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Subchronic Oral Toxicity in Guinea Pigs of Soot
from a Polychlorinated Biphenyl-Containing Transformer Fire

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Subchronic Oral Toxicity in Guinea Pigs of Soot From a Polychlorinated Biphenyl-Containing Transformer Fire. DeCaprio, A.P., Silkworth, J.B., McMartin, D.M., Rej, R., Pause R., and Kaminsky, L.S. (1982). Toxicol. Appl. Pharmacol. 00, 000-000. We have previously described the acute oral toxicity in guinea pigs of soot from a transformer fire at the State Office Building in Binghamton, New York. The soot was determined to contain high ppm concentrations of polychlorinated biphenyls, biphenylenes, dibenzodioxins, and dibenzofurans. The present study evaluates soot toxicity in guinea pigs receiving 0, 0.2, 1.9, 9.3, or 46.3 ppm soot in the feed for 90 days or 231.5 ppm for 32 days. At 231.5 ppm, body weight loss, thymic atrophy, bone marrow depletion, skeletal muscle and gastrointestinal tract epithelial degeneration, and fatty infiltration of hepatocytes were observed. Mortality had reached 35% by day 32 when survivors were killed, with total soot consumption of approximately 400 mg/kg. At 46.3 or 9.3 ppm soot a reduced rate of body weight gain was observed, with 30% mortality by day 90 at 46.3 ppm. Relative (to body) thymus weights were decreased in both groups, while relative spleen weights were increased at 46.3 ppm soot only. Salivary gland interlobular duct squamous metaplasia and focal lacrimal gland adenitis were detected histopathologically, while bone marrow depletion was noted only in females at the higher dose. Diminished serum alanine aminotransferase (ALT) activity in both sexes and decreased serum sodium levels in male and potassium levels in female animals were detected at both dose levels. Decreased γ -glutamyl transferase activity and red blood cell count, and elevated serum creatinine and triglycerides were observed only in animals fed 46.3 ppm soot. At 1.9 ppm soot, salivary gland duct metaplasia was observed in both sexes, along with decreased relative thymus weights, ALT activity, and serum sodium levels in male animals only. No effects attributable to soot exposure

were noted in animals receiving 0.2 ppm soot for 90 days. Total soot consumption in the 0.2, 1.9, 9.3, and 46.3 ppm dosage groups was 1.2, 12, 55, and 275 mg/kg, respectively. Although many of the observed effects were typical of acute exposure of guinea pigs to the Binghamton soot or to polychlorinated aromatic hydrocarbons in general, salivary gland duct metaplasia has not been previously reported. The results suggest a possibly increased toxicity of the soot in guinea pigs during prolonged as opposed to acute exposure, although variations in absorption due to effects of different vehicles (aqueous in the acute study versus the feed in this study) could account for some or all of this difference.

On February 5, 1981, a transformer fire in the State Office Building in Binghamton, New York resulted in the dispersal of a soot-like combustion product throughout the building. The dielectric and coolant fluid within the transformer was composed of the polychlorinated biphenyl (PCB) mixture Aroclor 1254 (65%), chlorinated benzenes (35%), and other trace additives. The building was subsequently closed and extensive hazard assessment and clean-up operations were begun. Chemical analysis of the soot revealed the presence of numerous congeners and isomers of polychlorinated biphenyls, naphthalenes, biphenylenes, dibenzofurans (PCDFs), and dibenzodioxins (PCDDs) (Stalling, 1981; Smith et al., 1982a). Based on an estimated PCDF content of 5 ppm in a sample of Aroclor 1254 similar to that present in the transformer fluid (Stalling, 1981), and on the analyzed PCDF and PCB contents of 320 and 5000 ppm, respectively, in an average soot sample (Smith et al., 1982b; Eadon et al., 1982), the pyrolysis of the fluid apparently resulted in a very substantial concentration increase of highly toxic PCDFs in the soot.

This incident is an example of what could be a significant public health problem since such PCB-filled transformers are widely utilized. Although PCDFs and PCDDs are among the compounds formed during combustion of PCBs (Buser et al., 1978), electrical capacitor fires (Jansson and Sundstrom, 1982), and incineration of municipal waste (Olie et al., 1977), there are few reports on the toxicological effects of such complex pyrolysates. Animal toxicity studies with the Binghamton soot were therefore initiated with the ultimate aim of developing risk assessment data for subsequent clean-up operations and reoccupation of the contaminated building. The complex chemical nature of the soot precluded hazard estimation based on the known toxicity of individual components, since not all components could be detected and quantitated, and because of the potential for synergistic or antagonistic effects. Acute toxicity studies of

the soot in guinea pigs, the species most sensitive to toxic effects of PCDFs and PCDDs (Kociba and Schwetz, 1982), indicated an oral LD50 of 410 mg/kg (Silkworth et al., 1982). A similar value was obtained with an organic extract of the soot, suggesting that the soot matrix did not affect the toxicity of the bound toxic components. A variety of dose-related pathological changes were observed, including pancreatic duct hyperplasia, salivary gland metaplasia, thymic atrophy, elevated serum triglycerides, and body weight loss. Similar effects have been reported during exposure to purified PCDDs (McConnell et al., 1978) and PCDFs (Moore et al., 1979). These acute studies indicated that the toxicity of the soot could not be ascribed solely to effects of the extremely toxic 2,3,7,8-TCDD and 2,3,7,8-TCDF isomers, but that other soot contaminants were major contributors to its overall toxicity.

The present investigation was designed to evaluate the subchronic oral toxicity of the soot in guinea pigs in order to establish a no-effect level and to determine target organs for risk assessment. An additional aim was to compare the effects of low-level, cumulative exposure to the soot with those produced by single acute exposures. The lack of data on subchronic exposure of guinea pigs to chlorinated aromatic hydrocarbons made dose selection difficult. Metabolism and excretion of 2,3,7,8-TCDD and 2,3,7,8-TCDF in the guinea pig are very slow, indicating that the toxicity of these compounds may be cumulative (Gasiewicz and Neal, 1979; Decad et al., 1981). LD50 values of 2,3,7,8-TCDD in this species were similar when the compound was given in either a single oral dose (McConnell et al., 1978), or in 4 weekly oral doses (Harris et al., 1973). These results suggested that cumulative mortality in guinea pigs fed soot might approach 50% after approximately 410 mg/kg had been ingested. Based on these considerations soot was incorporated into the feed in five dosage groups ranging from 0.2 to 231.5 ppm.

