS

Month on Study	Unexposed Controls N = 150	0.05 ppm Exposed N = 100	0.25 ppm Exposed N = 100	1.0 ppm Exposed N = 100	5.0 ppm Exposed N = 100
1	0%	0%	0%	0%	1%
2	0	0	1	3	3
3	0	0	1	3	3
4	0	1	1	3	3
5	0	1	1	3	3
6	0	1	1	3	3
7	0	1	1	3	3
8	0	1	2	3	3
9	0	2	2	3	3
10	0	2	2	4	3
11	0	2	2	4	3
12	0	2	2	4	4
13	1	2	2	4	4
14	1	2	2	4	4
15	2	2	2	4	4
16	4	2	2	6	5
17	5	2	3	6	6
18	5	4	5	6	7
19	6	6	6	7	7
20	9	10	9	12	8
21	15	19	16	12	9
22	22	20	20	16	12
23	27	31	29	19	22
24	34	39	37	26	36
25	40	45	43	33	41
26	57	69	56	46	54
27	72	71	64	58	63
28	77	79	66	63	68
29	81	81	76	69	73
30	84	82	76	81	81

Mouse mortality listed in Table 7 reveals a slight dose-related increase during exposure. These small differences are lessened by the sixth month postexposure among exposure groups but continue at a rate higher than unexposed controls.

TABLE 7. CUMULATIVE MORTALITY IN HYDRAZINE EXPOSED FEMALE C57BL/6 MICE (N = 400)

Time in Study (Months)	Set 1 Unexposed Controls	Set 1 0.05 ppm Exposed	Set 1 0.25 ppm Exposed	Set 2 Unexposed Controls	Set 2 1.0 ppm Exposed
1	1%	1%	0%	0%	1%
2	1	1	0	0	2
3	1	1	1	0	2
4	1	1	2	0	2
5	1	1	2	1	2
6	1	1	3	1	3
7	1	2	4	1	5
8	1	2	4	2	5
9	2	2	4	2	5
10	2	3	4	2	6
11	3	5	6	3	7
12	3	6	7	4	7
13	3	7	7	4	8
14	5	8	8	6	13
15	6	9	8	7	13
16	7	14	9	8	14
17	8	16	11	11	15
18	13	20	12	16	20
19	14	22	15	22	23
20	16	26	18	27	23
21	19	29	23	29	32
22	32	42	37	40	43
23	38	50	42	46	50
24	43	54	48	54	57
25	48	62	57	62	67
26	72	79	81	71	79
27	72	87	84	79	86

Pathology

Gross histopathology examinations were performed on all rodents that died during the course of the study or were sacrificed at completion of the postexposure period. Histopathologic examinations were conducted in accordance with the National Cancer Institute protocols on approximately 33 tissues from all animals with the exception of a few in which postmortem changes were extensive or cannibalism prevented examinations.

Surviving hamsters were sacrificed one-year postexposure, and their tissues were examined by pathologists of the Veterinary Science Division at Brooks Air Force Base. Tumor and nontumor nomenclature was developed by this group for automated data processing of the results from hamsters. Tumor incidence tables were compiled and statistical analyses, using the Fisher Exact Test, were performed by the UCI staff.

Since rat mortality was very low after one-year postexposure, 10% of the survivors were sacrificed and tissues collected as previously described. The study was terminated after 30 months (18 months postexposure), and all surviving rats were necropsied.

Mouse mortality approached 90% in the 18th postexposure month for the first set of animals including the 0.05 ppm and 0.25 ppm hydrazine-exposed mice, and their controls. The second set of mice including the 1.0 ppm hydrazine-exposure group and their controls were terminated at 132 weeks which was 3 weeks longer than the first set.

Tissues from both rats and mice were sent to the Huntingdon Research Centre in Huntingdon, England for histopathologic examination. Rats were examined by Dr. C. P. Cherry and mice by Dr. J. M. Offer under the supervision of Dr. D. E. Prentice.

Hamsters

Table 8 shows the tumor incidence in the various groups of exposed and control hamsters. The outstanding finding in hamsters is a statistically significant increase in benign nasal polyps. These tumors were seen in 16/160 of the 5.0 ppm exposed animals, and only one in the control group. The only other tumor types of possible importance are those of the gastrointestinal tract of the 5 and 1.0 ppm exposure groups. In the colon of the 5.0 ppm exposure group, there were 3 primary adenocarcinomas, one benign leiomyoma, and one benign papilloma and in the stomach there was a basal cell carcinoma in one animal. When these tumor types were separately subjected to the Fisher Exact Test, none showed statistical significance. There was a rather large incidence of cortical adenomas in the adrenals of all groups of exposed hamsters but with incidence rates lower than that in the control group and the same was true for carcinomas of the adrenal cortex. These types of tumor are commonly seen in aged hamsters. Incidence of other tumors in the various organs was low and no biologic significance is attached to the increase in benign thyroid adenomas limited to the 0.25 ppm hydrazine exposure group. While there was an increase in nasal polyps and gastrointestinal tumor incidence in the 5.0 ppm hydrazine exposure group, these effects equalled the decreased incidence of other tumor types so that the attack rates for malignant tumors or total tumor incidence was the same in unexposed controls and the highest exposure group.

TABLE 8. SELECTED† TUMORS FOUND IN MALE GOLDEN SYRIAN HAMSTERS AFTER INHALATION EXPOSURE TO HYDRAZINE

TUMOR TYPE	Unexposed Controls	0.25 ppm Exposed	1.0 ppm Exposed	5.0 ppm Exposed
Nares				
Polyp	1/181	0/154	1/148	16/160**
Lung				
Bronchogenic Carcinoma	1/179	0/154	1/146	0/155
Bronchogenic Adenoma	0/179	0/154	0/146	2/155
Spleen				
Hemangioma	1/160	1/129	0/130	2/138
Reticulo-endotheliomas	1/160	2/129	0/129	0/138
Lymph Nodes				
Reticulo-endotheliomas	5/167	5/143	5/140	6/146
Thyroid				
Carcinoma	1/145	1/117	0/127	0/137
Adenoma	0/145	4/117*	1/127	0/137
"C" Cell Adenoma	0/145	0/117	0/127	4/137
Parathyroid				
Adenoma	3/111	3/88	2/82	2/100
Adrenal				
Cortical Adenoma	32/177	18/155	19/141	23/153
Cortical Carcinoma	6/177	5/155	3/141	3/153
Stomach				
Papilloma	0/169	1/149	0/140	0/145
Basal Cell Carcinoma	0/169	0/149	2/140	1/145
Colon				
Adenocarcinoma	0/158	0/146	2/129	3/139
Leiomyoma	0/158	0/146	0/129	1/139
Papilloma	0/158	0/146	0/129	1/139
Total†† numbers of hamsters with:				
1. Benign Tumors	36	24	24	41
2. Malignant Tumors	18	20	15	16
3. Any Tumor	53/189	42/175	33/162	49/173

† Selection based on frequency of occurrence and those appearing to be exposure related.

* Significant at the 0.05 level as determined using the Fischer Exact Test.

** Significant at the 0.01 level as determined using the Fischer Exact Test.

†† Includes animals with any tumor.

The nonneoplastic histopathology findings for exposed hamsters included descriptions and discussion of many lesions which occasionally occurred more frequently than in control animals. These probably reflected acceleration of the aging process and exacerbation of chronic disease states to which hamsters are susceptible. Analysis of the incidence of such lesions would not elucidate the effect of hydrazine exposure on target organs. Therefore, the data were examined to select specific organ lesions which might have been related to exposure. This preliminary examination revealed that lesions in the nasal passages, lung, liver, spleen, lymph nodes, kidney, thyroid, adrenal, colon, and testes occurred more frequently in exposed animals and that, therefore, these organs could be possible sites of hydrazine injury.

A compilation for each exposure group of the numbers of each type of lesion in the 10 organs (Table 9) permitted the detection of significantly elevated incidence rates. An important observation emerged from the data in Table 9 that degenerative disease is increased significantly in hamsters exposed to high levels of hydrazine. This degenerative disease is characterized by amyloidosis in the livers, spleen, kidneys, thyroids, adrenals, and liver hemosiderosis, kidney mineralization, general degeneration of the adrenals, senile atrophy, aspermatogenesis, and hypospermatogenesis. In most cases, a dose response relationship can be seen. The implication is that the stress of 12 months of hydrazine exposure at the various dose levels tended to increase the degenerative process in a dose dependent manner.

TABLE 9. NONNEOPLASTIC HISTOLOGIC FINDINGS IN SELECTED ORGANS OF CONTROL AND HYDRAZINE-EXPOSED MALE HAMSTERS

LESION DESCRIPTION	Unexposed Control	0.25 ppm Exposed	1.0 ppm Exposed	5.0 ppm Exposed
Nares, Trachea, Bronchi				
Submucosal cysts	30/181(17)	29/154(19)	29/148(20)	36/160(23)
Rhinitis	4/181(2)	6/154(4)	9/148(6)	3/160(2)
Hyperplasia	0/181(0)	0/154(0)	2/148(1)	2/160(1)
Squamous metaplasia	0/181(0)	0/154(0)	0/148(0)	4/160(3)
Lung				
Adenomatosis	15/179(8)	22/154(14)	28/146(19)**	21/155(14)
Interstitial pneumonitis	28/179(16)	30/154(20)	38/146(26)*	27/155(17)
Bronchiolar hyperplasia	2/179(1)	2/154(1)	3/146(2)	4/155(3)
Liver				
Amyloidosis	42/180(23)	67/160(42)**	68/148(46)**	79/159(50)**
Hemosiderosis	42/180(23)	63/160(39)**	77/148(52)**	94/159(59)**
Bile duct hyperplasia	14/180(8)	31/160(19)**	28/148(19)*	44/159(28)**
Biliary cyst	45/180(25)	45/160(28)	42/148(28)	55/159(35)*
Spleen				
Amyloidosis	39/160(24)	39/129(30)	57/130(44)**	60/138(44)**
Lymph Nodes				
Lymphadenitis	6/167(4)	13/143(9)*	17/140(12)**	16/146(11)**
Lymphoid hyperplasia	15/167(9)	18/143(13)	15/140(11)	6/146(4)
Kidney				
Interstitial amyloidosis	15/179(8)	19/164(12)	21/145(15)	28/160(18)**
Glomerular amyloidosis	39/179(22)	53/164(32)*	67/145(46)**	77/160(48)**
Mineralization	55/179(31)	78/164(48)**	51/145(35)	82/160(51)**
Thyroid				
Amyloidosis	9/155(6)	20/117(17)**	11/127(9)	22/137(16)**
Adrenal				
Amyloidosis	38/177(22)	49/155(32)*	52/141(37)**	76/153(50)**
Degeneration	25/177(14)	29/155(19)	26/141(18)	34/153(22)*
Colon				
Colitis	10/148(7)	17/146(12)	13/129(10)	20/139(14)*
Testis				
Senile atrophy	33/185(18)	41/160(26)	40/149(27)*	55/159(35)**
Aspermatogenesis	27/185(15)	20/160(13)	18/149(12)	36/159(23)*
Hypospermatogenesis	33/185(18)	35/160(22)	38/149(26)	41/159(26)

( ) % incidence, rounded off to whole numbers.
* Significant at the 0.05 level as determined using the Fisher Exact Test.
** Significant at the 0.01 level as determined using the Fisher Exact Test.

Rats

Nasal epithelial tumors were observed only in hydrazine-exposed rats. The majority of the epithelial neoplasms were benign and were mainly classified as adenomatous nasal polyps. Small numbers of villous nasal polyps, muco-epidermoid papillomas, and squamous cell papillomas were also noted. The incidence of these benign and several malignant epithelial tumors (shown in Tables 10 and 11) was elevated significantly in the 5.0 ppm hydrazine-exposed rats of both sexes. An apparent dose response was noted in that the incidence and degree of significance of the benign tumors were less in the 1.0 ppm hydrazine-exposure groups (only 1 malignancy was observed in both sexes). No tumors of these types were seen in either control group of rats, and only 1 tumor of the 6 tumors seen was malignant in the 400 rats exposed to 0.05 and 0.25 ppm. Most of these tumors were seen after 2 years with the earliest occurring in a male rat at 88 weeks (36 weeks postexposure) and in a female rat at 98 weeks.

