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Diethylenetriamine  
l.b.

Project Report 40-45  
9 Pages  
April 7, 1977  
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CHEMICAL HYGIENE FELLOWSHIP  
Carnegie-Mellon Institute of Research  
Carnegie-Mellon University  
4400 Fifth Avenue  
Pittsburgh, Pa. 15213

Diethylenetriamine  
(1974-75 Results)

RECEIVED  
JUN 24 1983

Range Finding Toxicity and 7-Day Dietary Inclusion Studies

Sponsor: *Union Carbide Corporation*

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Summary

	<u>1974-75 Results</u>	<u>Previous Results</u> <sup>1</sup>
Stomach Intubation, rat LD50	1.62 ml/kg; undiluted	1.8 to 2.33 gm/kg; 1 ml = 0.10 gm in water (1941, 1948)
Intraperitoneal Injection, rat LD50	-	0.28 to 0.93 ml/kg; undiluted (1962, 1964)
Subcutaneous Injection, rat LD50	-	1.78 to 3.00 ml/kg; undiluted (1962, 1964)
Skin Penetration, rabbit LD50	0.707 ml/kg; undiluted	1.09 ml/kg; undiluted (1948)
Skin Penetration, guinea pig LD50	-	0.17 gm/kg; undiluted (1941)
Inhalation, rat Substantially saturated vapor	8 hr killed 0 of 6	8 hr killed 0 of 6 (1948, 1955)
Mist from saturation at 170°C	-	8 hr killed 4 of 6 (1948)
Uncovered Skin Irritation, rabbit	Moderate, Grade 6	Moderate, Grade 6 (1948)
Eye Injury, rabbit	Severe, Grade 8	Severe, Grade 8 (1948)
Seven-Day Dietary Inclusion, rat	Minimum effect at 0.61 gm/kg/day; no significant ill-effect at 0.24 gm/kg/day	-

<sup>1</sup> Smyth, Henry F., Jr. *et al.*, "Range Finding Toxicity Data List III"  
Journal of Industrial Hygiene and Toxicology, Vol. 31, No. 1, 60-62  
(January 1949) and Chemical Hygiene Fellowship (CHF) Reports 5-23 (1942),  
11-61 (1948) and 26-6 (1963).

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Interpretation

Diethylenetriamine was moderately toxic following single stomach intubation and covered dermal application routes of administration. Application of the undiluted material to uncovered rabbit skin resulted in necrosis in the current and previously-reported tests. Therefore, it is rated by the Chemical Hygiene Fellowship as a Department of Transportation (D.O.T.) "corrosive" although the actual 4-hr D.O.T. covered skin test was not performed. Application of a 10% dilution in distilled water resulted in trace irritation to rabbit skin. Severe corneal injury, with iritis, resulted from instillation of the material in rabbit eyes. No hazard is anticipated from the infrequent inhalation of substantially saturated vapor evolved at room temperature under normal handling conditions. Rats that received diethylenetriamine in their diets for 7 days were affected by 0.61 gm/kg/day (average); this is the minimum effect level (MiE). No significant effect, in the criteria examined, resulted at 0.24 gm/kg/day. The ratio of single peroral LD50/MiE was 2.66, probably indicating a low degree of chronicity.

The results of these latest range finding tests were similar to those done previously. Most of the previous results appear in report 11-61 (1948).

Included in the literature on diethylenetriamine is a study in which rabbits and guinea pigs received 1.0 and 0.6 mg/kg, respectively, for 6 months without effect (Trubko, E. I., Teplyakova, E. V., "Diethylenetriamine Studied in Connection with Determining its Hygienic Standard Levels in Reservoir Water". Gig. Sanit. 1972, 37 (7), 103-4 (Russ). One inhalation study (Brit. J. Industr. Med., 1970, 27, 1-18) consisted of 15 exposures, 6 hr per exposure, to 130 ppm without toxic effect among rats. During a study in Japan, subcutaneous injections (10 to 25 mg/kg/day) and daily topical applications (0.4 ml of 10% aqueous) reduced the life span of rats and affected kidneys, livers, spleens and adrenals (Fujino, Mitsuo, "Chronic Toxicity of Diethylenetriamine in Rats", Igaku Kenkyu 1970, 40 (2), 139-6).

Sample

Quantity: 2 quarts

Date Received: 7-26-74

CHF Sample No.: 37-417

Submitted By: R. V. Berthold

Division: Chemicals and Plastics  
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Charge No.: 01067

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Peroral, Single Dose to Rats

LD50 - 1.62 (1.18 to 2.24) ml/kg; undiluted.

Conditions - Standard.