METHODS

Animals and dosing. Male (250-350 g) and female (200-350 g) Hartley guinea pigs were obtained from a colony maintained in this center. Animals were randomly assigned to six dosage groups of 10 males and 10 females each, and were acclimated to a 12-hr on 12-hr off light cycle for 1 week. Room temperature was maintained at 22-24°C and relative humidity at 40-60%. Animals were housed individually in plastic cages (19 X 10.5 X 8 in.) on hardwood chips and were identified by numbered ear tags. Cages were equipped with polyester filter cage covers (Hazleton Systems, Inc., Aberdeen, Md.) to prevent cross-contamination.

Samples of soot were collected from stairwells of the third and fourth floors of the Binghamton, New York State Office Building and sieved through No. 40 copper wire mesh to remove inert debris. Sieved soot was incorporated into certified guinea pig chow (NIH-34) by a commercial feed processor (Zeigler Bros., Inc., Gardners, Pa), at concentrations of 0.2, 1.9, 9.3, 46.3, and 231.5 ppm. Groups received formulated or control feed and municipal tap water ad libitum for 90 days.

Observation and necropsy. Animals were evaluated daily for clinical signs of toxicity. Food consumption and body weights were measured weekly and the cumulative soot consumption was calculated. All surviving animals were killed at 90 days by CO₂ asphyxiation and subjected to complete necropsy. Major organs were weighed, and samples from 32 tissues were fixed in 10% neutral phosphate buffered formalin. Tissues were processed by standard paraffin techniques and sections stained with hematoxylin and eosin. Samples of blood and bladder urine were taken for clinical chemistry and hematological analysis.

Clinical chemistry. Serum enzymes (except sorbitol dehydrogenase) and triglycerides were determined using methods previously cited (Silkworth et al., 1982). Sorbitol dehydrogenase was determined by the method of Rose

and Henderson (1975). Bilirubin, total protein, albumin, creatinine, blood urea nitrogen (BUN), and glucose were determined with methods routinely used at this center. Sodium and potassium levels were determined by flame emission spectroscopy and calcium with atomic absorption spectroscopy. Serum chloride was measured with a Buchler Chloridometer. Urine pH, protein, glucose, ketones, and occult blood cell contents content were determined using Chemstrip 5 (Bio-Dynamics, Inc., Indianapolis, IN) reagent sticks. Urine specific gravity was measured by refractometry.

Chemical analysis of PCB concentrations in formulated feed. Assessment of actual concentrations of soot and of the homogeneity of its incorporation into guinea pig feed was performed using Aroclor 1254 concentration as an indicator for the soot. Samples (5 g) of feed were subjected to exhaustive soxhlet extraction in 1:1 acetone:hexane for 24 hr. Extracts were analyzed for PCB using packed column gas chromatography with electron capture detection (New York State Dept. of Health, 1982). Levels of incorporation were calculated based on an Aroclor 1254 concentration of 5000 ppm in the original soot (Eadon et al., 1982).

RESULTS

Soot incorporation into feed. Aroclor 1254 concentrations in the 231.5 and 46.3 ppm soot formulated feed levels were 1.10 and 0.27 $\mu\text{g/g}$ feed, respectively, compared with calculated values of 1.16 and 0.23 $\mu\text{g/g}$. Interfering extractants precluded the estimation of Aroclor concentrations in the 0.2, 1.9, and 9.3 ppm formulated feeds. Five samples from different regions of a barrel containing the 46.3 ppm feed were individually analyzed to determine homogeneity of soot incorporation. The mean and standard error for Aroclor concentration was 0.28 ± 0.02 $\mu\text{g/g}$ feed, with a range of 0.24 to 0.34 $\mu\text{g/g}$ feed.

Fig. 1 Clinical signs of toxicity. Both male (Fig. 1a) and female (Fig. 1b) animals displayed dose-related diminished body weight gain as compared to control animals. This effect was statistically significant ($p < 0.05$) in the 46.3 and 9.3 ppm dosage groups. Animals receiving 231.5 ppm soot in the feed exhibited a severe net body weight loss probably due to both decreased food consumption and toxic effects of the soot. Seven animals in this group died between days 28 and 31 of the study, and the surviving animals were killed and necropsied at 32 days. Food consumption (g/kg/day) in all other dose groups was not significantly different from that of the control group. Animals receiving food with 46.3 ppm soot began to show net body weight loss in the final week of the study. Three male and three female animals from this group died during the course of the study with gross pathology reflecting emaciation. Of these animals, two males and one female exhibited moderate to severe pneumonia. Deaths of one male control animal at 76 days and one male animal in the 9.3 ppm group at 32 days were due to pneumonia.

Body weights and estimated total soot consumption for each treatment group are shown in Table 1. Soot consumption in the 231.5 ppm dosage group had

approached the acute LD50 value of 410 mg/kg. The cumulative mortality of this group had reached 35% at the time of necropsy and all remaining animals were moribund. Total soot consumption in the 46.3, 9.3, 1.9, and 0.2 ppm groups represented approximately 67, 13, 3, and 0.3% of the acute oral LD50 dose, respectively, at termination.

On day 30, mold was detected in several barrels of the commercially-formulated control and soot-containing feeds. This mold was identified as several non-pathogenic strains of Aspergillus glaucus. Measures taken to eliminate the mold included the removal of contaminated feed from the metal feeders, cleaning and sterilization of these feeders, reduction of room humidity, and refrigeration of remaining feed stocks. No alterations in general health or food consumption in animals exposed to the mold were noted.

Gross pathology. Gross pathology in animals administered 231.5 ppm soot for 32 days or 46.3 ppm soot for 90 days consisted of varying degrees of emaciation and thymic atrophy. Gross observations in animals receiving 0.2, 1.9, or 9.3 ppm soot for 90 days were normal with the exception of thymic atrophy in males at 1.9 and in both sexes at 9.3 ppm. No grossly observable effects were noted in animals receiving 0.2 ppm soot.

