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# Subchronic Inhalation of Diethylamine Vapor in Fischer-344 Rats: Organ System Toxicity[1]

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Subchronic Inhalation of Diethylamine Vapor in Fischer-344-Rats: Organ System Toxicity. LYNCH, D. W., MOORMAN, W. J., STOBER, P., LEWIS, T. R., AND IVERSON, W. O. (1986). *Fundam. Appl. Toxicol.* **6,** 559–565. Male and female Fischer 344 (F-344) rats were exposed at 0, 25, or 250 ppm diethylamine (DEA) vapor, 6.5 hr per day, 5 days per week, for 24 weeks in order to assess cardiac and other organ system toxicity. Scheduled sacrifices were performed following 30, 60, and 120 days of exposure. During the first 2 weeks of exposure, the rats exposed at 250 ppm DEA did not gain weight. After 2 weeks, however, the rate of weight gain of these rats was greater than that of controls. Nevertheless, mean body weights for both sexes of rats exposed at 250 ppm DEA remained depressed compared to controls throughout the study. Sneezing, tearing, and reddened noses were seen in rats exposed at 250 ppm DEA. Histopathologic examinations revealed lesions of the nasal mucosa of rats exposed at 250 ppm DEA (rats exposed at 25 ppm were not evaluated). These lesions of the respiratory epithelium consisted of squamous metaplasia, suppurative rhinitis, and lymphoid hyperplasia. There were no pronounced treatment-related effects on organ weights, hematology, or clinical chemistry indices except for blood urea nitrogen which was elevated in rats of both sexes exposed at 250 ppm DEA for 24 weeks. In contrast to the high-dose animals, no treatment-related effects were observed in rats intermittently exposed at 25 ppm DEA for up to 24 weeks. No evidence of cardiotoxicity was seen in rats exposed to either DEA concentration for up to 24 weeks. 

Diethylamine (DEA) is widely used in industry as an organic intermediate, a corrosion inhibitor and a rubber accelerator, in pharmaceuticals, resins, pesticides, and dyes, in electroplating, and as a polymerization inhibitor. Annual production of DEA was approximately 7000 tons in 1976 (Schweizer *et al.*, 1978). The National Institute for Occupational Safety and Health (NIOSH) has estimated that about 67,000 workers are occupationally exposed to DEA (NIOSH, 1977).

DEA has a vapor pressure of 194 mm Hg (20°C) and has been reported to be irritating to the lung and nasal passages following inhalation exposure (Beard and Noe, 1981). Smyth *et al.* (1951) determined the acute inhalation toxicity of DEA and reported a 4-hr LC50 of 4000 ppm. The oral LD50 for rats was reported as 540 mg/kg, while the dermal LD50 in rabbits was reported to be 580 mg/kg. DEA was a skin irritant and a 10% dilution of DEA caused severe eye burns. Drotman and Lawhorn (1978) reported histologic evidence of liver damage and elevations of serum enzymes following ip administration of DEA to rats. In addition to these acute studies, Brieger

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and Hodes (1951) exposed rabbits at 50 and 100 ppm DEA vapor for 7 hr/day, 5 days/week for 6 weeks. All animals survived the exposures. Lungs from rabbits exposed at 100 ppm exhibited cellular infiltration and bronchopneumonia, livers showed marked parenchymatous degeneration with recent cell regeneration, and kidneys showed nephritis. Similar changes to a lesser degree were observed in animals exposed at 50 ppm DEA. In addition, there was a suggestion of very slight cardiac muscle degeneration in the animals exposed at 50 ppm DEA.

