SUBCHRONIC INHALATION OF TRIETHYLAMINE VAPOR IN FISCHER-344 RATS: ORGAN SYSTEM TOXICITY[a]

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Male and female F-344 rats were exposed at 0, 25, or 247 ppm triethylamine (TEA) vapor, 6 hr per day, 5 days per week for up to 28 weeks in order to characterize the subchronic organ system toxicity. Rats were weighed biweekly and scheduled sacrifices were performed following about 30, 60, and 120 days of exposure. No statistically significant treatment-related effects on organ weights, hematology, clinical chemistry, or electrocardiographic indices were observed. Body weight gain was not affected by TEA treatment. No physiologic or pathologic evidence of cardiotoxicity was seen in rats exposed to either TEA concen-

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Abbreviated title: Subchronic Inhalation of Triethylamine Vapor

Abbreviations: triethylamine—TEA; Fischer 344—F-344.

Key Words: triethylamine, subchronic inhalation toxicity; F-344 rats, triethylamine inhalation exposures; cardiotoxicity, absence in triethylamine-exposed rats.

[a]A preliminary report of this work was presented at the 26th Annual Meeting of the Society of Toxicology, Washington, D.C., February 24–27, 1987.

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Toxicology and Industrial Health, 6:3/4, pp. 403–414.

ISSN: 0748-2337

tration for up to 28 weeks. No gross or histopathologic lesions attributable to TEA exposure were noted in any of the organs examined, including the nasal passages. This latter finding is in marked contrast to previously reported findings from this laboratory in which squamous metaplasia, suppurative rhinitis, and lymphoid hyperplasia were found in the respiratory epithelium of F-344 rats exposed to the structurally related chemical, diethylamine, under the same conditions as this study (Lynch et al., 1986).

INTRODUCTION

Triethylamine (TEA) is produced from ethyl chloride and ammonia under heat and pressure and is used in the manufacture of wetting, penetrating, and waterproofing agents, as a corrosion inhibitor, and as a propellant (Sax and Lewis, 1987). Annual production of TEA was about 6,500 tons in 1976 (Schweizer et al., 1978). The National Institute for Occupational Safety and Health (NIOSH) has estimated that about 10,500 workers are potentially exposed to TEA in the workplace (NIOSH, 1977).

TEA has a vapor pressure of 54 mm Hg (20°C) and has been reported to be irritating to the lung and nasal passages of both laboratory animals and man following inhalation exposure (Beard and Noe, 1981). The acute inhalation toxicity of TEA to guinea pigs was reported by Carpenter et al. (1948). Four of six animals exposed at 2,000 ppm for 2 hr died, 2/6 exposed at 1,000 ppm for 4 hr died, and no deaths (0/6) were recorded following 4 hr exposures at 250 or 500 ppm TEA. Smyth et al. (1951) also investigated the acute inhalation toxicity of TEA and reported that one of six rats exposed at 1,000 ppm for 4 hrs died.

In addition to these acute studies, Brieger and Hodes (1951) exposed rabbits at 50 and 100 ppm TEA vapor for 7 hr/day, 5 days/week for 6 weeks. Lungs from rabbits exposed at 100 ppm exhibited hyperemia and edema, hemorrhages, moderate peribronchitis, and vascular thickening. The liver and kidneys showed parenchymatous degeneration with cell necrosis, and the heart showed congestion, edema, and muscular degeneration. Similar changes to a lesser degree were observed in the lungs and liver in animals exposed at 50 ppm TEA.

Several Russian investigators have also examined the toxicity of low levels of TEA. Tkachev (1971) exposed male rats to TEA at concentrations of 0.16, 1.71, and 13.01 mg/m^3 (0.04–3.25 ppm) for 3 months (other experimental details were not provided). TEA exposure did not affect weight gain, hemoglobin, RBC counts, oxygen consumption, prothrombin time, or the urinary excretion of phenols and sulfates. Exposure to the highest concentration of TEA produced thickening of the interalveolar septa and accumulation of acid mucopolysaccharides in the interstitial substance of the connective tissue of the alveoli. Kagan (1965) exposed rabbits orally to TEA at doses of 1 and 6 mg/kg for 7 months.

No effects were noted on protein synthesis by the liver, cholinesterase activity, or serum content of sulfhydryl groups, and only transient effects on hepatic carbohydrate metabolism were observed at the higher dose level.