Organ weights. Absolute organ weights of treated and control animals are summarized in Table 2. Organ weights in the 231.5 ppm dose group were not determined due to lack of suitable controls for comparison. Significant dose-related decreases were observed in absolute brain, liver, thymus, kidney, adrenal, and testes weights in males, and absolute thymus, kidney, and adrenal weights in females as compared to control weights. Thymus weight was a sensitive indicator of toxicity in male animals, with a significant decrease present at the 1.9 ppm level as compared to controls. Since absolute organ weights frequently reflect

body weight changes rather than specific target organ toxicity (Feron et al., 1973; Schärer, 1977), relative (to body weight) organ weights were also calculated (Table 3). Significant increases in the organ/body weight ratio were observed for brain, spleen, and testes. In contrast, decreases were observed in thymus/body weight ratios at the two highest dose levels in females and the three highest levels in males. No alterations in absolute or relative organ weights were observed in animals receiving 0.2 ppm soot.

Hematology. Dose-related hematological alterations relative to controls were observed only in animals at the 46.3 ppm dose level (Table 4). Erythrocyte counts were decreased in animals from both sexes in this dosage group and white cell counts and packed cell volume were lowered in females. Although these values were significantly different from control, they were generally within published normal ranges (Mitruka and Rawnsley, 1981). No alterations in white blood cell differential counts were noted.

Serum Chemistry. Serum alanine aminotransferase and γ -glutamyl transferase activities were decreased by soot exposure (Table 5). Activity of alanine aminotransferase decreased in a dose-related manner in male animals receiving 1.9, 9.3, and 46.3 ppm and in female animals at 9.3 and 46.3 ppm. Activity of γ -glutamyl transferase was depressed in male and female animals at the 46.3 ppm dose level. The decreases in serum enzyme levels observed at the higher doses are in contrast to effects expected from organ damage, and probably instead reflect decreases in organ and muscle mass. Results of other serum chemistry determinations are summarized in Table 6. Serum sodium levels were significantly lowered in male animals at the 1.9, 9.3, and 46.3 ppm dose levels, and potassium levels were decreased in female animals at 9.3 and 46.3 ppm. Serum triglyceride levels were significantly increased in animals receiving 46.3 ppm soot.

A relatively high triglyceride level in female control animals probably contributed to an apparently significant decrease in this component in serum from females receiving 0.2, 1.9, and 9.3 ppm soot. This decrease was not dose related and is thus unlikely to reflect soot exposure. Serum creatinine was significantly elevated in male and female guinea pigs at the 46.3 ppm dose level. Urinalysis did not reveal any alterations in pH or specific gravity attributable to soot exposure. No abnormal levels of protein, glucose, ketones, or red blood cells were detected in the urine of animals treated for 90 days.

Microscopic pathology. All tissues were examined for pathological alterations in the control, 9.3, 46.3, and 231.5 ppm dosage groups. The only tissues examined in the 0.2 and 1.9 ppm dosage groups were those identified as target tissues in the acute studies (Silkworth *et al.*, 1982), or which exhibited lesions at the three upper dose levels in the present study. A variety of dose-related pathological changes were observed in guinea pigs receiving Binghamton soot in the feed (Tables 7 and 8). Metaplasia of salivary gland interlobular duct epithelium was present in animals receiving 1.9, 9.3, or 46.3 ppm soot for 90 days or 231.5 ppm for 32 days (Fig. 2). All female animals at the 46.3 ppm dose level exhibited this lesion after 90 days. Epithelium having a severity grade of +1 was thickened by proliferating cells similar to those of the stratum spinosum of the skin. The lesion had progressed to squamous metaplasia in the 46.3 ppm group, with flattening and occasional keratinization of superficial epithelial cells (severity grade +2). Pancreatic duct goblet cell hyperplasia was frequently observed in male animals fed 46.3 ppm soot for 90 days and 231.5 ppm soot for 32 days. Goblet cells were considered hyperplastic when they occupied more than one-half of the circumference of the duct epithelium. Hyperplastic epithelium contained excessive numbers of goblet cells and was 25 to 35 μ m high

in contrast to the normal height of 10 to 17 μm . Although this lesion was also observed in female animals, its significance is questionable, since it was observed in 20% of female controls but not in male controls. Focal lacrimal gland adenitis was found in male animals at the 9.3, 46.3, and 231.5 ppm dose levels, and in female animals at the upper two dose levels. This was in contrast to the results of acute dosing, where the lesion was also observed in control animals (Silkworth et al., 1982). Depletion of hematopoietic cells from bone marrow (Fig. 3) was noted in 29% of female animals receiving 46.3 ppm soot for 90 days. Such depletion was also observed and was more severe in male and female animals receiving 231.5 ppm soot for 32 days. Focal interstitial nephritis was present in all groups after 90 days. This lesion was not observed in animals at the high dose level of 231.5 ppm after 32 days.

Solid or ring-shaped hyaline-like hepatocellular cytoplasmic inclusions were present primarily in animals receiving 9.3 and 46.3 ppm soot, but not in animals at the highest dose level. The number of inclusions ranged from approximately 4 to 10 per liver section (severity grade +1) to at least 10 per 250X microscopic field (severity grade +3). Focal hepatic necrosis similar to that described in normal guinea pigs by Cuba-Caparo and Myers (1977) was noted in animals from every group, including the control group. These lesions were also observed in previous acute studies (Silkworth et al., 1982) and were considered of no toxicological significance. Degenerative changes of skeletal muscle were present in two female animals in the 46.3 ppm group which died two weeks prior to completion of the study and in a male animal in the 231.5 ppm group. These lesions displayed shrunken fibers with the occasional loss of striations, proliferation of myoblasts, and foci of mineralization.

A variety of other pathological alterations were noted only in animals receiving 231.5 ppm soot for 32 days. Fatty infiltration was observed in liver from 57% of the male and 51% of the female animals at this dose level. Hepatocytes with fatty infiltration were scattered throughout the lobule and comprised 10 to 50% of the cells contained in a section. Degenerative changes of the stomach and intestine were occasionally seen in males from this group. These lesions consisted of mildly dilated crypts and a moderate number of pyknotic cells in the mucosa. Thinning of the thymic cortex was apparent in several animals receiving 231.5 ppm soot.

