

13 WEEK REPEATED INHALATION STUDY ON ETHYLENE DIBROMIDE (EDB)
IN MALE AND FEMALE RATS

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ABSTRACT

Male and female CDF (F-344) rats were exposed to 0, 3, 10 or 40 ppm ethylene dibromide, 6 hours/day, 5 days/week for 13 weeks for a total of 67-68 exposures in 95-96 days. Scheduled sacrifices occurred after 1, 6, and 13 weeks of exposure. Additional rats were held for a recovery period of 88-89 days and subsequently necropsied. Body weight data was obtained throughout the study and the animals were observed daily for signs of toxicity. Hematology, urinalysis and clinical chemistry parameters were measured. Gross and microscopic pathological examinations were conducted on selected tissues of all animals. Weights of various organs were recorded and organ/body weight ratios were calculated.

Rats exposed to 3 ppm EDB showed no consistent effect in any parameter measured. At 10 ppm, EDB caused slight epithelial hyperplasia of the nasal turbinates in animals necropsied after 1, 6 or 13 weeks of exposure; however, 88 days after the last exposure to EDB, no morphological difference from control animals was observed. Rats exposed to 40 ppm EDB showed a definite adverse response characterized by a decrease in body weight gain throughout the 13-week exposure period, an increase in liver and kidney weights after 6 and 13 weeks of exposure, and pathologic effects in the nasal epithelium. At this concentration the nasal turbinates of rats progressed from very slight hyperplasia of the epithelium after 1 week of exposure to EDB to hyperplasia and nonkeratinizing squamous metaplasia of the epithelium after 13 weeks of exposure to EDB. After a recovery period of at least 88 days, only a single focus of hyperplasia of the nasal epithelium in one rat and increased relative liver weights were apparent as residual effects from the subchronic exposure. It is believed that these observations would have returned to control limits if allowed a longer recovery period.

Therefore, while this study has shown that repeated subchronic exposure of rats to 10 or 40 ppm EDB induces pathologic changes in the respiratory epithelium of the nasal turbinates, a subsequent postexposure phase revealed a lack of progression of the lesions, with almost complete reversion toward normal histologic appearance of the nasal turbinates. In view of these findings, and the lack of any lesion subsequent to repeated exposure to 3 ppm EDB, short-term repeated exposure to

these concentrations of EDB would not be expected to result in any long term irreversible effects upon the nasal turbinates or other tissues of the body.

INTRODUCTION

The toxicological properties of Ethylene Dibromide (EDB) have been assessed in a number of studies over the past 25 years. Currently, the American Conference of Governmental Industrial Hygienists has listed EDB as having carcinogenic potential without an assigned TLV. Rowe et al. (1952) reported the single oral dose toxicity of EDB for several species of animals. These are listed in the following table.

<u>Species</u>	<u>Single Oral LD₅₀, mg/kg</u>
Mice - Females	420
Rats - Males	146
Rats - Females	117
Chickens	79
Guinea Pigs	110
Rabbits - Females	55

EDB can also be absorbed through the skin in toxic amounts. The LD₅₀ for skin absorption in rabbits is between 300 and 650 mg/kg. EDB is also irritating to the skin and the eyes.

Acute inhalation toxicity data are also included in the report of Rowe et al. (1952). The maximum survival times for rats exposed to EDB vapor are reported as follows:

	<u>EDB, ppm</u>	<u>Maximum Survival Times</u>
Rats both sexes	3000	6 minutes
	1600	12 minutes
	400	36 minutes
	200	2 hours
Guinea Pigs both sexes	400	2 hours
	200	7+ hours

Examination of female rats given single inhalation exposures to EDB gave these results (Rowe et al., 1952):

EDB, ppm	Hours of Exposure	
	With Adverse Effects	Without Adverse Effects
800	0.15	0.10
200	1.0	0.7
100	4.0	2.5
50	---	7.0

The adverse effects following these acute inhalation exposures included pulmonary congestion, edema, hemorrhage and inflammation. The livers showed hepatocellular degeneration and necrosis and the kidneys had slight inflammatory and degenerative changes.

Ethylene dibromide is reported to produce irritation of the mucous membranes, headache, vertigo, giddiness, nausea, vomiting, drowsiness and coma when inhaled (St. George, 1937). Thomas et al (1927) reported that guinea pigs exposed to 0.2-0.8% EDB for 30-150 minutes had nasal irritation.

Data on chronic vapor exposure of animals to EDB were also reported by Rowe et al. (1952). Animals were exposed for 7 hours/day, 5 days/week for periods of up to 6 months. The data are summarized in the attached Table 1.

In a carcinogenic bioassay conducted by the NCI (Olson et al., 1973) EDB was given by oral intubation to rats and mice. Squamous cell carcinomas of the stomach were found in rats as early as 10 weeks after the start of the study. The doses were changed within the 40-200 mg/kg/day range several times during the study. Table 2 summarizes the number of tumors noted.

Recent information indicates that a 2-year inhalation study being completed by NCI has identified nasal tumors in rats and mice exposed to 10 and 40 ppm EDB.

In view of the local irritating properties of EDB on the upper respiratory tract, this study was conducted to assess the possibility of EDB-induced nasal epithelial changes that may precede or accompany the development of nasal tumors in rodents.

This study would give perspective to the forthcoming tumor data from the NCI study by:

1. Allowing an assessment of whether or not various inflammatory, degenerative, necrotic, hyperplastic or metaplastic changes occur in the nasal epithelium prior to (or at doses lower than those leading to) the development of tumors,
2. Allowing an assessment of whether or not the exposure levels shown to induce nasal tumors in rodents are associated with adverse effects that would indicate a maximal tolerated dose (MTD) may have been exceeded in the chronic study at NCI.
3. Allowing a comparative assessment of those possible effects noted at higher exposure levels of 40 or 10 ppm with effects at a lower exposure level (3 ppm).

MATERIALS AND METHODS

General Study Design

A 13-week inhalation study of EDB at concentrations of 0, 3, 10, or 40 ppm was conducted with interim sacrifices of male rats after 1 week (5 exposures) and 6 weeks (29 exposures). Groups of control and exposed rats were retained for at least 88 days after the last exposure to assess the reversibility of effects observed after 13 weeks of exposure to EDB.

Body weights were obtained at least weekly throughout the study. Basic hematological and urinary parameters were measured prior to the 6 week and 13 week sacrifices. Urinalysis was also performed on animals in the recovery group. Clinical chemistry values were measured at the 1, 6, and 13 week scheduled necropsies. Weights of the brain, heart, liver, kidneys, testes (males only) and thymus were obtained and compared with the body weights of the rats. Tissues of lungs, bronchi, trachea, nasal turbinates, liver, kidneys, testes, ovaries, uterus, and oviducts were examined histopathologically from rats of all exposure levels at all scheduled necropsies.

Material. Production grade ethylene dibromide supplied by The Dow Chemical Company, Magnolia, Arkansas was used for this study. Gas chromatographic analysis of the test material was made prior to study initiation. The test material was also analyzed twice during the study and after the final exposure by the Dow Analytical Lab (Table 3).

Generation and Sampling of Vapor Concentrations of EDB. EDB was vaporized by metering the liquid at a calculated rate with a precision pump into a warmed vaporization flask (100°C). The vapors were swept from the flask with compressed air into the main chamber airflow. The chambers were 1 m³ stainless steel and glass Rochester-type chambers. The nominal concentration was calculated from the rate at which liquid EDB was dispensed and the total chamber airflow. The chamber concentration of EDB was analyzed at least 3 times/day by gas chromatography using a flame ionization detector. A 6' x 1/8" OD nickel column packed

with 10% SP-1000 on 100/200 mesh Chromosorb W (Supelco, Inc.) was used for the analysis. The carrier (helium), hydrogen and air flows were 54, 20, and 300 ml/min, respectively. The column and detector temperatures were 140° and 200°C, respectively. The retention time for the EDB peak was approximately one minute after injection of the air sample.

Animals. Four groups of CDF rats (9 weeks old) (Fischer 344 derived, Charles River Laboratories, Portage, MI) consisting of 40 male and 20 female rats were used. Rats were acclimated to the conditions of this laboratory for at least 13 days prior to the initial exposure to EDB. The animals were randomly assigned to the four groups using numbers generated by the program GRAND.CLIST (Computation Laboratory, The Dow Chemical Company). The CDF strain was chosen because of its current use in chronic toxicity/carcinogenicity studies in this laboratory and many other laboratories.

Serial sacrifices of 10 male rats/group were conducted after 1 (5 exposure days), 6 (29 exposure days) and 13 weeks (67 exposure days) and 10 female rats/group after 13 weeks (68 exposure days); the remaining 10 rats/sex/group were held and sacrificed after an 88-89 day post-exposure period for the purpose of assessing reversibility of any lesions that may be associated with exposure to EDB for 13 weeks.

Procedures. The concentrations studied were 0, 3, 10 and 40 ppm EDB. Exposures were 6 hours/day, 5 days/week. The animals were housed 2/cage during nonexposure periods and 5 or 10/cage for females and males, respectively, during exposure periods. Control animals were also housed in a chamber during exposure periods. Water and food (Purina Rat Chow) were withheld during the 6-hour exposure period but were available ad libitum at all other times. Rats were weighed twice prior to the start of the study, twice weekly for the first two weeks of the study and once weekly thereafter. Male rats exposed to the various concentrations of EDB for 5 days were initially exposed to EDB 6 days after the other groups were initially exposed. Consequently, their body weights were

statistically analyzed separately from the other groups. The groups necropsied after 6 or 13 weeks of exposure and the recovery groups were initially exposed to EDB at the same time and were statistically analyzed together. Animals were observed at the end of each exposure period and signs of toxicity noted and recorded. Particular attention was paid to the eyes and nose for clinical indications of irritation.

Clinical Determinations. Basic hematological and urinalysis determinations were conducted on 7 male rats/exposure level prior to their necropsy after 6 weeks and also on 7 rats/sex/exposure level prior to their necropsy after 13 weeks of exposure. Urinalysis on 7 rats/sex/exposure level was performed prior to the necropsy on animals in the recovery group. Clinical chemistry determinations was performed on all 10 animals/sex (if applicable)/exposure level at the time of necropsy for the serial sacrifices after 1, 6 and 13 weeks. Hematological parameters^a included a total erythrocyte count (RBC), total (WBC) and differential leukocyte counts, hemoglobin concentrations (HGB), and packed cell volume (PCV). Urinary parameters^b measured included specific gravity, pH, glucose, ketones, bilirubin, urobilinogen, occult blood and protein. Clinical chemistry measurements^c included blood urea nitrogen (BUN), serum glutamic pyruvate transaminase (SGPT), serum glutamic oxalacetic transaminase (SGOT), serum alkaline phosphatase (AP), glucose, and bilirubin. Serum bromide levels of rats exposed to EDB for 6 weeks were measured by neutron activation^d.

Pathology. Gross examination of the eyes of all rats was performed by a microscope slide technique at necropsy with observations recorded as part of the gross pathologic examination. At the time of each sacrifice, the eyes from 5 rats/sex (if applicable)/group were preserved in Zenker's solution. The eyes of the remaining rats were preserved in 10% formalin.

^aPCV-Microhematocrit Centrifuge, Clay-Adams Company, New York, RBC, WBC counts, Hgb - Coulter Counter Model 2B1 and hemoglobinometer, Coulter-Electronics, Hialeah, Florida.

^bSpecific gravity - T.S. Meter American Optical Company, Buffalo, NY, pH, glucose, protein, ketones, bilirubin, urobilinogen, occult blood-Bililabstix, Ames Company, Elkhart, Indiana.

^cSerum - Centrifichem System 400, Methods File, Union Carbide Corp., Rye, NY.

^dDow Analytical Lab Report 79-10895.

Gross necropsies were performed on all rats, with special attention given to assessing the presence or absence of inflammation of the upper respiratory tract. Rats were fasted overnight prior to necropsy. They were anesthetized with methoxyflurane and decapitated after clamping the trachea. The lungs and trachea of all animals were removed as a unit and inflated with 10% formalin from a hand held syringe. The nasal passageways were perfused with formalin fixative. Fasting body weights and organ weights for liver, kidneys, brain, heart, thymus, and testes (males) were obtained from all rats at each necropsy.

Representative specimens of the tissues indicated in Table 4 were taken from all animals and fixed in phosphate-buffered 10% formalin. The target tissues (lungs, bronchi, trachea, nasal turbinates (4 transverse planes), liver, kidney, testes, ovaries, uterus and oviducts) were processed by conventional histological methods, stained with hematoxylin and eosin and examined by light microscopy from all 10 rats/sex/group of each of the serial sacrifices after 1, 6, 13 weeks and the recovery group. Transverse sections through the decalcified nasal cavity were made perpendicular to the plane of the hard palate and the plane of the nasal septum at or near the following levels: 1) immediately caudal to the upper incisor teeth, 2) at the incisive papilla, 3) at the second palatal ridge, and 4) at the first upper molars.

Upon examination of the nasal turbinates, special attention was given to assessing the presence or absence of discernible inflammatory, degenerative, necrotic, hyperplastic or metaplastic changes.

Statistical Evaluation. Body weights, body weight gain, organ weights, urine specific gravity, hematology and clinical chemistry data were evaluated using an analysis of variance and Dunnett's test (Steel and Torrie, 1960). The level of significance was $p < 0.05$.

RESULTS

Chamber Analysis. Results of the chamber analysis are summarized in Table 5. Since the actual analytical concentrations are very close to the desired concentrations of 3, 10 or 40 ppm, these concentrations will be used throughout the report. The temperature range was similar within the chambers. Likewise, the relative humidity was nearly identical between the 4 chambers.