The mutagenic potential of TEA was evaluated by Isakova et al. (1971). Male Wistar rats were exposed at 1 mg/m^3 (0.25 ppm) and 10 mg/m^3 (2.5 ppm) TEA continuously for up to 90 days. The incidence of bone marrow cells with structural chromosome breaks did not exceed the control incidence (2%) at any time point, but the incidence of aneuploid cells was increased in rats exposed at the lower TEA concentration for 30 days.

Akesson et al. (1985) exposed human volunteers to TEA at 10–48 mg/m^3 (2.5–12 ppm) for 4–8 hours and reported transient decreased visual acuity and transient pronounced corneal edema. No effects were noted at the lowest concentration of 10 mg/m^3 (2.5 ppm), but effects were reported during 8 hr exposures at 18 mg/m^3 (4.5 ppm). In a follow-up study, Akesson et al. (1986) reported that 5/19 workers employed in a polyurethane foam production plant for a minimum of 4 years reported visual disturbances described as "foggy vision," "blue haze," and sometimes "halo phenomena" which were associated with TEA exposure. TEA concentrations ranged from 4–24 mg/m^3 (1–6 ppm) at selected sites within the plant where workers reported symptoms. No evidence of permanent eye disease was noted, and no effects were seen when TEA exposure concentrations were decreased to 6 mg/m^3 (1.5 ppm).

Akesson et al. (1988) reported that TEA and triethylamine-N-oxide were found in the plasma and urine of five healthy male volunteers exposed at 10–50 mg/m^3 (2.5–13 ppm) TEA for 4–8 hr. They reported a good correlation between the airborne TEA exposure levels and urinary TEA concentrations, and suggested that urinary TEA is useful as a biological monitor of TEA exposure.

TEA is regulated as an irritant and the Occupational Safety and Health Administration (OSHA) Permissible Exposure Limit for TEA is 10 ppm (OSHA, 1989). The American Conference of Governmental Industrial Hygienists (ACGIH) Threshold Limit Value (TLV®) for TEA is 10 ppm (ACGIH, 1986).

The objective of this study was to more fully investigate the subchronic toxicity of inhaled TEA in rats. Effects of inhaled TEA on other selected organ systems, including the heart, were also assessed.

MATERIALS

Chemical. Reagent grade TEA (Lot number G3M04), with a purity greater than 99.9% by weight, was obtained from MCB Manufacturing Chemists, Inc., Norwood, OH[c].

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

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

Vapor Generation and Monitoring. Rats were exposed at 25 or 247 ppm TEA for 6 hr/day, 5 days/week, excluding legal holidays, for 28 weeks. Exposure concentrations were selected to provide comparisons to previous toxicity determinations conducted in this laboratory with diethylamine at 25 and 250 ppm (Lynch et al., 1986). TEA vapor was generated by pumping liquid TEA at a constant flow rate (Fluid Metering Inc., Oyster Bay, NY) into the air stream of the tangential airfeed at the top of the exposure chambers. A fresh batch of TEA was used in the generation reservoir each day. TEA concentrations in the chamber were monitored 2–4 times per hour using a Wilks-Miran 1A Infrared Analyzer (Foxboro Analytical, Norwalk, CT) using the following instrument settings: wavelength 9 μm, pathlength 6.2 m, slit 1.0 mm. The instrument was calibrated by the closed loop calibration method. Adjustments were made to the generation system, as required, to maintain the exposure levels at the targeted concentrations.

Animals. Weanling caesarean-derived Fischer 344 rats [CDF (F-344)/Crl BR] obtained from Charles River Breeding Laboratories (Wilmington, MA) were used in the study. During a 2-week quarantine period, the rats were individually identified by ear tags and randomly assigned to each chamber (100 rats/chamber; 50 male and 50 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. A 12-hr on/12-hr off lighting schedule with lights on between 7 a.m. and 7 p.m. was maintained.

