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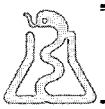

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90-Day Inhalation Toxicity of Dimethylamine in F344 Rats

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ABSTRACT. Dimethylamine (DMA) is a widely used commodity chemical with few toxicity data. Groups of 10 male and female F-344 rats were exposed by inhalation to 0, 5, 10, 20, 40 and 80 ppm of DMA for 6 hrs/day, 5 days/week for 90 days. The changes of body weight, organ weight, hematology, clinical chemistry, and histopathological changes were evaluated after the exposure. As the results, the body weight was significantly decreased at 80 ppm in male and female rats ($p<0.05$). The absolute lung weight showed no statistically significant changes in any group. In contrast, the relative lung weight significantly increased at 80 ppm in male and female rats ($p<0.05$). Erythrocytes, mean cell hemoglobin, leukocytes, neutrophil, and platelet numbers were significantly increased in male and female at 40 or 80 ppm of DMA ($p<0.05$, $p<0.01$). In addition, the serum values of total protein, urea nitrogen were increased in male and creatine kinase, total protein were increased in female rats at 40 or 80 ppm ($p<0.05$, $p<0.01$). Histopathological examinations of the male and female lung samples showed slight hyperplasia and congestion at 80 ppm. Taken together, our study revealed that maximum tolerated dose of DMA would be over 40 ppm.

Keywords: Inhalation, Dimethylamine, F344, Rats.

INTRODUCTION

Dimethylamine (DMA) is a flammable, colorless gas used as an intermediate in the manufacture of rubber accelerators and quaternary compound, pharmaceutical intermediates, fungicides and herbicides, solvents and rocket fuels. DMA is also used as a dehairing agent in leather processing (Steinhagen *et al.*, 1982). Annual production of DMA in Korea is reported to be up to 18,000 tons in 1994 (CISChem, 1995). Inhalation of DMA and direct contract with the aqueous solution are the most common routes of human exposure. Experimental sources have reported that DMA irritates respiratory tract, eyes, skin, and mucous membranes (Buckley *et al.*, 1985; McNulty and Heck, 1983; Steinhagen *et al.*, 1982). The threshold limit values (TLVs) of 5 ppm for DMA has been recommended by the American Conference of Governmental Industrial Hygienists (ACGIH) to protect respiratory tract irritation including tracheitis, bronchitis, pneumonitis, and pulmonary edema (ACGIH, 2002; Steinhagen *et al.*, 1982).

Several DMA inhalation studies have been reported. Animals repeatedly exposed to concentrations of approximately 100 to 200 ppm for 18~20 weeks showed irritation of the respiratory tract with pulmonary edema as well as hepatic injury (NIOSH, 1981). However, there is no enough data accumulated for DMA-induced toxicity by inhalation exposure. Therefore, this study was performed to evaluate the toxicity of DMA inhalation to get data applicable to health risk assessment. Here, we report the total 90 days inhalation toxicity study of DMA.

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MATERIALS AND METHODS

Chemical and animals

DMA gas (greater than 99.8% purity) was obtained from Fluka (Sigma-Aldrich Chemie GmbH, Switzer-

land). F344/NSlc rats of both sexes were purchased at the age of male 4 weeks, female 4.5 weeks from Charles River Korea (Seoul, Korea). The animals were acclimated for 10 days before the start of experiment. The animals were housed individually in stainless-steel wire hanging cages were placed in stainless steel inhalation exposure chambers (whole body type, 1.0 m^3, Dusturbo, Seoul, Korea). Environment in the chamber was maintained constant at a temperature of 21~23°C and a humidity of 35~70% with 12~15 air changes/hr. The exposure chambers were installed in a barrier system animal room. Lighting was controlled automatically to give a 12-h light/dark cycle from 08:00 to 20:00 h. The rats were given sterilized commercial pellet diet (Biogenomics, Seoul, Korea) and tap water *ad libitum*. Male and female rats weighting 105.9 ± 4.8 g, 87.3 ± 8.6 g were randomly assigned to 6 groups, respectively, and exposed DMA.

DMA exposure

A 90-day inhalation toxicity studies were conducted under the OECD Guidelines for Testing of Chemicals 412 and 413 (OECD, 1981; NIH, 1997; Senoh *et al.*, 2003). Groups of 10 rats of both sexes were exposed to DMA gas, and exposure concentration of 0, 5, 10, 20, 40, and 80 ppm based on the TLVs of 5 ppm (ACGIH, 2002) and dose response finding (DRF) study.

DMA gas was controlled by two-stage regulator (Harris, USA) and low-range flowmeter (Cole-Parmer, USA), and supplied to the inhalation exposure chambers. The DMA gas in the chamber was sampled with a personal sampler (Cole-Parmer, USA)on every 30 min/hr for 6 hr/day with a flow rate of 0.1 L/min. The concentration was measured with gas chromatography-flame ionized detector (GC-FID, Hewlett Packard, USA) (Veciana-Nogues *et al.*, 1995).