Several Russian investigators have also examined the toxicity of low levels of DEA. Tkachev (1971) reported thickening of interalveolar septa and accumulations of acid mucopolysaccharides in the interstitial substance of the alveolar connective tissue of rats exposed at 4.19 mg/m$^3$ DEA (1.4 ppm) for 3 months. Administration of oral DEA (3 mg/kg/day) concurrent with daily 7-hr inhalation exposures at 0.137 mg/m$^3$ (0.04 ppm) DEA was reported to prolong the period of acclimation of rats to cold exposure (Tkachev, 1974). The period of adaptation (assessed by body temperature and gas exchange) in rats exposed to DEA plus cold was increased to 2–3 months compared to 5–6 weeks in the rats exposed to cold alone. Kagan (1965) reported that rabbits and rats receiving oral doses of DEA (6 mg/kg) for up to 7 months showed no effects on liver function tests and a general lack of cumulative toxicity. Melnikova (1979) reported that the nervous and respiratory systems were the most susceptible organ systems following a single inhalation exposure at 55 mg/m$^3$ DEA (18 ppm).

DEA is regulated as an irritant and the Occupational Safety and Health Administration (OSHA) standard for DEA is 25 ppm and the American Conference of Governmental Industrial Hygienists (ACGIH) threshold limit value (TLV) for DEA is 10 ppm (ACGIH, 1980).

To more fully investigate the cardiac toxicity of inhaled DEA previously reported in the literature, a 6-month rat inhalation study was conducted. Effects of inhaled DEA on selected organ systems were also assessed.

## METHODS

*Chemical.* Reagent-grade DEA was obtained from MCB Manufacturing Chemists, Inc., Norwood, Ohio.[4] Lots 2J20 and J8L17 were used with the manufacturer's analyses indicating purities of 99.9% by weight.

*Chambers.* Exposures were conducted in three 4.5-m$^3$ stainless-steel and glass inhalation chambers (Hinners *et al.*, 1968). Chambers were operated under dynamic flow conditions with tangential airfeeds maintained at 1.1 m$^3$ per min (filtered/conditioned air) and at slightly negative pressures (− 0.25 cm of water) relative to ambient. Chamber airflows provided 12–15 air changes per hour. Temperature and humidity were maintained at 23 ± 3°C and 50 ± 10%, respectively.

*Vapor generation and monitoring.* Rats were exposed at 25 or 250 ppm DEA for 6.5 hr/day, 5 days/week for 6 months (118–123 exposure days). DEA vapor was generated by pumping liquid DEA at a constant flow rate (Fluid Metering Inc., Oyster Bay, N.Y.) into the air stream of the tangential airfeed at the top of the chambers. Fresh, liquid DEA was used in the generation reservoir each day. DEA concentrations in the chamber were monitored using a Wilks-Miran 1A infrared analyzer (Foxboro Analytical, Norwalk, Conn.) using the following instrument settings; wavelength 8.8 μm, pathlength 20.25 m, slit 2 mm. The instrument was calibrated by the closed-loop calibration method. Chamber atmospheres were monitored 2–4 times per hour, with adjustments made to the generation system as required to maintain the exposure levels at the targeted concentrations.

*Animals.* Six hundred weanling Caesarean-derived Fischer 344 rats [CDF (F-344)/Crl BR] obtained from Charles River Breeding Laboratories (Wilmington, Mass.) were used in the study. Rats were assigned to their respective treatment groups using a table of random numbers. After a 2-week quarantine period, the rats were individually identified by toe and ear clipping and assigned to each chamber (200 rats/chamber; 100 male and 100 female). Rats were screened for serological evidence of *Mycoplasma pulmonis* infection prior to the initiation of exposures and all results were negative. Rats were housed individually in stainless-steel wire-mesh cages within the chambers at all times. Food (Purina Laboratory Chow, Ralston Purina, St. Louis, Mo.) and tap water were available *ad libitum* except during the exposure periods. Rats were maintained on a 12-hr on/12-hr off lighting schedule with lights on between 7 AM and 7 PM.

*Animal observations.* Rats were observed twice daily for changes in appearance or demeanor. Body weights were

[4] Mention of a product or company name does not constitute endorsement by NIOSH.

recorded on the day preceding the first day of exposure and at 2-week intervals throughout the study. Body weight changes were computed by substracting the preexposure body weight for each animal from its body weight at the designated weighing interval.