Animal Observations. Twice daily observations were made for changes in appearance or demeanor. Body weights were recorded on the day preceding the first day of exposure, at 2-week intervals throughout the study (at the end of an exposure day), and immediately prior to scheduled sacrifice. Body weight changes were computed by subtracting the pre-exposure 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; Abbott Laboratories, North Chicago, IL) from each exposure group after 32–34 and 58–61 days of exposure. For the terminal sacrifice 10–20 male and female rats were randomly selected from each group after 125–127 exposure days. (The remaining rats in each group were used for another experiment and no pathologic examinations were con-

ducted). Prior to sacrifice rats were fasted overnight. A complete necropsy was performed, and lungs, liver, kidneys, and heart were weighed. Selected organs were fixed in 10% buffered formalin, embedded in paraffin, sectioned at 5 μm, stained with hematoxyline and eosin, and examined microscopically. The following tissues were examined histologically: lungs (following infusion with 10% formalin), liver, kidneys, heart, spleen, tracheobronchial lymph nodes, adrenals, urinary bladder, testes, seminal vesicles, uterus, ovaries, trachea, eyes and nasal passages (processed and cut as described by Buckley et al. 1985). Rats dying at other times during the study were refrigerated and necropsied within 12 hr whenever possible.

Clinical Chemistry-Hematology. The following clinical chemistry indices were measured at each scheduled sacrifice on a Gemsaec Centrifugal Analyzer (Electro-Nucleonics, Inc., Fairfield, NJ): alanine aminotransferase (ALT), aspartate aminotransferase (AST), creatine phosphokinase (CPK), blood urea nitrogen (BUN), creatinine (CRE) and sorbitol dehydrogenase (SDH). Hematology evaluations, conducted only at the terminal sacrifice, included hemoglobin, hematocrit, complete blood count and differential.

Electrophysiology. Electrocardiograms (ECGs) were recorded from 9–11 anesthetized rats/sex/group (ketamine/xylazine, 80 mg/kg/12 mg/kg, ip; Veterinary Products Bristol Laboratories, Syracuse, NY and Mobay Corp., Animal Health Div., Shawnee, KS) 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, NY). ECG waveforms were sampled and analyzed using a Healthgard CPT-5 computer system (Salt Lake City, UT). 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 by a veterinary cardiologist who did not have knowledge of the animal assignments into groups.

Statistical Evaluation. Multiple *t*-tests were used to compare initial body weights, while a multivariate analysis of variance was used to compare weight gains at each additional weighing period. 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). Pathology incidence data were evaluated using a χ^2 test. All comparisons between control and exposed animals were made at a statistical significant level of $\alpha = 0.05$. Results were considered significant when $p < 0.05$.

RESULTS

Vapor Exposure

The TEA chamber concentrations for the 28-week exposure period were 24.8 ± 1.3 and 247.3 ± 11.5 ($\bar{x}$ ± SD). Rats were exposed at 25 or 247 ppm

TEA for a maximum of 127 days, with an average of 5.80 and 5.82 hrs of exposure per day, respectively.

Animal Observations

Rats of both sexes tolerated the exposure at 25 ppm without exhibiting overt signs of toxicity. At 247 ppm TEA the rats kept their eyes closed and noses buried in their fur during the entire exposure period. Body weight gain was not statistically affected; however, there was a slight dose-related reduction which occurred in the TEA exposed male rats compared to the controls (data not shown).

Clinical Chemistry and Hematology

Hematologic analyses revealed no statistical differences in male or female rats exposed to TEA for 28 weeks (Table 1). Several clinical chemistry indices, i.e., SDH, ALT and creatinine, were elevated in one group of rats, or in only one

TABLE 1
Hematology Data from F-344 Rats Exposed to Inhaled Triethylamine Vapor for 28 Weeks