Dosage; ml/kg	Dead Dosed	Days to Death	Weight Change	Signs and/or Symptoms
4.0	5/5	0,0,1,1,1	-	Sluggish 2 min; prostrate 3 hr; death of 2 at 4 hr.
2.0	4/5	2,3,7,8	98 gm	Sluggish 10 min.
1.0	0/5	-	96 to 110 gm	Sluggish 10 min.

**Gross Pathology** - In victims, petechial hemorrhages of the lungs; stomachs liquid-filled, hemorrhaged; intestines liquid-filled, opaque, hemorrhaged, slightly yellow; kidneys and adrenals slightly congested; kidneys speckled; livers and spleens mottled. Nothing remarkable in survivors.

**Conclusions** - Moderately toxic following acute peroral intubation.

Skin Penetration, Single Dose to Rabbits

LD50 - 0.707 (0.324 to 1.54) ml/kg; undiluted.

Conditions - Standard. Dosed under polyethylene sheeting.

Dosage; ml/kg	Dead Dosed	Days to Death	Weight Change	Skin Irritation	Signs and/or Symptoms
1.0	3/4	2,5,6	-157 gm	necrosis	-
0.5	1/4	8	-181,-15, 212 gm	necrosis	-

**Gross Pathology** - In victims, congestion of lungs, livers, spleens and kidneys. Nothing remarkable in survivors.

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**Conclusions** - Moderately toxic following acute covered dermal application.

Inhalation, Single, by Rats

Conditions - Static exposure at 23°C. Procedure B of standard test procedures.

Procedure	Time	Concentration	Dead Dosed	Death	Weight Change	Signs and/or Symptoms
B	8 hr	Substantially saturated vapor	0/6	-	66 to 81 gm	-

Gross Pathology - Nothing remarkable.

Conclusions - No hazard is anticipated from the infrequent inhalation of substantially saturated vapor evolved at room temperature under normal handling conditions.

Skin Irritation, Rabbit, Uncovered

Conditions - Standard. Applied undiluted or in distilled water.

Conclusions - Necrosis on 2 of 2 rabbits from the undiluted material; no irritation on 2 rabbits, moderate capillary injection on 3 from a 10% dilution in distilled water. Grade 6.

Eye Irritation, Rabbit

Conditions - Standard. Instilled undiluted or in distilled water.

Conclusions - Severe corneal injury, with iritis, from 0.005 ml undiluted per eye; moderate corneal injury from 0.5 ml per eye of a 15% dilution in distilled water; trace corneal injury on one of 5 eyes from 5% in distilled water. Grade 8.

Seven-Day Dietary Inclusion, RatsProcedure

Diethylenetriamine was added to ground PURINA Chow and fed in the diet for 7 days. Groups of 5 male and 5 female Harlan-Wistar albino rats, 30 days of age at the start of the study, were randomly assigned to each dosage level and to each of 2 control levels.

Results

The results are summarized in Table 40-1 and a synopsis of pathology is given in Table 40-2.

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Inclusion of diethylenetriamine in the diet for 7 days resulted in moderate to severe body weight depression at attained dosages of 1.35 gm/kg/day for the males and 1.58 gm/kg/day for the females. These were the highest dosage levels. Liver weights of the male rats at their highest level were slightly depressed compared to those of one of the control groups. There were no other organ weight effects noted at any of the dosage levels for males or females. Body weights of female rats at 0.62 gm/kg/day were moderately depressed while the weights of males at the middle level, 0.60 gm/kg/day, were slightly depressed after 5 days compared to one of the control groups. No body weight or organ weight effects were observed at the lowest dosage level, 0.24 gm/kg/day.

On micropathological examination, the only remarkable lesions were instances of bile duct proliferation in livers from females at the middle level, hydronephrosis among a few males at the higher level and chronic tracheitis among females at the higher level. These findings were not strictly dosage-related or present in significantly large numbers. Therefore, our pathologist considered them as sporadic, common lesions not related to treatment.

#### Conclusions

The maximum no significant ill-effect level was 0.24 gm/kg/day based on body weight, liver and kidney weight, and micropathology. The ratio between the single peroral LD50 and the minimum effect level (MiE) for the 7-day feeding study was  $1.62 \text{ ml/kg} \div 0.61 \text{ gm/kg}$  (average) or 2.66, probably indicating a low degree of chronicity. The medium predicted minimum effect level for 90-day rat feeding is 0.20 gm/kg; that for two years is 0.11 gm/kg (Weil, *et al*, "Toxicology and Applied Pharmacology" 14, 426-431, 1969).

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Single Peroral Test

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Standard Test Procedures

In all tests, the nonfasted animals are maintained on appropriate Wayne diets and water *ad lib* except during period of manipulation or confinement. Dosage levels differ by a factor of 2 in a geometric series. LD50s or LC50s are calculated by the moving average method based on a 14-day observation period.