Animal Observations. Male rats exposed to 40 ppm EDB for 5 days exhibited eye and nasal irritation during the first exposure period. This was not observed in other animals scheduled for longer exposure or at different concentrations of EDB. No other effect relatable to ethylene dibromide exposure was observed.

Two non-exposure related deaths were observed in female rats from the 3 and 10 ppm exposure groups during the 88 day recovery period.

Body Weights. Mean body weights for male and female rats inhaling 0, 3, 10 or 40 ppm are shown in Tables 6-8. A decrease in body weight was observed in male rats exposed to 40 ppm EDB during the 13-week exposure period. Male rats exposed to 10 ppm EDB showed a significant decrease for the first two weeks of the study and occasionally thereafter. A statistically significant decrease in body weight was observed in female rats inhaling 40 ppm EDB on day 4 of the study. However, these significant differences were not nearly so evident when body weight gains were statistically analyzed (Figures 1-3 and Tables 9-11). The male rats inhaling 40 ppm ethylene dibromide still showed statistically decreased body weight gain during the 13-week exposure period but no change in body weight gain was observed at lower concentrations. The female rats inhaling 40 ppm EDB showed a decrease in body weight gain on day 4 and 14 of the study.

Hematology. The female rats exposed to 40 ppm EDB for 13 weeks had a statistical decrease in hematocrit and in hemoglobin that may have been the result of exposure (Table 12). No other measured hematological parameters revealed an effect attributable to exposure to EDB; the statistical increase in hematocrit of males exposed to 3 ppm EDB for 13 weeks and the statistical decrease in total white blood cell counts of males exposed to 3 or 10 ppm EDB for 6 weeks were considered to be of no toxicologic significance due to a lack of a dose response and the expected variability in this parameter.

Urinalysis. No treatment-related effects on urinalysis parameters were observed in any male rats exposed to EDB (Table 13). However, female rats exposed to 40 ppm EDB for 13 weeks showed a statistically significant decrease in specific gravity of the urine (Table 14) which was interpreted as treatment-related. After a recovery period of 88 days, the decrease in specific gravity was not observed.

Clinical Chemistry. As expected, serum bromide levels were significantly elevated in a dose-related manner above control values for all groups of male rats exposed to EDB for 6 weeks (Table 15). No other parameters, of those measured, exhibited a consistent effect due to exposure to ethylene dibromide; the statistical increases in total bilirubin noted in rats exposed to 3 or 10 ppm EDB for 13 weeks and the statistical decrease in SGPT values in rats exposed to 40 ppm EDB for 1 week were considered representative of the normal variation seen with these parameters and of no toxicologic significance.

Organ/Body Weight Ratios.

Values for terminal body weights, organ weights, and organ/body weight ratios for male and female rats are listed in Tables 16 and 17, respectively. After one week of exposure, there were no statistically significant differences in organ weights at any exposure level, although the absolute and relative liver weights were elevated slightly. The relative liver weights of male rats exposed to 40 ppm EDB were increased at each of the 3 subsequent necropsy intervals; this was considered to be the result of the exposure to 40 ppm EDB and the accompanying decrease in body

weight of this group. Female rats exposed to 10 or 40 ppm EDB for 13 weeks had elevated absolute (40 ppm only) and relative liver weight values. These liver weight changes observed in the female rats after exposure to 10 or 40 ppm EDB for 13 weeks were most likely due to exposure; these changes were not observed at necropsy in rats after an 88 day recovery period.

Kidney weights of male rats were increased after 6 weeks of exposure to 3 (relative basis only), 10 (relative basis only) and 40 ppm (absolute and relative basis) EDB. However, after 13 weeks of exposure, kidney weights were increased on a relative basis only in males exposed to 40 ppm EDB. Thus, the transient increase in relative body weights noted after 6 but not 13 weeks of exposure to 3 or 10 ppm EDB was considered to be of questionable significance. Kidney weights of female rats were not statistically different from control values at any of the exposure levels, but there was a trend toward increased relative kidney weights in female rats exposed to 40 ppm EDB for 13 weeks.

The weights of the brain, heart, thymus and testes were not considered to be directly affected by exposure to 3, 10, or 40 ppm EDB. The statistical increase in relative brain weights noted in males exposed to 40 ppm EDB for 6 or 13 weeks or 10 ppm EDB for 6 weeks were considered secondary reflections of the lower body weights of these groups. The statistical increase in relative weight of the thymus of male rats exposed to 10 ppm EDB for 13 weeks was considered an expression of the normal variability historically encountered in recording the weight of the thymus. The increase in relative weights of testes noted in the recovery group subsequent to exposure to 3, 10, or 40 ppm EDB were considered to be a secondary reflection of the lower body weight as compared to the control group sacrificed at that time. The same explanation applies to the decreased absolute testicular weights in males exposed to 40 ppm EDB for 13 weeks.

Pathology. Due to the numerous interim sacrifices and recovery portion of this study, the results of the gross and microscopic pathologic examinations (Tables 18-25) will be discussed separately.

6-Day Interim Sacrifice. The results of the gross pathologic observations for male rats terminated on day 6 of the study (5 exposure periods) are listed in Table 18. There were no grossly visible lesions considered to be related to treatment.

Histopathologic observations and the actual number of tissues examined microscopically from male rats terminated on day 6 of the study are listed in Table 19. Effects attributable to EDB were seen only in the most anterior section of the nasal turbinates. All male rats exposed to 40 ppm EDB showed very slight to slight scattered to diffuse hyperplasia of the respiratory epithelium of the turbinates. Five of ten male rats of this group showed very slight focal individual epithelial cell necrosis of the respiratory epithelium. Nine of ten male rats exposed to 10 ppm EDB showed isolated to scattered hyperplasia of the respiratory epithelium graded very slight to slight in degree. One rat of this group showed focal individual epithelial cell necrosis of the respiratory epithelium, very slight in degree. Examination of sections of nasal turbinates of rats exposed to 3 ppm EDB revealed no hyperplasia or other lesions related to exposure.

Most of the male rats of the control group showed varying distribution of slight submucosal and epithelial inflammation of the respiratory epithelium with focal aggregates of inflammatory cells in the lumen of the nasal turbinates. In addition, the tracheal submucosa of all male control rats showed a similar inflammatory response, accompanied by a hyperplastic response of the mucosal epithelium. This inflammation occurs at a highly variable rate in this laboratory. Male rats exposed to 3, 10 or 40 ppm showed a substantial decrease in the inflammatory reaction noted in both nasal turbinates and trachea in comparison to controls. This decrease in inflammation noted in the nasal turbinates

and trachea may or may not have been the result of exposure to EDB. All other histopathologic observations were considered to be spontaneous in nature and typical of rats of this age and strain.

40-Day Interim Sacrifice. The gross pathologic observations of male rats terminated on day 40 of the study (29 exposure periods) are listed in Table 20. There were no gross observations which were considered to be the result of exposure.

Histopathologic observations of male rats terminated on day 40 and the actual numbers of tissues examined microscopically are listed in Table 21. EDB exposure-related effects were again limited to the most anterior section of the respiratory epithelium of the nasal turbinates.

All male rats exposed to 40 ppm EDB showed very slight to slight multifocal to diffuse hyperplasia and very slight to slight multifocal individual epithelial cell necrosis of the respiratory epithelium. All male rats exposed to 10 ppm EDB showed very slight to slight hyperplasia of the respiratory epithelium with an isolated to diffuse distribution. Nasal turbinates of rats exposed to 3 ppm of EDB had no lesions attributed to the exposure. Male rats exposed to 40 ppm EDB had an increased incidence of slight focal atrophy of the renal tubules. This effect was not observed in rats necropsied after 1 or 13 weeks of exposure to EDB. In fact, after 1 week of exposure to EDB a decrease in the tubular atrophy of the kidneys was observed from the control group. No other histopathologic observations were considered to be related to exposure to ethylene dibromide.

95-96 Day Sacrifice. The gross pathologic observations of male and female rats on study for 95-96 days (67-68 exposure periods) are listed in Table 22. Five of ten male rats exposed to 40 ppm of EDB showed a decreased carcass size at the time of necropsy. In addition, five of ten female rats exposed to 40 ppm EDB showed very slight to slight diffuse paleness of the liver. No other grossly visible effects attributable to ethylene dibromide were observed.

Histopathologic observations on male and female rats sacrificed on day 95-96 of the study are listed in Table 23. Effects considered to be

related to EDB exposure were primarily limited to the most anterior sections of the nasal turbinates.

All male and female rats exposed to 40 ppm EDB showed very slight to slight diffuse or focal nonkeratinizing squamous metaplasia and hyperplasia of the respiratory epithelium. In addition, all male and most female rats exposed to 40 ppm showed very slight focal individual epithelial cell necrosis of the respiratory epithelium.

Nine of ten rats of each sex exposed to 10 ppm showed very slight to slight degrees of isolated to multifocal hyperplasia of the respiratory epithelium. One female rat of this exposure level showed very slight focal individual epithelial cell necrosis of the respiratory epithelium. The nasal turbinates of rats exposed to 3 ppm exhibited no lesions due to the exposure to ethylene dibromide. The increased incidence of subpleural mononuclear aggregates observed in the lung of rats exposed to EDB occurs at a highly variable rate in this strain of rats in this laboratory and is considered not toxicologically significant.

In view of the grossly observed very slight to slight degree of hepatic paleness, in 5 of 10 females, and the presence of hepatocellular cytoplasmic vacuolation in H&E stained sections of livers of 2 of 10 females exposed to 40 ppm EDB, Oil Red O stained liver sections from all female rats exposed to 0 or 40 ppm EDB were also examined. This revealed a very slight increase of fat within the liver sections of females exposed to 40 ppm EDB. Due to a lack of any significant increase of fat in the livers of females exposed to 40 ppm of EDB, and the absence of any grossly visible hepatic paleness at lower levels, tissues from the lower exposure groups were not stained with Oil Red O Stain.

88-89 Day Recovery Sacrifice. The gross observations of male and female rats on study for 94-95 days (67-68 exposure periods) and subsequently held for a recovery period of at least 88 days are listed in Table 24. One female each from the 3 and 10 ppm groups died spontaneously during the recovery period. Necropsy of these two female rats showed a generalized acute bacterial septicemia, with bacterial organisms noted in various organs and tissues. These deaths were not considered to be related to previous exposure to vapors of EDB. There were no gross pathologic observations which were considered to be related to exposure.

Histopathologic observations of male and female rats of this recovery group are listed in Table 25. Examination of the sections of the nasal turbinates revealed no evidence of progression of the epithelial hyperplasia or metaplasia that had been previously noted at the 1, 6 or 13 week sacrifices. The nasal turbinates of all 10 males previously exposed to 10 or 40 ppm ethylene dibromide had no discernible changes in comparison to controls as a result of the exposure. Of the 10 females previously exposed to 40 ppm EDB, 9 of the 10 females had no evidence of hyperplasia, metaplasia or other exposure-related pathologic effects within the nasal turbinates. One female rat exposed to 40 ppm EDB had a single focus of epithelial hyperplasia noted in the respiratory epithelium of the nasal turbinates which was probably the sole remnant from the previous exposure to EDB.

Examination of the nasal turbinates of females previously exposed to 10 ppm of EDB revealed no evidence of epithelial hyperplasia that had been noted during the exposure. As with the interim sacrifices, there were no exposure-related observations in the nasal turbinates of male or female rats exposed previously to 3 ppm of EDB.

CONCLUSIONS

In this study, rats were exposed to 0, 3, 10, or 40 ppm EDB for 1, 6 or 13 weeks and an additional group of rats were held for an 88-89 day recovery period following the 13 week exposure. Rats exposed to 3 ppm EDB showed no consistent effect in any parameter measured. Exposure to 10 ppm EDB caused hyperplasia of the respiratory epithelium of the nasal turbinates, but no effects in the other tissues examined. Examination of the nasal turbinates and other tissues from the recovery group revealed no differences from controls in the 10 ppm group thus indicating a lack of progression of the lesion.

Rats exposed to 40 ppm EDB had multiple indications of toxicity as indicated by a decrease in body weight gain, an increase in liver and/or kidney weights and pathologic changes in the nasal turbinates. At this concentration the nasal turbinates of rats progressed from very slight hyperplasia of the respiratory epithelium after 1 week of exposure to hyperplasia and nonkeratinizing squamous metaplasia of the respiratory epithelium after 13 weeks of exposure. After a recovery period of 88-89 days there was essentially complete reversibility of the lesions, with only a slight hyperplasia in the nasal epithelium of one rat that would have been expected to return to within control limits if allowed a slightly longer recovery period.

A preliminary report from the NCI Bioassay Program revealed a high incidence of tumors of the respiratory system of rats exposed to 10 and 40 ppm EDB for 2 years. These tumors in rats were primarily located in the upper respiratory system and described as primary adenomas, and carcinomas and adenocarcinomas of the nasal cavity. These findings appear consistent with those of the study reported herein which demonstrated that exposure of rats to 10 or 40 ppm EDB for as little as five days was sufficient to produce hyperplastic (10 ppm) and focal necrotic (40 ppm) alteration in the nasal respiratory epithelium. That such effects would progress in severity even to neoplasia following two years of exposure to these EDB concentrations is not surprising. However these considerations must also be tempered by the finding that the lesions of the nasal turbinates produced by exposure of rats to EDB for 90 days in the present study were reversible and nearly completely

so within about the same time span used to produce the effect. In view of these findings and the lack of any observable effect in rats of the 3 ppm exposure group, these data indicate that short-term exposure to EDB would not likely result in any irreversible effects on the upper respiratory tract or other tissues of the body.