Exposure levels (ppm)	RBC $\times 10^6$	WBC $\times 10^3$	Hb g/dl	HCT
		Male Rats		
0	8.59 ± 0.60[a]	7.46 ± 6.07	16.39 ± 0.82	43.0 ± 2.9
	(7.52–9.92)[b]	(2.00–27.40)	(15.4–18.0)	(38–48)
	15[c]	15	11	11
25	8.71 ± 0.57	7.04 ± 6.63	16.51 ± 0.93	42.7 ± 3.0
	(7.04–9.59)	(2.60–33.40)	(14.9–17.7)	(38–47)
	20	20	10	10
247	8.80 ± 0.53	7.69 ± 7.05	16.74 ± 0.67	43.3 ± 1.5
	(7.65–9.57)	(2.30–25.30)	(15.7–18.1)	(41–45)
	17	17	10	10
		Female Rats		
0	7.99 ± 0.46	5.15 ± 3.96	16.48 ± 1.12	41.4 ± 2.4
	(6.91–8.88)	(1.90–19.90)	(15.0–18.8)	(38–45)
	19	19	10	10
25	8.06 ± 0.46	4.54 ± 3.29	16.23 ± 1.03	40.9 ± 2.1
	(7.26–8.98)	(1.20–14.00)	(14.8–18.0)	(38–44)
	19	19	10	10
247	7.93 ± 0.48	5.93 ± 5.06	16.12 ± 0.74	40.7 ± 1.7
	(7.05–9.04)	(1.70–25.20)	(14.9–17.6)	(38–43)
	19	19	10	10

[a] $\bar{x}$ ± SD.
[b] (Range).
[c] Number of animals.

sex of rats, at one of the scheduled interim sacrifices. These changes were not attributed to TEA exposure since they were sporatic in occurrence and not concentration related (Table 2).

Absolute and Relative Organ Weights

No consistent statistically significant differences in absolute or relative organ weights were seen in rats exposed to TEA and killed at any of the scheduled sacrifices. Lung weights and lung-to-body weight ratios were increased in all four groups of male and female rats exposed to TEA for 28 weeks, and absolute heart weights were increased in both groups of male rats exposed to TEA for the same period (Table 3).

Electrophysiology

Representative electrocardiographic data are presented in Table 4. No statistically significant differences were observed in any of the indices which were recorded and analyzed from rats exposed to either TEA concentration for 28 weeks.

Gross and Histopathology

There were no gross pathologic observations in rats which were considered to be related to treatment with the test chemical. All rats survived the exposures except for one female rat in the 25 ppm TEA group which was sacrificed due to malocclusion (week 6), two 250 ppm TEA female rats which died following an accidental injury (week 3), and one 250 ppm male rat which died during the exposure period (week 8). These deaths could not be attributed to TEA exposure. Microscopic evaluation of tissues from animals exposed for up to 28 weeks failed to reveal lesions that could be attributed to chemical exposure. Chronic inflammation of the lungs was seen in both sexes of rats in all groups, including the controls, exposed for 28 weeks. Liver lesions consisting of minimal foci of necrosis were detected in males of all three groups exposed for 28 weeks. Neoplastic lesions, unrelated to chemical exposure, included: one nephroblastoma, 25 ppm TEA female, interim sacrifice; one pituitary adenoma, 250 ppm TEA male, final sacrifice; and one thyroid follicular cell adenoma, control female, final sacrifice.

DISCUSSION

In this study, F-344 rats of both sexes were exposed at 0, 25, or 247 ppm TEA for up to 127 exposure days. Rats exposed to TEA showed no statistically significant differences compared to the controls in any of the measured indices. This finding is surprising and is in marked contrast to previously reported findings from this laboratory in which squamous metaplasia, suppurative rhinitis, and lymphoid hyperplasia were found in the respiratory epithelium of the nasal passages of F-344 rats exposed to the diethyl-substituted amine, diethylamine,

TABLE 2
Terminal Clinical Chemistry Results for F-344 Rats Exposed to Inhaled Triethylamine Vapor for 28 Weeks