Nonneoplastic pathologic changes in female and male rats are listed in Tables 12 and 13. Varying degrees of acute inflammation were observed in the nasal cavity, larynx and/or trachea in some rats from the control and all treated groups. The incidence and severity of the inflammatory changes were greatest in male and female rats from the group receiving 5.0 ppm, and in some of these affected animals, they were associated with focal hyperplasia and/or squamous metaplasia of the epithelium of the nasal cavity, larynx, and trachea. These histopathologic changes were observed in rats dying during the study as well as in the animals killed at the 2-year interim sacrifice and at the 2 1/2-year terminal sacrifice.

The more severe grades of chronic respiratory disease were seen in the lungs in some rats from the groups exposed to 5.0 ppm hydrazine, and to a lesser degree, in males exposed at 0.05 ppm dying during the study as well as those killed at the 2-year interim and 2 1/2-year terminal sacrifice. None of the males or the females exposed to 0.25 and 1.0 ppm showed epithelial hyperplasia. The morphologic changes included peribronchial/peribronchiolar lymphoid hyperplasia, pneumonia, bronchopneumonia, and bronchiectatic abscesses. Inflammatory changes of the larynx and trachea were most severe in the 5.0 ppm exposed groups of both male and female rats and were statistically different from all other groups at the 0.01 level. An increase of this nature was also seen to a lesser degree in the 0.05 ppm exposed males.

TABLE 10. SELECTED TUMORS FOUND IN FEMALE FISCHER 344 RATS AFTER INHALATION EXPOSURE TO HYDRAZINE

TUMOR TYPE	Unexposed Controls (N = 147)	Exposed 0.05 ppm (N = 99)	Exposed 0.25 ppm (N = 100)	Exposed 1.0 ppm (N = 97)	Exposed 5.0 ppm (N = 98)
Nasal cavity:					
Epithelial (Benign)	0 (0)	1 (1)	0 (0)	4 (4)*	31 (32)**
Epithelial (Malignant)	0 (0)	0 (0)	0 (0)	0 (0)	5 (5)**
Pituitary:					
Adenoma	59 (40)	28 (28)	35 (35)	33 (34)	40 (41)
Adenocarcinoma	9 (6)	6 (6)	2 (2)	6 (6)	6 (6)
Thyroid:					
Adenoma	9 (6)	2 (2)	4 (4)	7 (7)	7 (7)
Carcinoma	17 (12)	1 (1)	8 (8)	15 (15)	5 (5)
Adrenals:					
Phaeochromocytoma	10 (7)	3 (3)	6 (6)	9 (9)	12 (12)
Uterus:					
Adenoma	1 (0)	0 (0)	0 (0)	2 (2)	3 (3)
Adenocarcinoma	10 (7)	4 (4)	5 (5)	7 (7)	6 (6)
Endometrial stromal sarcoma	0 (0)	2 (2)	1 (1)	1 (1)	3 (3)
Lymphoreticular tissue:					
Leukemias	41 (28)	18 (18)	21 (21)	13 (13)	13 (13)
Sarcomas	4 (3)	4 (4)	4 (4)	2 (2)	6 (6)
Mammary gland:					
Adenoma	4 (3)	4 (4)	6 (6)	8 (8)	8 (8)
Fibroadenoma	28 (19)	20 (20)	11 (11)	18 (19)	19 (19)
Adenocarcinoma	2 (1)	1 (1)	2 (2)	2 (2)	3 (3)
Liver:					
Liver cell tumor	3 (2)	0 (0)	0 (0)	6 (6)	3 (3)
Lung:					
Bronchial adenoma	0 (0)	0 (0)	0 (0)	0 (0)	1 (1)
Total number of female rats with tumors:	144/147 (98)	95/99 (96)	43/100 (93)	83/97 (86)	95/98 (97)

( ) % incidence.
* Significant at the 0.05 level, control vs. test.
** Significant at the 0.01 level, control vs. test.

TABLE 11. SELECTED TUMORS FOUND IN MALE FISCHER 344 RATS AFTER INHALATION EXPOSURE TO HYDRAZINE

TUMOR TYPE	Unexposed Controls (N = 149)	Exposed 0.05 ppm (N = 99)	Exposed 0.25 ppm (N = 99)	Exposed 1.0 ppm (N = 98)	Exposed 5.0 ppm (N = 99)
Nasal Cavity:					
Epithelial (Benign)	0 (0)	2 (2)	2 (2)	10 (10)**	66 (67)**
Epithelial (Malignant)	0 (0)	1 (1)	0 (0)	1 (1)	6 (6)**
Pituitary:					
Adenoma	62 (42)	31 (31)	29 (29)	27 (28)	26 (26)
Adenocarcinoma	4 (3)	0 (0)	5 (5)	4 (4)	5 (5)
Thyroid:					
Adenoma	15 (10)	5 (5)	7 (7)	9 (9)	2 (2)
Adenomacarcinoma	7 (5)	6 (6)	5 (5)	9 (9)	13 (13)*
Adrenals:					
Phaeochromocytoma	16 (11)	14 (14)	13 (13)	18 (18)	11 (11)
Testes:					
Interstitial cell tumor	104 (70)	80 (81)	73 (74)	83 (85)	74 (75)
Prostate:					
Squamous carcinoma	1 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Liver:					
Liver cell tumors	9 (6)	11 (11)	8 (8)	6 (6)	4 (4)
Lung:					
Bronchial adenoma	0 (0)	0 (0)	0 (0)	0 (0)	3 (3)
Lymphoreticular tissue:					
Leukemias	36 (24)	20 (20)	28 (28)	22 (22)	10 (10)
Sarcomas	8 (5)	9 (9)	3 (3)	6 (6)	3 (3)
Total number of male rats with tumors:	130/149 (87)	78/99 (79)	77/99 (78)	79/98 (81)	80/99 (81)

( ) % incidence.
* Significant at the 0.05 level, control vs. test.
** Significant at the 0.01 level, control vs. test.

TABLE 12. PATHOLOGIC CHANGES SEEN IN FEMALE FISCHER 344 RATS AFTER INHALATION EXPOSURE TO HYDRAZINE

LESION	Unexposed Controls	Exposed 0.05 ppm	Exposed 0.25 ppm	Exposed 1.0 ppm	Exposed 5.0 ppm
Nasal:					
Squamous metaplasia	28/145(19)	18/97(19)	23/98(23)	24/94(26)	28/95(29)**
Epithelial hyperplasia	3/145(2)	2/97(2)	4/98(4)	5/94(5)	9/95(9)*
Larynx:					
Squamous metaplasia	6/138(4)	2/91(2)	2/91(2)	4/91(20	14/91(15)**
Inflammation	22/38(16)	11/91(12)	4/91(4)	10/91(11)	48/91(53)**
Trachea:					
Squamous metaplasia	0/147(0)	0/96(0)	0/97(0)	0/95(0)	6/98(6)**
Inflammation	0/147(0)	3/96(3)	1/97(1)	4/95(4)*	29/98(30)**
Lung:					
Epithelial hyperplasia	0/147(0)	0/97(0)	0/100(0)	1/97(1)	3/98(3)
Adenomatosis	7/147(5)	3/97(3)	3/100(3)	4/97(4)	3/98(3)
Heart:					
Myocardial degeneration	125/147(85)	82/97(85)	91/100(91)	83/97(86)	89/98(91)
Myocardial fibrosis	49/147(33)	24/97(25)	24/100(24)	26/97(27)	23/98(23)
Thymus:					
Regression	85/147(58)	55/97(57)	59/100(59)	46/97(47)	50/98(51)
Lymph Nodes:					
Hyperplasia	3/147(2)	2/97(2)	4/100(4)	3/97(3)	11/98(11)**
Liver:					
Hepatocyte degeneration	18/147(12)	15/97(15)	14/100(14)	13/97(13)	15/98(15)
Hepatic hyperplasia	57/147(39)	42/97(43)	36/100(36)	58/97(60)**	64/98(65)**
Kidney:					
Progressive glomerulonephrosis	82/147(56)	34/97(35)	52/100(52)	54/97(56)	79/98(81)*
Uterus:					
Polyps	26/147(18)	23/97(24)	21/100(21)	19/97(20)	19/98(19)
Cystic endometrial hyperplasia	2/147(1)	1/97(1)	4/100(4)	1/97(1)	7/98(7)*
Endometritis	8/147(5)	5/97(5)	0/100(0)	6/97(6)	21/98(21)**
Squamous metaplasia	3/147(2)	1/97(1)	1/100(1)	0/97(0)	2/98(2)
Ovary:					
Atrophy	15/147(10)	13/97(13)	3/100(3)	15/97(15)	22/98(22)*
Ovaduct:					
Salpingitis	0/147(0)	0/97(0)	0/100(0)	1/97(1)	20/98(20)**

** Significant at 0.01 level, control vs. test.
* Significant at 0.05 level, control vs. test.
() = % incidence.

TABLE 13. PATHOLOGIC CHANGES SEEN IN MALE FISCHER 344 RATS AFTER INHALATION EXPOSURE TO HYDRAZINE

TUMOR	Unexposed Controls	Exposed 0.05 ppm	Exposed 0.25 ppm	Exposed 1.0 ppm	Exposed 5.0 ppm
Nasal:					
Squamous metaplasia	24/146(16)	19/96(20)	24/94(26)	25/97(26)	47/99(47)**
Epithelial hyperplasia	4/146(3)	9/96(9)*	3/94(3)	4/97(4)	21/99(21)**
Larynx:					
Squamous metaplasia	2/141(1)	2/95(2)	2/91(2)	3/91(3)	18/92(20)**
Inflammation	14/141(9)	42/95(44)**	7/91(8)	14/91(15)	72/92(78)**
Trachea:					
Squamous metaplasia	0/145(0)	0/97(0)	0/98(0)	0/95(0)	10/97(10)**
Inflammation	5/145(3)	17/97(18)**	2/98(2)	2/95(2)	52/97(54)**
Lung:					
Epithelial hyperplasia	0/149(0)	6/99(6)**	0/99(0)	0/98(0)	6/99(6)**
Adenomatosis	6/149(4)	9/99(9)	7/99(7)	9/98(9)	4/99(4)
Heart:					
Myocardial degeneration	98/149(66)	71/99(72)	73/99(74)	76/98(78)*	82/99(83)*
Myocardial fibrosis	104/149(70)	67/99(68)	68/99(69)	73/98(74)	52/99(53)
Thymus:					
Regression	67/149(45)	43/99(43)	57/99(58)*	48/98(49)	44/99(44)
Lymph Nodes:					
Hyperplasia	4/149(3)	5/99(5)	3/99(3)	5/98(5)	5/99(5)
Liver:					
Hepatocyte degeneration	18/149(12)	20/99(20)	16/99(20)	12/98(12)	7/99(7)
Hepatic hyperplasia	58/149(39)	39/99(39)	40/99(40)	41/99(41)	42/99(42)
Kidney:					
Progressive glomerulonephrosis	137/149(92)	90/99(90)	93/99(94)	90/98(92)	90/99(91)
Testes:					
Atrophy	119/149(80)	85/99(86)	77/99(78)	85/98(87)	84/99(85)
Interstitial hyperplasia	29/149(19)	12/99(12)	18/99(18)	11/98(11)	13/99(13)*
Prostate:					
Hyperplasia	8/149(5)	1/99(1)	11/99(11)	9/98(9)	13/99(13)

** Significant at 0.01 level, control vs. test.
* Significant at 0.05 level, control vs. test.
() = % incidence.

A significant increase in lymph node hyperplasia was seen only in female rats exposed to the highest concentration of hydrazine.

The incidence of focal liver cell hyperplasia tended to be greater in treated as compared to control female rats only at the inhalation exposure levels of 1.0 ppm and 5.0 ppm. This effect was seen in female rats dying during the study and in those killed at the 2-year interim sacrifice, but it was not noted in female rats killed at the 2 1/2-year terminal sacrifice. There was no difference in the incidence of liver cell hyperplasia in treated as compared to control male rats.

Acute endometritis was noted more frequently in female rats from the groups receiving 5.0 ppm than in the controls or in rats from the groups receiving 0.05 ppm, 0.25 ppm, or 1.0 ppm. Acute salpingitis was present only in rats from the highest dosage group with the exception of one female from the 1.0 ppm dosage level and killed at termination.

Mice

Many microscopic variations from normal were seen in the aging mice, both control and hydrazine exposed groups. The only lesion of statistical significance, an increased incidence of pulmonary adenomas in the 1.0 ppm hydrazine exposed mice, when compared with one control group but not both is shown in Table 14. This small increase in tumor incidence over unexposed control mice is similar to that previously reported in Swiss mice (MacEwen et al., 1974). An increased incidence of ovarian tubular adenomas was also noted in the group of mice exposed to 1.0 ppm hydrazine. This increase was not statistically significant at the 0.05 confidence level.