DISCUSSION

We have previously reported a spectrum of clinical and pathological effects in guinea pigs exposed to acute, oral doses of transformer-fire soot from the Binghamton State Office Building (Silkworth et al., 1982). Generally the effects were typical of those observed after acute exposure to chlorinated aromatic hydrocarbons (McConnell et al., 1978; Moore et al., 1979). The present report describes findings in guinea pigs receiving soot in the feed for 90 days. Toxic effects were seen at lower total dose levels of soot as compared with effects of acute exposure. These effects, which included thymic atrophy and salivary gland duct metaplasia, were observed in male animals receiving a total of 12 mg soot/kg, or 0.13 mg soot/kg/day. Salivary gland metaplasia was also noted in female guinea pigs at this dose. In contrast, an acute oral dose of 10 mg soot/kg produced no detectable toxicological effects, and a dose of 100 mg soot/kg resulted only in elevated serum triglycerides in male animals and thymic atrophy in female animals. Although these comparisons suggest an increased toxicity of soot components with prolonged exposure, variations in absorption due to the effects of the different vehicles (aqueous in the acute study versus the feed in this study) could account for some or all of this difference. Higher dose levels of soot produced toxic effects not predicted from the acute dosing studies. Spleen to body weight ratios were significantly increased in animals receiving 46.3 ppm soot. This increase probably represents a direct toxic effect and was not secondary to body weight changes, since spleen/body weight ratios usually decrease during restricted weight gain (Feron et al., 1973; Schärer, 1977). Bone marrow depletion and decreased erythrocyte counts were noted in animals at this dose level and thus the increased relative spleen weight might represent an adaptive response by the organ to provide an alternate

hematopoietic center. Similar changes have been reported in rats receiving oral doses of 2,3,7,8-TCDD for 90 days (Kociba et al., 1976). Brain/body and testes/body relative organ weight changes most likely reflect decreased body weight gain rather than specific organ toxicity.

There are no reports concerning subchronic or chronic toxicity of PCDDs or PCDFs in guinea pigs. It is therefore difficult to compare the subchronic toxicity of the Binghamton soot with known effects of its components and comparisons can only be based on the well-characterized effects of acute exposure (McConnell et al., 1978; Gasiewicz and Neal, 1979; Huff et al., 1980). Thymic atrophy, bone marrow hypoplasia, and decreased body weight gain are typically encountered during acute PCDD and PCDF exposure in guinea pigs, and such effects were prominent in animals receiving Binghamton soot for 90 days. Elevated serum triglycerides are also indicative of acute polychlorinated aromatic hydrocarbon exposure in guinea pigs, and may reflect altered utilization of exogenous nutrients. Such increased levels were observed during acute exposure to the Binghamton soot and in animals fed 46.3 ppm soot for 90 days. Body weight gain was significantly lower in the 9.3 and 46.3 ppm groups as compared to control rates. Feed consumption in animals administered soot was not different from that of control animals, indicating that the decreased weight gain was a toxic effect rather than a reflection of reduced nutrient intake. Thymic atrophy was probably the most reliable indicator of soot toxicity, since it was apparent at a low dose level (1.9 ppm in male animals) and was highly correlated with total soot exposure. Decreased thymus weights indicate the potential for diminished immune response as a result of exposure to these compounds (McConnell et al., 1978). Although cellular depletion was not marked in the thymus of treated animals, thinning of thymic cortex was confirmed in several animals

receiving 231.5 ppm soot for 32 days. Alterations in the immune response and thymic atrophy have been reported in experimental animals after exposure to 2,3,7,8-TCDD (Vos et al., 1973) and 2,3,7,8-TCDF (Luster et al., 1979).

Guinea pigs receiving 231.5 ppm Binghamton soot in the feed for 32 days exhibited additional lesions characteristic of acute exposure to these compounds, including skeletal muscle degeneration, fatty change in hepatocytes, and degeneration of gastrointestinal tract epithelium. In contrast, other commonly reported effects (e.g., renal pelvis hyperplasia, adrenal hemorrhage, and testicular atrophy) were not marked in guinea pigs fed Binghamton soot.

Other clinical and pathological effects observed in the present study have not previously been reported in guinea pigs exposed acutely to purified PCDD or PCDF congeners. The elevated serum creatinine levels observed in animals receiving 46.3 ppm soot suggests an impairment of glomerular filtration, although indicators of glomerular pathology (e.g., elevated BUN and serum sodium) were not observed. Lowered serum sodium levels in male and potassium levels in female animals are also not characteristic of PCDD or PCDF exposure in guinea pigs. The significance and mechanism of these serum alterations remains obscure. Salivary gland duct epithelium metaplasia was also highly correlated with soot exposure. This lesion may be species-specific, since it was not reported in rats fed pure 2,3, 7,8-TCDD for 90 days (Kociba et al., 1976) or two years (Kociba et al., 1978).

Lethality due to soot exposure was encountered in the 46.3 and 231.5 ppm dosage groups. Animals in the highest dosage group exhibited a progressive body weight loss similar to that observed during acute dosing regimens. Seven animals (35%) in this group died after consuming approximately 400 mg soot/kg, although it is likely that all the remaining animals would have died within a

short time thereafter. In addition, the rapid weight loss observed in this group suggests that the total dose required for lethality had actually been consumed much earlier in the study. In the 46.3 ppm dose group, lethality reached 30% after consumption of approximately 225 mg soot/kg. These results can be compared with the acute LD50 value of 410 mg soot/kg. Based on chemical analyses of the soot (Smith et al., 1982b), the amount of soot consumed by animals at the 46.3 ppm dose level would result in a dose of 0.27 µg 2,3,7,8-TCDD/kg and 11 µg 2,3,7,8-TCDF/kg, while total exposure to these compounds at the 1.9 ppm dose level would be 14 and 580 ng/kg, respectively. As a basis for comparison, LD50 values in guinea pigs have been reported as 0.6-2.5 µg/kg for 2,3,7,8-TCDD (Schwetz et al., 1973; Silkworth et al., 1982) and 5-10 µg/kg for 2,3,7,8-TCDF (Huff et al., 1980). It is apparent that many of the other soot components must have contributed to the observed toxicity at low dose levels. Chemical analysis of the soot has revealed the presence of many additional PCDD and PCDF congeners along with potentially toxic polychlorinated biphenyls, biphenylenes, and naphthalenes (Stalling, 1981; Smith et al., 1982b).