Exposure levels (ppm)	AST IU	ALT IU	BUN mg/dl	CPK IU	Creatinine mg/dl	LDH IU	SDH IU
			Male Rats				
0	125.8 ± 36.8[a]	87.6 ± 36.4	21.27 ± 1.85	371.6 ± 167.1	0.68 ± 0.12	475.0 ± 162.1	10.08 ± 5.64
	(80–184)[b]	(49–171)	(19–25)	(140–697)	(0.5–0.8)	(198–654)	(4.3–20.7)
	11[c]	11	11	11	11	11	11
25	166.9 ± 154.4	114.0 ± 117.2	20.70 ± 1.77	481.9 ± 243.9	0.74 ± 0.19	524.2 ± 236.8	10.85 ± 11.11
	(76–600)	(54–445)	(18–23)	(212–920)	(0.5–1.1)	(246–1102)	(2.5–41.4)
	10	10	10	10	10	10	10
247	119.9 ± 34.1	82.8 ± 18.7	21.20 ± 1.62	512.5 ± 355.0	0.73 ± 0.27	466.3 ± 237.5	7.80 ± 2.91
	(73–179)	(55–144)	(18–24)	(117–1201)	(0.4–1.2)	(189–930)	(4.0–12.6)
	10	10	10	10	10	10	10
			Female Rats				
0	98.9 ± 28.5	63.4 ± 12.8	23.3 ± 2.58	342.7 ± 276.4	0.66 ± 0.12	366.3 ± 150.7	5.56 ± 3.03
	(67–155)	(38–81)	(21–30)	(99–972)	(0.5–0.8)	(171–678)	(1.5–11.5)
	10	10	10	10	10	10	10
25	107.1 ± 42.2	65.6 ± 27.2	21.5 ± 1.27	431.8 ± 468.6	0.61 ± 0.24	390.7 ± 224.4	5.26 ± 3.44
	(54–194)	(39–120)	(20–24)	(126–1656)	(0.3–1.0)	(70–700)	(1.7–12.7)
	10	10	10	10	10	10	10
247	77.0 ± 11.9	48.7 ± 8.2	21.3 ± 2.26	206.5 ± 101.0	0.58 ± 0.27	207.3 ± 83.1	2.85 ± 1.26
	(65–106)	(40–68)	(19–25)	(69–378)	(0.1–0.9)	(73–290)	(1.2–4.9)
	10	10	10	10	10	10	10

[a] $\bar{x}$ ± SD.
[b] (Range).
[c] Number of animals.

TABLE 3
Terminal Body Weights, Organs Weights, and Organ-to-Body Weight Ratios for F-344 Rats Exposed to Inhaled Triethylamine Vapor for 28 Weeks

Exposure levels (ppm)	Body wt (g)	Lung		Heart		Kidney		Liver	
		g	g/body wt ratio × 100	g	g/body wt ratio × 100	g	g/body wt ratio × 100	g	g/body wt ratio × 100
Male Rats									
0	376 ± 17.7[a]	2.11 ± 0.36	0.59 ± 0.10	1.13 ± 0.08	0.32 ± 0.03	2.39 ± 0.32	0.67 ± 0.09	10.68 ± 0.80	2.98 ± 0.22
	(345–414)[b]	(1.73–2.77)	(0.48–0.78)	(1.03–1.27)	(0.28–0.38)	(1.81–2.89)	(0.49–0.79)	(9.54–12.72)	(2.73–3.57)
	25[c]	14	14	15	15	15	15	15	15
25	372 ± 23.2	2.18 ± 0.36	0.61 ± 0.09	1.18 ± 0.15	0.33 ± 0.03	2.39 ± 0.29	0.67 ± 0.08	10.59 ± 1.01	2.96 ± 0.21
	(310–409)	(1.52–2.80)	(0.44–0.76)	(0.95–1.48)	(0.28–0.39)	(1.89–2.87)	(0.52–0.77)	(8.18–12.25)	(2.56–3.34)
	24	20	20	20	20	20	20	20	20
247	371 ± 20.9	2.29 ± 0.37	0.63 ± 0.10	1.16 ± 0.21	0.32 ± 0.06	2.31 ± 0.35	0.64 ± 0.09	10.75 ± 0.87	2.97 ± 0.16
	(345–404)	(1.73–2.97)	(0.50–0.78)	(0.98–1.89)	(0.27–0.55)	(1.62–2.81)	(0.49–0.77)	(9.46–12.78)	(2.73–3.28)
	24	19	19	19	19	19	19	19	19
Female Rats									
0	206 ± 12.6	1.44 ± 0.14	0.72 ± 0.06	0.74 ± 0.06	0.37 ± 0.03	1.55 ± 0.14	0.78 ± 0.07	6.21 ± 0.40	3.13 ± 0.17
	(186–235)	(1.25–1.82)	(0.61–0.85)	(0.65–0.84)	(0.33–0.46)	(1.19–1.80)	(0.64–0.92)	(5.44–7.39)	(2.75–3.46)
	25	19	19	20	20	20	20	20	20
25	197 ± 11.1	1.49 ± 0.14	0.80 ± 0.07[d]	0.73 ± 0.07	0.39 ± 0.03	1.47 ± 0.16	0.79 ± 0.08	6.10 ± 0.66	3.25 ± 0.24
	(171–212)	(1.29–1.73)	(0.68–0.89)	(0.59–0.86)	(0.32–0.44)	(1.24–1.78)	(0.67–0.95)	(4.79–7.23)	(2.78–3.65)
	24	20	20	20	20	20	20	20	20
247	199 ± 11.7	1.46 ± 0.13	0.76 ± 0.06	0.74 ± 0.07	0.38 ± 0.03	1.52 ± 0.14	0.79 ± 0.08	6.06 ± 0.57	3.14 ± 0.31
	(176–225)	(1.24–1.77)	(0.63–0.86)	(0.67–0.94)	(0.33–0.45)	(1.30–1.80)	(0.67–0.93)	(5.15–7.04)	(2.68–3.67)
	23	20	20	20	20	20	20	20	20