Study of inhalation toxicity

The animals were observed daily for their clinical signs and mortality. Their body weight, food consumption were measured weekly throughout the study period. The day following the last exposure, the animals were anesthetized, and blood, organ samples was collected for further studies. For blood analysis, erythrocytes, mean cell volume, hemoglobin, leukocytes, neutrophil, lymphocyte, monocyte, eosinophil, basophil, and platelets were determined using a hematological autoanalyzer (Coulter T540 hematology system, Coulter World Headquarters, USA). Serun biochemical analysis was carried out to determine the levels of alkaline phosphatase, creatine kinase, creatinine, total protein, albumin, alanine aminotransferase, and total bilirubin using a biochemical autoanalyzer (VITALAB, Merck, Netherlands). Organ weights of the heart, right kidney, liver, lung, right testis, right ovary, and thymus were recorded before fixation with 10% buffered formalin. Other tissues such as brain, pituitary gland, trachea, spleen, adrenal, pancreas, thyroid, and uterus were collected and preserved in 10% formalin and subsequently processed for microscopic examinations.

Statistical analysis

Data were expressed as means ± S.D. Multiple variance of analysis and Duncan's multiple range tests were used.

RESULTS

Concentration of DMA in the exposure chambers

The concentration of DMA gas in the exposure chambers were maintained constant throughout the 6 hrs exposure period with satisfactory accuracy and precision (Fig. 1).

Body weight development and general observations

The body weight gain of rats exposed to 80 ppm of DMA was significantly suppressed compared to control group ($P<0.05$). No changes food consumption was observed during the 90-day experiment in all groups

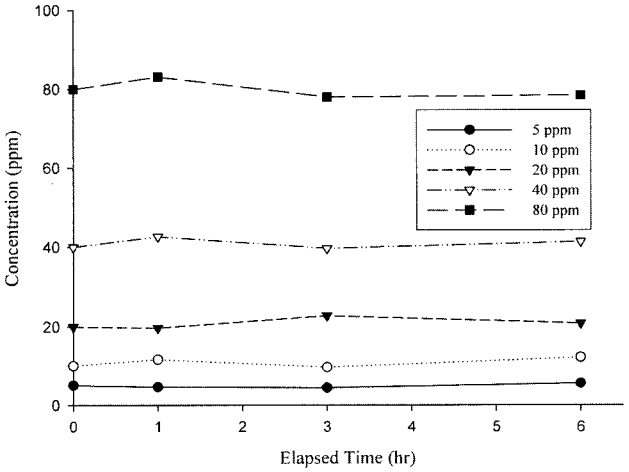

Fig. 1. Concentration of dimethylamine in the inhalation chamber for 6 hours. The dimethylamine concentrations in each inhalation chamber were controlled with mixing of dimethylamine and HEPA-filtered air. Dimethylamine chamber concentrations were monitored by gas chromatograph equipped with flame ionization detector. The variations of dimethylamine concentrations for 6 hours were less than 20% for mean dimethylamine concentrations in each inhalation chamber.

Table 1. Absolute and relative organ weights of male rats in the 90-day inhalation study of dimethylamine[a]

Items	Control	5 ppm	10 ppm	20 ppm	40 ppm	80 ppm
n	10	10	10	10	10	10
Necropsy body wt.	283.6 ± 16.5	281.2 ± 13.0	276.5 ± 11.0	286.9 ± 3.7	290.5 ± 17.2	256.9 ± 18.1*
Heart						
Absolute	0.87 ± 0.09	0.92 ± 0.17	0.85 ± 0.08	0.95 ± 0.11	0.93 ± 0.10	0.92 ± 0.17
Relative	0.31 ± 0.03	0.33 ± 0.06	0.31 ± 0.03	0.33 ± 0.04	0.32 ± 0.03	0.33 ± 0.05
Kidney						
Absolute	1.03 ± 0.12	1.03 ± 0.04	0.95 ± 0.05	1.06 ± 0.10	1.09 ± 0.15	0.91 ± 0.08
Relative	0.36 ± 0.04	0.37 ± 0.02	0.35 ± 0.02	0.37 ± 0.03	0.38 ± 0.04	0.36 ± 0.04
Liver						
Absolute	6.50 ± 1.88	7.77 ± 1.02	7.20 ± 1.14	6.85 ± 0.69	8.03 ± 0.80	7.16 ± 0.80
Relative	2.29 ± 0.61	2.76 ± 0.33	2.61 ± 0.45	2.39 ± 0.25	2.76 ± 0.18	2.79 ± 0.26
Lung						
Absolute	1.53 ± 0.32	1.69 ± 0.40	1.56 ± 0.25	1.36 ± 0.25	1.62 ± 0.17	1.74 ± 0.22
Relative	0.54 ± 0.10	0.60 ± 0.13	0.56 ± 0.10	0.44 ± 0.19	0.58 ± 0.07	0.65 ± 0.11*
Testis						
Absolute	1.51 ± 0.13	1.55 ± 0.16	1.56 ± 0.11	1.48 ± 0.10	1.57 ± 0.12	1.55 ± 0.29
Relative	0.53 ± 0.04	0.55 ± 0.05	0.56 ± 0.04	0.48 ± 0.04	0.54 ± 0.04	0.61 ± 0.24
Thymus						
Absolute	0.23 ± 0.04	0.21 ± 0.04	0.24 ± 0.07	0.25 ± 0.06	0.26 ± 0.02	0.22 ± 0.06
Relative	0.08 ± 0.01	0.07 ± 0.02	0.09 ± 0.03	0.09 ± 0.02	0.09 ± 0.01	0.09 ± 0.02