Results from the present investigation have indicated a possible enhanced toxicity of Binghamton State Office Building soot in guinea pigs during prolonged versus acute exposure. A total dose of 1.2 mg soot/kg (0.013 mg/kg/ day) was determined to produce no toxic effects. Higher doses produced effects generally attributable to exposure to polychlorinated aromatic hydrocarbons, although some observed changes have not been previously reported as effects of these compounds. A comparison of the acute oral LD50 value of the soot in guinea pigs with that of pure 2,3,7,8-TCDD indicated that the acute toxicity of the soot was

equivalent to that which would be produced by a dose of soot containing 58 ppm 2,3,7,8-TCDD (Eadon et al., 1982). Based on this calculation, soot consumption at the no-effect level in this study resulted in a total intake of toxic components equivalent to a dose of 70 ng 2,3,7,8-TCDD/kg (0.78 ng/kg/day). Thus, the toxic dose of soot at the lowest effect level was equivalent to 700 ng 2,3,7,8-TCDD/kg (7.8 ng/kg/day). This contrasts with data from rats, where a total dose of 650 ng 2,3,7,8-TCDD/kg given over 90 days produced no toxic effects (Kociba et al., 1976). A preliminary study has revealed no overt toxicity in rats fed 231.5 ppm Binghamton soot for 35 days, confirming the lower sensitivity of this species to toxic soot components. The guinea pig has proved extremely sensitive to toxicity induced by exposure to the Binghamton soot, and may therefore be useful in providing further data for hazard assessment.

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Table 1

Body Weights and Soot Consumption in Guinea Pigs After 90-Day Administration of Binghamton Soot in the Feed

Dose	Sex	Body weight ^a (g)	% of initial body weight	Daily soot consumption (mg/kg/day)	Total soot consumption (mg/kg)
Control	M	712 ± 27 (9)	209	---	---
	F	594 ± 15 (10)	183	---	---
0.2 ppm	M	734 ± 17 (10)	204	0.013	1.2
	F	591 ± 19 (10)	185	0.013	1.2
1.9 ppm	M	663 ± 29 (10)	181	0.13	11.7
	F	605 ± 23 (10)	177	0.13	11.9
9.3 ppm	M	596 ± 30 (9)	157 ^c	0.62	56.1
	F	551 ± 23 (10)	161 ^b	0.59	53.0
46.3 ppm	M	498 ± 25 (7)	130 ^d	2.76	248.6
	F	423 ± 37 (7)	128 ^d	3.33	299.6
231.5 ppm ^e	M	288 ± 17 (6)	77 ^d	~12.9	~400
	F	235 ± 14 (7)	71 ^d	~12.9	~400

^a Values expressed as $\bar{X} \pm$ standard error (n).

^b Significantly different from control (Student's t-test), $p < 0.05$.

^c $p < 0.01$

^d $p < 0.001$

^e Necropsy at 32 days. Statistical comparisons made using control animal weights at day 32.

Table 2

Absolute Organ Weights in Guinea Pigs Fed Binghamton Soot for 90 Days

Absolute Organ Weights (g) ^a								
Dose	Sex	Brain	Liver	Spleen	Thymus	Kidney	Adrenal	Testes
Control	Male	3.721 ± 0.047	35.936 ± 5.681	0.601 ± 0.023	0.455 ± 0.039	4.588 ± 0.170	0.267 ± 0.011	4.523 ± 0.159
0.2 ppm		3.761 ± 0.050	27.609 ± 1.530	0.587 ± 0.055	0.480 ± 0.032	4.737 ± 0.218	0.299 ± 0.015	4.549 ± 0.189
1.9 ppm		3.757 ± 0.054	31.081 ± 2.660	0.596 ± 0.037	0.351 ± 0.026 ^b	4.246 ± 0.176	0.276 ± 0.016	4.505 ± 0.169
9.3 ppm		3.570 ± 0.053 ^b	31.230 ± 2.269	0.598 ± 0.046	0.254 ± 0.021 ^d	3.910 ± 0.125 ^c	0.237 ± 0.012	3.741 ± 0.220 ^b
46.3 ppm		3.531 ± 0.032 ^c	23.058 ± 1.700 ^b	0.601 ± 0.034	0.212 ± 0.015 ^d	3.375 ± 0.134 ^d	0.206 ± 0.016 ^c	3.575 ± 0.163 ^d
Control	Female	3.598 ± 0.060	24.221 ± 2.922	0.737 ± 0.047	0.674 ± 0.028	4.017 ± 0.171	0.239 ± 0.011	
0.2 ppm		3.708 ± 0.076	24.145 ± 2.766	0.696 ± 0.046	0.624 ± 0.050	3.911 ± 0.138	0.240 ± 0.011	
1.9 ppm		3.619 ± 0.037	25.706 ± 1.806	0.708 ± 0.042	0.645 ± 0.053	4.063 ± 0.199	0.253 ± 0.015	
9.3 ppm		3.600 ± 0.046	26.410 ± 2.115	0.582 ± 0.025 ^c	0.535 ± 0.032 ^c	3.560 ± 0.111 ^b	0.197 ± 0.007 ^c	
46.3 ppm		3.398 ± 0.076	21.849 ± 1.138	0.674 ± 0.044	0.261 ± 0.040 ^d	3.116 ± 0.183 ^c	0.173 ± 0.010 ^d	

^a Values expressed as $\bar{x} \pm$ standard error.

^b Significantly different from control (Student's t-test), $p < 0.05$

^c $p < 0.01$.

^d $p < 0.001$.

Table 3

Relative Organ Weights in Guinea Pigs Fed Binghamton Soot for 90 Days

Relative Organ Weights (g/g body weight X 100) ^a								
Dose	Sex	Brain	Liver	Spleen	Thymus	Kidney	Adrenal	Testes
Control	Male	0.529 ± 0.020	5.156 ± 0.897	0.085 ± 0.005	0.064 ± 0.004	0.647 ± 0.019	0.038 ± 0.002	0.640 ± 0.026
0.2 ppm		0.515 ± 0.015	3.749 ± 0.151	0.080 ± 0.007	0.065 ± 0.004	0.644 ± 0.020	0.041 ± 0.002	0.619 ± 0.017
1.9 ppm		0.575 ± 0.022	4.899 ± 0.662	0.090 ± 0.005	0.052 ± 0.002 ^b	0.643 ± 0.011	0.042 ± 0.002	0.683 ± 0.016
9.3 ppm		0.611 ± 0.030 ^b	5.370 ± 0.550	0.102 ± 0.009	0.043 ± 0.002 ^d	0.662 ± 0.019	0.040 ± 0.002	0.628 ± 0.020
46.3 ppm		0.723 ± 0.044 ^c	4.630 ± 0.240	0.122 ± 0.007 ^c	0.041 ± 0.003 ^d	0.681 ± 0.014	0.041 ± 0.002	0.721 ± 0.019 ^b
Control	Female	0.609 ± 0.016	4.076 ± 0.503	0.124 ± 0.007	0.114 ± 0.004	0.676 ± 0.020	0.040 ± 0.001	
0.2 ppm		0.635 ± 0.027	4.138 ± 0.619	0.118 ± 0.007	0.105 ± 0.006	0.664 ± 0.017	0.041 ± 0.002	
1.9 ppm		0.605 ± 0.021	4.227 ± 0.184	0.119 ± 0.011	0.106 ± 0.007	0.672 ± 0.020	0.042 ± 0.002	
9.3 ppm		0.662 ± 0.027	4.853 ± 0.445	0.106 ± 0.004 ^b	0.097 ± 0.003 ^b	0.650 ± 0.015	0.036 ± 0.001 ^b	
46.3 ppm		0.841 ± 0.074 ^d	5.496 ± 0.687	0.162 ± 0.007 ^c	0.060 ± 0.006 ^d	0.752 ± 0.031	0.042 ± 0.003	

^a Values expressed as $\bar{x} \pm$ standard error.