Toxicity Terminology for Peroral and 24-Hr Dermal LD50s (A)/Inhalation 4-Hr LC50 (B)

	A, gm/kg	B, ppm		A, gm/kg	B, ppm
Extremely low order	> 15	> 100M	Highly	0.05-0.5	100-1M
Slightly	5-15	10M-100M	Seriously	0.01-0.05	10-100
Moderately	0.5-5	1M-10M	Dangerously	< 0.001	< 10

Peroral. Compounds administered by stomach intubation to Wistar derived male rats, 90-120 grams in weight and 3 to 4 weeks of age, reared in our own colony.

Skin Penetration. Male albino rabbits, 3 to 5 months of age, are immobilized during the 24-hour contact period with the compound retained under impervious sheeting on the clipped intact skin of the trunk. Thereafter, excess fluid is removed to prevent ingestion. Maximum dosage that can be retained is 16 to 20 ml/kg.

Inhalation. Procedure A. Concentrated vapor is generated in a gas washing bottle by passing dried air at 2.5 liters/min through a fritted glass disc immersed to a depth of at least 1-1/2 inches in the chemical which is delivered to rats in a 9-liter glass exposure chamber. Mean vapor concentration is calculated from the loss in weight of the liquid or estimated from the vapor pressure at the actual temperature of the chemical during aeration.

Procedure B. Substantially saturated vapor is prepared by spreading 50 grams of chemical over 200 cm<sup>2</sup> area on shallow tray placed near the top of a 120-liter glass chamber which is then sealed for at least 16 hours while an intermittently operated fan agitates the internal chamber atmosphere. Rats are then introduced in a gasketed drawer-type cage designed and operated to minimize vapor loss.

Procedure C. Mist, vapor and any oxidation or decomposition products of the chemical held at 170°C are generated and delivered as in A.

Procedure D. Vapor at metered concentration, not checked analytically, is generated by feeding the liquid at a constant rate down the inside of a spirally corrugated surface of a minimally heated one-inch Pyrex tube, through which metered air is passed. Resultant vapor is delivered as in A.

Procedure E. Spray - Solutions or suspensions are atomized in a glass VAPONEFRIN nebulizer using dried compressed air at 9 liters/min (corrected) and 22 psi. The resultant aerosol of droplets averaging 2 microns in diameter is conducted directly into a 60-liter cubic glass chamber containing rats. Mean aerosol concentration is calculated from the amount of material atomized.

Procedure F. Dust - Dust clouds are generated by a baffled Wright Dust Feed through which air is passed at 14 liters/min (uncorrected) at 5 psi. The dust is delivered directly to a 120-liter plexiglas chamber containing rats. Airborne dust concentrations are measured gravimetrically every half hour.

Skin Irritation. Chemical is applied in 0.01 ml amounts to clipped, uncovered intact skin of 5 rabbit bellies either undiluted or in progressive dilutions of 10, 1, 0.1, and 0.01% in solvent. Ten grades are recognized based on appearance of moderate or marked capillary injection, erythema, edema or necrosis within 24 hours. No injury from undiluted = Grade 1.

Eye Irritation. Eyes not staining with 5% fluorescein in 20 seconds contact are accepted. Single instillation of 0.005, 0.02, 0.10 or 0.5 ml undiluted or of 0.5 ml of 40, 15, 5 and 1% dilutions are made into conjunctival sac of 5 rabbits. Read immediately unstained and after fluorescein at 24 hours, with ten grades recognized. Trace or no injury from 0.5 ml undiluted = Grade 1.

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Table 40-1

Summary of Results of 7 Days of Inclusion of Diethylenetriamine  
in the Diet of Rats