The occurrence of non-neoplastic lesions in the C57BL/6 mice used in this study was similar in all groups with no apparent treatment effects.

TABLE 14. SELECTED TUMOR INCIDENCE IN CONTROL AND HYDRAZINE EXPOSED FEMALE C57BL/6 MICE

	Set 1			Set 2	
TUMOR TYPE	Unexposed Controls (N = 385)	Exposed 0.05 ppm (N = 364)	Exposed 0.25 ppm (N = 382)	Unexposed Controls (N = 378)	Exposed 1.0 ppm (N = 379)
Pituitary					
Adenoma	152 (39)	94 (26)	101 (26)	109 (29)	64 (17)
Carcinoma	7 (2)	10 (3)	3 (1)	8 (2)	2 (1)
Thyroid					
Adenoma	17 (4)	25 (7)	19 (5)	34 (9)	22 (6)
Carcinoma	2 (1)	1 (0)	1 (0)	2 (1)	1 (0)
Uterus					
Adenocarcinoma	0 (0)	1 (0)	0 (0)	0 (0)	0 (0)
Lymphoreticular Tissue					
Leukemias	4 (1)	5 (2)	11 (3)	5 (1)	0 (0)
Sarcomas	145 (38)	154 (42)	150 (39)	154 (41)	139 (37)
Mammary Gland					
All tumors	1 (0)	1 (0)	0 (0)	1 (0)	0 (0)
Liver					
Liver cell tumor	4 (1)	9 (2)	6 (2)	6 (2)	11 (3)
Lung					
Adenoma	8 (2)	3 (1)	5 (1)	4 (1)	12 (3)*
Adenocarcinoma	2 (1)	1 (0)	2 (1)	3 (1)	3 (1)
Ovary					
Tubular adenoma	12/369(3)	10/340(3)	11/365(3)	13/365(4)	23/361(6)
Total number of mice with tumors:	170/385(44)	177/364(49)	177/382(46)	193/379(46)	157/385(42)

* Significant at 0.05 level, control vs. test
() = % incidence.

Dogs

An unexposed male control dog died 32 months postexposure due to respiratory failure following extensive hemorrhage into the thoracic cavity. The hemorrhage resulted from rupture of numerous small capillaries formed in response to pyogranulomatous reaction involving the lung, pericardium, and diaphragm. Bacterial cultures made from the material in this lesion isolated a Corynebacterium organism.

BSP (Bromsulfalein) retention time was measured in all dogs at bimonthly intervals during the study. There was no indication that liver function was affected by exposure to either 0.25 or 1.0 ppm hydrazine exposure daily for the one-year period. However, during the postexposure phase of the study, commencing at 34 months postexposure, one male dog from the 1.0 ppm hydrazine exposure group exhibited intermittent increases in SGPT values. BSP retention time measured when these increases occurred was never greater than that of control animals nor was the liver palpable on examination. After multiple episodes of this cyclic event, the animal was sacrificed at 36 months postexposure and tissues examined. A control dog was also sacrificed for comparative pathology. Changes in the liver of the exposed dog were revealed as groups of swollen cells that had water clear cytoplasm. The change was seen with multifocal distribution.

The surviving 21 dogs were sacrificed at 38 months postexposure (50 months on study). Incidence of histopathologic lesions seen in various tissues of all the dogs exposed to 0.25 ppm or 1.0 ppm hydrazine and controls is given in Table 15.

Only two tumors were seen, both in one dog exposed to 0.25 ppm hydrazine. There was a hemangioma of endothelial cells of the splenic capsule. Also seen was a low grade papillary carcinoma of epithelial tissue at the mucocutaneous border of the anus. Four months postexposure, a rectal tumor had been detected in this dog which prompted a biopsy of a growth on the surface of the rectum. Histologic examination revealed a low grade adenocarcinoma. This diagnosis was confirmed at 27 months postexposure when the tumor was removed and examined. The tumor pathology listed in Table 15 shows that surgical removal of the tumor 11 months prior to sacrifice was incomplete.

There will be no attempt here to attach significance to the findings of tumors in one 0.25 ppm exposed dog and the hepatocytic clear cell change seen in the liver of one 1.0 ppm hydrazine exposed dog. These findings, along with the remainder of the non-neoplastic lesions seen in the incidence table, are interpreted as incidental findings not unusual in dogs of this age.

TABLE 15. INCIDENCE OF HISTOLOGIC LESIONS IN BEAGLE DOGS EXPOSED TO INHALED HYDRAZINE AND THEIR UNEXPOSED CONTROLS (N = 8)

LESION TYPE	1.0 PPM EXPOSURE GROUP	0.25 PPM EXPOSURE GROUP	UNEXPOSED CONTROLS
Pituitary			
Multilocular cysts	4	6	7
Thyroid			
C-cell hyperplasia	5	6	8
Lymphocytic infiltration	0	1	0
Thymus			
Ultimobronchial cyst	4	2	3
Atrophy	0	0	1
Hepatocyte			
Vacuolization	6	4	6
Pigmentation	5	7	7
Clear cell change	1	0	0
Heart			
Endocardiosis	5	5	3
Lung			
Eosinophilic granuloma	1	0	0
Granulomatous inflammation	0	0	1
Fibrosis, multifocal	2	3	3
Squamous metaplasia	1	0	0
Acute inflammation	0	0	1
Splenic Capsule			
Nodular hyperplasia	2	3	2
Hemangioma	0	1	0
Kidney			
Collecting Tubules			
Mineralization	7	5	3
Casts	1	2	0
Convoluted Tubules			
Pigmentation	3	4	3
Gall Bladder			
Cystic hyperplasia	2	4	1
Pancreas			
Hypertrophy	1	3	0
Nasal Mucosa			
Chronic inflammation	0	3	0
Alveolus			
Acute inflammation	0	0	1
Anus			
Adenocarcinoma	0	1	0
Uterus[a]			
Distension	0	2	0
Subserosa cyst	0	1	2
Endometrial cyst	0	1	0
Testes[a]			
Senile atrophy	1	2	2
Prostate[a]			
Cyst	0	0	1

[a]N = 4

SECTION IV

DISCUSSION

This study differed from those performed previously in one or more of the following factors: use of the inhalation route, the free base rather than the sulfate salt, and different strains of rats, Fischer 344, and mice, C57BL/6. Unexpectedly, mice were the most resistant species to the oncogenic effects of hydrazine, showing only a questionable increase in benign lung tumors at the highest level tested, 1.0 ppm. This concentration was the highest tested in mice during the present study since a prior study had shown 5.0 ppm killed half of the mice during exposure. This borderline increase of lung tumors in mice exposed to hydrazine contrasts with previous studies with hydrazine sulfate in which mice developed significantly more lung tumors than other species at comparable levels of exposure. A previous report of hydrazine inhalation exposures (MacEwen et al., 1974) indicated a dose related increase in alveolargenic carcinomas in female mice exposed to 1.0 ppm and 5.0 ppm hydrazine in a strain (ICR) that normally has a high incidence of these tumors.

Although the respiratory system appears to be the primary site of hydrazine-induced tumors in rats and mice, previous studies had shown the lung to be the specific target organ. Under our study conditions, the nasal cavities were the sites of the most striking tumor development. In rats, dose related numbers of benign tumors and, at the highest exposure level, small numbers of malignant tumors of the nasal turbinates were characteristic of inhalation exposure to hydrazine. In hamsters, a species which had been resistant to tumor development after oral administration of hydrazine sulfate in previous studies, a significant incidence of nasal polyps resulted from exposure to 5.0 ppm hydrazine. Rats exhibited a small incidence of bronchial adenomas at the highest level of exposure. Although mathematical significance was not obtained because of the small numbers of tumors, one in females and three in males, the incidences had biological significance since no tumors appeared in controls or at any but the highest dose. No other tumor was induced or increased over natural incidence in any of the species tested.

Comparing the daily and total doses used in some previous studies with those obtained in this experiment (Table 16) shows that we obtained total doses which were 5 - 20 times lower. Estimated doses for our study were calculated using the following animal factors: rat weight - 300 g; rat minute volume - 100 ml; mouse weight - 35 g; mouse minute volume - 25 ml; hamster weight - 140 g; hamster minute volume - 54 ml. The data for humans is the normal therapeutic dose of INH used in cases of tuberculosis.

TABLE 16. DOSES OF HYDRAZINE ADMINISTERED IN VARIOUS STUDIES

			mg/kg/day	mg/kg/Study
This Study				
	N_2H_4	Mice	0.34	85
		Rats	0.8	195
		Hamsters	0.93	229
Biancifiori et al. (1964)				
Mice	INH		57.0	14342
	as N_2H_4		13.3	3350
	Hydrazine Sulfate		32.3	8086
	as N_2H_4		8.1	2021
Toth (1969)				
Mice	Hydrazine Sulfate		20.0	9100
	as N_2H_4		5.0	2275
Severi and Biancifiori (1968)				
Rats	Hydrazine Sulfate		40.0	19040
	as N_2H_4		10.0	4760
Toth (1972a)				
Hamsters		Hydrazine Sulfate	16.4	8050
		as N_2H_4	4.1	2010
Humans		INH	5.0	3650
		as N_2H_4	1.25	913

Since hydrazine sulfate and INH appeared similar in inducing lung tumors in albino mice, extrapolation of the results to man might be illuminated by epidemiologic studies on tuberculosis patients receiving 5 mg/kg/day INH for up to two years.

Hammond et al. (1967), using data from a large prospective study of lung cancer in a population of more than 1 million, showed an excess of deaths due to lung cancer (45 cases versus 36.5 expected) among 18,963 tuberculosis patients, 10% of whom had received INH treatment. The excess was not significant at the p 0.05 level.

A number of studies have been reported by Ferebee (1970) in which tuberculosis cases were given 5 mg INH/kg bw daily for 1 year and observed for 10 years. In 10,531 patients treated in mental institutions and 12,439 household contacts treated prophylactically there was no indication of an increase in the frequency of cancer deaths after 10 years of observation, in comparison with approximately similar numbers of controls given placebos.

The epidemiologic evidence to date, therefore, indicates that the extensive therapeutic use of INH has not led to any detectable increase in lung tumors in the human population involved. It appears that the positive results obtained in mice are not extrapolatable to man in the case of INH and possibly for hydrazine as well since INH and hydrazine appear to be equivalent in the induction of mouse lung adenomas and adenocarcinomas. Moreover, induction of lung adenomas in the C57BL/6 mice used in our study was of borderline mathematical significance at the 1.0 ppm level when concurrent controls were used for comparison, and this significance disappeared when the older group of controls was used. It appears that adenomas are commonly present at a 1-2% incidence in this strain and that exposure to hydrazine does not significantly increase the incidence. As noted earlier, the mice were not exposed to 5.0 ppm because previous repeated exposures of mice to the higher level for 6 months caused 50% mortality.

The only remaining tumor types in this study that require analysis for estimation of oncogenicity of hydrazine are the nasal adenomas and adenocarcinomas in rats and the nasal polyps in hamsters.

The nasal polyps in hamsters and nasal turbinate tumors in rats noted after one year high level repeated exposures to hydrazine could only be seen at the microscopic level. They were not life threatening and were only one among the many chronic toxic effects of the hydrazine exposure, most significant of which were the increased mortality seen at the higher concentrations during exposure in this and previously reported studies and the increased incidence of hyaline related disease in hamsters. The irritative effect of the higher level hydrazine concentrations which is weakly basic with an ammoniacal odor is apparent by the greatly increased inflammatory response of the upper airways of both male and female rats. The inflammatory response was accompanied by an increase in metaplastic changes in squamous cells of the trachea, larynx and nasal passages. Similar effects have been noted with long-term exposure of Fischer 344 rats to formaldehyde (Chemical Regulation Reporter, 1980) in which a 43% incidence of nasal squamous cell carcinomas was induced after 18 month's exposure to 15 ppm. Here, too, many of the tumors were not grossly visible until decalcification and sectioning of the nasal turbinates had been carried out. (Progress Report on CIIT Formaldehyde Studies - 1/16/80). Studies at CIIT also revealed that 15 ppm formaldehyde produced multifocal squamous metaplasia as was seen at the high level in our study.