^b Significantly different from control (Student's t-test), $p < 0.05$

^c $p < 0.01$.

^d $p < 0.001$.

Table 4

Hematological Values in Guinea Pigs Fed Binghamton Soot for 90 Days^a

Dose	Sex	Red Cell Count ($\times 10^6/\text{mm}^3$)	White Cell Count ($\times 10^3/\text{mm}^3$)	Platelet Count ($\times 10^4/\text{mm}^3$)	Packed Cell Volume (%)
Control	Male	5.95 \pm 0.20	5.67 \pm 0.80	25.00 \pm 2.43	48.0 \pm 1.1
0.2 ppm		5.24 \pm 0.13 ^c	6.90 \pm 0.81	e.n.d.	47.7 \pm 0.7
1.9 ppm		5.90 \pm 0.18	7.48 \pm 1.42	19.83 \pm 2.74	47.7 \pm 0.8
9.3 ppm		5.34 \pm 0.21	7.31 \pm 1.09	23.00 \pm 4.64	44.0 \pm 1.0 ^b
46.3 ppm		5.17 \pm 0.18 ^b	3.79 \pm 0.41	17.57 \pm 2.51	43.9 \pm 3.2
Control	Female	5.50 \pm 0.14	7.80 \pm 1.08	29.78 \pm 5.07	43.9 \pm 0.8
0.2 ppm		4.83 \pm 0.15 ^c	6.93 \pm 0.89	e.n.d.	46.1 \pm 0.6 ^b
1.9 ppm		5.31 \pm 0.12	6.53 \pm 1.09	18.40 \pm 1.63 ^b	45.2 \pm 1.2
9.3 ppm		5.17 \pm 0.13	5.18 \pm 0.65	27.10 \pm 2.77	43.8 \pm 0.7
46.3 ppm		5.04 \pm 0.15 ^b	4.57 \pm 0.67 ^b	26.00 \pm 1.76	39.1 \pm 0.7 ^d

^a Values expressed as $\bar{X} \pm$ standard error.

^b Significantly different from control (Student's t-test), $p < 0.05$.

^c $p < 0.01$.

^d $p < 0.001$.

^e not determined.

Table 5

Serum Enzyme Values^a from Guinea Pigs Receiving Binghamton Soot for 90 Days

Dose	Sex	Lactate Dehydrogenase (uM/min/L)	Aspartate Aminotransferase (uM/min/L)	Alanine Aminotransferase (uM/min/L)	γ -Glutamyl Transferase (uM/min/L)	Alkaline Phosphatase (uM/min/L)	Sorbitol Dehydrogenase (uM/min/L)
Control	Male	250 \pm 42	60 \pm 11	65 \pm 11	11.4 \pm 1.2	103.2 \pm 7.3	93 \pm 19
0.2 ppm		237 \pm 29	62 \pm 9	41 \pm 4	10.8 \pm 0.2	112.0 \pm 12.2	70 \pm 17
1.9 ppm		289 \pm 39	69 \pm 12	39 \pm 2 ^b	10.7 \pm 1.0	92.0 \pm 10.1	80 \pm 21
9.3 ppm		309 \pm 60	74 \pm 18	27 \pm 3 ^c	9.0 \pm 0.5	105.2 \pm 6.8	68 \pm 17
46.3 ppm		251 \pm 37	47 \pm 6	25 \pm 3 ^c	8.2 \pm 0.3 ^b	107.6 \pm 11.1	56 \pm 7
Control	Female	226 \pm 24	49 \pm 8	33 \pm 2	10.5 \pm 0.7	106.7 \pm 5.0	84 \pm 17
0.2 ppm		174 \pm 22	48 \pm 6	23 \pm 1 ^d	8.9 \pm 0.8	101.1 \pm 3.3	49 \pm 9
1.9 ppm		157 \pm 7 ^b	40 \pm 3	27 \pm 3	8.2 \pm 0.4 ^c	105.1 \pm 8.1	57 \pm 7
9.3 ppm		221 \pm 55	58 \pm 16	22 \pm 1 ^d	9.1 \pm 0.3	117.2 \pm 9.1	99 \pm 34
46.3 ppm		189 \pm 15	53 \pm 15	20 \pm 2 ^d	8.4 \pm 0.5 ^b	103.4 \pm 6.9	51 \pm 7

^a Data expressed as $\bar{x} \pm$ standard error, n = 5 to 10 per group.^b Significantly different from control (Student's t-test), p < 0.05.^c p < 0.01.^d p < 0.001.