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QUALITY ASSURANCE STATEMENT

This report represents data generated prior to the enactment of the FDA Good Laboratory Practice Regulations. The study was conducted according to standards used in this laboratory at that time. The report accurately reflects all of the data generated. All data and reports are located at the submitting laboratory.

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TABLE 1

CHRONIC VAPOR TOXICITY OF ANIMALS EXPOSED TO ETHYLENE DIBROMIDE^a

<u>Species</u>	<u>Concentration</u>	<u>Number of Exposures</u>	<u>Results</u>
Rats (10 F)	100 ppm	7 in 9 days	3 of 10 died after one, five and seven exposures; survivors looked "unhealthy"; blood in stomachs; lung, liver and kidney weight increases; blood nonprotein nitrogen, BUN and plasma prothrombin clotting time values normal; Microscopic exam.: Thickening of alveolar walls, leucocytic infiltration of lungs, cloudy swelling of liver, congestion and hemosiderosis of spleen.
Rabbits (4 F)	100 ppm	4 in 4 days	3 of 4 died after second and third exposures; Microscopic exam.: widespread central fatty degeneration of liver with some necrosis.
Rats (20/sex/group)	50 ppm	63 in 91 days	50% mortality of male rats due to pneumonia and upper respiratory tract infections (not compound related). Males: increased lung, liver and kidney weights decreased testes weights Females: increased liver and kidney weights decreased spleen weights Blood normal; lung damage in males but no histopathological changes in heart, liver, kidneys, spleen or testes.
Guinea Pigs (M, F 8/group)	50 ppm	57 in 80 days	No increase in mortality; Body weight decrease; Organ weight increase; Microscopic exam.: Slight central fatty degradation in all livers and slight interstitial congestion and edema with slight parenchymatous degeneration of the tubular epithelium in 8 or 14 kidney sections examined.
Rabbits (1 F, 1 M)	50 ppm	59 in 84 days	No effects except slight liver and kidney weight increases
Monkeys (1 F, 1 M)	50 ppm	49 in 70 days	Both appeared ill, nervous and unkempt; Body weight loss; Blood chemistry normal; Liver weight increase with slight central fatty degeneration; Slight kidney weight increase; Other organs normal
Rats (20 F, 20 M)	25 ppm	151 in 213 days	No effects
Guinea Pigs (8 F, 8 M)	25 ppm	145 in 205 days	No effects
Rabbits (1 F, 1 M)	25 ppm	152 in 214 days	No effects
Monkeys (1 F, 1 M)	25 ppm	156 in 220 days	No effects

^aRowe, V.K., Spencer, H. C., McCollister, D.D., Hollingsworth, R. L., Adams, E. M., Toxicity of Ethylene Dibromide Determined on Experimental Animals, A.M.A. Arch. Ind. Hyg. and Occup. Med. 6, 158-73 (1952).

TABLE 2

NUMBER OF STOMACH SQUAMOUS CARCINOMAS IN RATS
RECEIVING ETHYLENE DIBROMIDE BY ORAL GAVAGE^a

<u>Compound</u>	<u>Week</u>	<u>Species</u>	<u>Sex</u>	80-200 mg/kg/day			40-100 mg/kg/day			Controls		
				<u>Stomach Squamous Carcinoma</u>	<u>Died Without Tumors</u>	<u>Sur- viving</u>	<u>Stomach Squamous Carcinoma</u>	<u>Died Without Tumors</u>	<u>Sur- viving</u>	<u>Stomach Squamous Carcinoma</u>	<u>Died Without Tumors</u>	<u>Sur- viving</u>
EDB	54	Rat	M	31	19	0	49	1	0	0	11	9
EDB	54	Rat	F	14	27	9	24	17	9	0	0	19
EDB	42	Mouse	M	1	20	29	3	6	41	0	1	19
EDB	42	Mouse	F	1	20	29	2	1	47	0	0	20

^aOlson, W.A., Habermann, R. T., Weisburger, E. K., Ward, J. M., Weisburger, J. H., Brief Communication: Induction of Stomach Cancer in Rats and Mice by Halogenated Aliphatic Fumigants, J. Nat'l Cancer Inst., 51 (6), 1993-5, (1973).

TABLE 3
ANALYSIS OF THE ETHYLENE DIBROMIDE SAMPLE
USED IN THE 13-WEEK INHALATION STUDY

	Weight %			
	Analysis <u>1^a</u>	Analysis <u>2^b</u>	Analysis <u>3^b</u>	Analysis <u>4^b</u>
Ethylene Dibromide	99.84	99.58	99.64	99.6
Unknown (probably ethylene)		0.02	N.D.	N.D.
Vinyl Bromide	~0.03	0.01	0.01	0.01
Ethyl Bromide		0.29	0.27	0.25
Methylene Chloride		N.D.	N.D.	N.D.
Bromochloromethane		N.D.	N.D.	N.D.
Methylene Bromide and/or 1-bromo-2-chloroethane		0.01	0.01	0.01
2-Chloroethanol		0.02	0.02	0.02
Bromoform		0.02	0.01	0.02
2-Bromoethanol		0.01	0.01	0.03
1,1,2-Tribromoethane		0.02	0.02	0.02
Bis(2-bromoethyl)ether		0.02	0.01	0.03

N.D. = Not detected.

^aPersonal communication from J. C. Warren, Jr., Quality Control Lab., Dow Chemical USA, Magnolia, Arkansas.

^bDow Analytical Lab

TABLE 4
REPRESENTATIVE TISSUE SPECIMENS OBTAINED AT AUTOPSY FROM ALL RATS

esophagus	peripheral nerve
salivary glands	trachea ^a
stomach	lungs (bronchi) ^a
small intestine	nasal turbinates ^a
large intestine	sternum
pancreas	spleen
liver ^a	thymus
kidneys ^a	lymph nodes (thoracic, mesenteric)
urinary bladder	heart
prostate	aorta
accessory sex glands	skeletal muscle
epididymides	adrenal glands
testes ^a	thyroid gland
ovaries ^a	parathyroid gland
oviducts ^{a,b}	adipose tissue
brain cerebrum	skin
cerebellum	any gross lesion or mass
brain stem	uterus ^a
pituitary gland	
spinal cord	

^aThese target tissues were examined by conventional histological methods.

^bTissue was evaluated histologically only to the extent that it was included in routine sections of the adjacent larger organs.

TABLE 5

CHAMBER AIR ANALYSIS FOR ETHYLENE DIBROMIDE EXPOSURES

Exposure Concentration (ppm)	<u>0</u>	<u>3</u>	<u>10</u>	<u>40</u>
Analytical Concentration $\bar{X} \pm \text{S.D.}$				
1 week exposure		3.1 $\pm$ 0.2	9.7 $\pm$ 1.0	39.6 $\pm$ 0.5
6 week exposure		3.0 $\pm$ 0.2	10.7 $\pm$ 2.2	39.6 $\pm$ 2.2
13 week exposure		3.0 $\pm$ 0.4	10.3 $\pm$ 1.7	39.8 $\pm$ 1.8
Nominal Concentration $\bar{X} \pm \text{S.D.}$				
1 week exposure		3.5 $\pm$ 0.7	9.7 $\pm$ 0.5	39.4 $\pm$ 1.9
6 week exposure		3.3 $\pm$ 0.5	10.9 $\pm$ 2.3	40.3 $\pm$ 2.3
13 week exposure		3.2 $\pm$ 0.4	10.7 $\pm$ 1.7	40.3 $\pm$ 2.2 (males) 40.2 $\pm$ 2.4 (females)
Coefficient of Variation, %				
1 week exposure		6.5	10.3	1.3
6 week exposure		6.7	20.6	5.6
13 week exposure		13.3	16.5	4.5
Daily Temperature, °C, cumulative				
Minimum, $\bar{X} \pm \text{S.D.}$	21 $\pm$ 1	23 $\pm$ 2	20 $\pm$ 1	23 $\pm$ 1
Maximum, $\bar{X} \pm \text{S.D.}$	26 $\pm$ 1	27 $\pm$ 2	26 $\pm$ 1	28 $\pm$ 1
Daily Relative Humidity, %, cumulative	46 $\pm$ 5	43 $\pm$ 3	44 $\pm$ 2	43 $\pm$ 3

TABLE 6
MEAN BODY WEIGHT VALUES OF MALE RATS
EXPOSED TO ETHYLENE DIBROMIDE FOR ONE WEEK

Days on test	Control	DOSE LEVEL PPM		
		3	10	40
-2	214.1±8.5	216.2± 8.4	213.5±12.8	215.7± 9.3
1	223.6±8.4	224.9± 7.9	222.1±12.6	229.1±10.8
4	232.5±8.1	231.3±15.3	231.5±12.9	229.1±10.8

No values were significantly different from controls by Dunnett's test,
p <0.05.

TABLE 7

MEAN BODY WEIGHT VALUES (GRAMS) OF MALE RATS
MAINTAINED ON ETHYLENE DIBROMIDE FOR 13 WEEK

DAYS ON TEST	DOSE LEVEL PPM			
	CONTRL	3	10	40
-2	196±6	192±10	189±10**	189±10**
1	212±6	208±10	206±10*	207±11
4	215±6	214±11	212±10*	206±11**
7	222±9	216±11	214±10*	212±12**
11	241±9	235±13	231±11**	228±11**
14	244±10	239±13	236±11*	232±11**
20	235±12	232±16	226±15	220±18**
24	253±11	248±14	246±13	237±15**
27	259±8	251±15*	247±12**	238±14**
35	258±15	259±17	251±13	250±14
42	269±13	282±17	278±13	272±13**
49	307±13	299±16	296±14	290±14**
55	317±14	309±17	304±15*	297±14**
63	327±14	319±17	315±16	307±13**
69	325±15	324±16	320±16	311±14*
76	337±16	331±16	328±17	316±13**
83	344±18	335±17	333±17	320±14**
90	351±19	341±17	337±17*	326±15**
97	357±22	345±20	342±17	335±18*
104	367±20	353±22	346±18	344±16*
111	368±19	360±22	355±17	355±20
118	379±19	363±22	357±18	356±20
125	384±19	363±22	361±17*	360±19*
131	376±19	370±23	364±17	365±20
139	386±20	375±23	369±17	373±21
146	392±21	374±25	371±18	373±20
152	386±21	378±24	372±17	375±19

TABLE 7 (CONT.)

MEAN BODY WEIGHT VALUES (GRAMS) OF MALE RATS
MAINTAINED ON ETHYLENE DIBROMIDE FOR 13 WEEK

DAYS ON TEST	DOSE LEVEL PPM			
	CONTROL	3	10	40
159	399±21	381±25	377±16	383±20
166	401±23	385±22	380±16	385±22
173	406±21	387±25	381±16*	386±21
180	407±23	396±27	386±17	392±25

* STATISTICALLY SIGNIFICANT DEVIATION FROM CONTROL USING DUNNETT'S
TEST, $p < 0.05$.

TABLE 8

MEAN BODY WEIGHT VALUES (GRAMS) OF FEMALE RATS
MAINTAINED ON ETHYLENE DIBROMIDE FOR 13 WEEK

DAYS ON TEST	DOSE LEVEL PPM			
	CONTRL	3	10	40
-2	129± 6	127± 6	127± 6	129± 5
1	139± 6	139± 6	139± 7	139± 6
4	141± 6	142± 7	142± 7	135± 7*
7	141± 6	141± 8	141± 7	140± 6
11	152± 8	151± 7	152± 7	150± 6
14	154± 8	152± 7	154± 8	151± 7
20	153±10	151± 8	153± 8	151± 8
24	161±10	159± 7	161± 9	158± 8
27	159±11	157± 6	161± 9	158± 7
35	161±12	161± 7	162±11	162± 6
42	172±11	171± 8	173±11	171± 8
49	179±12	176± 8	179±10	179± 7
55	182±11	179± 7	181±11	179± 7
63	185±11	185± 8	188±11	185± 8
69	188±12	188± 8	190±11	188± 8
76	192±11	191± 9	193±12	188± 9
83	193±10	192± 9	195±11	192± 9
90	196±10	194± 9	195±13	193±10
97	199±11	195±15	192±14	195±10
104	197±12	195±14	195±14	196±13
111	193±13	193±13	196±13	197±13
118	189±13	186±12	192±13	189±12
125	192±14	197±12	199±12	192±12
131	191±13	192±11	196±13	195±13
139	190±12	189±12	194±14	190±13
146	192±12	191±11	196±14	192±11
152	192±13	189±10	194±16	190±13

TABLE 8 (CONT.)

MEAN BODY WEIGHT VALUES (GRAMS) OF FEMALE RATS
MAINTAINED ON ETHYLENE DIBROMIDE FOR 13 WEEK

DAYS ON TEST	DOSE LEVEL PPM			
	CONTROL	3	10	40
159	398±21	361±25	377±16	383±20
166	401±23	385±22	380±16	385±22
173	406±21	387±25	381±16*	386±21
180	407±23	396±27	386±17	392±25

* STATISTICALLY SIGNIFICANT DEVIATION FROM CONTROL USING DUNNETT'S
TEST, $p < 0.05$.

TABLE 9
MEAN BODY WEIGHT GAIN VALUES (GRAMS) OF MALE RATS
MAINTAINED ON ETHYLENE DIBROMIDE FOR ONE WEEK

<u>Days on test</u>	<u>Control</u>	<u>DOSE LEVEL PPM</u>		
		<u>3</u>	<u>10</u>	<u>40</u>
-2	0±0	0±0	0±0	0±0
1	9±3	8±2	9±2	11±4
4	18±3	19±3	18±3	13±4*

*Statistically significant from control value by Dunnett's test, $p < 0.05$.