Formaldehyde is a long and much used chemical in human experience. If it were a strong human carcinogen, one might expect that indications would have been noted in those groups heavily exposed. Although results of epidemiologic investigations are not available, there is no striking evidence of increased nasal cancer, a relatively rare neoplasm, in embalmers or other workers exposed to formaldehyde. The reaction of rats and hamsters to formaldehyde and hydrazine may be specifically associated with reactions of the rodent turbinate epithelium to irritants rather than to general carcinogenicity on the part of the chemicals. Although there were increases in some types of tumors as a result of chronic high level exposures to hydrazine, the total incidence of all tumor types was not significantly different from unexposed control male hamsters, male and female rats and male mice. This was true even at levels which caused increased mortality, a variety of chronic pathologic tissue changes, and retarded growth rates. Concurrent with the appearance of respiratory lesions were significant decreases in the incidence of leukemias in male and female rats and of cortical adenomas of the adrenals in hamsters.

We conclude from these long-term inhalation studies on 800 male golden syrian hamsters, 2000 female C57BL/6 mice and 1100 male and female Fischer 344 rats that hydrazine is a relatively weak tumorigen capable of inducing respiratory tumors, primarily benign, in a dose related incidence at 1.0 and 5.0 ppm. Repeated daily exposures to hydrazine concentrations above 5.0 ppm resulted in early death of rodents and of dogs at levels as low as 5.0 ppm. This was usually associated with malnutrition during chronic exposure.

Based upon these studies, the current OSHA Threshold Limit Value of 1.0 ppm for hydrazine is unsatisfactory while the ACGIH recommended TLV of 0.1 ppm appears to be a low risk exposure level.

APPENDIX

TABLE 17. MEAN BODY WEIGHTS IN GRAMS (±S.D.) OF MALE RATS EXPOSED TO HYDRAZINE FOR ONE YEAR

Week of Exposure	Control (N = 150)	0.05 ppm (N = 100)	0.25 ppm (N = 100)	1.0 ppm (N = 100)	5.0 ppm (N = 100)
-2	181 ± 20	176 ± 24	177 ± 12	177 ± 22	180 ± 19
-1	197 ± 21	193 ± 24	195 ± 23	195 ± 24	197 ± 17
2	246 ± 18	227 ± 17**	229 ± 14**	223 ± 20**	173 ± 21**
4	268 ± 19	256 ± 20**	246 ± 15**	249 ± 21**	212 ± 20**
6	291 ± 19	270 ± 19**	261 ± 16**	261 ± 22**	238 ± 21**
8	307 ± 19	289 ± 21**	277 ± 16**	283 ± 26**	258 ± 18**
10	317 ± 19	308 ± 21**	306 ± 16**	295 ± 24**	271 ± 19**
12	333 ± 20	307 ± 21**	301 ± 21**	298 ± 24**	281 ± 19**
14	341 ± 20	316 ± 20**	309 ± 19**	314 ± 24**	299 ± 22**
16	347 ± 21	319 ± 21**	316 ± 20**	313 ± 25**	283 ± 20**
18	356 ± 21	334 ± 18**	319 ± 16**	325 ± 25**	305 ± 19**
20	363 ± 22	342 ± 17**	309 ± 19**	335 ± 25**	308 ± 20**
22	368 ± 22	341 ± 19**	302 ± 19**	335 ± 26**	316 ± 20**
24	370 ± 22	343 ± 19**	319 ± 18**	341 ± 26**	301 ± 23**
26	375 ± 23	346 ± 22**	338 ± 19**	351 ± 26**	317 ± 11**
28	380 ± 24	351 ± 18**	347 ± 19**	350 ± 18**	328 ± 19**
30	381 ± 23	351 ± 19**	343 ± 21**	343 ± 27**	331 ± 21**
32	386 ± 24	354 ± 21**	345 ± 20**	357 ± 27**	335 ± 21**
34	388 ± 24	351 ± 19**	344 ± 35**	357 ± 28**	340 ± 21**
36	392 ± 25	361 ± 20**	356 ± 25**	355 ± 32**	321 ± 24**
38	402 ± 25	359 ± 21**	364 ± 26**	362 ± 29**	351 ± 32**
40	411 ± 25	364 ± 21**	352 ± 23**	366 ± 29**	346 ± 26**
42	411 ± 25	370 ± 22**	366 ± 24**	370 ± 29**	354 ± 30**
44	416 ± 26	369 ± 23**	363 ± 24**	369 ± 29**	354 ± 25**
46	421 ± 27	360 ± 27**	363 ± 28**	376 ± 28**	358 ± 26**
48	422 ± 29	371 ± 24**	371 ± 25**	377 ± 29**	355 ± 26**
50	430 ± 32	373 ± 25**	374 ± 25**	379 ± 32**	359 ± 28**
52	432 ± 28	376 ± 24**	394 ± 25**	374 ± 31**	336 ± 31**

TABLE 17. CONTINUED

Week of Exposure	Control (N = 150)	0.05 ppm (N = 100)	0.25 ppm (N = 100)	1.0 ppm (N = 100)	5.0 ppm (N = 100)
Postexposure					
4	428 ± 28	375 ± 21**	382 ± 38**	384 ± 32**	366 ± 26**
8	429 ± 27	376 ± 22**	376 ± 25**	386 ± 34**	354 ± 26**
12	428 ± 27	387 ± 22**	387 ± 28**	392 ± 34**	366 ± 27**
18	439 ± 33	405 ± 23**	402 ± 38**	412 ± 34**	384 ± 29**
22	441 ± 35	407 ± 25**	417 ± 34**	412 ± 35**	395 ± 31**
26	442 ± 36	405 ± 24**	421 ± 31**	411 ± 34**	398 ± 30**
30	446 ± 38	412 ± 27**	426 ± 34**	418 ± 36**	395 ± 32**
35	429 ± 53	409 ± 33**	402 ± 38	415 ± 40*	390 ± 38**
39	430 ± 36	412 ± 32**	415 ± 49*	405 ± 46**	394 ± 34**
44	439 ± 32	399 ± 34**	412 ± 32**	400 ± 41**	396 ± 29**
48	422 ± 40	394 ± 33**	395 ± 22**	399 ± 41**	383 ± 35**
53	410 ± 40	396 ± 38**	400 ± 29	401 ± 42	378 ± 33
57	393 ± 34	386 ± 39	393 ± 26	385 ± 35	362 ± 43**
61	389 ± 39	381 ± 35	385 ± 53	317 ± 38**	359 ± 36**
66	385 ± 39	379 ± 25	377 ± 20	365 ± 46	350 ± 30**
70	377 ± 23	355 ± 28**	361 ± 32	359 ± 45	345 ± 35**
74	360 ± 30	351 ± 32	347 ± 32	354 ± 45	327 ± 52*
77	347 ± 43	334 ± 30	322 ± 51	337 ± 43	342 ± 41

** Significant at 0.01 level, control vs. test.
* Significant at 0.05 level, control vs. test.

TABLE 18. MEAN BODY WEIGHTS IN GRAMS (±S.D.) OF FEMALE RATS EXPOSED TO HYDRAZINE FOR ONE YEAR

Week of Exposure	Control (N = 150)	0.05 ppm (N = 100)	0.25 ppm (N = 100)	1.0 ppm (N = 100)	5.0 ppm (N = 100)
-2	136 ± 9	134 ± 9	134 ± 9	134 ± 8	134 ± 9
-1	141 ± 9	138 ± 8*	138 ± 8*	139 ± 6	139 ± 8
2	159 ± 10	149 ± 9**	158 ± 9	139 ± 9**	106 ± 16**
4	167 ± 11	161 ± 11**	157 ± 10**	153 ± 10**	140 ± 11**
6	172 ± 10	163 ± 11**	158 ± 10**	157 ± 12**	154 ± 12**
8	178 ± 11	169 ± 10**	167 ± 9**	170 ± 10**	161 ± 11**
10	179 ± 11	177 ± 10	183 ± 11**	169 ± 11**	169 ± 11**
12	182 ± 11	177 ± 9**	173 ± 9**	170 ± 10**	169 ± 10**
14	183 ± 11	177 ± 11**	176 ± 10**	179 ± 10*	172 ± 10**
16	182 ± 12	173 ± 10**	181 ± 11	178 ± 10**	167 ± 10**
18	187 ± 12	188 ± 11	181 ± 10**	184 ± 9*	180 ± 9**
20	189 ± 13	197 ± 10**	161 ± 12**	188 ± 10	178 ± 10**
22	193 ± 13	193 ± 10	157 ± 10**	191 ± 10	180 ± 11**
24	190 ± 13	194 ± 10**	178 ± 10**	190 ± 13	180 ± 10**
26	190 ± 13	194 ± 14*	182 ± 13**	193 ± 12	181 ± 11**
28	195 ± 14	201 ± 11**	189 ± 12**	197 ± 12	190 ± 11**
30	196 ± 14	201 ± 11**	190 ± 12**	198 ± 11	182 ± 10**
32	197 ± 14	197 ± 14	185 ± 10**	199 ± 12	189 ± 12**
34	199 ± 15	199 ± 14	195 ± 11**	196 ± 11	194 ± 10**
36	204 ± 15	202 ± 12	199 ± 11**	197 ± 11	192 ± 10**
38	204 ± 16	194 ± 13**	204 ± 12	190 ± 11**	188 ± 12**
40	209 ± 17	198 ± 12**	194 ± 13**	196 ± 11**	190 ± 10**
42	209 ± 19	198 ± 12**	199 ± 14**	198 ± 16**	194 ± 11**
44	211 ± 18	204 ± 13**	200 ± 12**	195 ± 17**	192 ± 10**
46	216 ± 20	207 ± 13**	197 ± 14**	200 ± 11**	198 ± 12**
48	219 ± 20	210 ± 14**	205 ± 14**	204 ± 12**	194 ± 12**
50	225 ± 20	208 ± 14**	213 ± 15**	205 ± 13**	206 ± 13**
52	226 ± 22	213 ± 13**	221 ± 15**	207 ± 13**	196 ± 12**

TABLE 18. CONTINUED

Week of Exposure	Control (N = 150)	0.05 ppm (N = 100)	0.25 ppm (N = 100)	1.0 ppm (N = 100)	5.0 ppm (N = 100)
Postexposure					
4	241 ± 24	217 ± 14**	221 ± 16**	220 ± 14**	219 ± 12**
8	252 ± 26	225 ± 16**	225 ± 18**	222 ± 17**	220 ± 14**
12	261 ± 28	233 ± 17**	232 ± 19**	230 ± 19**	225 ± 13**
18	268 ± 30	242 ± 21**	244 ± 21**	236 ± 20**	229 ± 15**
22	276 ± 31	247 ± 22**	248 ± 24**	243 ± 24**	239 ± 17**
26	279 ± 33	248 ± 24**	253 ± 24**	250 ± 26**	246 ± 20**
30	287 ± 31	257 ± 24**	260 ± 27**	260 ± 27**	256 ± 25**
35	280 ± 32	258 ± 24**	259 ± 29**	261 ± 27**	255 ± 23**
39	279 ± 33	260 ± 22**	261 ± 29**	267 ± 31*	260 ± 23**
44	288 ± 33	264 ± 23**	266 ± 29**	273 ± 27**	264 ± 27**
48	290 ± 34	260 ± 25**	268 ± 26**	272 ± 30**	267 ± 24**
53	294 ± 29	263 ± 32**	268 ± 28**	279 ± 28**	275 ± 23**
57	281 ± 31	263 ± 24**	267 ± 29**	270 ± 27	268 ± 21*
61	282 ± 41	267 ± 29	270 ± 29	273 ± 29	264 ± 24*
66	288 ± 28	261 ± 21**	264 ± 26**	259 ± 21**	253 ± 20**
70	285 ± 31	254 ± 22**	265 ± 37*	249 ± 30**	255 ± 24**
74	286 ± 27	255 ± 27**	274 ± 24	257 ± 24**	255 ± 22**
77	281 ± 23	255 ± 30**	273 ± 25	248 ± 36**	245 ± 22**