Table 6

Serum Chemistry Values^a from Guinea Pigs Receiving Binghamton Soot for 90 Days

Dose	Sex	Bilirubin (mg/dl)	Glucose (mg/dl)	BUN (mg/dl)	Total protein (g/dl)	Albumin (g/dl)	Globulin (g/dl)	Na ⁺ (mEq/l)	K ⁺ (mEq/l)	Ca ⁺⁺ (mg/dl)	Cl ⁻ (mEq/l)	Triglycerides (mg triolein equivalent/dl)	Creatinine (mg/dl)
Control		0.2 ± 0.0	175 ± 19	26 ± 1	5.4 ± 0.1	3.5 ± 0.1	1.9 ± 0.1	147 ± 1	10.4 ± 0.3	13.2 ± 0.2	107 ± 1	94 ± 8	0.5 ± 0.0
0.2 ppm	Male	0.3 ± 0.0	250 ± 13	22 ± 1	5.4 ± 0.1	3.6 ± 0.1	2.0 ± 0.1	143 ± 2	10.3 ± 0.4	13.5 ± 0.1	106 ± 1	98 ± 23	0.5 ± 0.0
1.9 ppm		0.0 ± 0.0 ^d	203 ± 11	25 ± 1	6.4 ± 0.4 ^c	3.6 ± 0.3	2.8 ± 0.4 ^c	141 ± 1 ^c	10.4 ± 0.2	13.6 ± 0.1	105 ± 1	93 ± 7	0.6 ± 0.0
9.3 ppm		0.2 ± 0.0	192 ± 12	23 ± 1	5.3 ± 0.1	3.4 ± 0.1	1.9 ± 0.1	139 ± 2 ^c	9.7 ± 0.3	13.0 ± 0.1	104 ± 1 ^b	127 ± 16	0.5 ± 0.0
46.3 ppm		0.2 ± 0.0	223 ± 14	26 ± 1	5.2 ± 0.1	3.5 ± 0.1	1.9 ± 0.1	140 ± 2 ^b	9.4 ± 0.5	13.1 ± 0.2	105 ± 1	176 ± 22 ^c	0.7 ± 0.0 ^c
Control	Female	0.2 ± 0.0	221 ± 16	23 ± 1	5.5 ± 0.1	3.5 ± 0.1	1.9 ± 0.1	148 ± 1	10.9 ± 0.3	13.2 ± 0.2	106 ± 1	144 ± 6	0.5 ± 0.0
0.2 ppm		0.3 ± 0.0	200 ± 12	26 ± 1	5.5 ± 0.1	3.5 ± 0.1	2.0 ± 0.1	146 ± 1	10.2 ± 0.3	13.3 ± 0.1	106 ± 1	91 ± 6 ^d	0.5 ± 0.0
1.9 ppm		0.0 ± 0.0 ^d	208 ± 8	24 ± 1	5.6 ± 0.2	3.6 ± 0.1	2.1 ± 0.2	145 ± 1	10.3 ± 0.3	13.2 ± 0.2	104 ± 1	73 ± 8 ^d	0.4 ± 0.0
9.3 ppm		0.3 ± 0.0 ^d	204 ± 8	24 ± 1	5.7 ± 0.1	3.8 ± 0.1	2.0 ± 0.0	147 ± 1	9.7 ± 0.3 ^c	13.1 ± 0.1	106 ± 1	101 ± 14 ^b	0.5 ± 0.0
46.3 ppm		0.2 ± 0.0	173 ± 18	26 ± 2	5.3 ± 0.1	3.5 ± 0.1	1.9 ± 0.1	147 ± 2	9.0 ± 0.4 ^c	13.2 ± 0.2	107 ± 2	164 ± 23 ^d	0.6 ± 0.0 ^b

^a Data expressed as $\bar{x} \pm$ standard error, n = 5 to 10 per group.^b Significantly different from control (Student's t-test), p < 0.05.^c p < 0.01.^d p < 0.001.

Table 7
Frequency of Microscopic Lesions in Male Guinea Pigs^a

	Dose																	
	Control			0.2 ppm			1.9 ppm			9.3 ppm			46.3 ppm			231.5 ppm		
	No. ^b	%	Grade ^c	No.	%	Grade	No.	%	Grade	No.	%	Grade	No.	%	Grade	No.	%	Grade
Salivary gland, metaplasia of duct epithelium	0/9	0		0/10	0		2/10	20	1 ± 0	4/9	44	1 ± 0	4/7	57	2 ± 1	3/7	43	1 ± 0
Pancreas, goblet cell hyperplasia of duct epithelium	0/9	0		0/10	0		2/10	20		1/9	11		4/7	57		3/7	43	
Lacrimal gland, focal adenitis	0/9	0		0/10	0		0/10	0		4/9	44	1 ± 0	4/7	57	1 ± 0	3/7	43	1 ± 1
Bone marrow, cellular depletion	0/9	0								0/9	0		0/7	0		4/7	57	2 ± 1
Skeletal muscle, degeneration	0/9	0								0/9	0		0/7	0		1/7	14	
Liver, focal necrosis	5/9	55		5/10	50		3/10	30		1/9	11		5/7	71		2/7	29	
Liver, fatty infiltration	0/9	0		0/10	0		0/10	0		0/9	0		0/7	0		4/7	57	2 ± 1
Liver, bile duct hyperplasia	1/9	11	1 ± 0	0/10	0		3/10	30	1 ± 0	0/9	0		2/7	29	1 ± 0	0/7	0	
Liver, hepatocellular cytoplasmic inclusion bodies	0/9	0		0/10	0		0/10	0		4/10	40	2 ± 0	5/7	71	2 ± 1	0/7	0	
Kidney, focal interstitial nephritis	3/9	33		5/10	50		4/10	40		5/9	55		5/7	71		0/7	0	
Thymus, thinning of cortex	0/9	0								0/9	0		0/7	0		1/6	17	
Stomach, degeneration	0/9	0								0/9	0		0/7	0		2/5	40	
Small intestine, degeneration	0/9	0								0/9	0		0/7	0		1/7	14	
Large intestine, degeneration	0/9	0								0/9	0		0/7	0		1/7	14	
Testis, unilateral degeneration	0/9	0								2/9	22		0/7	0		0/7	0	

^a Animals surviving for 90 days, except 32 days for 231.5 ppm group.

^b Data expressed as no. of positive findings/no. of animals examined.

^c Data expressed as $\bar{x} \pm$ standard deviation.