TABLE 10

MEAN BODY WEIGHT GAIN VALUES (GRAMS) OF MALE RATS
MAINTAINED ON ETHYLENE DIBROMIDE FOR 13 WEEK

DAYS ON TEST	DOSE LEVEL PPM			
	CONTROL 0 ± 0	3 0 ± 0	10 0 ± 0	40 0 ± 0
1	16 ± 2	16 ± 2	17 ± 2	19 ± 3**
4	22 ± 3	22 ± 3	23 ± 3	18 ± 3**
7	25 ± 3	27 ± 4	25 ± 3	23 ± 3
11	45 ± 4	44 ± 5	43 ± 4	39 ± 4**
14	47 ± 4	46 ± 5	43 ± 4	44 ± 5**
20	39 ± 10	41 ± 12	40 ± 10	32 ± 14*
24	55 ± 9	57 ± 9	55 ± 3	49 ± 9**
27	53 ± 5	59 ± 10	53 ± 5	50 ± 10**
35	52 ± 10	57 ± 13	53 ± 9	61 ± 8
42	71 ± 3	90 ± 12	39 ± 3	85 ± 7
49	109 ± 3	108 ± 12	107 ± 3	103 ± 8
55	113 ± 9	117 ± 11	115 ± 9	110 ± 9*
53	123 ± 10	127 ± 11	127 ± 10	120 ± 7*
59	125 ± 10	132 ± 10	131 ± 10	124 ± 8
75	139 ± 11	139 ± 10	139 ± 11	129 ± 7**
83	145 ± 13	143 ± 11	144 ± 10	134 ± 9**
90	153 ± 14	149 ± 12	143 ± 11	139 ± 10**
97	157 ± 17	155 ± 15	153 ± 12	148 ± 12
104	157 ± 15	153 ± 17	158 ± 11	157 ± 13
111	153 ± 14	159 ± 17	155 ± 11	167 ± 14
113	179 ± 13	172 ± 17	153 ± 12	170 ± 14
125	134 ± 14	172 ± 17	171 ± 12	172 ± 13
131	175 ± 15	130 ± 12	175 ± 10	177 ± 15
139	135 ± 15	134 ± 18	130 ± 10	135 ± 15
145	192 ± 15	134 ± 20	131 ± 3	185 ± 15
152	135 ± 15	135 ± 19	133 ± 10	187 ± 14

TABLE 10 (CONT.)

MEAN BODY WEIGHT GAIN VALUES (GRAMS) OF MALE RATS
MAINTAINED ON ETHYLENE DIBROMIDE FOR 13 WEEK

DAYS ON TEST	DOSE LEVEL PPM			
	CONTR.	3	10	40
159	193±15	190±20	183±10	195±16
155	201±13	195±17	190±10	197±17
173	205±15	197±20	192±10	198±16
130	207±17	203±23	197±10	205±20

* STATISTICALLY SIGNIFICANT DEVIATION FROM CONTROL USING DUNNETT'S
TEST, $p < 0.05$.

TABLE 11

MEAN BODY WEIGHT GAIN VALUES (GRAMS) OF FEMALE RATS
MAINTAINED ON ETHYLENE DIBROMIDE FOR 13 WEEK

DAYS ON TEST	DOSE LEVEL PP4			
	CONTROL 0 ± 0	3 0 ± 0	10 0 ± 0	40 0 ± 0
1	10 ± 2	12 ± 2*	12 ± 2	10 ± 2
4	12 ± 3	14 ± 4	14 ± 2	5 ± 4**
7	12 ± 3	14 ± 3	14 ± 3	11 ± 4
11	23 ± 4	24 ± 2	25 ± 3	21 ± 3
14	25 ± 4	25 ± 3	25 ± 3	22 ± 4*
20	24 ± 7	23 ± 6	25 ± 5	22 ± 5
24	32 ± 5	32 ± 4	33 ± 5	29 ± 5
27	30 ± 7	29 ± 5	33 ± 5	29 ± 5
35	33 ± 3	33 ± 4	35 ± 7	35 ± 4
42	43 ± 2	42 ± 6	45 ± 7	42 ± 5
49	50 ± 3	50 ± 5	52 ± 7	50 ± 5
55	53 ± 7	52 ± 5	54 ± 7	50 ± 5
59	57 ± 3	57 ± 7	50 ± 3	56 ± 7
59	59 ± 3	50 ± 7	52 ± 7	59 ± 5
75	53 ± 7	52 ± 7	55 ± 9	59 ± 7
83	55 ± 5	54 ± 7	58 ± 3	63 ± 3
90	57 ± 5	57 ± 6	55 ± 9	64 ± 9
97	71 ± 9	71 ± 7	55 ± 3	67 ± 3
104	70 ± 3	72 ± 7	59 ± 3	69 ± 11
111	55 ± 9	70 ± 5	59 ± 9	59 ± 11
113	51 ± 10	53 ± 6	55 ± 7	61 ± 10
125	55 ± 11	74 ± 5	73 ± 3	64 ± 10
131	54 ± 10	53 ± 4	59 ± 7	67 ± 12
139	52 ± 10	55 ± 4	57 ± 3	52 ± 12
145	55 ± 10	53 ± 4	70 ± 3	54 ± 11
152	54 ± 11	55 ± 3	55 ± 10	52 ± 12
159	59 ± 10	72 ± 4	73 ± 10	68 ± 11

TABLE 11 (CONT.)

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MEAN BODY WEIGHT GAIN VALUES (GRAMS) OF FEMALE RATS
MAINTAINED ON ETHYLENE DIBROMIDE FOR 13 WEEK

	DOSE LEVEL PPM			
159	59±10	72± 4	73±10	66±11
155	55± 9	59± 4	70± 9	64±12
173	57±10	71± 4	73±11	67±12
130	57±11	72± 5	70±11	67±12

* STATISTICALLY SIGNIFICANT DEVIATION FROM CONTROL USING DUNNETT'S
TEST, $p < 0.05$.

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TABLE 12

MEAN ($\pm$ SD) HEMATOLOGY VALUES FOR RATS EXPOSED TO ETHYLENE DIBROMIDE BY INHALATION

Exposure level	Sex	Length of Exposure (weeks)	HCT %	RBC $\times 10^6/\text{mm}^3$	Hgb gm/100cc	WBC $\times 10^3/\text{mm}^3$	Differential Count %					
							Neut					
							Seg	B/J	Lymph	Mono	Eos	Baso
0	Male	6	50.6 $\pm$ 4.1	8.13 $\pm$ 0.49	16.5 $\pm$ 0.6	16.4 $\pm$ 1.7	23	1/0	69	6	1	0
3	Male	6	48.4 $\pm$ 1.9	8.16 $\pm$ 0.29	16.3 $\pm$ 0.5	14.2 $\pm$ 1.1 *	24	1/0	69	5	1	0
10	Male	6	47.9 $\pm$ 0.7	8.26 $\pm$ 0.24	16.3 $\pm$ 0.5	14.3 $\pm$ 0.8 *	23	1/0	69	5	2	0
40	Male	6	47.4 $\pm$ 1.6	8.26 $\pm$ 0.14	16.2 $\pm$ 0.2	16.7 $\pm$ 1.7	29	1/0	63	6	1	0
0	Male	13	47.9 $\pm$ 1.3	8.51 $\pm$ 0.33	16.2 $\pm$ 0.6	15.1 $\pm$ 1.8	26	0/0	68	5	1	0
3	Male	13	51.3 $\pm$ 1.7*	8.44 $\pm$ 0.17	16.5 $\pm$ 0.6	15.8 $\pm$ 2.3	20	1/0	73	5	1	0
10	Male	13	49.6 $\pm$ 1.4	8.35 $\pm$ 0.42	16.2 $\pm$ 0.6	15.4 $\pm$ 2.9	26	1/0	68	5	0	0
40	Male	13	49.7 $\pm$ 1.0	8.67 $\pm$ 0.23	16.1 $\pm$ 0.3	12.6 $\pm$ 0.6	17	1/0	77	5	0	0
0	Female	13	49.6 $\pm$ 1.9	8.07 $\pm$ 0.26	16.6 $\pm$ 0.4	12.5 $\pm$ 1.3	16	1/0	76	6	1	0
3	Female	13	48.6 $\pm$ 0.9	7.83 $\pm$ 0.17	16.2 $\pm$ 0.4	13.2 $\pm$ 2.7	20	1/0	73	5	1	0
10	Female	13	48.1 $\pm$ 0.9	7.87 $\pm$ 0.44	16.1 $\pm$ 0.5	11.8 $\pm$ 1.1	24	1/0	69	5	1	0
40	Female	13	47.4 $\pm$ 1.6*	7.74 $\pm$ 0.44	15.7 $\pm$ 0.8*	12.0 $\pm$ 1.3	19	1/0	73	6	1	0

*Significantly different from control by Dunnett's test $p < 0.05$.

TABLE 13

MEAN ($\pm$ S.D.) URINALYSIS VALUES FOR MALE RATS EXPOSED TO ETHYLENE DIBROMIDE BY INHALATION

Exposure Level (ppm)	Length of Exposure (weeks)	Sample Size	Specific Gravity	pH	Glucose	Protein ^a	Ketones ^a	Bilirubin	Blood ^a	Urobilinogen
0	6	7	1.056 $\pm$ 0.017 ^d	7 $\pm$ 1	- ^b	1+(2) 2+(5)	1+(7)	-	tr(1)	1(7)
3	6	7	1.053 $\pm$ 0.005	7 $\pm$ 1	-	1+(4) 2+(3)	1+(7)	-	tr(1)	1(7)
10	6	7	1.042 $\pm$ 0.021	7 $\pm$ 1	-	1+(3) 2+(4)	1+(6)	-	-	1(7)
40	6	7	1.047 $\pm$ 0.017	7 $\pm$ 1	-	1+(3) 2+(4)	1+(7)	-	-	1(7)
0	13	6	1.064 $\pm$ 0.002	6 $\pm$ 1	-	1+(2) 2+(2) 3+(2)	-	-	-	1(6)
3	13	7	1.067 $\pm$ 0.002	6 $\pm$ 0	-	2+(6) 3+(1)	-	-	-	1(7)
10	13	7	1.059 $\pm$ 0.007	7 $\pm$ 1	-	2+(5) 3+(2)	-	-	-	1(7)
40	13	7	1.057 $\pm$ 0.007	6 $\pm$ 0	-	2+(7)	-	-	-	1(7)
0	13 ^c	7	1.065 $\pm$ 0.006	7 $\pm$ 0.5	-	3+(3) 4+(4)	1+(6)	-	-	1(7)
3	13 ^c	7	1.064 $\pm$ 0.007	7 $\pm$ 1	-	2+(1) 3+(3) 4+(3)	1+(7)	-	-	1(7)
10	13 ^c	7	1.064 $\pm$ 0.007	7.5 $\pm$ 1	-	2+(1) 3+(5) 4+(1)	1+(6)	-	-	1(7)
40	13 ^c	7	1.060 $\pm$ 0.005	7 $\pm$ 1	-	2+(2) 3+(3) 4+(2)	1+(7)	-	-	1(7)

^aNumber in parenthesis is the number of samples in which the indicated observation was made.^bIndicates a negative finding.^cAnimals were exposed to EDB for 13 weeks, allowed an 88-89 day recovery period and then necropsied.^d $\bar{X} \pm$ S.D.No values were significantly different from control by Dunnett's test, $p < 0.05$.

TABLE 14

MEAN ($\pm$ S.D.) URINALYSIS VALUES FOR FEMALE RATS EXPOSED TO ETHYLENE DIBROMIDE BY INHALATION

Exposure Level (ppm)	Length of Exposure (weeks)	Sample Size	Specific Gravity	pH	Glucose	Protein ^a	Ketones ^a	Bilirubin	Blood ^a	Urobilinogen ^a
0	13	7	1.066 $\pm$ 0.004 ^d	6 $\pm$ 0	- ^b	1+(4) 2+(2) 3+(1)	-	-	tr(1)	1(7)
3	13	7	1.061 $\pm$ 0.005	7 $\pm$ 1	-	1+(4) 2+(3)	-	-	-	1(7)
10	13	6	1.063 $\pm$ 0.006	6 $\pm$ 0	-	tr(1) 1 $\pm$ 2 2+(4)	-	-	-	1(7)
40	13	7	1.043 $\pm$ 0.010*	7 $\pm$ 0	-	tr(5) 1 $\pm$ (2)	-	-	-	1(7)
0	13 ^c	7	1.065 $\pm$ 0.006	7 $\pm$ 0.5	-	3+(3) 4+(4)	1+(6)	-	-	1(7)
3	13 ^c	7	1.064 $\pm$ 0.007	7 $\pm$ 1	-	2+(1) 3+(3) 4+(3)	1+(7)	-	-	1(7)
10	13 ^c	7	1.068 $\pm$ 0.008	6 $\pm$ 0.5	-	1+(4) 2+(2) 3+(1)	tr(2) 1+(5)	-	-	1(7)
40	13 ^c	7	1.067 $\pm$ 0.005	6.5 $\pm$ 0.5	-	1+(4) 2+(3)	tr(3) 1+(4)	-	-	1(7)

^aNumber in parenthesis is the number of samples in which the indicated observation was made.^bIndicates a negative finding.^cAnimals were exposed to EDB for 13 weeks allowed an 88-89 day recovery period and then necropsied.^d $\bar{X} \pm$ S.D.*Values were significantly different from control by Dunnett's test, $p < 0.05$.