n: number of animal. Significant differences as compared with control; * $P<0.05$.
[a]Organ weights and body weights are given in grams; relative organ weight is given as mg organ weight/g body weight × 100 (mean ± standard deviation).

Table 2. Absolute and relative organ weights of female rats in the 90-day inhalation study of dimethylamine[a]

Items	Control	5 ppm	10 ppm	20 ppm	40 ppm	80 ppm
n	10	10	10	10	10	10
Necropsy body wt.	175.1 ± 4.5	180.8 ± 6.4	172.3 ± 4.6	170.8 ± 10.0	169.8 ± 9.4	164.6 ± 4.3*
Heart						
Absolute	0.67 ± 0.14	0.66 ± 0.06	0.65 ± 0.17	0.65 ± 0.11	0.62 ± 0.06	0.58 ± 0.26
Relative	0.38 ± 0.13	0.36 ± 0.03	0.38 ± 0.14	0.38 ± 0.05	0.37 ± 0.04	0.35 ± 0.14
Kidney						
Absolute	0.64 ± 0.07	0.71 ± 0.19	0.63 ± 0.05	0.62 ± 0.03	0.64 ± 0.07	0.62 ± 0.06
Relative	0.37 ± 0.04	0.39 ± 0.11	0.37 ± 0.02	0.37 ± 0.02	0.38 ± 0.06	0.37 ± 0.04
Liver						
Absolute	4.66 ± 0.50	4.69 ± 0.34	4.37 ± 0.49	4.31 ± 0.47	4.35 ± 0.30	4.27 ± 0.47
Relative	2.66 ± 0.27	2.60 ± 0.29	2.54 ± 0.26	2.52 ± 0.14	2.57 ± 0.25	2.60 ± 0.29
Lung						
Absolute	1.06 ± 0.14	1.17 ± 0.25	1.03 ± 0.11	0.99 ± 0.21	1.32 ± 0.36	1.21 ± 0.27
Relative	0.60 ± 0.08	0.65 ± 0.19	0.60 ± 0.07	0.58 ± 0.16	0.59 ± 0.08	0.72 ± 0.14*
Ovary						
Absolute	0.06 ± 0.02	0.06 ± 0.02	0.05 ± 0.02	0.05 ± 0.02	0.05 ± 0.02	0.06 ± 0.03
Relative	0.03 ± 0.01	0.03 ± 0.01	0.03 ± 0.01	0.03 ± 0.01	0.03 ± 0.01	0.03 ± 0.01
Thymus						
Absolute	0.21 ± 0.03	0.20 ± 0.09	0.18 ± 0.03	0.19 ± 0.06	0.18 ± 0.05	0.22 ± 0.03
Relative	0.12 ± 0.02	0.11 ± 0.05	0.10 ± 0.02	0.11 ± 0.04	0.09 ± 0.02	0.11 ± 0.02

n: number of animal. Significant differences as compared with control; * $P<0.05$.
[a]Organ weights and body weights are given in grams; relative organ weight is given as mg organ weight/g body weight × 100 (mean ± standard deviation).

(data not shown). In addition, the DMA gas-exposed animals did not show any distinct behavioral changes.