*Sacrifice schedule.* Ten male and ten female rats were randomly selected and sacrificed (35 mg/kg pentobarbital sodium, ip) from each exposure group after 30 and 60 days of exposure. Fifty male and fifty female rats were randomly selected and sacrificed from each group after 120 exposure days. The remaining rats were not examined. Rats were fasted overnight prior to scheduled sacrifice and subjected to a complete gross necropsy.

All major organs and tissues were visually inspected, fixed in 10% buffered Formalin, embedded in paraffin, sectioned at 5$\mu$m, stained with hematoxylin and eosin, and examined microscopically. The following tissues were examined histologically: lungs (following perfusion with Formalin), liver, kidneys, heart, spleen, tracheobronchial lymph nodes, adrenals, testes, seminal vesicles, ovaries, uterus, trachea, eye, urinary bladder, and from selected animals, nares. Nares were processed and cut into sections as described by Buckley *et al.* (1985). Only sections from the first two levels were of acceptable quality to allow for microscopic examination. Lungs, liver, kidneys, heart and reproductive organs were weighed at each scheduled sacrifice. Rats dying at other times during the study were immediately refrigerated and necropsied within 12 hr whenever possible.

*Clinical chemistry–hematology.* Clinical chemical indices, selected to assist in the evaluation of suspected target organ toxicity, were measured on a GEMSAEC centrifugal analyzer (Electro-Nucleonics, Inc., Fairfield, N.J.). These included alanine aminotransferase (ALT), aspartate aminotransferase (AST), creatine phosphokinase (CPK), blood urea nitrogen (BUN), creatinine (CRE), and soribitol dehydrogenase (SDH). Hematology evaluations, conducted only at the terminal sacrifice, included hemoglobin, hematocrit, and complete and differential blood counts. Blood was collected at each scheduled sacrifice from the inferior vena cava.

*Electrophysiology.* Electrocardiograms (ECGs) were recorded from 10 anesthetized rats/sex/group (35 mg/kg secobarbital, ip) at the terminal sacrifice. Data were recorded with rats lying in a prone position using an Electronics for Medicine DR-12 photographic oscillograph (White Plains, N.Y.). ECG waveforms were sampled and analyzed using a Healthgard CPT-5 computer system (Salt Lake City, Utah). Leads I, II, and III, avR, avL, and avF were recorded from each animal for 5-sec durations. Heart rate, axes, and amplitudes of the P wave, QRS complex, and T wave, as well as durations of various intervals, were computed and compared among exposure groups. Each ECG tracing was also evaluated "in blind" by a veterinary cardiologist.

*Statistical evaluation.* A one-way analysis of variance was used to compare initial body weights, while a multivariate analysis of variance was used to compare weight gains at each additional weighing period. If significant group differences were indicated, the results were analyzed by Duncan's multiple range test (Winer, 1971). Organ weights, organ-to-body weight ratios, hematology, clinical chemistry, and electrocardiographic indices of the groups were compared by sex and length of exposure using the Kruskal–Wallis test (Hollander and Wolfe, 1973). If significant group differences were indicated, a pairwise test was performed. Pathology incidence data were evaluated using a $\chi^2$ test. For all statistical comparisons between control and exposed animals, an overall experimentwise error rate of $\alpha = 0.05$ was maintained. Results were considered significant when $p < 0.05$.

## RESULTS

### *Vapor Exposures*

The DEA chamber concentrations for the 24-week exposure period were 26 ± 0.5 and 251 ± 0.9 ppm ($\bar{x} \pm SD$). Henceforth exposure concentrations will be reported as 25 or 250 ppm since the actual measured values were not substantially different from these targeted levels. Rats were exposed at 25 or 250 ppm DEA vapor for a maximum of 123 and 118 days, respectively, with an average of 6.5 hr of exposure per day.