TABLE 15
MEAN ($\pm$ S.D.) CLINICAL CHEMISTRY VALUES OF MALE RATS EXPOSED TO ETHYLENE DIBROMIDE

<u>Exposure Level</u>	<u>Length of Exposure (weeks)</u>	<u>BUN mg/100ml</u>	<u>SGPT mU/ml</u>	<u>SGOT¹ mU/ml</u>	<u>AP mU/ml</u>	<u>Glucose mg/100ml</u>	<u>T. Bilirubin mg/100ml</u>	<u>Serum Bromide ppm</u>
0	1	14 $\pm$ 1	19 $\pm$ 2	88 $\pm$ 29	167 $\pm$ 11	156 $\pm$ 8	0.2 $\pm$ 0.0	N.D.
3	1	14 $\pm$ 1	18 $\pm$ 3	82 $\pm$ 25	170 $\pm$ 13	170 $\pm$ 15	0.2 $\pm$ 0.1	N.D.
10	1	14 $\pm$ 1	18 $\pm$ 3	89 $\pm$ 3	174 $\pm$ 13	153 $\pm$ 9	0.2 $\pm$ 0.1	N.D.
40	1	14 $\pm$ 2	16 $\pm$ 4*	81 $\pm$ 34	170 $\pm$ 10	154 $\pm$ 15	0.2 $\pm$ 0.1	N.D.
0	6	14 $\pm$ 1	21 $\pm$ 5	101 $\pm$ 18	102 $\pm$ 18	135 $\pm$ 9	0.3 $\pm$ 0.1	10.3 $\pm$ 0.1
3	6	14 $\pm$ 2	20 $\pm$ 3	118 $\pm$ 31	98 $\pm$ 8	128 $\pm$ 11	0.2 $\pm$ 0.0	42 $\pm$ 2*
10	6	13 $\pm$ 1	19 $\pm$ 5	108 $\pm$ 34	94 $\pm$ 8	129 $\pm$ 9	0.2 $\pm$ 0.1	114 $\pm$ 3*
40	6	14 $\pm$ 2	21 $\pm$ 4	106 $\pm$ 30	101 $\pm$ 5	132 $\pm$ 12	0.3 $\pm$ 0.1	379 $\pm$ 12*
0	13	14 $\pm$ 1	19 $\pm$ 3	77 $\pm$ 13	68 $\pm$ 3	142 $\pm$ 9	0.1 $\pm$ 0.1	N.D.
3	13	13 $\pm$ 2	21 $\pm$ 4	87 $\pm$ 25	69 $\pm$ 8	135 $\pm$ 10	0.2 $\pm$ 0.1*	N.D.
10	13	13 $\pm$ 1	20 $\pm$ 3	71 $\pm$ 7	67 $\pm$ 3	137 $\pm$ 17	0.2 $\pm$ 0.0*	N.D.
40	13	13 $\pm$ 1	20 $\pm$ 1	83 $\pm$ 8	73 $\pm$ 5	144 $\pm$ 25	0.1 $\pm$ 0.0	N.D.

*Significantly different from control values by Dunnett's test, $p < 0.05$.

N.D. = No data

TABLE 16
MEAN ($\pm$ S.D.) ORGAN WEIGHTS AND ORGAN TO BODY WEIGHT RATIOS
FOR MALE RATS EXPOSED TO ETHYLENE DIBROMIDE BY INHALATION

Exposure Level	Length of Exposure (wks)	Body Weight	Liver		Kidney		Brain		Heart		Thymus		Testes	
			g	g/100g	g	g/100g	g	g/100g	g	g/100g	g	g/100g	g	g/100g
0	1	206.5 $\pm$ 6.4	6.09 $\pm$ 0.28	2.95 $\pm$ 0.05	1.69 $\pm$ 0.07	0.82 $\pm$ 0.02	1.76 $\pm$ 0.02	0.85 $\pm$ 0.03	0.68 $\pm$ 0.04	0.33 $\pm$ 0.01	0.29 $\pm$ 0.03	0.14 $\pm$ 0.01	2.74 $\pm$ 0.11	1.33 $\pm$ 0.04
1	1	204.7 $\pm$ 14.6	6.07 $\pm$ 0.51	2.96 $\pm$ 0.11	1.64 $\pm$ 0.12	0.80 $\pm$ 0.03	1.75 $\pm$ 0.07	0.86 $\pm$ 0.06	0.68 $\pm$ 0.05	0.33 $\pm$ 0.01	0.28 $\pm$ 0.04	0.14 $\pm$ 0.02	2.69 $\pm$ 0.20	1.31 $\pm$ 0.04
0	1	206.9 $\pm$ 11.8	6.14 $\pm$ 0.46	2.97 $\pm$ 0.13	1.71 $\pm$ 0.11	0.83 $\pm$ 0.03	1.77 $\pm$ 0.05	0.86 $\pm$ 0.03	0.67 $\pm$ 0.04	0.32 $\pm$ 0.01	0.30 $\pm$ 0.02	0.14 $\pm$ 0.01	2.69 $\pm$ 0.15	1.30 $\pm$ 0.04
10	1	204.8 $\pm$ 9.3	6.24 $\pm$ 0.44	3.04 $\pm$ 0.10	1.72 $\pm$ 0.11	0.84 $\pm$ 0.03	1.77 $\pm$ 0.04	0.86 $\pm$ 0.04	0.65 $\pm$ 0.04	0.32 $\pm$ 0.01	0.28 $\pm$ 0.03	0.14 $\pm$ 0.01	2.73 $\pm$ 0.11	1.33 $\pm$ 0.05
0	6	261.2 $\pm$ 7.5	7.10 $\pm$ 0.22	2.72 $\pm$ 0.10	1.90 $\pm$ 0.06	0.73 $\pm$ 0.02	1.86 $\pm$ 0.03	0.71 $\pm$ 0.02	0.79 $\pm$ 0.03	0.30 $\pm$ 0.01	0.30 $\pm$ 0.03	0.11 $\pm$ 0.01	2.84 $\pm$ 0.11	1.09 $\pm$ 0.06
3	6	253.1 $\pm$ 12.9	6.85 $\pm$ 0.46	2.71 $\pm$ 0.10	1.93 $\pm$ 0.11	0.76 $\pm$ 0.02*	1.85 $\pm$ 0.05	0.73 $\pm$ 0.03	0.79 $\pm$ 0.05	0.31 $\pm$ 0.02	0.30 $\pm$ 0.05	0.12 $\pm$ 0.02	2.90 $\pm$ 0.12	1.15 $\pm$ 0.06
10	6	252.9 $\pm$ 10.1	7.00 $\pm$ 0.27	2.77 $\pm$ 0.06	1.95 $\pm$ 0.10	0.77 $\pm$ 0.03*	1.87 $\pm$ 0.03	0.74 $\pm$ 0.03*	0.78 $\pm$ 0.05	0.31 $\pm$ 0.01	0.33 $\pm$ 0.06	0.13 $\pm$ 0.02	2.88 $\pm$ 0.11	1.14 $\pm$ 0.04
10	6	244.8 $\pm$ 13.1*	7.36 $\pm$ 0.52	3.01 $\pm$ 0.11*	2.06 $\pm$ 0.12*	0.84 $\pm$ 0.03*	1.84 $\pm$ 0.04	0.75 $\pm$ 0.03*	0.76 $\pm$ 0.02	0.31 $\pm$ 0.01	0.29 $\pm$ 0.04	0.12 $\pm$ 0.01	2.77 $\pm$ 0.25	1.13 $\pm$ 0.07
0	13	321.3 $\pm$ 14.9	7.99 $\pm$ 0.40	2.47 $\pm$ 0.07	2.33 $\pm$ 0.08	0.72 $\pm$ 0.03	1.96 $\pm$ 0.02	0.61 $\pm$ 0.03	0.91 $\pm$ 0.04	0.28 $\pm$ 0.01	0.24 $\pm$ 0.03	0.07 $\pm$ 0.01	3.05 $\pm$ 0.13	0.95 $\pm$ 0.04
3	13	320.6 $\pm$ 14.2	8.12 $\pm$ 0.62	2.53 $\pm$ 0.10	2.37 $\pm$ 0.15	0.74 $\pm$ 0.02	1.95 $\pm$ 0.04	0.61 $\pm$ 0.02	0.91 $\pm$ 0.05	0.28 $\pm$ 0.01	0.27 $\pm$ 0.02	0.08 $\pm$ 0.01	3.12 $\pm$ 0.15	0.97 $\pm$ 0.04
10	13	321.0 $\pm$ 16.1	8.30 $\pm$ 0.47	2.59 $\pm$ 0.05	2.38 $\pm$ 0.10	0.74 $\pm$ 0.02	1.94 $\pm$ 0.06	0.60 $\pm$ 0.03	0.93 $\pm$ 0.05	0.29 $\pm$ 0.01	0.28 $\pm$ 0.02	0.09 $\pm$ 0.01*	3.08 $\pm$ 0.17	0.96 $\pm$ 0.04
10	13	299.0 $\pm$ 10.2*	8.20 $\pm$ 0.48	2.74 $\pm$ 0.09*	2.41 $\pm$ 0.12	0.80 $\pm$ 0.04*	1.92 $\pm$ 0.03*	0.64 $\pm$ 0.03*	0.86 $\pm$ 0.03	0.29 $\pm$ 0.01	0.25 $\pm$ 0.05	0.08 $\pm$ 0.02	2.84 $\pm$ 0.17*	0.95 $\pm$ 0.07
0	13 ^a	390.2 $\pm$ 21.6	10.29 $\pm$ 0.76	2.64 $\pm$ 0.10	2.77 $\pm$ 0.19	0.71 $\pm$ 0.03	1.96 $\pm$ 0.06	0.50 $\pm$ 0.03	0.98 $\pm$ 0.05	0.25 $\pm$ 0.01	0.19 $\pm$ 0.02	0.05 $\pm$ 0.01	3.20 $\pm$ 0.14	0.82 $\pm$ 0.04
3	13 ^a	371.6 $\pm$ 20.7	9.41 $\pm$ 0.64	2.53 $\pm$ 0.08	2.62 $\pm$ 0.16	0.71 $\pm$ 0.02	1.95 $\pm$ 0.06	0.53 $\pm$ 0.03	0.95 $\pm$ 0.06	0.26 $\pm$ 0.01	0.19 $\pm$ 0.03	0.05 $\pm$ 0.01	3.19 $\pm$ 0.14	0.86 $\pm$ 0.03*
10	13 ^a	366.4 $\pm$ 16.9*	9.49 $\pm$ 0.45	2.59 $\pm$ 0.09	2.60 $\pm$ 0.13	0.71 $\pm$ 0.03	1.96 $\pm$ 0.04	0.54 $\pm$ 0.03*	0.98 $\pm$ 0.03	0.27 $\pm$ 0.01	0.18 $\pm$ 0.03	0.05 $\pm$ 0.01	3.23 $\pm$ 0.11	0.88 $\pm$ 0.03*
10	13 ^a	370.8 $\pm$ 19.2	10.18 $\pm$ 0.69	2.75 $\pm$ 0.13*	2.74 $\pm$ 0.20	0.74 $\pm$ 0.03	1.96 $\pm$ 0.04	0.53 $\pm$ 0.02	0.97 $\pm$ 0.05	0.26 $\pm$ 0.01	0.17 $\pm$ 0.02	0.05 $\pm$ 0.00	3.18 $\pm$ 0.09	0.86 $\pm$ 0.03*

*significantly different from control by Dunnett's test, $p < 0.05$.

Animals were exposed to EDB for 13 weeks, allowed an 88-89 day recovery period and then necropsied.

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TABLE 17
MEAN ($\pm$ S.D.) ORGAN WEIGHTS AND ORGAN TO BODY WEIGHT RATIOS
FOR FEMALE RATS EXPOSED TO ETHYLENE DIBROMIDE BY INHALATION

Exposure Level	Length of Exposure (wks)	Body Weight	Liver		Kidney		Brain		Heart		Thymus	
			g	g/100g	g	g/100g	g	g/100g	g	g/100g	g	g/100g
0	13	184.1 $\pm$ 9.3	4.57 $\pm$ 0.17	2.49 $\pm$ 0.08	1.44 $\pm$ 0.04	0.78 $\pm$ 0.04	1.82 $\pm$ 0.02	0.99 $\pm$ 0.05	0.60 $\pm$ 0.02	0.33 $\pm$ 0.01	0.21 $\pm$ 0.03	0.12 $\pm$ 0.02
3	13	181.1 $\pm$ 7.6	4.60 $\pm$ 0.15	2.54 $\pm$ 0.08	1.44 $\pm$ 0.07	0.80 $\pm$ 0.04	1.82 $\pm$ 0.02	1.01 $\pm$ 0.02	0.60 $\pm$ 0.04	0.33 $\pm$ 0.02	0.22 $\pm$ 0.03	0.12 $\pm$ 0.02
10	13	181.0 $\pm$ 9.1	4.79 $\pm$ 0.34	2.65 $\pm$ 0.14*	1.48 $\pm$ 0.06	0.82 $\pm$ 0.02	1.82 $\pm$ 0.03	1.01 $\pm$ 0.05	0.60 $\pm$ 0.04	0.33 $\pm$ 0.02	0.24 $\pm$ 0.05	0.13 $\pm$ 0.02
40	13	176.3 $\pm$ 7.9	4.97 $\pm$ 0.22*	2.82 $\pm$ 0.10*	1.50 $\pm$ 0.08	0.85 $\pm$ 0.05	1.82 $\pm$ 0.06	1.03 $\pm$ 0.05	0.59 $\pm$ 0.03	0.34 $\pm$ 0.02	0.23 $\pm$ 0.03	0.13 $\pm$ 0.02
0	13 ^a	186.2 $\pm$ 14.4	4.75 $\pm$ 0.71	2.54 $\pm$ 0.22	1.46 $\pm$ 0.12	0.78 $\pm$ 0.04	1.79 $\pm$ 0.05	0.96 $\pm$ 0.07	0.58 $\pm$ 0.04	0.31 $\pm$ 0.02	0.14 $\pm$ 0.01	0.07 $\pm$ 0.01
3	13 ^a	181.0 $\pm$ 10.3	4.49 $\pm$ 0.38	2.48 $\pm$ 0.13	1.47 $\pm$ 0.14	0.81 $\pm$ 0.04	1.78 $\pm$ 0.05	0.98 $\pm$ 0.05	0.61 $\pm$ 0.06	0.33 $\pm$ 0.02	0.14 $\pm$ 0.02	0.08 $\pm$ 0.01
10	13 ^a	185.4 $\pm$ 15.9	4.75 $\pm$ 0.38	2.57 $\pm$ 0.10	1.54 $\pm$ 0.12	0.83 $\pm$ 0.06	1.77 $\pm$ 0.05	0.96 $\pm$ 0.06	0.62 $\pm$ 0.06	0.33 $\pm$ 0.02	0.14 $\pm$ 0.02	0.08 $\pm$ 0.02
40	13 ^a	181.8 $\pm$ 12.2	4.62 $\pm$ 0.35	2.54 $\pm$ 0.08	1.49 $\pm$ 0.12	0.82 $\pm$ 0.03	1.78 $\pm$ 0.03	0.98 $\pm$ 0.06	0.61 $\pm$ 0.04	0.33 $\pm$ 0.02	0.13 $\pm$ 0.02	0.07 $\pm$ 0.01

*Significantly different from control by Dunnett's test, $p < 0.05$.