Table 8
Frequency of Microscopic Lesions in Female Guinea Pigs^a

	Dose																	
	Control			0.2 ppm			1.9 ppm			9.3 ppm			46.3 ppm			231.5 ppm		
	No. ^b	%	Grade ^c	No.	%	Grade	No.	%	Grade	No.	%	Grade	No.	%	Grade	No.	%	Grade
Salivary gland, metaplasia of duct epithelium	0/10	0		0/10	0		2/10	20	1 ± 0	3/10	30	1 ± 0	7/7	100	2 ± 0	1/7	14	1 ± 0
Pancreas, goblet cell hyperplasia of duct epithelium	2/10	20		1/10	10		3/10	30		3/10	30		3/7	43		0/7	0	
Lacrimal gland, focal adenitis	0/10	0		1/10	10		0/10	0		0/10	0		5/7	57	1 ± 0	3/7	43	1 ± 0
Bone marrow, cellular depletion	0/10	0								0/10	0		2/7	29	1 ± 0	5/7	57	2 ± 1
Skeletal muscle, degeneration	0/10	0								0/10	0		0/7	0		0/7	0	
Liver, focal necrosis	4/10	40		1/10	10		1/10	10		1/10	10		2/7	29		1/7	14	
Liver, fatty infiltration	0/10	0		0/10	0		0/10	0		1/10	10	1 ± 0	0/7	0		4/7	51	1 ± 0
Liver, bile duct hyperplasia	0/10	0		2/10	20		0/10	0		0/10	0		1/7	14	2 ± 0	0/7	0	
Liver, hepatocellular cytoplasmic inclusion bodies	0/10	0		0/10	0		1/10	10	3 ± 0	8/10	80	2 ± 1	5/7	57	1 ± 1	0/7	0	
Kidney, focal interstitial nephritis	6/10	60		7/10	70		6/10	60		7/10	70		3/7	43		0/7	0	
Thymus, thinning of cortex	0/10	0								0/10	0		0/7	0		3/7	43	
Stomach, degeneration	0/10	0								0/10	0		0/7	0		0/7	0	
Small intestine, degeneration	0/10	0								0/10	0		0/7	0		0/7	0	
Large intestine, degeneration	0/10	0								0/10	0		0/7	0		0/7	0	

^a Animals surviving for 90 days, except 32 days for 231.5 ppm group.

^b Data expressed as no. of positive findings/no. of animals examined.

^c Data expressed as $\bar{x} \pm$ standard deviation.

LEGENDS

- Fig. 1: Body weight changes in (a) male and (b) female guinea pigs receiving soot from the Binghamton State Office Building transformer fire in the feed. Asterisks indicate individual mortalities during the observation period. Values significantly different from control ($p < 0.05$) at 46.3 and 231.5 ppm soot dose levels from day 6 onward, and at 1.9 ppm soot from day 14 onward.
- Fig. 2: Interlobular duct of salivary gland from (a) control guinea pig and (b) guinea pig receiving 46.3 ppm Binghamton soot in the feed for 90 days. Stratified squamous epithelium has replaced the normal columnar cells of this duct.
- Fig. 3: Bone marrow of sternum from (a) control guinea pig and (b) guinea pig receiving 231.5 ppm Binghamton soot in the feed for 32 days. Hematopoietic cells are markedly reduced in number in marrow from treated animals.

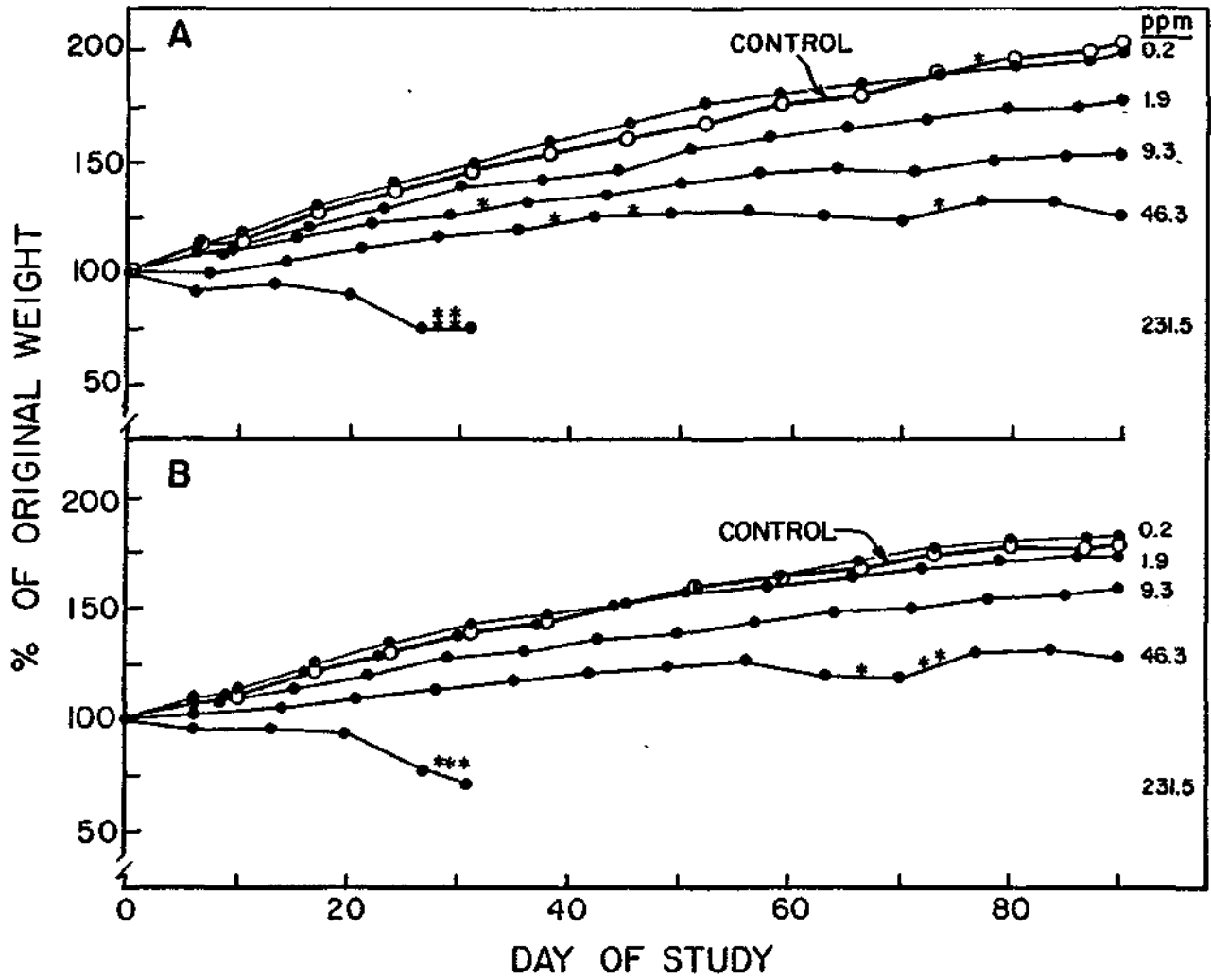


Fig 1



94G Control bone marrow 100X

Fig. 9a



Bone marrow: 107X, 425/19p

Fig. 9b



Fig. 2a



Fig. 2b

94-B
11-B
Comp. Control - 107X