### *Animal Observations*

Rats of both sexes tolerated the exposure at 25 ppm DEA without developing overt signs of toxicity. At 250 ppm, however, both sexes exhibited evidence of the strong irritant properties of this concentration of diethylamine. Animal observations included sneezing, tearing, squinting and attempted avoidance of the DEA by burying their noses in their fur during the entire exposure period. Mean body weights of both male and female rats exposed at 250 ppm DEA demonstrated an initial, transient cessation of weight gain evident at the first weighing period which followed the initial 2 weeks of exposure (Fig. 1). Mean body weight gains of the rats exposed at 250 ppm DEA were significantly reduced compared to the control groups at Week 2 and remained re-

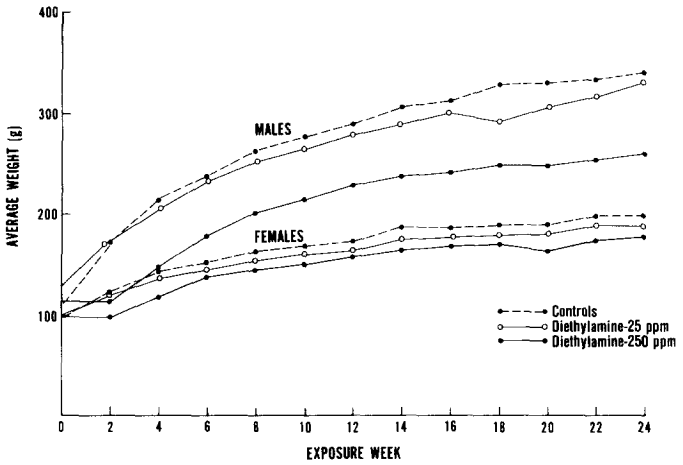


FIG. 1. Mean body weights of male and female F-344 rats intermittently exposed to diethylamine vapor for 24 weeks.

duced at each subsequent weighing period. The mean body weight gain of the rats exposed at 250 ppm was significantly greater than both the control and 25 ppm DEA groups at 9 of 10 subsequent weighing periods following the fourth week of exposure.

*Clinical Chemistry and Hematology*

Hematologic analyses revealed no consistent statistical differences in male of female rats exposed to DEA. Several clinical chemistry indices, e.g., SDH and CPK, were elevated in one group of rats, or in only one sex of rats, at one of the scheduled interim sacrifices. These changes were not attributed to DEA exposure. Creatinine levels were significantly elevated in female rats exposed at both 25 and 250 ppm DEA for 24 weeks, while BUN levels were significantly elevated in rats of both sexes exposed at 250 ppm DEA for 24 weeks. These changes, however, could not be correlated with any observed gross or histologic renal damage.

*Electrophysiology*

No statistically significant differences were observed in any of the electrocardiographic indices which were recorded and analyzed from rats exposed to DEA.

*Absolute and Relative Organ Weights*

No consistent changes in absolute or relative organ weights were seen in rats exposed to DEA and sacrificed following 30 and 60 days of exposure (data not shown). Representative absolute and relative organ weights from rats exposed to DEA for 24 weeks are presented in Table 1. Absolute lung weights were significantly decreased and lung-to-body weight ratios were significantly increased in male rats exposed at 250 DEA for 24 weeks. Similar changes were noted for absolute lung weight and heart-to-body weight ratios for female rats. While statistically significant, these changes appear to reflect the statistically reduced mean body weights of the rats exposed at 250 ppm DEA rather than indicating toxic effects on these organs. Some histologic damage, however, was noted in the lungs of rats exposed to DEA (see next section). No other effects on organ weights or organ-to-body weight ratios of rats were considered to be related to DEA exposure.