[a] $\bar{x}$ ± SD.
[b] (Range).
[c] Number of animals.
[d] Statistically different from control, $p < 0.05$.

TABLE 4
Representative Electrocardiographic Data from F-344 Rats Exposed to Inhaled Triethylamine Vapor for 28 Weeks

Exposure levels (ppm)	Heart rate/min	PQ interval (msec)	QT interval (msec)
	Male Rats		
0	267 ± 45[a]	54 ± 11	87 ± 10
	(210–380)[b]	(40–70)	(80–110)
	10[c]	10	10
25	256 ± 25	48 ± 8	83 ± 19
	(210–300)	(40–60)	(60–120)
	11	11	11
247	259 ± 20	53 ± 7	86 ± 7
	(230–290)	(40–60)	(80–100)
	10	10	10
	Female Rats		
0	238 ± 27	50 ± 5	98 ± 17
	(210–290)	(40–60)	(80–120)
	10	10	10
25	218 ± 24	54 ± 9	103 ± 10
	(180–250)	(40–70)	(90–120)
	9	9	9
247	233 ± 22	49 ± 5	100 ± 15
	(210–270)	(40–60)	(80–120)
	11	11	11

[a] $\bar{x}$ ± SD.
[b] (Range).
[c] Number of animals.

under the same conditions as this study (Lynch et al. 1986). The fact that diethylamine is a stronger base than TEA (Beard and Noe, 1981) may explain, at least in part, the difference in toxicity observed under essentially identical exposure conditions.

Kinney et al. (1984) reported that acute 6-hr exposures (74-760 ppm) of rats to the structurally related chemical trimethylamine produced dose-dependent nasal cavity and turbinate irritation ranging from very mild to severe. While nasal cavity lesions were not found in rats exposed at 25 or 247 ppm TEA for up to 28 weeks in the current study, nasal lesions were produced in our laboratory following acute exposures of rats to 1,000 ppm TEA (unpublished results).

The primary purpose of the current study was to further investigate the subchronic inhalation toxicity of TEA. In addition, we investigated organ system toxicity, and in particular, the cardiac toxicity (heart muscle degeneration) pro-

duced by TEA exposure in rabbits (100 ppm, 7 hr/day, 5 days/wk for 6 wk) as reported by Brieger and Hodes (1951). We were unable to confirm these findings in rats, as no evidence of cardiac muscle degeneration or any changes in electrocardiograms or related clinical chemistry indices were seen in any of the rats exposed to TEA for up to 28 weeks. The data from the current study suggest that inhaled TEA, at the concentrations tested, does not induce cardiotoxicity in rats. The negative findings in rats, when compared to the cardiotoxicity reported in rabbits, may reflect a species difference in susceptibility to TEA-induced cardiotoxicity. An alternative explanation is that the effects reported in rabbits (congestion, edema, and muscular degeneration) were secondary to the pulmonary changes observed, and, therefore, TEA did not induce any direct cardiotoxicity. In summary, a lack of organ system toxicity, including cardiotoxicity, was noted in rats intermittently exposed at 25 or 247 ppm TEA vapor (approximately 25 times the current OSHA PEL) for up to 28 weeks.

ACKNOWLEDGMENTS

The authors thank Amir Kahn, Terry Boyle, George Madden, Barbara Dames, Melissa Penza, Fred Phipps, John Clark, Cheryl Adkins, Brenda Ellis, and Jannia Braun for technical and clerical assistance.

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