As shown in Table 1, 2, the absolute lung weight showed no statistically significant changes in any group. However, the relative lung weight was increased significantly at 80 ppm in both male and female rats ($P<0.05$). No other organ weights, including the heart, right kidney, liver, right testis, ovary, and thymus showed any

Table 3. Hematology data of male rats in the 90-day inhalation study of dimethylamine[a]

Items	Control	5 ppm	10 ppm	20 ppm	40 ppm	80 ppm
n	10	10	10	10	10	10
Erythrocytes (10^6/μl)	9.69 ± 0.45	9.74 ± 0.56	8.89 ± 2.20	8.69 ± 2.46	9.81 ± 0.41	14.64 ± 0.69**
Mean cell volume (fl)	48.46 ± 8.60	48.24 ± 7.12	48.14 ± 7.63	46.90 ± 7.14	48.39 ± 4.65	48.80 ± 5.90
Hemoglobin (g/dl)	18.03 ± 2.60	17.77 ± 1.94	15.81 ± 3.96	15.61 ± 4.24	18.29 ± 1.83	17.28 ± 1.04
Mean cell hemoglobin (pg)	18.62 ± 0.58	18.27 ± 0.90	17.78 ± 1.04	18.10 ± 1.13	24.64 ± 2.50*	27.97 ± 3.20**
Mean cell hemoglobin concentration (g/dl)	38.46 ± 1.50	37.85 ± 2.00	36.99 ± 2.36	38.54 ± 2.28	38.50 ± 1.47	36.81 ± 2.31
Leukocytes (10^3/μl)	13.99 ± 4.15	15.21 ± 2.42	13.86 ± 1.94	13.68 ± 1.23	15.49 ± 1.38	18.75 ± 1.86*
Leukocyte differential						
Neutrophil (%)	32.19 ± 2.67	35.53 ± 11.54	32.86 ± 9.14	33.50 ± 4.38	37.57 ± 2.77*	44.41 ± 9.81*
Lymphocyte (%)	56.69 ± 7.08	51.03 ± 9.43	58.12 ± 11.24	55.18 ± 8.82	52.62 ± 9.17	48.89 ± 10.63
Monocyte (%)	8.40 ± 2.41	8.85 ± 1.64	7.23 ± 2.35	7.39 ± 1.29	8.41 ± 1.32	6.43 ± 4.62
Eosinophil (%)	3.33 ± 1.44	3.36 ± 1.16	3.53 ± 1.58	3.37 ± 0.50	3.20 ± 0.28	3.35 ± 1.38
Basophil (%)	1.13 ± 0.16	1.18 ± 0.16	1.09 ± 0.15	1.10 ± 0.13	1.12 ± 0.14	1.28 ± 0.27
Platelets (10^3/μl)	687.9 ± 57.9	637.1 ± 53.0	627.7 ± 45.3	614.1 ± 83.2	674.6 ± 41.2	827.7 ± 70.1**

n: number of animal. Significant differences as compared with control; * $P<0.05$, ** $P<0.01$.
[a]Mean ± standard deviation.

Table 4. Hematology data of female rats in the 90-day inhalation study of dimethylamine[a]

Items	Control	5 ppm	10 ppm	20 ppm	40 ppm	80 ppm
n	10	10	10	10	10	10
Erythrocytes (10^6/μl)	9.14 ± 1.53	8.92 ± 1.20	8.50 ± 1.39	9.12 ± 0.43	8.66 ± 1.36	8.81 ± 2.39
Mean cell volume (fl)	52.36 ± 2.57	52.57 ± 6.45	52.14 ± 7.80	50.31 ± 4.64	52.58 ± 6.83	52.21 ± 8.53
Hemoglobin (g/dl)	18.12 ± 8.71	15.30 ± 2.16	16.00 ± 2.71	17.01 ± 1.03	16.49 ± 3.07	16.65 ± 2.60
Mean cell hemoglobin (pg)	19.11 ± 1.08	19.38 ± 1.12	18.83 ± 1.12	18.67 ± 1.23	22.07 ± 1.16*	25.24 ± 2.27**
Mean cell hemoglobin concentration (g/dl)	36.54 ± 2.07	36.89 ± 2.20	36.10 ± 2.35	37.12 ± 2.62	36.53 ± 2.18	36.26 ± 2.46
Leukocytes (10^3/μl)	13.09 ± 1.74	12.82 ± 0.78	12.24 ± 1.47	12.84 ± 1.69	12.47 ± 1.17	12.39 ± 1.04
Leukocyte differential						
Neutrophil (%)	34.73 ± 6.87	34.75 ± 10.94	30.32 ± 7.53	39.78 ± 5.45	46.41 ± 4.42*	42.76 ± 5.18*
Lymphocyte (%)	54.11 ± 5.54	52.46 ± 8.86	56.93 ± 8.16	49.51 ± 11.52	47.38 ± 9.62	50.68 ± 7.46
Monocyte (%)	8.67 ± 3.32	11.04 ± 3.35	11.32 ± 3.40	9.96 ± 2.63	5.97 ± 4.36	6.03 ± 2.28
Eosinophil (%)	1.19 ± 0.14	1.28 ± 0.12	1.12 ± 0.07	1.23 ± 0.16	1.17 ± 0.12	1.35 ± 0.38
Basophil (%)	0.34 ± 0.08	0.32 ± 0.16	0.37 ± 0.12	0.36 ± 0.17	0.38 ± 0.13	0.35 ± 0.09
Platelets (10^3/μl)	641.1 ± 125.6	667.4 ± 177.6	705.7 ± 184.8	736.3 ± 194.5	869.9 ± 129.2*	911.4 ± 124.1**

n: number of animal. Significant differences as compared with control; * $P<0.05$, ** $P<0.01$.
[a]Mean ± standard deviation.

significant change.