*Gross and Histopathology*

There were no gross pathologic observations in rats which were considered to be related to

TABLE 1

TERMINAL BODY WEIGHT, ORGAN WEIGHTS, AND ORGAN TO BODY WEIGHT RATIOS FOR F-344 RATS EXPOSED TO INHALED DIETHYLAMINE VAPOR FOR 24 WEEKS

| Exposure levels (ppm) | Body wt (g) | Lung | | Heart | |
|---|---|---|---|---|---|
| | | g | g/body wt ratio × 100 | g | g/body wt ratio × 100 |
| | | | Male rats | | |
| 0 | 329.6 ± 18.1[a]<br>(288–377)[b]<br>61[c] | 2.30 ± 0.24<br>(1.81–2.90)<br>31 | 0.70 ± 0.06<br>(0.59–0.89)<br>31 | 0.93 ± 0.07<br>(0.67–1.05)<br>31 | 0.29 ± 0.02<br>(0.25–0.32)<br>31 |
| 25 | 331.1 ± 20.5<br>(254–373)<br>79 | 2.35 ± 0.25<br>(2.06–2.89)<br>20 | 0.71 ± 0.08<br>(0.58–0.85)<br>20 | 0.96 ± 0.10<br>(0.78–1.20)<br>20 | 0.29 ± 0.03<br>(0.23–0.35)<br>20 |
| 250 | 259.6 ± 15.8*<br>(230–298)<br>77 | 1.90 ± 0.19*<br>(1.45–2.26)<br>20 | 0.78 ± 0.05*<br>(0.71–0.88)<br>20 | 0.76 ± 0.08*<br>(0.60–0.90)<br>20 | 0.31 ± 0.02<br>(0.28–0.36)<br>20 |
| | | | Female rats | | |
| 0 | 191.3 ± 10.6<br>(172–215)<br>58 | 1.74 ± 0.15<br>(1.39–2.06)<br>29 | 0.90 ± 0.07<br>(0.75–1.05)<br>29 | 0.64 ± 0.04<br>(0.58–0.73)<br>29 | 0.33 ± 0.02<br>(0.30–0.37)<br>29 |
| 25 | 198.6 ± 10.9<br>(169–230)<br>80 | 1.75 ± 0.16<br>(1.48–2.01)<br>20 | 0.89 ± 0.07<br>(0.73–1.04)<br>20 | 0.68 ± 0.05*<br>(0.60–0.80)<br>20 | 0.34 ± 0.02<br>(0.31–0.41)<br>20 |
| 250 | 176.0 ± 13.1*<br>(136–238)<br>70 | 1.58 ± 0.22*<br>(1.07–2.05)<br>20 | 0.92 ± 0.13<br>(0.62–121)<br>20 | 0.65 ± 0.08<br>(0.57–0.89)<br>20 | 0.38 ± 0.04*<br>(0.31–0.50)<br>20 |

[a] $\bar{x} \pm$ SD.
[b] (Range).
[c] Number of animals.
* Statistically significant difference versus controls, $p < 0.05$.

treatment with the test material. Ten female rats exposed at 250 ppm DEA were found dead following 12 weeks of exposure. Gross examination of these rats showed evidence of dehydration which was attributed to a malfunction of an isolated portion of the automatic watering system which affected only these 10 rats and was not due to DEA exposure. No other animals died or were killed in moribund condition during the 24-week exposures. In the testes of male rats exposed at 250 ppm DEA there was a slight increase in occurrence of hypospermatogenesis, degeneration of seminiferous tubules, and mineralization within the tubules compared to controls. However, in most cases, these changes were unilateral and were not considered to be related to DEA exposure. Histological changes, considered to be possibly related to DEA exposure, were confined primarily to the nares and lungs. A slight, though statistically significant increase in the incidence of bronchiolar lymphoid hyperplasia was noted in rats of both sexes exposed at 25 ppm DEA. However, this lung lesion was seen in all groups, including the controls, and the incidence was not dose

related. Hence, this lesion was not considered to be related to DEA exposure.