	Male Rats				
				A	B
Dosage goal, gm/kg	1.65	0.65	0.25	0.0	0.0
Concentration in diet, %	1.27	0.53	0.21	0.0	0.0
Dosage attained, gm/kg/day	1.35	0.60	0.24	0.0	0.0
Diet consumed, gm/rat/day	14.4	16.3	17.6	18.4	16.7
<u>Body weight change, gm</u>					
1 day of doses	-0.4 <sup>b, b<sup>x</sup></sup>	3.2	6.4	4.4	5.2
5 days of doses	17.0 <sup>c, b</sup>	23.6 <sup>a, -</sup>	27.4	30.2	27.2
7 days of doses	34.6 <sup>b, a</sup>	43.6	49.0	53.2	47.0
Liver weight, gm	6.78 <sup>a, -</sup>	7.49	8.42	8.62	7.46
Liver wt as % of body wt	4.42	4.46	4.85	4.66	4.42
Kidney weight, gm	1.51	1.56	1.62	1.69	1.54
Kidney wt as % of body wt	0.99	0.93	0.93	0.92	0.92
Mortality	0	0	0	0	0
	Female Rats				
				A	B
Dosage goal, gm/kg	1.65	0.65	0.25	0.0	0.0
Concentration in diet, %	1.43	0.57	0.21	0.0	0.0
Dosage attained, gm/kg/day	1.58	0.62	0.24	0.0	0.0
Diet consumed, gm/rat/day	13.6	14.0	14.3	14.1	15.7
<u>Body weight change, gm</u>					
1 day of doses	-3.4 <sup>c, c</sup>	2.2 <sup>-, a</sup>	3.4	3.6	6.2
5 days of doses	9.2 <sup>c, c</sup>	15.4 <sup>a, b</sup>	21.6	21.0	25.2
7 days of doses	21.0 <sup>c, c</sup>	28.6 <sup>-, b</sup>	36.2	35.2	39.2
Liver weight, gm	5.83	6.48	6.81	6.70	7.10
Liver wt as % of body wt	4.39	4.55	4.66	4.88	4.66
Kidney weight, gm	1.37	1.35	1.39	1.34	1.38
Kidney wt as % of body wt	0.96	0.95	0.96	0.98	0.91
Mortality	0	0	0	0	0

<sup>a</sup>0.05 > P > 0.01<sup>b</sup>0.01 > P > 0.001<sup>c</sup>P < 0.001

<sup>x</sup>1st letter of superscript denotes degree of significance versus control group A;  
2nd letter denotes degree of significance versus control group B.

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Diethylenetriamine

Rats		
	A	B
0.25	0.0	0.0
0.21	0.0	0.0
0.24	0.0	0.0
17.6	18.4	16.7
6.4	4.4	5.2
27.4	30.2	27.2
49.0	53.2	47.0

8.42	8.62	7.46
4.85	4.66	4.42
1.62	1.69	1.54
0.93	0.92	0.92
0	0	0

Male Rats		
	A	B
0.25	0.0	0.0
0.21	0.0	0.0
0.24	0.0	0.0
14.3	14.1	15.7

3.4	3.6	6.2
21.6	21.0	25.2
36.2	35.2	39.2
6.81	6.70	7.10
4.66	4.88	4.66
1.39	1.34	1.38
0.96	0.98	0.91
0	0	0

<sup>c</sup>P < 0.001

versus control group A;  
group B.

Table 40-2  
Synopsis of Pathology of Rats that Received Diethylenetriamine in their Diets for 7 Days

	Males				Females			
	1.65	0.65	0.25	0.00	1.65	0.65	0.25	0.00
Total Number Examined Grossly:	5	5	5	5	5	5	5	5
LIVER: Number Examined	(M)	(M)	(M)	(M)	(M)	(M)	(M)	(M)
Bile duct proliferation	2	0	0	2	0	3	2	0
Round cell foci	0	2	1	1	1	3	3	1
KIDNEY: Number Examined	5	5	5	5	5	5	5	5
Hydronephrosis	2	1	0	0	1	0	2	1
Hydronephrosis	(M)	(M)	(M)	(M)	(M)	(M)	(M)	(M)
Round cell foci	0	0	1	0	0	0	1	0
Tubular regeneration	0	0	0	0	0	0	0	0
LUNG: Number Examined	5	5	5	5	5	5	5	5
Pneumonia	0	0	1	1	0	0	0	0
Inhaled blood due to kill	0	0	1	0	0	0	0	0
Inhaled blood	(M)	(M)	(M)	(M)	(M)	(M)	(M)	(M)
TRACHEA: Number Examined	5	5	5	5	5	5	5	5
Dilated tracheal glands	0	0	0	0	0	0	0	1
Purulent tracheitis	0	0	1	0	0	0	0	0
Chronic tracheitis	1	2	2	2	4	5	3	1
UTERUS: Number Examined	-	-	-	-	5	0	0	5
Dilated	(M)	(M)	(M)	(M)	(M)	(M)	(M)	(M)
COLON: Number Examined	5	0	0	5	0	0	0	5
Section parasites	0	-	-	1	0	-	-	0
BRAIN: Number Examined	5	5	5	5	5	5	5	5
Granulomas, parasitic	0	0	1	0	0	0	0	0

C = Gross

M = Microscopic

The following tissues were examined microscopically on the 1.65 and 0.0 gm/kg levels: lung, liver, kidneys, heart, spleen, adrenal, thyroids, parathyroids, trachea, esophagus, stomach, duodenum, pancreas, colon, urinary bladder, pituitary, brain and prostate, testis, epididymis or uterus and ovary. On the 0.65 and 0.25 gm/kg levels the lung, liver, kidney, heart, spleen, adrenal, thyroids, parathyroids, trachea, esophagus and brain were examined microscopically.