Hematological parameters

At terminal sacrifice major points of statistically significant changes in hematological parameters were observed. Erythrocytes were significantly increased in the male exposed to 80 ppm ($P<0.01$). Mean cell hemoglobin was increased in the male and female exposed to 40, 80 ppm ($P<0.05$, $P<0.01$). Leukocytes was significantly increased in the male exposed to 80 ppm ($P<0.05$). Neutrophil was significantly increased in the male and female exposed to 40, 80 ppm ($P<0.05$). Platelets were significantly increased in the male exposed to 80 ppm ($P<0.01$) and the female exposed to 40, 80 ppm ($P<0.05$, $P<0.01$). Other hematological parameters were remained unchanged by DMA exposure (Table 3, 4).

Clinical chemistry parameters

Creatine kinase was significantly increased in the female exposed to 40, 80 ppm ($P<0.01$). Total protein was significantly increased in the male exposed to 40 ppm ($P<0.05$) and the female exposed to 40, 80 ppm ($P<0.05$, $P<0.01$). Urea nitrogen was significantly increased in the male exposed to 40, 80 ppm ($P<0.05$). Alkaline phosphatase, creatinine, albumin, alanine aminotransferase, and total bilirubin levels were not affected by DMA exposure (Table 5, 6).

Histopathological changes

Figure 4, 5 and Table 7, 8 shows the incidence of

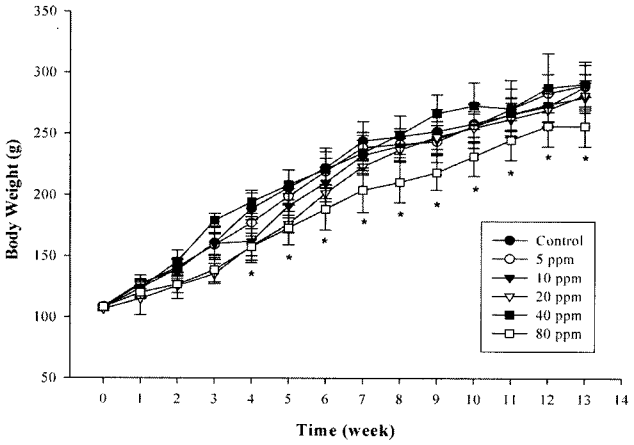

Fig. 2. Body weight of male rats exposed to dimethylamine during the 90-day inhalation toxicity study. Six groups of 10 male rats were exposed to dimathylamine at concentrations of 0, 5, 10, 20, 40, and 80 ppm for 6 hours/day, 5 days/week for 90 days. The rats exposed to the dimethylamine showed changes in body weight during the 90 days ex periment. Significant differences as compared with control; * $P<0.05$.

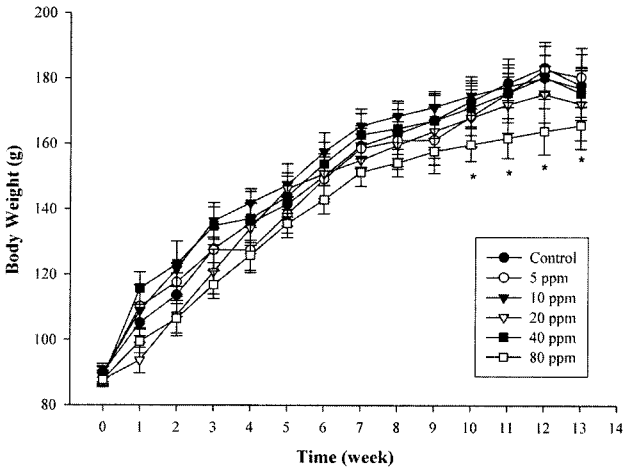

Fig. 3. Body weight of female rats exposed to dimethylamine during the 90-day inhalation toxicity study. Six groups of 10 male rats were exposed to dimethylamine at concentrations of 0, 5, 10, 20, 40, and 80 ppm for 6 hours/day, 5 days/week for 90 days. The rats exposed to the dimethylamine showed changes in body weight during the 90 days experiment. Significant differences as compared with control; * $P<0.05$.

lung lesions in the male and female rats exposed to DMA for 90-day. In the 0, 5, 10, 20, and 40 ppm groups, no significant changes was found in the terminal bronchiole, and alveolar space with thin alveolar septa. In contrast, in the 80 ppm male and female