^a Animals were exposed to EDB for 13 weeks, allowed an 88-89 Day recovery period and then necropsied.

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TABLE 18

GROSS PATHOLOGIC OBSERVATIONS ON MALE RATS EXPOSED TO
VAPORS OF ETHYLENE DIBROMIDE (6 DAYS ON STUDY)

<u>Exposure Concentration (ppm)</u>	<u>0</u>	<u>3</u>	<u>10</u>	<u>40</u>
<u>Number of rats examined</u>	<u>10</u>	<u>10</u>	<u>10</u>	<u>10</u>
No visible lesions	2	2	4	5
<u>GENERAL</u>				
Accessory spleen present	1	0	0	0
Necrosis and atrophy of the tip of the tail	1	0	0	0
<u>SALIVARY GLANDS</u>				
Edema	1	0	0	0
<u>EYES</u>				
Corneal cloudiness	4	2	4	1
<u>LUNGS</u>				
Single circumscribed red focus	1	4	2	0
Few circumscribed red foci	4	1	0	2
<u>LIVER</u>				
Diaphragmatic hernia	0	0	1	0
<u>URINARY BLADDER</u>				
Organized plug within lumen	1	1	0	0

Data listed as number of rats with the listed observation.

TABLE 19

HISTOPATHOLOGIC OBSERVATIONS ON MALE RATS
EXPOSED TO VAPORS OF ETHYLENE DIBROMIDE (6 DAYS ON STUDY)

Exposure Concentration (ppm)	0	3	10	40
Number of Rats Examined	10	10	10	10
<u>NASAL TURBINATES</u> (Number of tissues examined microscopically)	10	10	10	10
Hyperplasia of respiratory epithelium				
- isolated, very slight to slight	0	0	1	0
- focal, very slight to slight	0	0	4	0
- scattered, very slight to slight	0	0	4	3
- multifocal, very slight to slight	0	0	0	3
- diffuse, very slight to slight	0	0	0	4
Individual epithelial cell necrosis, respiratory epithelium				
- focal, very slight	0	0	1	5
Epithelial inflammation, respiratory epithelium				
- focal, slight	5	0	0	0
- multifocal, slight	0	0	1	0
Submucosal inflammation, respiratory epithelium				
- focal, slight	2	1	0	0
- scattered, slight	3	0	0	0
- multifocal, slight	5	0	1	0
Submucosal inflammation, olfactory epithelium				
- focal, slight	1	0	0	0
Inflammatory cells in lumen				
- focal, very slight	4	0	0	0
<u>TRACHEA</u> (Number of tissues examined microscopically)	10	10	10	10
Submucosal aggregates of mononuclear cells				
- focal, slight	0	2	0	3
- multifocal, slight	0	0	0	1
- diffuse, moderate	10	0	2	0
Epithelial hyperplasia				
- diffuse, slight	10	3	6	8
Inflammatory cells in lumen				
- focal, slight	3	0	0	0
<u>LUNGS/BRONCHI</u> (Number of tissues examined microscopically)	10	10	10	10
Peribronchiolar aggregates of mononuclear cells				
- focal, slight	10	10	9	10
Subpleural aggregates of mononuclear cells				
- focal, slight	8	4	8	6
- multifocal, slight	1	0	0	0
Aggregates of alveolar macrophages				
- focal, slight	2	1	2	1
Interstitial inflammation				
- focal, slight	1	0	0	1
Perivascular aggregate of mononuclear cells				
- focal, slight	1	0	0	0
Inflammation and fibrosis of pleura				
- focal, slight	2	0	0	0
<u>LIVER</u> (Number of tissues examined microscopically)	10	10	10	10
Aggregates of mononuclear cells				
- focal, slight	6	3	5	8
Periportal aggregates of mononuclear cells				
- focal, slight	0	1	1	2
Single focus of hepatocellular necrosis and accompanying inflammation				
- slight	0	2	0	2
Single area of biliary hyperplasia, fibrosis, and inflammation				
- moderate	0	0	1	0
Single focus of hepatocellular alteration				
- slight	0	0	1	0
Biliary hyperplasia				
- multifocal, slight	0	1	0	0

TABLE 19 (cont.)

HISTOPATHOLOGIC OBSERVATIONS ON MALE RATS
EXPOSED TO VAPORS OF ETHYLENE DIBROMIDE (6 DAYS ON STUDY)

<u>Exposure Concentration (ppm)</u>	<u>0</u>	<u>3</u>	<u>10</u>	<u>40</u>
<u>Number of Rats Examined</u>	<u>10</u>	<u>10</u>	<u>10</u>	<u>10</u>
<u>KIDNEYS</u> (Number of tissues examined microscopically)	10	10	10	10
Atrophy of renal tubules				
- focal, slight	4	1	0	0
Aggregate of mononuclear cells				
- focal, slight	1	0	1	0
<u>TESTES</u> (Number of tissues examined microscopically)	10	10	10	10
Unilateral decreased spermatogenesis				
- focal, very slight	0	1	0	0
- focal, moderate	0	0	1	0
<u>SPLEEN</u> (Number of tissues examined microscopically)	1	0	0	0
Accessory spleen	1	0	0	0
<u>THYROID</u> (Number of tissues examined microscopically)	4	3	3	5
Hemorrhage				
- focal, slight	0	1	0	0
Aggregates of mononuclear cells and debris within follicles				
- focal, slight	0	1	0	0
<u>Additional tissues examined microscopically and showing no visible lesions</u>				
ESOPHAGUS	10	10	10	10
AORTA	5	4	1	0
LARGE MEDIASTINAL ARTERY	5	7	8	7
THORACIC LYMPH NODE	4	2	3	3
PARATHYROID	2	1	1	2
PANCREAS	1	0	0	1
THYMUS	0	1	0	1
PHARYNX	0	1	4	2

TABLE 20

GROSS PATHOLOGIC OBSERVATIONS ON MALE RATS EXPOSED TO
VAPORS OF ETHYLENE DIBROMIDE (40 DAYS ON STUDY)

<u>Exposure Concentration (ppm)</u>	<u>0</u>	<u>3</u>	<u>10</u>	<u>40</u>
<u>Number of rats examined</u>	<u>10</u>	<u>10</u>	<u>10</u>	<u>10</u>
No visible lesions	6	6	6	4
<u>EYES</u>				
Corneal cloudiness	2	2	3	2
Decreased in size with cataract formation - unilateral (possibly congenital)	0	0	0	2
Focal intraocular opacity	0	0	1	0
<u>LUNGS</u>				
Single circumscribed red focus	1	0	2	3
Few circumscribed red foci	1	1	0	1
<u>LIVER</u>				
Diffuse paleness	1	1	0	0
<u>URINARY BLADDER</u>				
Organized plug within lumen	0	1	0	0
<u>STOMACH</u>				
Hemolyzed blood clot within lumen	0	1	0	0
Pinpoint focus on glandular mucosa	0	1	0	0
<u>MESENTERIC TISSUE</u>				
Tag of strangulated omental fat	1	0	0	0

Data listed as number of rats with the listed observation.

TABLE 21

HISTOPATHOLOGIC OBSERVATIONS ON MALE RATS
EXPOSED TO VAPORS OF ETHYLENE DIBROMIDE (40 DAYS ON STUDY)

Exposure Concentration (ppm)	0	3	10	40
Number of Rats Examined	10	10	10	10
<u>NASAL TURBINATES</u> (Number of tissues examined microscopically)	10	10	10	10
Hyperplasia of respiratory epithelium				
- isolated, very slight to slight	0	0	3	0
- focal, very slight to slight	0	0	2	0
- scattered, very slight to slight	0	0	1	0
- multifocal, very slight to slight	0	0	3	2
- diffuse, very slight to slight	0	0	1	8
Individual epithelial cell necrosis, respiratory epithelium				
- focal, very slight	0	0	0	5
- multifocal, slight	0	0	0	5
Epithelial inflammation, respiratory epithelium				
- multifocal, slight	0	0	0	1
Submucosal inflammation, respiratory epithelium				
- focal, slight	0	2	0	1
- scattered, slight	0	0	0	1
- multifocal, slight	0	0	0	1
Submucosal inflammation, olfactory epithelium				
- focal, moderate	1	0	0	0
Submucosal inflammation of olfactory epithelium				
- multifocal, slight	0	0	0	1
<u>TRACHEA</u> (Number of tissues examined microscopically)	10	9	10	10
Submucosal aggregates of mononuclear cells				
- focal, slight	3	4	0	1
- multifocal, slight	0	0	0	1
Epithelial hyperplasia				
- diffuse, slight	0	0	0	1
<u>LUNGS/BRONCHI</u> (Number of tissues examined microscopically)	10	10	10	10
Peribronchiolar aggregates of mononuclear cells				
- focal, slight	10	10	10	10
Subpleural aggregates of mononuclear cells				
- focal, slight	7	7	7	5
Aggregates of alveolar macrophages				
- focal, slight	1	0	2	1
Interstitial inflammation				
- focal, slight	1	1	0	1
Inflammation and fibrosis of pleura				
- focal, slight	0	0	0	1
<u>LIVER</u> (Number of tissues examined microscopically)	10	10	10	10
Aggregates of mononuclear cells				
- focal, slight	4	2	4	4
- multifocal, slight	6	8	6	5
Periportal aggregates of mononuclear cells				
- focal, slight	0	1	1	0
Increased cytoplasmic vacuolization				
- diffuse, slight	1	0	0	0
- diffuse, moderate	0	1	0	0
Capsular fibrosis				
- focal, slight	1	0	0	0
Aggregate of mast cells				
- focal, slight	0	0	0	1
<u>KIDNEYS</u> (Number of tissues examined microscopically)	10	10	10	10
Atrophy of renal tubules				
- focal, slight	3	2	1	8
Aggregates of mononuclear cells				
- focal, slight	1	3	0	0
Dilated renal tubule with eosinophilic cast formation				
- focal, slight	0	1	0	0
Interstitial inflammation				
- focal, slight	0	0	0	1

TABLE 21 (cont.)

HISTOPATHOLOGIC OBSERVATIONS ON MALE RATS
EXPOSED TO VAPORS OF ETHYLENE DIBROMIDE (40 DAYS ON STUDY)

Exposure Concentration (ppm)	0	3	10	40
Number of Rats Examined	10	10	10	10
<u>TESTES</u> (Number of tissues examined microscopically)	10	10	10	10
Hyperplasia of spermatogenic cells				
- focal, slight	1	0	0	0
Unilateral decreased spermatogenesis				
- multifocal, pronounced	1	0	0	0
- focal, moderate	1	0	0	1
- diffuse, pronounced	0	0	0	1
Sperm granuloma	0	0	0	1
Mineralization				
- focal, slight	0	0	0	1
<u>THYROID</u> (Number of tissues examined microscopically)	6	7	7	7
Aggregates of mononuclear cells and debris within follicles				
- focal, slight	0	1	0	0
<u>LACRIMAL GLAND</u> (Number of tissues examined microscopically)	2	0	0	2
Interstitial inflammation				
- focal, slight	1	0	0	0
- diffuse, moderate	1	0	0	2
<u>Additional tissues examined microscopically and showing no visible lesions</u>				
ESOPHAGUS	10	9	10	10
AORTA	4	2	2	2
LARGE MEDIASTINAL ARTERY	7	6	4	5
THORACIC LYMPH NODE	5	4	3	5
THYROID	6	7	7	7
PARATHYROID	3	2	7	5
THYMUS	2	3	0	2
PHARYNX	0	0	0	2
PANCREAS	0	1	0	0
STOMACH	0	1	0	0

TABLE 22

GROSS OBSERVATIONS ON MALE AND FEMALE RATS
EXPOSED TO VAPORS OF ETHYLENE DIBROMIDE (95-96 DAYS ON STUDY)

Sex	Males				Females			
	0	3	10	40	0	3	10	40
Dose in ppm	10	10	10	10	10	10	10	10
Number of rats in group								
No visible lesions	2	3	4	2	7	7	6	4
<u>General</u>								
Inflammatory reaction in ear at site of identification tag	2	3	1	2	1	1	1	1
Alopecia reaction in ear at site of identification tag	0	0	0	1	0	0	0	0
Alopecia on bridge of nose	0	0	0	0	0	0	1	0
Decreased size of carcass	0	0	0	5	0	0	0	0
Strangulated tag of epididymal fat	0	0	0	1	0	0	0	0
<u>Liver</u>								
Pale focus	0	1	0	0	0	0	0	0
Scattered pale foci	0	0	0	0	0	0	0	1
Diaphragmatic herniation	0	1	0	0	0	0	2	0
Diffuse paleness - very slight to slight	0	0	0	0	0	0	0	5
<u>Kidneys</u>								
Fibrous adhesions and contraction of central portion of one kidney	0	0	0	0	0	0	1	0
<u>Lungs</u>								
Few circumscribed foci	7	2	3	2	0	0	0	0
<u>Eyes</u>								
Corneal cloudiness - unilateral	1	1	3	5	2	2	0	2
Corneal cloudiness - bilateral	2	3	2	0	0	0	0	0
<u>Stomach</u>								
Focal gastric hemorrhage	1	0	0	0	0	0	0	0
<u>Urinary Bladder</u>								
Organized plug in lumen	1	0	1	0	0	0	0	0

Data listed as number of rats with the listed observation.