** Significant at the 0.01 level, control vs. test.
* Significant at the 0.01 level, control vs. test.

TABLE 19. MEAN BODY WEIGHTS IN GRAMS (±S.D.) OF HAMSTERS EXPOSED TO HYDRAZINE FOR ONE YEAR

Week of Exposure	Control (N = 200)	0.25 ppm (N = 200)	1.0 ppm (N = 200)	5.0 ppm (N = 200)
-3 days	115 ± 7	116 ± 7	114 ± 7	115 ± 7
-1 day	115 ± 7	116 ± 7	114 ± 7	114 ± 7
2	122 ± 9	117 ± 8**	116 ± 8**	113 ± 9**
4	129 ± 10	120 ± 9**	122 ± 11**	119 ± 11**
6	131 ± 10	120 ± 10**	115 ± 14**	115 ± 12**
8	132 ± 11	125 ± 11**	127 ± 13**	120 ± 13**
10	134 ± 12	130 ± 12**	133 ± 15	125 ± 14**
12	137 ± 13	134 ± 13*	135 ± 15	128 ± 15**
14	137 ± 13	134 ± 13	135 ± 16	131 ± 14**
16	139 ± 14	136 ± 13*	131 ± 22**	132 ± 14**
18	141 ± 14	135 ± 13**	134 ± 16**	131 ± 13**
20	141 ± 15	136 ± 14**	133 ± 16**	133 ± 14**
22	142 ± 15	132 ± 14**	131 ± 16**	127 ± 13**
24	142 ± 14	133 ± 14**	134 ± 16**	125 ± 14**
26	143 ± 15	134 ± 13**	134 ± 16**	124 ± 14**
28	143 ± 16	136 ± 14**	134 ± 15**	126 ± 13**
30	144 ± 15	134 ± 14**	136 ± 16**	127 ± 14**
32	144 ± 16	131 ± 14**	130 ± 17**	130 ± 13**
34	144 ± 16	133 ± 15**	135 ± 16**	130 ± 15**
36	145 ± 15	134 ± 14**	132 ± 17**	127 ± 13**
38	145 ± 15	136 ± 14**	136 ± 16**	131 ± 12**
40	144 ± 15	136 ± 14**	134 ± 16**	127 ± 13**
42	145 ± 15	135 ± 14**	136 ± 16**	123 ± 13**
44	143 ± 16	138 ± 14**	136 ± 16**	124 ± 12**
46	142 ± 16	135 ± 14**	136 ± 16**	125 ± 13**
48	143 ± 16	134 ± 13**	132 ± 16**	121 ± 13**
50	142 ± 16	130 ± 13**	132 ± 16**	121 ± 13**
52	140 ± 16	129 ± 13**	135 ± 17**	122 ± 15**

TABLE 19. CONTINUED

Week of Exposure	Control (N = 200)	0.25 ppm (N = 200)	1.0 ppm (N = 200)	5.0 ppm (N = 200)
Postexposure				
4	132 ± 18	122 ± 15**	128 ± 18	115 ± 15**
8	125 ± 18	120 ± 16*	124 ± 18	111 ± 13**
12	123 ± 19	119 ± 15	124 ± 18	108 ± 14**
17	123 ± 18	123 ± 15	129 ± 19*	115 ± 12**
21	130 ± 17	128 ± 14	133 ± 19	119 ± 15**
26	138 ± 15	132 ± 13*	137 ± 17	123 ± 13**
30	140 ± 17	133 ± 13*	134 ± 18	126 ± 13**
35	138 ± 21	133 ± 13	134 ± 19	126 ± 14**
39	136 ± 19	133 ± 14	135 ± 17	128 ± 14**
43	137 ± 19	131 ± 14	136 ± 17	134 ± 22
48	134 ± 16	128 ± 18	137 ± 18	127 ± 14
52	130 ± 16	132 ± 19	145 ± 37	125 ± 17

** Significant at 0.01 level, control vs. test.
* Significant at 0.05 level, control vs. test.

TABLE 20. GROUP MEAN VALUES ± STANDARD DEVIATIONS OF RED BLOOD COUNTS (x 10^6) FOR DOGS EXPOSED TO HYDRAZINE FOR ONE YEAR

Week of Exposure	Unexposed Controls	0.25 ppm Exposure Group	1.0 ppm Exposure Group
-7	6.30 ± .54	6.33 ± .40	6.13 ± .47
-3	6.23 ± .28	6.28 ± .39	6.23 ± .29
-1	6.42 ± .39	6.31 ± .42	6.54 ± .13
2	5.46 ± .53	4.68 ± .93*	4.93 ± .51
4	5.74 ± .50	5.46 ± .65	5.99 ± .42
6	6.22 ± .38	5.96 ± .45	6.28 ± .38
8	6.05 ± .56	5.09 ± .87	5.23 ± .80*
10	5.74 ± .48	5.33 ± .46	5.24 ± .64
12	6.56 ± .47	6.34 ± .43	6.10 ± .32*
14	5.84 ± .60	5.42 ± .46	5.28 ± .38*
16	6.84 ± .35	6.36 ± .44*	6.18 ± .38**
18	6.49 ± .34	6.18 ± .40	5.91 ± .97
20	6.77 ± .48	6.46 ± .30	6.05 ± .65**
22	6.71 ± .49	6.67 ± .38	6.64 ± .43
26	6.66 ± .42	5.97 ± .56**	6.38 ± .33
28	6.88 ± .43	6.28 ± .55*	6.23 ± .27**
30	6.73 ± .43	6.23 ± .49*	6.43 ± .40
32	6.57 ± .42	6.44 ± .45	6.54 ± .48
34	6.30 ± .35	6.11 ± .56	6.01 ± .68
36	6.83 ± .31	6.38 ± .29	6.11 ± .66**
38	6.76 ± .36	6.40 ± .29	6.39 ± .56
40	7.13 ± .53	6.23 ± .43**	6.17 ± .43**
42	6.43 ± .32	6.62 ± .39	6.25 ± .57
44	6.70 ± .62	6.80 ± .54	6.50 ± .55
46	6.18 ± .33	6.15 ± .32	5.91 ± .31
48	6.58 ± .58	6.53 ± .72	6.56 ± .50
50	5.94 ± .47	5.89 ± .53	5.63 ± .42
52	6.67 ± .51	6.52 ± .54	5.92 ± .30**
Postexposure			
2	6.90 ± .58	5.99 ± .52**	5.56 ± .37**
5	6.45 ± .37	5.53 ± .46**	5.31 ± .35**
9	5.70 ± .53	4.78 ± .44**	5.50 ± .52
14	5.70 ± .32	6.04 ± .38	6.20 ± .42*
33	7.01 ± .45	7.09 ± .42	7.19 ± .65
83	Lost	Lost	Lost
96	6.99 ± .61	7.15 ± .55	7.03 ± .34
121	7.56 ± .44	7.66 ± .49	7.58 ± .56
152	7.94 ± .54	7.69 ± .81	7.43 ± 1.03

** Significant at 0.01 level, control vs. test.
* Significant at 0.05 level, control vs. test.

TABLE 21. GROUP MEAN VALUES ± STANDARD DEVIATIONS OF WHITE BLOOD CELL COUNTS (x 10^3) FOR DOGS EXPOSED TO HYDRAZINE FOR ONE YEAR

Week of Exposure	Unexposed Controls	0.25 ppm Exposure Group	1.0 ppm Exposure Group
-7	9.4 ± 1.8	9.7 ± 1.9	11.7 ± 2.2*
-3	7.9 ± 1.3	8.2 ± 2.1	9.1 ± 2.2
-1	8.1 ± 1.7	8.8 ± 2.1	9.7 ± 1.3
2	11.0 ± .41	10.5 ± 2.1	11.4 ± 1.7
4	13.2 ± 3.0	14.0 ± 4.1	13.4 ± 4.6
6	12.9 ± 4.6	12.0 ± 3.0	14.9 ± 4.6
8	10.3 ± 2.4	13.0 ± 3.3	13.0 ± 3.6
10	12.8 ± 7.9	12.3 ± 2.8	13.7 ± 2.6
12	10.8 ± 3.4	13.4 ± 3.5	13.6 ± 3.3
14	10.0 ± 3.9	10.7 ± 2.7	11.4 ± 3.2
16	10.5 ± 3.5	12.0 ± 2.4	13.0 ± 3.9
18	9.6 ± 2.5	11.3 ± 2.0	11.1 ± 2.6
20	11.2 ± 2.5	11.2 ± 2.3	11.4 ± 3.1
22	10.6 ± 3.0	12.4 ± 2.9	12.7 ± 3.1
26	9.1 ± 2.7	12.0 ± 2.9	13.3 ± 3.8
28	10.7 ± 3.3	11.0 ± 3.0	12.0 ± 2.7
30	11.3 ± 4.6	10.8 ± 3.3	9.9 ± 2.8
32	12.5 ± 4.2	12.5 ± 3.0	12.8 ± 2.8
34	10.9 ± 2.9	11.1 ± 2.5	11.5 ± 3.8
36	9.8 ± 3.1	11.7 ± 2.7	13.9 ± 3.6*
38	11.8 ± 5.2	12.8 ± 4.3	12.5 ± 4.1
40	9.8 ± 3.8	12.3 ± 3.6	12.7 ± 3.5
42	9.4 ± 2.1	11.6 ± 3.9	12.0 ± 1.7
44	11.2 ± 5.4	10.8 ± 2.7	15.7 ± 4.5
46	10.0 ± 4.1	10.9 ± 3.5	14.0 ± 3.9*
48	11.0 ± 3.8	12.4 ± 2.4	14.3 ± 2.3*
50	9.1 ± 2.2	11.9 ± 2.9*	11.9 ± 1.9*
52	10.7 ± 3.1	12.6 ± 3.3	11.9 ± 1.9
Postexposure			
2	8.7 ± 2.7	12.7 ± 6.1	12.7 ± 1.6**
5	9.3 ± 3.2	15.8 ± 6.7*	14.5 ± 3.0*
9	12.4 ± 3.4	16.0 ± 5.9	15.1 ± 3.0
14	10.0 ± 3.5	10.6 ± 3.2	11.6 ± 3.1
33	11.7 ± 3.4	10.2 ± 2.6	11.7 ± 2.0
83	8.7 ± 2.5	9.5 ± 2.6	10.1 ± 3.0
96	9.7 ± 0.8	12.3 ± 3.2	12.9 ± 2.0**
121	8.8 ± 1.5	11.4 ± 6.3	10.4 ± 2.7
152	10.5 ± 2.8	15.1 ± 15.1	11.8 ± 2.1

** Significant at 0.01 level, control vs. test.
* Significant at 0.05 level, control vs. test.

TABLE 22. GROUP MEAN VALUES ± STANDARD DEVIATIONS OF HEMATOCRIT (Vols. %) FOR DOGS EXPOSED TO HYDRAZINE FOR ONE YEAR

Week of Exposure	Unexposed Controls	0.25 ppm Exposure Group	1.0 ppm Exposure Group
-7	44 ± 2	45 ± 2	45 ± 1
-3	43 ± 2	44 ± 3	44 ± 2
-1	44 ± 3	44 ± 3	46 ± 2
2	41 ± 4	41 ± 3	44 ± 2
4	40 ± 4	40 ± 3	44 ± 2*
6	42 ± 2	43 ± 3	43 ± 2
8	45 ± 3	43 ± 3	44 ± 3
10	48 ± 2	46 ± 3	45 ± 3
12	46 ± 2	46 ± 2	44 ± 2
14	48 ± 2	48 ± 2	46 ± 3
16	48 ± 2	46 ± 3	44 ± 1**
18	47 ± 2	47 ± 2	46 ± 3
20	48 ± 3	46 ± 2	43 ± 4**
22	46 ± 3	46 ± 3	46 ± 2
26	47 ± 2	44 ± 3*	47 ± 3
28	46 ± 2	46 ± 3	46 ± 2
30	46 ± 2	46 ± 2	46 ± 2
32	47 ± 2	44 ± 3*	44 ± 3*
34	48 ± 2	46 ± 3	46 ± 4
36	48 ± 2	45 ± 2*	43 ± 5*
38	48 ± 2	46 ± 2	45 ± 5
40	48 ± 3	45 ± 3	44 ± 3*
42	45 ± 3	46 ± 3	44 ± 4
44	47 ± 4	49 ± 3	46 ± 4
46	46 ± 3	47 ± 2	44 ± 2
48	47 ± 3	45 ± 5	44 ± 3
50	47 ± 2	45 ± 4	42 ± 3**
52	50 ± 1	47 ± 3*	42 ± 2**
Postexposure			
2	50 ± 2	45 ± 3**	41 ± 2**
5	50 ± 2	46 ± 3**	46 ± 2**
9	50 ± 2	46 ± 3**	49 ± 1
14	46 ± 2	49 ± 2*	50 ± 1**
33	49 ± 3	49 ± 2	49 ± 4
83	47 ± 3	50 ± 2	49 ± 3
96	47 ± 4	49 ± 3	48 ± 3
121	49 ± 2	51 ± 3	50 ± 3
152	47 ± 4	48 ± 4	46 ± 6