Table 5. Serum biochemical data of male rats in the 90-day inhalation study of dimethylamine[a]

Items	Control	5 ppm	10 ppm	20 ppm	40 ppm	80 ppm
n	10	10	10	10	10	10
Alkaline phosphatase (mg/dl)	272.3 ± 78.1	297.2 ± 86.5	283.6 ± 91.8	245.8 ± 34.4	302.9 ± 86.6	281.3 ± 62.8
Creatine kinase (mg/dl)	182.5 ± 45.2	212.3 ± 40.2	186.4 ± 33.4	190.3 ± 54.7	205.3 ± 59.4	182.6 ± 56.2
Creatinine (mg/dl)	0.58 ± 0.34	0.61 ± 0.31	0.93 ± 0.52	0.78 ± 0.64	1.03 ± 0.48	0.95 ± 0.40
Total protein (g/dl)	7.59 ± 0.89	7.03 ± 1.88	7.14 ± 1.58	8.52 ± 1.97	10.62 ± 1.69*	8.54 ± 1.77
Albumin (g/dl)	5.65 ± 1.52	5.86 ± 0.66	5.92 ± 0.57	5.54 ± 0.86	6.92 ± 2.66	6.45 ± 1.42
Urea nitrogen (mg/dl)	15.22 ± 2.32	13.31 ± 3.91	15.97 ± 1.03	14.45 ± 4.60	20.27 ± 2.70*	21.13 ± 3.34*
Alanine aminotransferase (mg/dl)	24.70 ± 4.72	23.80 ± 6.76	24.00 ± 3.94	25.10 ± 5.67	30.50 ± 5.52	29.70 ± 12.96
Total bilirubin (mg/dl)	0.51 ± 0.20	0.57 ± 0.45	0.55 ± 0.28	0.56 ± 0.17	0.52 ± 0.24	0.63 ± 0.12

n: number of animal. Significant differences as compared with control: * $P<0.05$.
[a]Mean ± standard deviation.

Table 6. Serum biochemical data of female rats in the 90-day inhalation study of dimethylamine[a]

Items	Control	5 ppm	10 ppm	20 ppm	40 ppm	80 ppm
n	10	10	10	10	10	10
Alkaline phosphatase (mg/dl)	235.5 ± 78.9	296.1 ± 67.3	269.2 ± 84.7	266.5 ± 40.3	243.1 ± 35.2	253.5 ± 63.3
Creatine kinase (mg/dl)	175.1 ± 29.2	176.3 ± 47.5	163.4 ± 33.1	188.0 ± 34.0	224.5 ± 21.8**	226.2 ± 28.6**
Creatinine (mg/dl)	0.63 ± 0.12	0.71 ± 0.25	0.68 ± 0.14	0.75 ± 0.21	0.72 ± 0.28	0.78 ± 0.31
Total protein (g/dl)	6.29 ± 2.93	7.51 ± 1.36	8.22 ± 3.26	7.51 ± 2.10	11.24 ± 2.04*	13.51 ± 4.32**
Albumin (g/dl)	5.96 ± 2.60	5.18 ± 3.65	6.26 ± 1.49	5.68 ± 1.17	6.57 ± 2.36	6.30 ± 1.21
Urea nitrogen (mg/dl)	15.84 ± 3.27	16.20 ± 5.20	18.11 ± 3.65	18.54 ± 4.65	20.69 ± 5.23	19.16 ± 3.82
Alanine aminotransferase (mg/dl)	23.00 ± 3.56	24.20 ± 5.27	23.68 ± 4.06	26.50 ± 3.57	25.80 ± 5.88	20.90 ± 8.69
Total bilirubin (mg/dl)	0.31 ± 0.19	0.39 ± 0.25	0.38 ± 0.24	0.41 ± 0.28	0.35 ± 0.24	0.32 ± 0.16

n: number of animal. Significant differences as compared with control; * $P<0.05$, ** $P<0.01$.
[a]Mean ± standard deviation.