TABLE 23

HISTOPATHOLOGIC OBSERVATIONS ON MALE AND FEMALE RATS EXPOSED TO
VAPOURS OF ETHYLENE DIBROMIDE VIA INHALATION (95-96 DAYS ON STUDY)

Sex	Males				Females			
	0	3	10	40	0	3	10	40
Dose in ppm	10	10	10	10	10	10	10	10
Number of rats examined	10	10	10	10	10	10	10	10
Nasal Turbinates (Number of tissues examined microscopically)	10	10	10	10	10	10	10	10
Nonkeratinizing squamous metaplasia and hyperplasia of the respiratory epithelium								
- focal, very slight to slight	0	0	0	0	0	0	0	1
- diffuse, very slight to slight	0	0	0	10	0	0	0	9
Hyperplasia of the respiratory epithelium								
- isolated, very slight to slight	0	0	3	0	0	0	1	0
- focal, very slight to slight	0	0	2	0	0	0	4	0
- scattered, very slight to slight	0	0	2	0	0	0	1	0
- multifocal, very slight to slight	0	0	2	0	0	0	3	0
Individual epithelial cell necrosis of the respiratory epithelium								
- focal, very slight	0	0	0	10	0	0	1	9
Epithelial inflammation of the respiratory epithelium								
- focal, very slight	2	3	0	1	0	2	0	0
Submucosal inflammation of the respiratory epithelium								
- focal, slight	5	6	6	2	5	4	5	3
- scattered, slight	1	0	0	0	2	1	3	0
- multifocal, slight	1	2	3	0	1	2	1	0
Submucosal inflammation of the olfactory epithelium								
- focal, slight	0	0	1	3	0	0	0	0
Trachea (Number of tissues examined microscopically)	10	10	10	10	10	10	10	10
Submucosal aggregates of mononuclear cells								
- focal, slight	3	5	3	2	6	7	2	0
Lungs/Bronchi (Number of tissues examined microscopically)	10	10	10	10	10	10	10	10
Peribronchiolar aggregates of mononuclear cells								
- focal, slight	10	10	10	9	10	10	9	9
Subpleural aggregates of mononuclear cells								
- focal, slight	0	2	5	1	1	2	3	4
Aggregates of alveolar macrophages								
- focal, slight	0	0	1	1	0	2	1	0
Interstitial inflammation								
- focal, slight	0	0	1	1	0	0	0	0
Hemorrhage								
- focal, slight	0	0	1	0	0	0	0	0
Perivascular aggregates of mononuclear cells								
- focal, slight	0	0	0	0	2	0	0	0
Granuloma								
- focal, very slight	1	0	0	0	0	0	0	0
Thickening of pleura								
- focal, slight	0	0	1	0	0	0	0	0
Liver (Number of tissues examined microscopically)	10	10	10	10	10	10	10	10
Aggregates of mononuclear cells								
- focal, slight	10	9	6	8	6	8	6	4
Aggregates of mononuclear cells								
- multifocal, slight	0	1	1	0	0	0	0	3
Periportal aggregates of mononuclear cells								
- focal slight	0	0	2	1	2	0	2	0

Data listed as number of rats with the listed observation.

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TABLE 23 (cont.)

HISTOPATHOLOGIC OBSERVATIONS ON MALE AND FEMALE RATS EXPOSED TO
VAPORS OF ETHYLENE DIBROMIDE VIA INHALATION (95-96 DAYS ON STUDY)

Sex	Males				Females			
	0	3	10	40	0	3	10	40
Dose in ppm	10	10	10	10	10	10	10	10
Number of rats examined								
<u>Liver (Cont'd)</u>								
Single focus of hepatocellular necrosis and accompanying inflammation								
- slight	0	1	0	2	2	1	0	2
Subcapsular microgranuloma								
- focal, slight	0	0	0	0	0	1	0	0
Hepatocellular cytoplasmic vacuolation, suggestive of fatty change								
- diffuse, slight	0	0	0	0	0	0	0	2
<u>LIVER - Oil Red O Stain</u>								
(Number of tissues examined)	0	0	0	0	9	0	0	10
Negative	0	0	0	0	7	0	0	5
1+	0	0	0	0	1	0	0	3
2+	0	0	0	0	1	0	0	1
3+	0	0	0	0	0	0	0	1
<u>Kidneys (Number of tissues examined microscopically)</u>								
Atrophy of renal tubules	10	10	10	10	10	10	10	10
- focal, slight	8	8	9	9	2	1	1	2
Aggregates of mononuclear cells								
- focal, slight	2	1	2	2	2	0	1	1
Interstitial inflammation								
- focal, slight	2	0	0	0	0	1	0	0
Dilated renal tubules with eosinophilic cast formation								
- focal, slight	0	0	0	1	0	0	0	0
Mineralized debris								
- focal, slight	0	0	0	0	0	0	2	0
Area of tubular atrophy, interstitial fibrosis and inflammation, pigment accumulation, focal inflammatory cells in collecting ducts and hyperplasia of renal pelvis epithelium	0	0	0	0	0	0	1	0
<u>Lacrimal Gland (Number of tissues examined microscopically)</u>								
Interstitial inflammation	2	0	0	0	0	0	0	0
- focal, slight	1	0	0	0	0	0	0	0
<u>Uterus (Number of tissues examined microscopically)</u>								
Dilatation of lumen	-	-	-	-	10	10	10	10
<u>Additional tissues examined microscopically and showing no visible lesions</u>								
Testes	10	10	10	10	-	-	-	-
Ovary(ies)	-	-	-	-	10	10	10	10
Oviducts	-	-	-	-	10	10	10	10
Esophagus	9	10	10	10	10	10	10	10
Aorta	4	4	4	6	2	3	4	4
Large Mediastinal Artery(ies)	5	6	4	1	3	1	3	4
Thyroid	3	1	2	5	1	0	2	2
Parathyroid	3	0	0	4	1	0	2	1
Thoracic Lymph Node	6	7	7	6	6	5	4	4
Thymus	1	0	1	0	1	0	1	0
Hard Palate	2	0	0	0	0	0	0	0
Stomach	1	0	0	0	0	0	0	0
Urinary Bladder	1	0	0	0	2	2	3	3

Data listed as number of rats with the listed observation.

- = Not applicable.

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TABLE 24

GROSS PATHOLOGIC OBSERVATIONS ON MALE AND FEMALE RATS EXPOSED BY INHALATION
TO VAPOURS OF ETHYLENE DIBROMIDE (EDB) (94-95 DAYS ON STUDY)
AND HELD FOR A RECOVERY PERIOD OF 88-89 DAYS

Sex	Males				Females			
Dose in ppm	0	3	10	40	0	3	10	40
Number of rats dying spontaneously	0	0	0	0	0	1	1	0
Number of rats in group	10	10	10	10	10	10	10	10
No visible lesions	4	5	5	4	4	7	5	7
<u>General</u>								
Inflammatory reaction at site of ear tag	1	1	1	3	1	0	1	0
Tag of strangulated omental fat	0	2	0	0	0	0	0	0
Slight alopecia of the facial region	0	0	0	0	1	0	0	0
Perineal soiling	0	0	0	0	0	0	1*	0
Soiling around external nares and oral cavity	0	0	0	0	0	0	1*	0
Very slight postmortem autolysis	0	0	0	0	0	0	1*	0
<u>Eyes</u>								
Focal corneal cloudiness - unilateral	3	1	3	2	2	1	1	0
Focal lenticular cloudiness - unilateral	0	1	0	0	0	0	0	0
Slight enlargement - unilateral	0	0	0	0	0	1	0	0
<u>Liver</u>								
Pale yellow area	0	0	0	1	0	0	0	0
Pale areas	0	0	0	0	1	0	0	0
Nodular protrusion of liver into herniated diaphragm	0	0	0	0	0	1*	0	1
Herniation of diaphragm involving the liver sometimes producing a pale area	0	0	0	0	2	1	0	0
Congested	0	0	0	0	0	0	1*	0
Slight pale accentuation of the lobular pattern	0	0	0	1	0	0	0	0
<u>Kidneys</u>								
Congested	0	0	0	0	0	0	1*	0
<u>Lungs</u>								
Few circumscribed foci	2	3	1	2	2	0	0	1
Dark, congested and edematous	0	0	0	0	0	0	1*	0
<u>Pituitary</u>								
Increased size	0	0	0	0	0	0	1*	0
<u>Thoracic Cavity</u>								
Hydrothorax	0	0	0	0	0	0	1*	0
<u>Adrenal</u>								
Dark focus	0	0	0	0	0	0	1*	0
<u>Uterus</u>								
Small structure free within lumen	0	0	0	0	0	0	1	0
Distended with fluid containing few suspended particles	0	0	0	0	0	0	1	0
Inflammatory material in horns	0	0	0	0	0	0	0	1
<u>Ovary</u>								
Periovarian cyst	0	0	0	0	1	0	1	0
Increased size with accumulation of inflammatory material	0	0	0	0	0	0	0	1

Data listed as number of rats with the listed observation.

*Observation on rat dying during study.

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TABLE 25

HISTOPATHOLOGIC OBSERVATIONS ON MALE AND FEMALE RATS EXPOSED BY INHALATION
TO VAPORS OF ETHYLENE DIBROMIDE (EDB) (94-95 DAYS ON STUDY)
AND HELD FOR A RECOVERY PERIOD OF 88-89 DAYS

Sex	Males				Females			
Dose (ppm)	0	3	10	40	0	3	10	40
Number of rats dying spontaneously	0	0	0	0	0	1	1	0
Number of rats examined	10	10	10	10	10	10	10	10
<u>NASAL TURBINATES</u> (number of tissues examined)	10	10	10	10	10	10	10	10
Epithelial hyperplasia of respiratory epithelium								
- single focus	0	0	0	0	0	0	0	1
Epithelial inflammation of respiratory epithelium								
- focal, slight	0	0	0	1	0	0	0	0
Submucosal inflammation, respiratory epithelium								
- focal, slight	0	0	0	1	6	1	6	3
Submucosal inflammation, olfactory epithelium								
- focal, slight	0	0	0	0	1	0	0	0
Inflammatory cells in lumen - focal, slight	0	0	0	1	0	0	0	0
Focal flattening of ciliated respiratory epithelium								
- isolated, very slight	3	0	0	3	0	0	0	0
<u>LUNGS/BRONCHI</u> (number of tissues examined)	10	10	10	10	10	10	10	10
Peribronchiolar aggregates of mononuclear cells								
- focal, slight	7	8	8	10	9	10	10	10
Peribronchiolar aggregates of mononuclear cells								
- multifocal, slight	3	0	0	0	1	0	0	0
Subpleural aggregates of mononuclear cells								
- focal, slight	6	3	4	3	3	2	3	3
Subpleural aggregates of mononuclear cells								
- multifocal, slight	0	0	0	0	0	1*	0	0
Aggregates of alveolar macrophages								
- focal, slight	0	1	1	0	0	0	0	0
Interstitial inflammation - focal, very slight	0	0	0	0	0	0	0	1
Interstitial inflammation - focal, slight	1	0	2	0	0	0	0	0
Hemorrhage - focal, slight	0	0	1	0	0	0	0	0
Perivascular aggregates of mononuclear cells								
- focal, slight	1	0	0	0	0	1	0	0
Inflammation and fibrosis of pleura								
- focal, slight	0	0	1	0	0	0	0	0
Acute pulmonary edema and congestion with multiple bacterial colonies	0	0	0	0	0	0	1*	0
Alveolar hyperplasia and interstitial inflammation								
- multifocal, slight	0	0	0	0	1	0	0	0
Aggregate of mononuclear cells								
- focal, slight	0	0	0	0	0	0	1	0
<u>LIVER</u> (number of tissues examined)	10	10	10	10	10	10	10	10
Aggregates of mononuclear cells								
- focal, slight	7	6	7	8	3	3	5	3
Aggregates of mononuclear cells								
- multifocal, slight	3	1	2	1	3	0	0	1
Periportal aggregates of mononuclear cells								
- focal, slight	5	0	2	2	2	3	5	5
Single focus of hepatocellular necrosis and accompanying inflammation - slight	2	0	1	0	0	0	0	0
Subcapsular microgranuloma - focal, slight	2	1	0	0	0	0	0	0
Cytoplasmic vacuolization - focal, slight	3	3	4	4	0	0	0	0

Data listed as the number of rats with the listed observation.