** Significant at 0.01 level, control vs. test.
* Significant at 0.05 level, control vs. test.

TABLE 23. GROUP MEAN VALUES ± STANDARD DEVIATIONS OF HEMOGLOBIN (g %) FOR DOGS EXPOSED TO HYDRAZINE FOR ONE YEAR

Week of Exposure	Unexposed Controls	0.25 ppm Exposure Group	1.0 ppm Exposure Group
-7	14.9 ± 0.7	15.2 ± 0.6	15.2 ± 0.6
-3	14.9 ± 0.5	15.1 ± 0.8	15.1 ± 0.6
-1	15.1 ± 1.1	15.0 ± 0.7	15.6 ± 0.6
2	14.2 ± 1.1	13.6 ± 1.0	14.8 ± 0.6
4	13.9 ± 1.3	13.9 ± 0.8	15.0 ± 0.7*
6	14.6 ± 0.6	14.8 ± 1.0	15.0 ± 0.9
8	15.8 ± 1.1	14.8 ± 1.1	14.9 ± 1.1
10	16.1 ± 0.9	15.4 ± 1.1	15.1 ± 1.0
12	15.8 ± 0.9	15.9 ± 0.9	15.0 ± 0.4
14	16.6 ± 0.9	16.7 ± 0.9	15.8 ± 1.1
16	16.6 ± 0.7	15.8 ± 1.2	15.1 ± 0.5**
18	16.5 ± 0.7	15.7 ± 0.8	15.2 ± 1.0**
20	16.4 ± 0.9	15.8 ± 0.8	14.8 ± 1.3**
22	15.9 ± 1.2	15.7 ± 1.0	15.6 ± 1.1
26	16.0 ± 0.7	14.8 ± 1.1*	15.8 ± 1.0
28	15.9 ± 0.9	15.7 ± 1.1	15.6 ± 0.6
30	16.0 ± 0.8	15.8 ± 0.5	15.7 ± 0.8
32	16.6 ± 0.7	15.0 ± 0.9**	15.1 ± 1.0**
34	16.7 ± 0.7	15.9 ± 1.3	15.7 ± 1.3
36	16.3 ± 0.8	15.1 ± 0.8*	14.3 ± 1.4**
38	16.4 ± 0.8	15.8 ± 1.3	15.0 ± 1.5*
40	17.2 ± 1.4	15.3 ± 1.0**	15.3 ± 1.4**
42	16.2 ± 1.2	16.0 ± 1.1	15.2 ± 1.4
44	16.3 ± 1.4	16.1 ± 1.1	15.0 ± 1.4
46	16.8 ± 1.0	16.6 ± 0.9	15.7 ± 0.8*
48	16.4 ± 1.4	15.3 ± 1.4	15.0 ± 1.1
50	16.1 ± 0.8	15.3 ± 1.3	14.2 ± 1.3**
52	16.8 ± 0.7	15.9 ± 0.9*	14.2 ± 0.6**
Postexposure			
2	17.5 ± 0.9	16.1 ± 1.1**	14.5 ± 0.6**
5	17.2 ± 0.5	16.0 ± 0.9**	16.0 ± 0.9**
9	17.2 ± 0.6	16.0 ± 0.9**	16.9 ± 0.5
14	16.3 ± 0.6	16.9 ± 0.8	17.2 ± 0.6**
33	17.2 ± 1.0	17.1 ± 0.8	17.3 ± 1.6
83	15.9 ± 0.9	17.1 ± 0.9*	17.1 ± 1.0*
96	16.5 ± 1.1	16.8 ± 1.0	17.0 ± 1.0
121	17.3 ± 0.6	17.9 ± 1.0	17.3 ± 0.7
152	15.8 ± 1.2	15.8 ± 1.5	15.5 ± 1.8

** Significant at 0.01 level, control vs. test.
* Significant at 0.05 level, control vs. test.

TABLE 24. GROUP MEAN VALUES ± STANDARD DEVIATIONS OF SODIUM (mEq/L) FOR DOGS EXPOSED TO HYDRAZINE FOR ONE YEAR

Week of Exposure	Unexposed Controls	0.25 ppm Exposure Group	1.0 ppm Exposure Group
-7	148 ± 2	147 ± 2	148 ± 3
-3	148 ± 2	148 ± 2	149 ± 2
-1	150 ± 2	150 ± 1	150 ± 2
2	150 ± 2	150 ± 2	150 ± 2
4	145 ± 1	145 ± 2	146 ± 2
6	150 ± 1	148 ± 3	147 ± 3*
8	148 ± 1	149 ± 1	150 ± 2**
10	149 ± 1	148 ± 2	150 ± 1
12	150 ± 1	149 ± 2	149 ± 1
14	150 ± 1	151 ± 2	150 ± 2
16	149 ± 1	150 ± 1	149 ± 1
18	150 ± 2	149 ± 1*	149 ± 1
20	150 ± 2	153 ± 1**	152 ± 1
22	152 ± 2	152 ± 1	151 ± 1
26	152 ± 2	149 ± 2*	150 ± 2
28	154 ± 1	150 ± 2**	151 ± 2**
30	149 ± 2	149 ± 2	147 ± 2*
32	153 ± 2	153 ± 2	154 ± 3
34	142 ± 1	142 ± 1	144 ± 2**
36	151 ± 2	150 ± 1	149 ± 2**
38	153 ± 3	151 ± 2	154 ± 2
40	150 ± 3	149 ± 1	149 ± 2
42	147 ± 1	148 ± 2	147 ± 2
44	145 ± 1	145 ± 1	146 ± 2
46	150 ± 2	150 ± 1	151 ± 1
48	149 ± 2	146 ± 1**	146 ± 1**
50	152 ± 2	151 ± 4	147 ± 2**
52	153 ± 2	149 ± 2**	150 ± 1**
Postexposure			
2	151 ± 2	150 ± 3	149 ± 2
5	151 ± 2	150 ± 2	150 ± 3
9	149 ± 2	148 ± 2	148 ± 2
14	148 ± 2	150 ± 3	149 ± 1
33	Lost	Lost	Lost
83	Lost	Lost	Lost
96	151 ± 2	150 ± 3	150 ± 2
121	153 ± 2	153 ± 1	154 ± 1
152	152 ± 1	152 ± 2	152 ± 2

** Significant at 0.01 level, control vs. test.
* Significant at 0.05 level, control vs. test.

TABLE 25. GROUP MEAN VALUES ± STANDARD DEVIATIONS OF POTASSIUM (mEq/L) FOR DOGS EXPOSED TO HYDRAZINE FOR ONE YEAR

Week of Exposure	Unexposed Controls	0.25 ppm Exposure Group	1.0 ppm Exposure Group
-7	4.4 ± 0.3	4.7 ± 0.3*	4.4 ± 0.3*
-3	5.0 ± 0.4	5.2 ± 0.2	4.8 ± 0.3
-1	4.8 ± 0.4	5.1 ± 0.2	4.9 ± 0.3
2	4.7 ± 0.3	5.0 ± 0.2	4.7 ± 0.3
4	4.4 ± 0.2	4.8 ± 0.3**	4.8 ± 0.3*
6	4.7 ± 0.3	5.0 ± 0.2*	4.8 ± 0.2
8	4.7 ± 0.2	4.6 ± 0.2	5.0 ± 0.2**
10	4.7 ± 0.1	4.7 ± 0.2	4.9 ± 0.1*
12	4.3 ± 0.2	4.8 ± 0.2**	4.7 ± 0.1**
14	4.3 ± 0.2	4.7 ± 0.3**	4.6 ± 0.2
16	4.4 ± 0.2	4.7 ± 0.3*	4.6 ± 0.2
18	4.3 ± 0.2	4.8 ± 0.2**	4.6 ± 0.1**
20	4.5 ± 0.3	5.0 ± 0.2**	4.7 ± 0.3
22	4.5 ± 0.2	5.0 ± 0.2**	4.7 ± 0.2
26	4.4 ± 0.2	4.6 ± 0.2	4.6 ± 0.2
28	4.5 ± 0.3	4.7 ± 0.3	4.7 ± 0.3
30	4.5 ± 0.1	4.7 ± 0.2*	4.7 ± 0.3
32	4.7 ± 0.2	4.5 ± 0.2	4.6 ± 0.3
34	4.3 ± 0.4	4.1 ± 0.4	4.1 ± 0.2
36	4.6 ± 0.3	4.7 ± 0.2	4.7 ± 0.2
38	4.5 ± 0.3	4.7 ± 0.2*	5.0 ± 0.3**
40	4.6 ± 0.3	4.9 ± 0.2*	4.7 ± 0.3
42	4.5 ± 0.3	4.9 ± 0.2**	4.8 ± 0.1**
44	4.4 ± 0.2	4.6 ± 0.2	4.6 ± 0.2
46	4.6 ± 0.2	5.1 ± 0.2**	4.6 ± 0.3
48	4.9 ± 0.2	4.9 ± 0.2	4.8 ± 0.2
50	4.7 ± 0.3	5.1 ± 0.2**	4.7 ± 0.2
52	5.0 ± 0.2	5.1 ± 0.1	5.1 ± 0.3
Postexposure			
2	4.9 ± 0.3	4.8 ± 0.3	5.2 ± 0.2
5	4.8 ± 0.3	5.1 ± 0.4	5.1 ± 0.4
9	4.7 ± 0.3	4.6 ± 0.2	4.6 ± 0.3
14	4.6 ± 0.2	4.8 ± 0.3	4.6 ± 0.2
33	Lost	Lost	Lost
83	Lost	Lost	Lost
96	4.5 ± 0.2	4.6 ± 0.2	4.5 ± 0.3
121	4.6 ± 0.3	4.9 ± 0.2	4.7 ± 0.3
152	5.0 ± 0.4	5.3 ± 0.4	4.9 ± 0.4

** Significant at 0.01 level, control vs. test.
* Significant at 0.05 level, control vs. test.

TABLE 26. GROUP MEAN VALUES ± STANDARD DEVIATIONS OF CALCIUM (mg/100 ml) FOR DOGS EXPOSED TO HYDRAZINE FOR ONE YEAR

Week of Exposure	Unexposed Controls	0.25 ppm Exposure Group	1.0 ppm Exposure Group
-7	10.2 ± 0.9	9.9 ± 0.3	10.2 ± 0.4
-3	10.0 ± 0.6	9.8 ± 0.2	10.1 ± 0.4
-1	10.3 ± 0.4	10.1 ± 0.3	10.0 ± 0.5
2	10.1 ± 0.6	10.1 ± 0.3	10.3 ± 0.5
4	9.9 ± 0.6	9.9 ± 0.4	10.0 ± 0.3
6	9.8 ± 0.4	10.0 ± 0.3	10.1 ± 0.3*
8	9.8 ± 0.6	9.7 ± 0.4	10.1 ± 0.5
10	9.9 ± 0.4	9.9 ± 0.3	10.1 ± 0.3
12	10.2 ± 0.4	10.2 ± 0.6	10.3 ± 0.6
14	9.9 ± 0.4	10.4 ± 0.2*	10.3 ± 0.3*
16	9.8 ± 0.4	9.9 ± 0.4	9.9 ± 0.4
18	10.2 ± 0.4	10.3 ± 0.4	10.5 ± 0.3*
20	10.3 ± 0.4	10.4 ± 0.4	10.9 ± 0.4**
22	10.1 ± 0.4	10.4 ± 0.3	10.6 ± 0.5*
26	10.5 ± 0.5	10.3 ± 0.5	10.5 ± 0.5
28	10.6 ± 0.4	10.6 ± 0.4	10.7 ± 0.4
30	10.2 ± 0.4	9.9 ± 0.4	10.4 ± 0.4
32	10.1 ± 0.4	10.2 ± 0.3	10.4 ± 0.4
34	9.8 ± 0.3	10.0 ± 0.6	9.9 ± 0.5
36	10.1 ± 0.3	10.1 ± 0.4	9.9 ± 0.6
38	10.5 ± 0.4	10.3 ± 0.3	10.4 ± 0.5
40	9.7 ± 0.3	9.8 ± 0.5	9.7 ± 0.5
42	9.9 ± 0.4	9.9 ± 0.5	9.8 ± 0.5
44	9.8 ± 0.4	9.8 ± 0.4	9.7 ± 0.5
46	9.5 ± 0.3	9.9 ± 0.3**	9.6 ± 0.4
48	10.1 ± 0.3	9.7 ± 0.4	9.9 ± 0.5
50	9.9 ± 0.4	9.8 ± 0.3	9.7 ± 0.5
52	9.9 ± 0.3	9.5 ± 0.4*	9.6 ± 0.4
Postexposure			
2	10.0 ± 0.4	9.3 ± 0.8*	9.8 ± 0.5
5	10.1 ± 0.4	9.9 ± 0.5	10.1 ± 0.4
9	9.8 ± 0.4	9.4 ± 0.3	9.9 ± 0.3
14	9.9 ± 0.4	9.8 ± 0.4	9.8 ± 0.3
33	10.5 ± 0.3	10.6 ± 0.4	10.6 ± 0.4
83	10.2 ± 0.3	10.2 ± 0.2	10.0 ± 0.2
96	10.6 ± 0.2	10.4 ± 0.2	10.4 ± 0.3
121	10.1 ± 0.4	10.0 ± 0.2	9.9 ± 0.4
152	10.0 ± 0.4	9.9 ± 0.3	9.9 ± 0.4