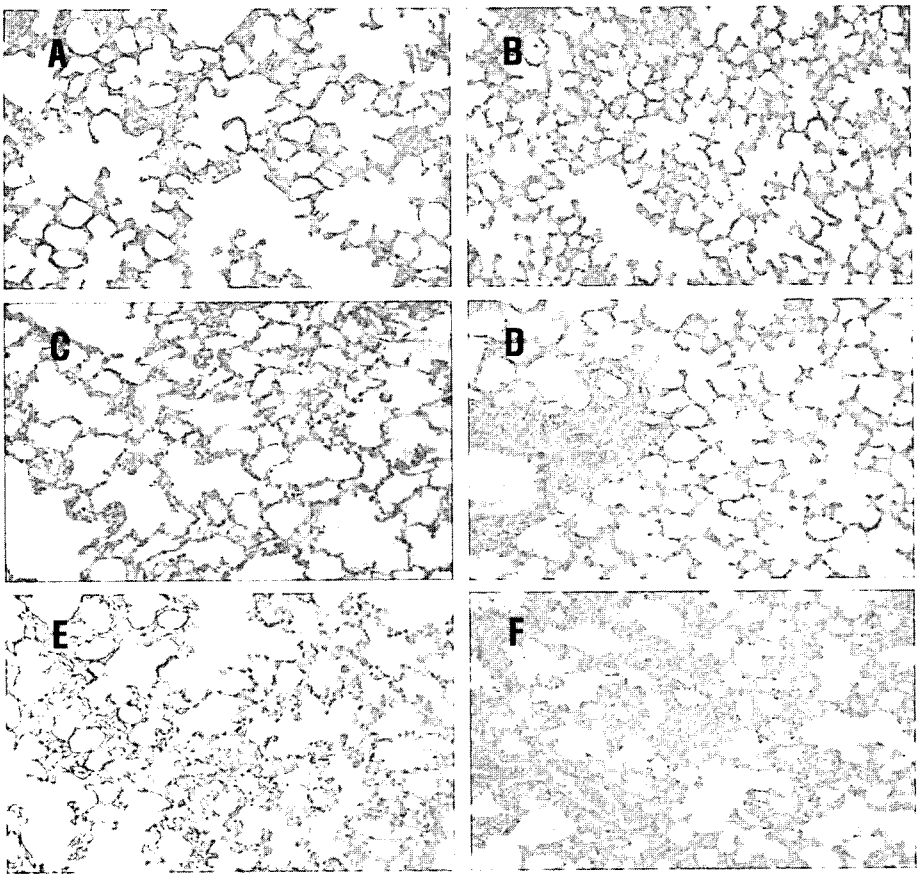

Fig. 4. Histopathological changes of lung from male rats exposed to dimethylamine (0, 5, 10, 20, 40, 80 ppm) and control. (A) Control group showed normal terminal bronchiole, and alveolar septa. In the exposed groups (5, 10, 20, 40 ppm), no significant change was found in the terminal bronchiole, and alveolar space with thin alveolar septa (B-E). In the F group (80 ppm) rats, slightly and randomly distributed epithelial hyperplasia was noted in the bronchioles and alveoli. Hematoxylin & Eosin, Magnification 200 ×.

rats, slightly and randomly distributed epithelial hyperplasia was noted in the bronchioles and alveoli. The others did not show any distinct histopathological changes.

DISCUSSION

Of all the short-chain aliphatic amines, dimethylamine has been investigated frequently owing to its ability to act both *in vitro* and *in vivo* as a presursor of carcinogenic dimethylnitrosamine (Mirvish, 1975). Excess amounts of both dimethylamine and dimethylnitrosamine have been measured in the intestine of chronic renal failure patients giving rise to concern (Dunn *et al.*, 1990), and dimethylnitrosamine has been detected in human urine, its presence being attributed to the nitrosation of dimethylamine catalysed by nitrogen oxides within the modern urban atmosphere (Garland *et al.*, 1986).

Our study clearly showed that inhalation exposure of DMA for 90 days caused some characteristic histopathologic adverse effects on the lung, while other organs were not affected. These results were well matched with the change of relative lung weight which was significantly increased at 80 ppm in male and female rats. Single environmental chemical esposure is not common, rather more than one chemical may be co-exposed to humanbeing. Therefore, co-exposure of different chemicals may produce unexpected endpoint. In this, study, DMA alone exhibited characteristic toxicity. The toxicity, however, may be associated with severe damage if DMA is co-exposed with other chemicals. In fact, DMA with sodium nitrite caused severe DNA damage whereas each single chemical did not produce such genotoxic effects (Ohsawa *et al.*, 2003).

In conclusion, it was found that inhalation exposed to rats of DMA gas for 90-day induced adverse effects on the lung were affected histopathological changes at 80