*Observation noted only in rat dying during study.

TABLE 25 (cont.)

HISTOPATHOLOGIC OBSERVATIONS ON MALE AND FEMALE RATS EXPOSED BY INHALATION
TO VAPORS OF ETHYLENE DIBROMIDE (EDB) (94-95 DAYS ON STUDY)
AND HELD FOR A RECOVERY PERIOD OF 88-89 DAYS

Sex	Males				Females			
Dose (ppm)	0	3	10	40	0	3	10	40
Number of rats dying spontaneously	0	0	0	0	0	1	1	0
Number of rats examined	10	10	10	10	10	10	10	10
<u>LIVER</u> (cont'd)								
Cytoplasmic vacuolization - multifocal, slight	4	2	0	2	0	0	0	0
Biliary hyperplasia - focal, slight	5	1	2	2	0	0	1*	1
Biliary hyperplasia - multifocal, slight	1	0	0	0	0	1	0	1
Retention cyst	1	0	0	0	0	0	0	0
Periportal fibrosis - focal, slight	0	0	0	0	0	0	0	1
Bacterial colonies present in RE cells	0	0	0	0	0	0	1*	0
Focal hepatic necrosis - very slight	0	0	0	0	0	0	1*	0
Capsular inflammation and bacterial colonies - focal, slight	0	0	0	0	0	1*	0	0
Capsular inflammation and fibrosis - moderate	0	0	0	0	1	0	0	0
<u>KIDNEYS</u> (number of tissues examined)	10	10	10	10	10	10	10	10
Atrophy of renal tubules - focal, slight	6	8	7	9	0	1	1	0
Atrophy of renal tubules - multifocal, slight	2	0	0	0	0	0	0	0
Aggregates of mononuclear cells - focal, slight	4	3	2	0	1	2	1	2
Interstitial inflammation - focal, slight	3	0	1	1	0	0	0	0
Dilated renal tubules with eosinophilic cast formation - focal, slight	6	4	4	8	1	1	1	0
Mineralized debris - focal, slight	0	0	0	0	0	0	0	1
Dilated renal tubules - focal, slight	1	0	0	2	0	0	0	0
Bacterial colonies in renal tubules	0	0	0	0	0	1*	1*	0
<u>TRACHEA</u> (number of tissues examined)	10	10	10	10	10	10	10	10
Submucosal aggregates of mononuclear cells - focal, slight	4	1	4	4	2	6	3	3
Submucosal aggregates of mononuclear cells - multifocal, slight	1	0	0	0	0	0	0	0
Epithelial hyperplasia - focal, slight	1	0	0	0	0	0	0	0
<u>TESTES</u> (number of tissues examined)	10	10	10	10	-	-	-	-
Unilateral decreased spermatogenesis - focal, moderate	1	0	1	0	-	-	-	-
Sperm granuloma	0	0	0	1	-	-	-	-
Mineralization - focal, slight	1	0	0	0	-	-	-	-
<u>OVARY</u> (number of tissues examined)	-	-	-	-	10	10	10	10
Pyogranulomatous inflammatory reaction	-	-	-	-	0	0	0	1
Acute suppurative inflammation and bacterial colonies	-	-	-	-	0	1*	1*	0
<u>UTERUS</u> (number of tissues examined)	-	-	-	-	10	10	10	10
Dilatation of the lumen	-	-	-	-	1	0	1	0
Endometrial hyperplasia - slight	-	-	-	-	0	0	0	1
Endometrial changes consistent with phases of the estrus cycle	-	-	-	-	0	2	4	3

Data listed as the number of rats with the listed observation.

- = Not applicable.

*Observation noted only in rat dying during study.

TABLE 25 (cont.)

HISTOPATHOLOGIC OBSERVATIONS ON MALE AND FEMALE RATS EXPOSED BY INHALATION
TO VAPORS OF ETHYLENE DIBROMIDE (EDB) (94-95 DAYS ON STUDY)
AND HELD FOR A RECOVERY PERIOD OF 88-89 DAYS

Sex	Males				Females			
Dose (ppm)	0	3	10	40	0	3	10	40
Number of rats dying spontaneously	0	0	0	0	0	1	1	0
Number of rats examined	10	10	10	10	10	10	10	10
<u>THYROID</u> (number of tissues examined)	7	9	10	8	9	9	10	7
Follicular cyst	0	0	1	0	0	1	0	0
<u>MEDIASTINAL TISSUES</u> (number of tissues examined)	10	10	10	10	10	10	10	10
Acute suppurative inflammation, edema, and congestion	0	0	0	0	0	1*	1*	0
<u>PITUITARY GLAND</u> (number of tissues examined)	0	0	0	0	0	0	1	0
Focal hyperplasia	0	0	0	0	0	0	1*	0
<u>ADRENAL GLAND</u> (number of tissues examined)	0	0	0	0	0	0	1	0
Focal hematocyst	0	0	0	0	0	0	1*	0
<u>MISCELLANEOUS</u>								
Generalized acute bacterial septicemia	0	0	0	0	0	1*	1*	0
<u>ADDITIONAL TISSUES EXAMINED MICROSCOPICALLY AND SHOWING NO VISIBLE LESIONS</u>								
Esophagus	10	10	9	9	9	10	10	10
Large Mediastinal Artery(ies)	8	7	9	8	8	7	8	7
Aorta	5	3	3	3	2	0	1	2
Thoracic Lymph Node	8	7	7	8	6	5	6	10
Thyroid	7	9	10	8	9	9	10	7
Parathyroid	5	7	9	7	5	6	9	4
Thymus	0	0	1	0	1	0	2	0
Oviducts	-	-	-	-	10	10	10	10
Pharynx	0	0	0	0	2	1	1	0
Urinary Bladder	0	0	0	0	5	4	4	4
Large Intestine	0	0	0	0	1	0	0	0

Data listed as the number of rats with the listed observation.

- = Not applicable.

*Observation noted only in rat dying during study.

FIGURE 1

BODY WEIGHT GAIN FOR MALE RATS EXPOSED TO
ETHYLENE DIBROMIDE FOR 1 WEEK

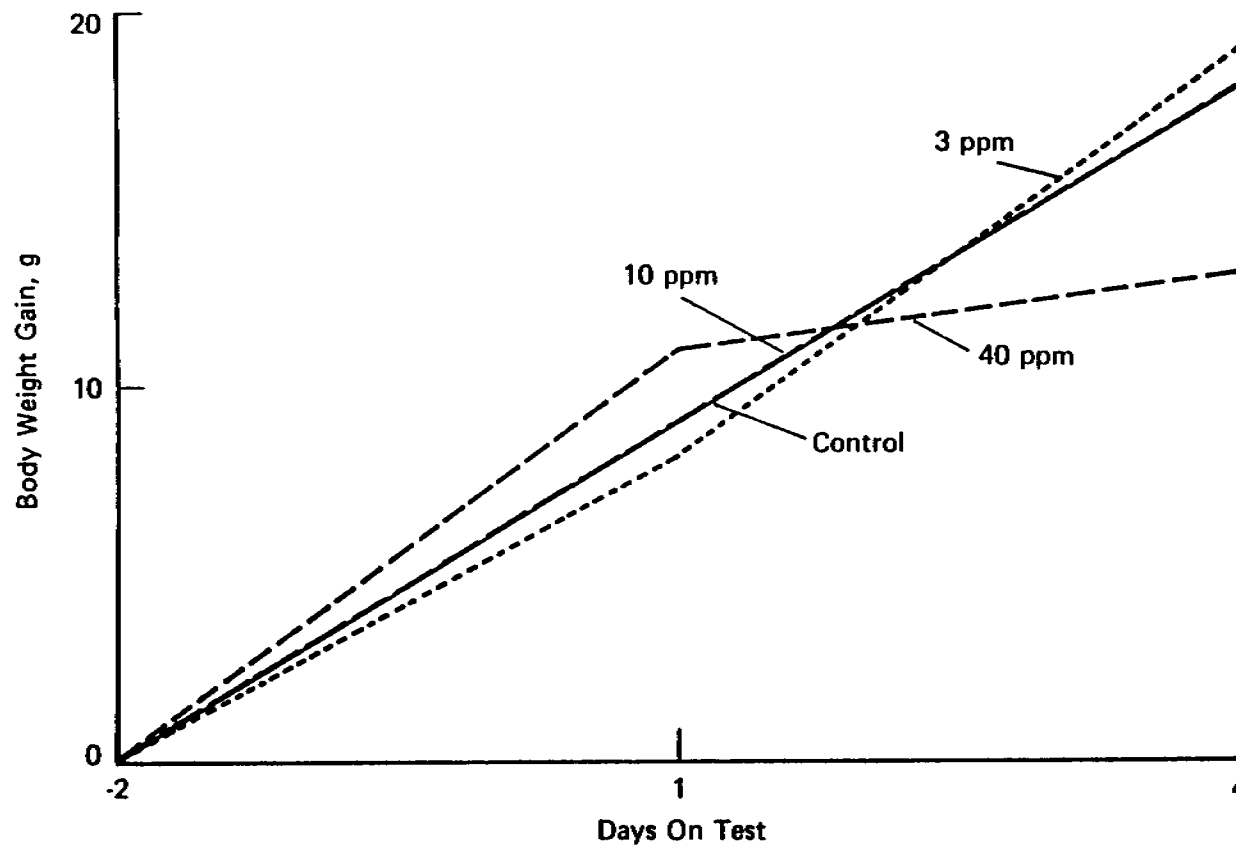
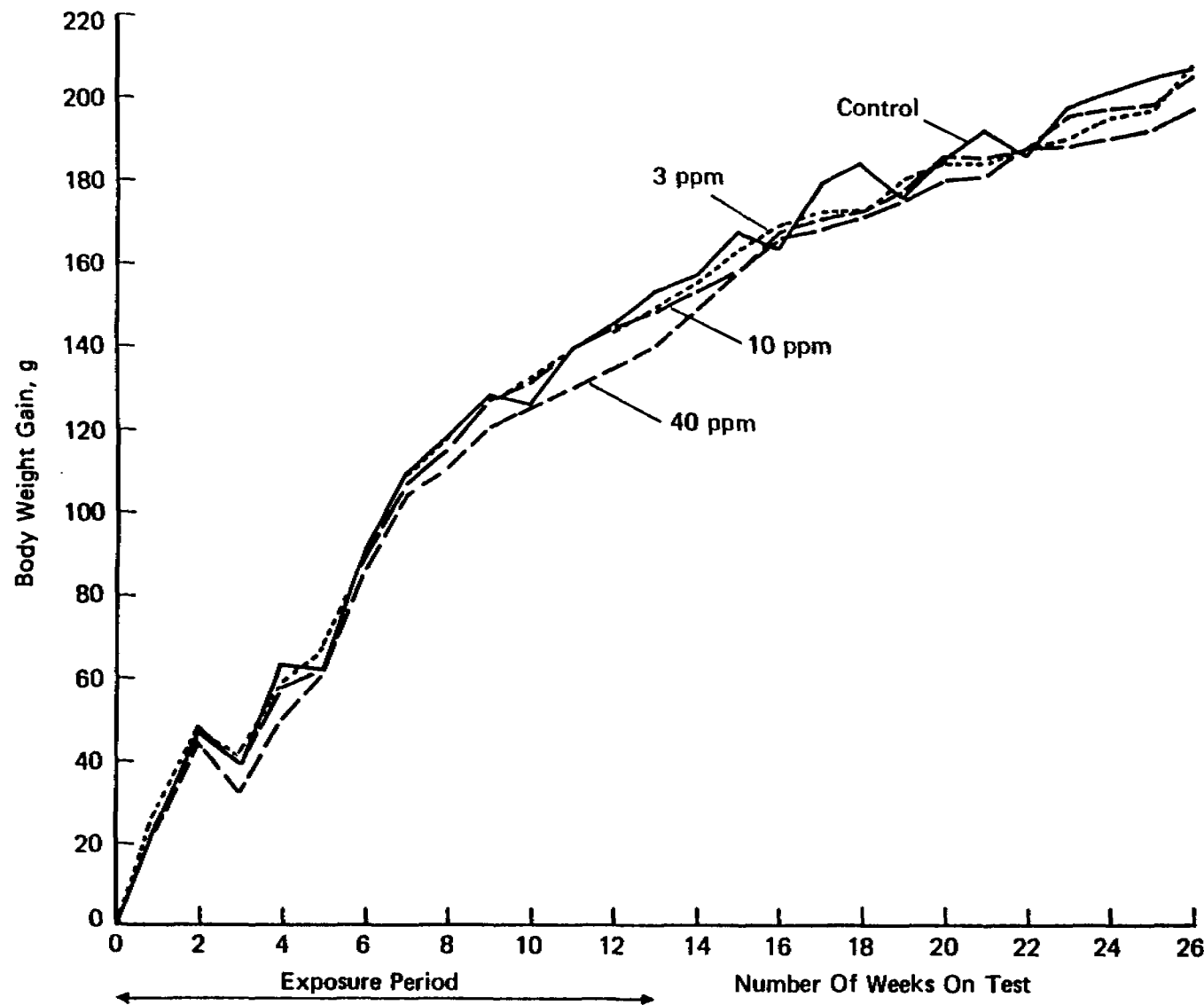


FIGURE 2

BODY WEIGHT GAIN OF MALE RATS EXPOSED TO
ETHYLENE DIBROMIDE FOR 13 WEEKS



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FIGURE 3

BODY WEIGHT GAIN OF FEMALE RATS EXPOSED TO
ETHYLENE DIBROMIDE FOR 13 WEEKS