** Significant at 0.01 level, control vs. test.
* Significant at 0.05 level, control vs. test.

TABLE 27. GROUP MEAN VALUES ± STANDARD DEVIATIONS OF TOTAL PROTEIN (g/dl) FOR DOGS EXPOSED TO HYDRAZINE FOR ONE YEAR

Week of Exposure	Unexposed Controls	0.25 ppm Exposure Group	1.0 ppm Exposure Group
-7	6.4 ± 0.3	6.2 ± 0.4	6.2 ± 0.3
-3	6.3 ± 0.3	6.1 ± 0.4	6.3 ± 0.2
-1	6.3 ± 0.2	6.2 ± 0.3	6.3 ± 0.3
2	6.5 ± 0.2	6.3 ± 0.3	6.3 ± 0.2
4	6.5 ± 0.3	6.3 ± 0.3	6.4 ± 0.3
6	6.6 ± 0.2	6.4 ± 0.3	6.8 ± 0.2
8	6.6 ± 0.3	6.4 ± 0.4	6.6 ± 0.2
10	6.2 ± 0.1	6.5 ± 0.3*	6.8 ± 0.3**
12	6.4 ± 0.3	6.9 ± 0.3**	7.0 ± 0.3**
14	6.4 ± 0.1	6.6 ± 0.3	6.6 ± 0.2*
16	6.5 ± 0.1	6.5 ± 0.3	6.8 ± 0.3**
18	6.4 ± 0.1	6.7 ± 0.4*	6.8 ± 0.1**
20	6.6 ± 0.1	6.5 ± 0.4	7.0 ± 0.3**
22	6.8 ± 0.2	6.8 ± 0.4	7.1 ± 0.2*
26	6.8 ± 0.3	6.9 ± 0.3	7.1 ± 0.4
28	6.7 ± 0.2	6.8 ± 0.4	7.2 ± 0.3**
30	6.1 ± 0.3	6.2 ± 0.2	6.9 ± 0.4**
32	6.3 ± 0.2	6.5 ± 0.3	6.9 ± 0.4**
34	6.2 ± 0.3	6.4 ± 0.4	6.7 ± 0.3*
36	6.2 ± 0.2	6.2 ± 0.3	6.4 ± 0.5
38	6.2 ± 0.2	6.5 ± 0.3	6.9 ± 0.5**
40	6.1 ± 0.5	6.2 ± 0.6	6.3 ± 0.3
42	6.4 ± 0.3	6.6 ± 0.5	6.8 ± 0.4
44	6.5 ± 0.2	6.7 ± 0.2	6.8 ± 0.4*
46	6.2 ± 0.2	6.9 ± 0.3**	7.0 ± 0.4**
48	6.3 ± 0.2	6.4 ± 0.4	6.7 ± 0.4*
50	6.2 ± 0.2	6.3 ± 0.2	6.6 ± 0.3**
52	6.3 ± 0.1	6.2 ± 0.4	6.6 ± 0.5
Postexposure			
2	6.3 ± 0.2	6.1 ± 0.6	6.6 ± 0.5
5	6.7 ± 0.3	6.5 ± 0.4	6.8 ± 0.3
9	6.4 ± 0.3	6.5 ± 0.3	6.9 ± 0.3**
14	6.7 ± 0.3	6.7 ± 0.4	6.9 ± 0.4
33	6.2 ± 0.3	6.3 ± 0.4	6.4 ± 0.1
83	6.2 ± 0.4	6.2 ± 0.2	6.2 ± 0.4
96	6.5 ± 0.3	6.3 ± 0.3	6.5 ± 0.3
121	6.3 ± 0.2	6.3 ± 0.3	6.4 ± 0.2
152	6.8 ± 0.2	6.6 ± 0.3	6.7 ± 0.2

** Significant at 0.01 level, control vs. test.
* Significant at 0.05 level, control vs. test.

TABLE 28. GROUP MEAN VALUES ± STANDARD DEVIATIONS OF ALBUMIN (g/dl) FOR DOGS EXPOSED TO HYDRAZINE FOR ONE YEAR

Week of Exposure	Unexposed Controls	0.25 ppm Exposure Group	1.0 ppm Exposure Group
-7	2.6 ± 0.3	2.5 ± 0.3	2.4 ± 0.4
-3	2.7 ± 0.3	3.0 ± 0.5	2.8 ± 0.5
-1	2.6 ± 0.5	2.6 ± 0.4	2.6 ± 0.4
2	2.9 ± 0.6	2.9 ± 0.5	2.4 ± 0.5
4	3.1 ± 0.2	2.9 ± 0.2	3.1 ± 0.2
6	3.3 ± 0.5	3.1 ± 0.2	3.2 ± 0.3
8	3.3 ± 0.3	3.1 ± 0.2	3.2 ± 0.3
10	3.3 ± 0.2	3.1 ± 0.2	3.2 ± 0.2
12	3.3 ± 0.3	3.3 ± 0.2	3.2 ± 0.3
14	4.7 ± 0.3	4.5 ± 0.2	4.5 ± 0.1*
16	5.2 ± 0.3	5.0 ± 0.3	4.7 ± 0.2*
18	4.4 ± 0.2	4.4 ± 0.2	4.5 ± 0.2
20	4.4 ± 0.3	4.3 ± 0.2	4.1 ± 0.6
22	4.8 ± 0.4	5.0 ± 0.2	4.9 ± 0.3
26	4.4 ± 0.3	4.1 ± 0.3	3.9 ± 0.3**
28	4.5 ± 0.2	4.1 ± 0.4*	4.2 ± 0.4
30	4.3 ± 0.3	4.1 ± 0.2	4.1 ± 0.1*
32	4.3 ± 0.2	4.0 ± 0.1*	4.6 ± 0.6
34	4.4 ± 0.2	4.3 ± 0.2	4.3 ± 0.3
36	4.4 ± 0.2	4.3 ± 0.2	4.3 ± 0.3
38	4.4 ± 0.2	4.4 ± 0.1	4.4 ± 0.2
40	4.4 ± 0.3	4.1 ± 0.3	4.2 ± 0.3
42	4.0 ± 0.1	3.9 ± 0.2	3.9 ± 0.1
44	4.1 ± 0.3	3.8 ± 0.2*	3.9 ± 0.3
46	4.2 ± 0.2	4.2 ± 0.2	4.1 ± 0.3
48	4.4 ± 0.4	4.4 ± 0.4	4.1 ± 0.2
50	3.1 ± 0.2	3.2 ± 0.2	3.2 ± 0.2
52	2.9 ± 0.3	2.8 ± 0.3	2.5 ± 0.2*
Postexposure			
2	2.4 ± 0.3	2.5 ± 0.4	2.7 ± 0.5
5	3.5 ± 0.3	3.3 ± 0.3	3.2 ± 0.2*
9	3.4 ± 0.4	3.2 ± 0.2	3.2 ± 0.3
14	3.5 ± 0.4	3.4 ± 0.3	3.3 ± 0.3
33	2.9 ± 0.3	3.0 ± 0.2	2.8 ± 0.3
83	3.3 ± 0.4	3.3 ± 0.3	3.2 ± 0.3
96	3.8 ± 0.2	3.7 ± 0.1	3.8 ± 0.2
121	3.4 ± 0.1	3.4 ± 0.2	3.5 ± 0.2
152	3.5 ± 0.2	3.3 ± 0.2	3.4 ± 0.3

** Significant at 0.01 level, control vs. test.
* Significant at 0.05 level, control vs. test.

TABLE 29. GROUP MEAN VALUES ± STANDARD DEVIATIONS OF GLOBULIN (g/dl) FOR DOGS EXPOSED TO HYDRAZINE FOR ONE YEAR

Week of Exposure	Unexposed Controls	0.25 ppm Exposure Group	1.0 ppm Exposure Group
-7	3.8 ± 0.4	3.7 ± 0.4	3.8 ± 0.6
-3	3.6 ± 0.4	3.1 ± 0.7	3.5 ± 0.6
-1	3.7 ± 0.5	3.6 ± 0.3	3.7 ± 0.5
2	3.6 ± 0.6	3.4 ± 0.6	3.9 ± 0.4
4	3.3 ± 0.2	3.3 ± 0.3	3.2 ± 0.3
6	3.4 ± 0.4	3.4 ± 0.3	3.6 ± 0.2
8	3.3 ± 0.2	3.3 ± 0.3	3.5 ± 0.2
10	2.9 ± 0.2	3.3 ± 0.2**	3.6 ± 0.2**
12	3.1 ± 0.2	3.5 ± 0.2**	3.7 ± 0.3**
14	1.7 ± 0.2	2.0 ± 0.3*	2.2 ± 0.2**
16	1.3 ± 0.3	1.6 ± 0.4	2.1 ± 0.4**
18	2.0 ± 0.2	2.3 ± 0.4*	2.4 ± 0.2**
20	2.2 ± 0.2	2.2 ± 0.3	2.9 ± 0.5**
22	1.9 ± 0.3	1.8 ± 0.3	2.2 ± 0.2*
26	2.4 ± 0.4	2.7 ± 0.3	3.2 ± 0.5**
28	2.2 ± 0.3	2.7 ± 0.3**	2.9 ± 0.3**
30	1.8 ± 0.4	2.1 ± 0.3	2.9 ± 0.4**
32	2.1 ± 0.2	2.5 ± 0.3**	2.2 ± 0.7
34	1.9 ± 0.2	2.0 ± 0.3	2.4 ± 0.3**
36	1.8 ± 0.1	2.0 ± 0.3	2.0 ± 0.4
38	1.8 ± 0.2	2.2 ± 0.3	2.5 ± 0.4**
40	1.7 ± 0.3	2.1 ± 0.3*	2.1 ± 0.3*
42	2.4 ± 0.3	2.7 ± 0.3	2.9 ± 0.4*
44	2.4 ± 0.3	2.8 ± 0.2**	2.9 ± 0.5*
46	1.9 ± 0.3	2.7 ± 0.2**	2.9 ± 0.4**
48	2.0 ± 0.3	2.0 ± 0.3	2.6 ± 0.2**
50	3.1 ± 0.2	3.1 ± 0.2	3.5 ± 0.3**
52	3.4 ± 0.2	3.4 ± 0.4	4.1 ± 0.4**
Postexposure			
2	3.9 ± 0.4	3.6 ± 0.3	3.9 ± 0.7
5	3.3 ± 0.3	3.3 ± 0.1	3.6 ± 0.3*
9	3.0 ± 0.5	3.3 ± 0.3	3.6 ± 0.4**
14	3.2 ± 0.6	3.3 ± 0.3	3.6 ± 0.6
33	3.3 ± 0.2	3.3 ± 0.4	3.5 ± 0.4
83	2.9 ± 0.3	2.9 ± 0.2	3.1 ± 0.4
96	2.7 ± 0.3	2.6 ± 0.3	2.7 ± 0.3
121	2.9 ± 0.3	2.9 ± 0.2	2.9 ± 0.2
152	3.4 ± 0.4	3.3 ± 0.2	3.4 ± 0.3