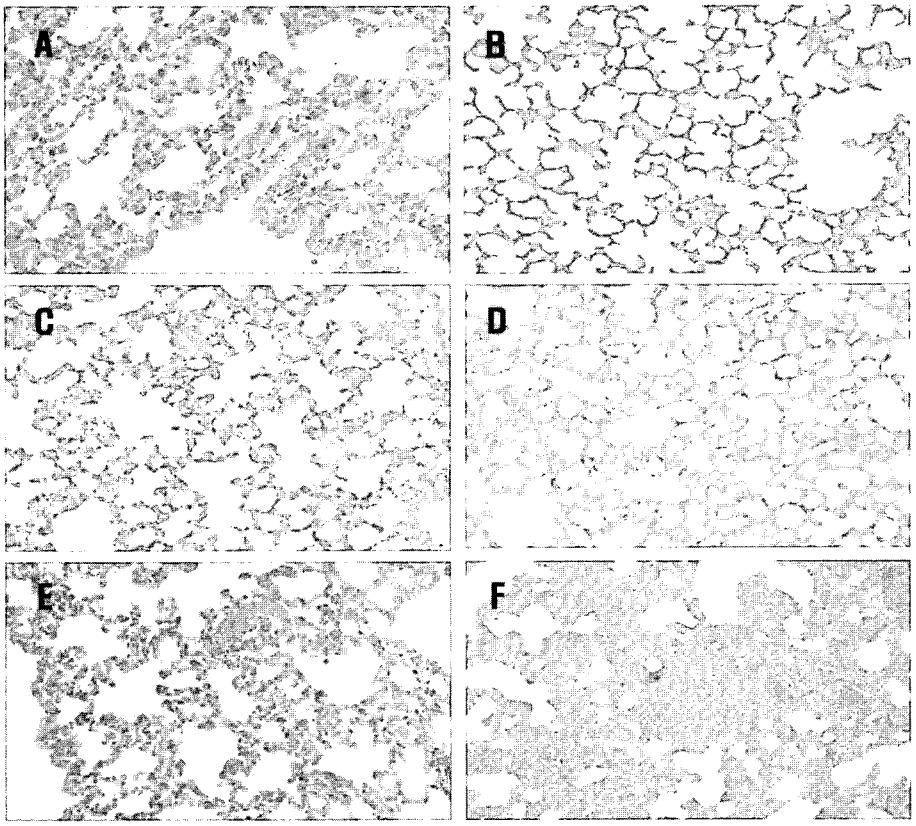

Fig. 5. Histopathological changes of lung from female rats exposed to dimethylamine (5, 10, 20, 40, 80 ppm) and control. (A) Control group showed normal terminal bronchiole, and alveolar septa. In the exposed groups (5, 10, 20, 40 ppm), no significant change was found in the terminal bronchiole, and alveolar space with thin alveolar septa (B-E). In the F group (80 ppm) rats, mild hyperplasia and congestion were observed in the bronchioles and alveoli. Hematoxylin & Eosin, 200 ×.

Table 7. Histopathological findings in male F344 rats

Concentration (ppm)	0	5	10	20	40	80
n	10	10	10	10	10	10
Heart	N[a]	N	N	N	N	N
Kidney						
- Vaculoation	N	N	N	N	N	N
Liver						
- Cell swelling	N	N	N	N	N	N
Lung						
- Hyperplasia	N	N	N	N	N	1
- Congestion	N	N	N	N	N	1
Testis	N	N	N	N	N	N
Thymus	N	N	N	N	N	N
Brain	N	N	N	N	N	N
Pituitary	N	N	N	N	N	N
Nasal cavity	N	N	N	N	N	N
Trachea	N	N	N	N	N	N
Spleen	N	N	N	N	N	N
Adrenal	N	N	N	N	N	N

Note: Sis groups of 10 male rats were exposed to DMA at concentrations of 0, 5, 10, 20, 40, and 80 ppm for 6 hours/day, 5 days/week, for 90 days. The rats exposed to the DMA showed changes in histopathological findings during the 90 days experiment. n, Number of animal.
[a]N, no significant histopathological changes.

Table 8. Histopathological findings in female F344 rats

Concentration (ppm)	0	5	10	20	40	80
n	10	10	10	10	10	10
Heart	N[a]	N	N	N	N	N
Kidney						
- Vaculoation	1	N	N	N	N	N
Liver						
- Cell swelling	N	N	N	N	N	N
Lung						
- Hyperplasia	N	N	N	N	N	2
- Congestion	N	N	N	N	N	2
Ovary	N	N	N	N	N	N
Thymus	N	N	N	N	N	N
Brain	N	N	N	N	N	N
Pituitary	N	N	N	N	N	N
Nasal cavity	N	N	N	N	N	N
Trachea	N	N	N	N	N	N
Spleen	N	N	N	N	N	N
Adrenal	N	N	N	N	N	N

Note: Sis groups of 10 female rats were exposed to DMA at concentrations of 0, 5, 10, 20, 40, and 80 ppm for 6 hours/day, 5 days/week, for 90 days. The rats exposed to the DMA showed changes in histopathological findings during the 90 days experiment. n, Number of animal.
[a]N, no significant histopathological changes.

ppm in male and female rats. In the hematological and clinical chemistry, some significant changes of several parameters were observed in the male and female exposed to 40 and 80 ppm, but these findings were considered to be of no toxicological significance. Accordingly, it was considered that over 40 ppm of DMA exposure would induce the toxicological effects.

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