The group distributions for squamous metaplasia, lymphoid hyperplasia, and suppurative rhinitis in the nares of both male and female rats exposed at 250 ppm DEA for 24 weeks were significantly increased over the distributions for controls (Table 2). Most of the rats exposed at 250 ppm DEA and examined for nasal lesions had an acute inflammatory exudate present in the nasal cavity (nares from rats exposed at 25 ppm DEA were not examined). Inflammation of the nasal passages was manifested by increased numbers of lymphocytes and plasmacytes in the lamina propria and hyperplasia of lymphoid tissue in the DEA-exposed animals as compared to the controls. The inflammatory changes were located primarily at level two, i.e., approximately one-third of the distance from the posterior aspect of the incisor teeth to the incisive papilla. The region just anterior to the incisor teeth also showed inflammatory changes, but not as pronounced. Mild to moderate squamous metaplasia of the respiratory mucosa occurred in focal areas of the middle portions of the nasal septum and lateral walls of the nasal cavity primarily at level two. All other microscopic changes were considered to be spontaneous in nature and unrelated to treatment with the test material.

TABLE 2

HISTOPATHOLOGIC LESIONS OBSERVED IN THE NASAL PASSAGES OF F-344 RATS EXPOSED TO INHALED DIETHYLAMINE VAPOR FOR 24 WEEKS

| Lesion | Exposure level (ppm) 0 | 250 |
|---|---|---|
| | Male rats | |
| Squamous metaplasia | 0/9[a] | 8/14* |
| Suppurative rhinitis | 0/9 | 13/14* |
| Lymphoid hyperplasia | 0/9 | 7/14* |
| | Female rats | |
| Squamous metaplasia | 0/5 | 13/13* |
| Suppurative rhinitis | 0/5 | 13/13* |
| Lymphoid hyperplasia | 1/5 | 6/13* |

[a] Number positive/number examined.

* Statistically significant difference versus controls, $p < 0.05$.

## DISCUSSION

In this study, F-344 rats of both sexes were exposed at 0, 25, or 250 ppm DEA for 30, 60, or 120 exposure days. Rats exposed at 25 ppm showed no effect in any measured parameter.

Rats exposed at 250 ppm DEA exhibited evidence of toxicity indicated by a decrease in body weight and histopathologic changes in the nares. The incidence of the bronchiolar lymphoid hyperplasia in the lungs of the exposed animals, however, did not increase with increasing DEA exposure. Hence, this histologic change in the lungs was considered not to be of toxicologic significance in terms of DEA exposure. Interestingly, histopathological effects have been reported in the nares of rats following both acute and subchronic inhalation exposures to a structurally related chemical, dimethylamine. Steinhagen *et al.* (1982) reported that acute 6-hr exposures of F-344 rats to high levels of dimethylamine (600 to 6100 ppm) produced a spectrum of pathological changes in the nasal passages, including severe congestion, ulcerative rhinitis, and necrosis of the nasal turbinates. Buckley *et al.* (1983) reported significantly decreased body weight gain and concentration-dependent lesions confined to the nasal passages in rats exposed at 175 ppm dimethylamine for 6 months. The finding of pathologic damage in the nasal passages of rats exposed at 250 ppm DEA is not surprising since inhalation of aliphatic amines has been reported to produce irritation of the nose, throat, and lungs (Beard and Noe, 1981). Further research to investigate the time course, threshold, and incidence of the nasal lesions in animals exposed to DEA is warranted.

The primary purpose of the current study was to further investigate heart muscle degen-

eration reported by Brieger and Hodes (1951). However, we were unable to duplicate their findings as no evidence of cardiac muscle degeneration nor any changes in electrocardiograms or related clinical chemistry indices were seen in any of the rats exposed to DEA for up to 24 weeks. This apparent discrepancy may not, in fact, be real as Brieger and Hodes (1951) reported only very slight heart muscle degeneration which was an inconsistent, non-dose-related finding. The data from the current study suggest that inhaled DEA, at the concentrations tested, does not induce cardiotoxicity in rats, and that the previously reported heart muscle degeneration in rabbits may not have been related to DEA exposure. An alternative explanation is that the negative findings reflect a species difference in susceptibility to DEA cardiotoxicity. In summary, while a number of exposure-related effects were found in rats exposed at 250 ppm DEA, a lack of toxicity was noted in rats intermittently exposed at 25 ppm DEA for up to 24 weeks.

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