** Significant at 0.01 level, control vs. test.
* Significant at 0.05 level, control vs. test.

TABLE 30. GROUP MEAN VALUES ± STANDARD DEVIATIONS OF ALBUMIN/GLOBULIN RATIOS FOR DOGS EXPOSED TO HYDRAZINE FOR ONE YEAR

Week of Exposure	Unexposed Controls	0.25 ppm Exposure Group	1.0 ppm Exposure Group
-7	0.7 ± 0.2	0.7 ± 0.1	0.7 ± 0.2
-3	0.8 ± 0.2	1.0 ± 0.4	0.9 ± 0.3
-1	0.7 ± 0.2	0.7 ± 0.2	0.7 ± 0.2
2	0.9 ± 0.3	0.9 ± 0.3	0.6 ± 0.2
4	0.9 ± 0.1	0.9 ± 0.1	1.0 ± 0.1
6	1.0 ± 0.3	0.9 ± 0.1	0.9 ± 0.1
8	1.0 ± 0.1	0.9 ± 0.1	0.9 ± 0.1
10	1.1 ± 0.1	1.0 ± 0.1**	0.9 ± 0.1**
12	1.1 ± 0.2	1.0 ± 0.1	0.9 ± 0.2**
14	2.8 ± 0.5	2.3 ± 0.4*	2.1 ± 0.3**
16	4.0 ± 0.9	3.6 ± 2.0	2.3 ± 0.5**
18	2.3 ± 0.3	1.9 ± 0.3*	1.9 ± 0.3*
20	2.0 ± 0.3	2.0 ± 0.3	1.5 ± 0.4**
22	2.6 ± 0.5	2.8 ± 0.4	2.2 ± 0.3
26	1.9 ± 0.4	1.5 ± 0.3	1.3 ± 0.3**
28	2.1 ± 0.3	1.6 ± 0.3**	1.5 ± 0.3**
30	2.6 ± 0.8	2.0 ± 0.4	1.5 ± 0.2**
32	2.1 ± 0.3	1.6 ± 0.2**	2.4 ± 1.1
34	2.4 ± 0.3	2.1 ± 0.2*	1.9 ± 0.3**
36	2.4 ± 0.2	2.2 ± 0.3	2.2 ± 0.4
38	2.4 ± 0.3	2.1 ± 0.3*	1.8 ± 0.3**
40	2.6 ± 0.4	2.0 ± 0.2**	2.1 ± 0.4*
42	1.7 ± 0.3	1.5 ± 0.1	1.4 ± 0.2*
44	1.7 ± 0.3	1.4 ± 0.1**	1.4 ± 0.3**
46	2.3 ± 0.5	1.5 ± 0.1**	1.5 ± 0.3**
48	2.3 ± 0.6	2.3 ± 0.6	1.6 ± 0.1**
50	1.0 ± 0.1	1.0 ± 0.1	0.9 ± 0.1
52	0.9 ± 0.2	0.8 ± 0.2	0.6 ± 0.1**
Postexposure			
2	0.6 ± 0.2	0.7 ± 0.1	0.7 ± 0.3
5	1.1 ± 0.2	1.0 ± 0.1	0.9 ± 0.1**
9	1.2 ± 0.3	1.0 ± 0.1	0.9 ± 0.2
14	1.2 ± 0.3	1.0 ± 0.1	1.0 ± 0.2
33	0.9 ± 0.1	0.9 ± 0.1	0.8 ± 0.2
83	1.2 ± 0.2	1.1 ± 0.2	1.0 ± 0.2
96	1.5 ± 0.2	1.5 ± 0.2	1.4 ± 0.2
121	1.2 ± 0.1	1.2 ± 0.1	1.2 ± 0.1
152	1.1 ± 0.2	1.0 ± 0.1	1.0 ± 0.1

** Significant at 0.01 level, control vs. test.
* Significant at 0.05 level, control vs. test.

TABLE 31. GROUP MEAN VALUES ± STANDARD DEVIATIONS OF SGPT (IU/L) FOR DOGS EXPOSED TO HYDRAZINE FOR ONE YEAR

Week of Exposure	Unexposed Controls	0.25 ppm Exposure Group	1.0 ppm Exposure Group
-7	19 ± 5	23 ± 5	23 ± 7
-3	22 ± 6	26 ± 11	49 ± 50
-1	21 ± 12	28 ± 8	33 ± 16
2	20 ± 6	25 ± 7	18 ± 4
4	35 ± 29	22 ± 9	14 ± 3
6	22 ± 7	21 ± 2	11 ± 6**
8	20 ± 6	27 ± 5*	21 ± 5
10	20 ± 8	18 ± 2	14 ± 4
12	22 ± 5	21 ± 3	14 ± 4**
14	28 ± 9	25 ± 11	17 ± 4*
16	26 ± 9	17 ± 3*	35 ± 26
18	22 ± 4	21 ± 2	16 ± 3**
20	31 ± 8	33 ± 4	28 ± 3
22	28 ± 8	23 ± 4	19 ± 3*
26	30 ± 13	25 ± 3	20 ± 3
28	25 ± 6	25 ± 2	20 ± 3
30	28 ± 6	25 ± 5	23 ± 3*
32	29 ± 5	36 ± 37	22 ± 10
34	29 ± 7	21 ± 3**	22 ± 3*
36	32 ± 9	31 ± 4	27 ± 5
38	32 ± 10	26 ± 6	26 ± 10
40	29 ± 9	25 ± 6	68 ± 126
42	28 ± 7	23 ± 4	29 ± 22
44	29 ± 7	19 ± 3**	20 ± 13
46	31 ± 9	19 ± 3**	26 ± 23
48	31 ± 7	15 ± 3**	15 ± 5**
50	25 ± 6	17 ± 3**	31 ± 39
52	23 ± 7	16 ± 3*	14 ± 7**
Postexposure			
2	30 ± 17	30 ± 12	42 ± 29
5	21 ± 10	25 ± 11	30 ± 28
9	20 ± 6	19 ± 2	30 ± 34
14	21 ± 3	23 ± 2	27 ± 16
33	49 ± 18	57 ± 30	61 ± 42
83	--	--	--
96	36 ± 10	48 ± 16	47 ± 29
121	32 ± 7	44 ± 23	57 ± 70
152	40 ± 17	55 ± 26	60 ± 46

** Significant at 0.01 level, control vs. test.
* Significant at 0.05 level, control vs. test.

TABLE 32. GROUP MEAN VALUES ± STANDARD DEVIATIONS OF ALKALINE PHOSPHATASE (IU/L) FOR DOGS EXPOSED TO HYDRAZINE FOR ONE YEAR

Week of Exposure	Unexposed Controls	0.25 ppm Exposure Group	1.0 ppm Exposure Group
-7	6.7 ± 2.0	7.5 ± 1.9	7.3 ± 2.7
-3	6.5 ± 1.8	6.5 ± 2.9	7.1 ± 2.9
-1	5.7 ± 1.4	6.4 ± 2.3	7.1 ± 4.2
2	5.8 ± 1.8	7.5 ± 3.3	7.4 ± 3.1
4	6.1 ± 1.4	5.1 ± 1.6	4.6 ± 2.0
6	5.3 ± 1.3	5.3 ± 1.5	5.7 ± 2.8
8	4.7 ± 1.3	5.4 ± 1.5	5.1 ± 2.4
10	6.2 ± 1.8	6.0 ± 1.8	6.9 ± 1.9
12	5.7 ± 1.9	7.1 ± 2.2	6.2 ± 2.6
14	5.3 ± 2.7	5.0 ± 1.3	5.1 ± 1.9
16	4.1 ± 1.3	5.1 ± 1.5	5.5 ± 2.6
18	3.6 ± 1.1	4.5 ± 1.4	5.1 ± 3.2
20	3.7 ± 0.9	5.3 ± 1.9*	5.5 ± 3.9
22	3.4 ± 0.9	4.9 ± 1.8	4.1 ± 1.9
26	3.9 ± 0.8	4.7 ± 1.4	4.7 ± 2.1
28	3.4 ± 0.6	3.9 ± 1.0	3.8 ± 1.6
30	3.9 ± 0.9	4.2 ± 1.3	4.4 ± 1.5
32	3.6 ± 1.1	4.4 ± 1.8	4.0 ± 1.9
34	3.7 ± 1.0	3.9 ± 1.6	4.2 ± 2.4
36	3.2 ± 0.5	3.1 ± 0.9	3.2 ± 1.6
38	4.0 ± 1.5	4.0 ± 1.2	3.6 ± 1.2
40	3.3 ± 0.8	3.7 ± 1.4	3.3 ± 1.1
42	3.7 ± 0.6	3.7 ± 1.0	3.6 ± 0.9
44	3.6 ± 0.8	3.4 ± 1.1	3.1 ± 0.7
46	3.7 ± 0.8	3.6 ± 1.0	3.1 ± 0.9
48	3.8 ± 0.7	3.7 ± 1.3	3.6 ± 0.8
50	3.7 ± 1.3	3.8 ± 1.4	3.2 ± 1.4
52	2.9 ± 1.0	3.7 ± 1.3	3.6 ± 2.1
Postexposure			
2	2.9 ± 0.8	4.4 ± 2.2	3.5 ± 1.5
5	4.0 ± 1.0	4.6 ± 0.7	4.2 ± 1.3
9	3.5 ± 1.0	5.4 ± 2.3	4.3 ± 1.8
14	3.3 ± 1.4	4.3 ± 1.4	3.7 ± 2.0
33	Lost	Lost	Lost
83	34.6 ± 25.5[1]	31.9 ± 11.2[1]	29.3 ± 25.0[1]
96	5.1 ± 3.2	8.2 ± 4.2	6.8 ± 5.0
121	4.0 ± 1.4	4.7 ± 2.8	3.6 ± 2.3
152	5.2 ± 2.9	7.3 ± 3.4	6.0 ± 3.3

** Significant at 0.01 level, control vs. test.
* Significant at 0.05 level, control vs. test.
[1] Different method of analysis used.

TABLE 33. GROUP MEAN VALUES ± STANDARD DEVIATIONS OF GLUCOSE (mg/dl) FOR DOGS EXPOSED TO HYDRAZINE FOR ONE YEAR

Week of Exposure	Unexposed Controls	0.25 ppm Exposure Group	1.0 ppm Exposure Group
-7	109 ± 6	105 ± 8	109 ± 8
-3	97 ± 5	98 ± 3	96 ± 13
-1	97 ± 10	94 ± 8	103 ± 11
2	108 ± 9	98 ± 8*	107 ± 5
4	116 ± 9	98 ± 6**	90 ± 7**
6	109 ± 4	90 ± 7**	97 ± 11**
8	113 ± 6	110 ± 8	93 ± 10**
10	109 ± 7	104 ± 7	95 ± 9**
12	107 ± 7	87 ± 9**	79 ± 6**
14	103 ± 6	95 ± 5*	88 ± 10**
16	103 ± 5	92 ± 5**	102 ± 7
18	105 ± 6	79 ± 7**	94 ± 7**
20	123 ± 6	116 ± 6*	117 ± 6
22	126 ± 9	103 ± 8**	113 ± 10*
26	132 ± 7	116 ± 7**	112 ± 8**
28	131 ± 5	115 ± 6**	110 ± 8**
30	127 ± 6	105 ± 7**	115 ± 5**
32	131 ± 6	113 ± 7**	105 ± 8**
34	129 ± 8	114 ± 4**	100 ± 11**
36	112 ± 6	105 ± 8	85 ± 10**
38	121 ± 9	102 ± 7**	91 ± 10**
40	115 ± 9	108 ± 5	109 ± 11
42	121 ± 6	111 ± 5**	102 ± 13**
44	114 ± 9	108 ± 6	87 ± 12**
46	120 ± 10	107 ± 10*	96 ± 14**
48	105 ± 8	101 ± 5	109 ± 7
50	122 ± 7	118 ± 9	111 ± 11*
52	98 ± 5	95 ± 8	110 ± 9**
Postexposure			
2	110 ± 7	104 ± 9	97 ± 8**
5	126 ± 8	117 ± 10	106 ± 13**
9	125 ± 7	114 ± 7	103 ± 15**
14	122 ± 8	122 ± 6	114 ± 11
33	97 ± 12	99 ± 6	96 ± 11
83	97 ± 3	93 ± 11	102 ± 10
96	104 ± 9	105 ± 7	107 ± 10
121	99 ± 6	101 ± 6	105 ± 8
152	95 ± 6	97 ± 9	98 ± 9

** Significant at 0.01 level, control vs. test.
* Significant at 0.05 level, control vs. test.

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