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THE ACUTE TOXICITY OF POLYETHYLENE GLYCOL 200 IN LABORATORY ANI--ETC(U)
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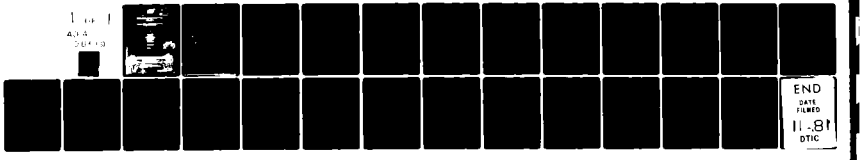

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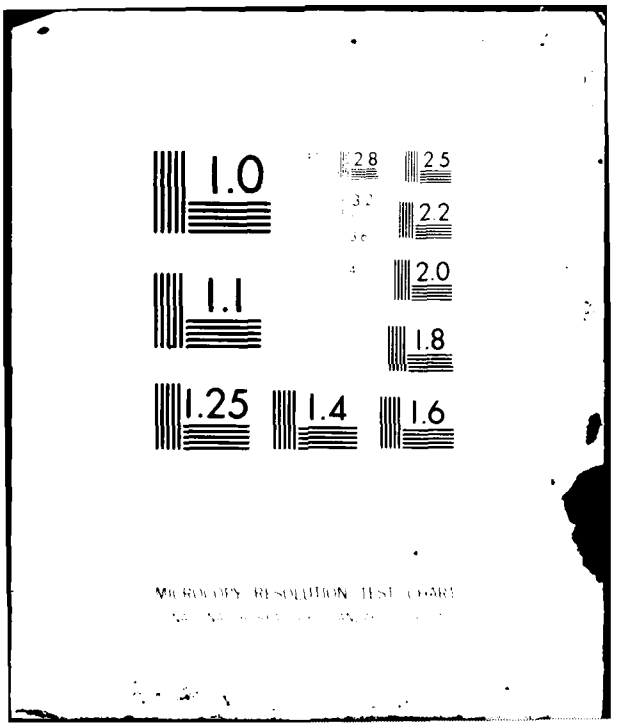
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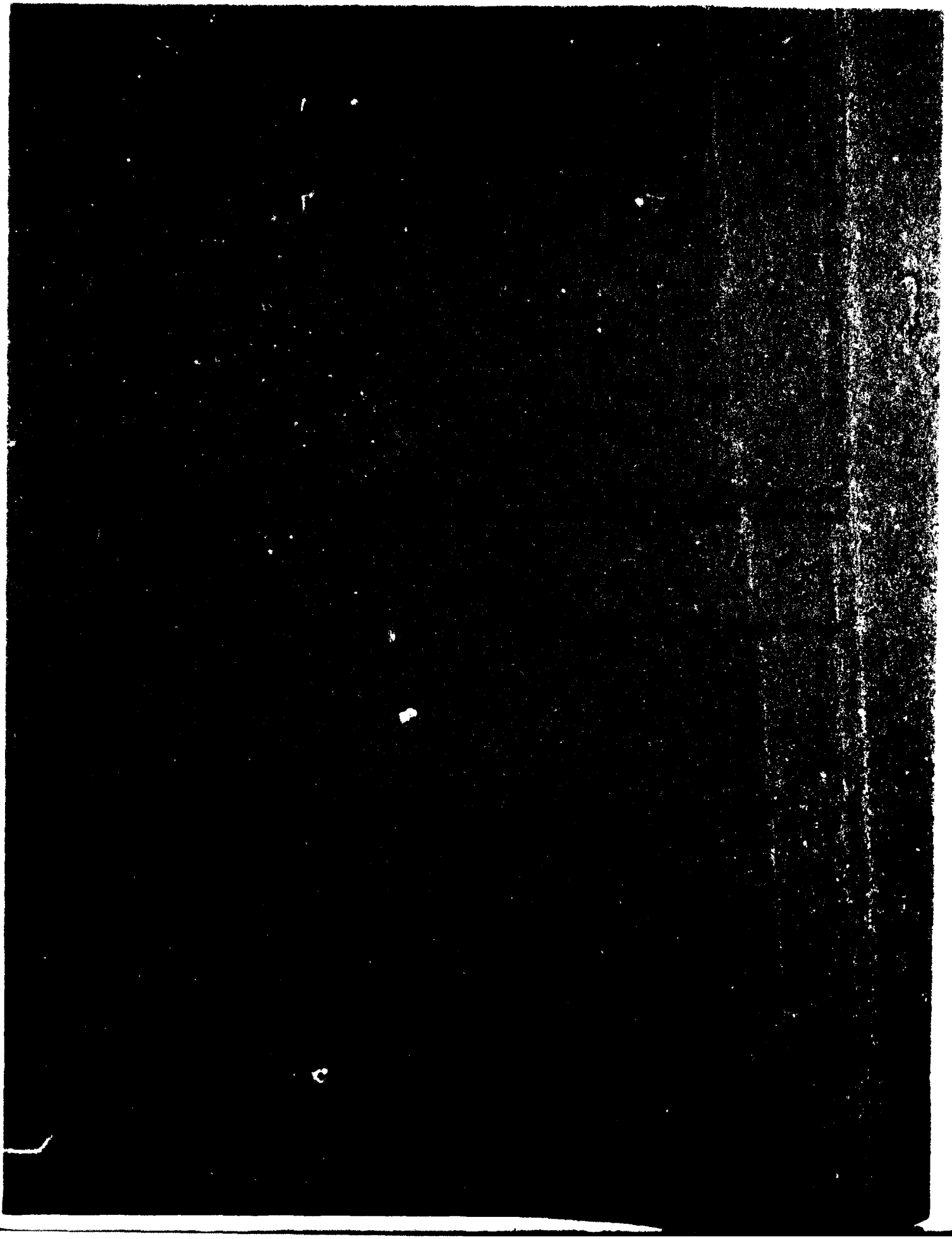

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20. ABSTRACT (Continue on reverse side if necessary and identify by block number)

Mice and rats were exposed to polyethylene glycol 200 (PEG 200) aerosols by the inhalation route for 6 hours at a concentration of 2,516 mg/m^3. The LCt50 for PEG 200 is greater than the 905,760 mg min/m^3 used in this study. No biologically significant alterations in blood chemistry,

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hematology, or pulmonary resistance were found. No mutations or pathological abnormalities could be attributed to the PEG 200 exposure. Intravenous and oral toxicity tests in rats place PEG 200 in the relatively harmless class.

PREFACE

The work described in this report was authorized under Project 1L162622A554 (TA4-E) Smoke Toxicology and was conducted using approved Animal Care and Use Committee Protocol PEM 79-9 for acute inhalation and PEN-79-14 for acute toxicology.

The work was started in September 1979 and completed in December 1980. The experimental data are contained in notebooks 9699, 9783, and CSL-81-0018. Data from blood tests are computerized in the files of the Toxicology Branch, Research Division, Chemical Systems Laboratory. Pathological findings are recorded in a pathology accession book, in a yearly protocol book, and computerized in the Comparative Pathology and Surgery Branch, Biomedical Laboratory.

In conducting the research described in this report, the investigators adhered to the "Guide for the Care and Use of Laboratory Animals," as promulgated by the Committee on Revision of the Guide for Laboratory Animal Facilities and Care of the Institute of Laboratory Resources, National Research Council.

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The authors also acknowledge the assistance of Messrs. John F. Miller and Franklin Tittle for preparation of blood samples and portions of the statistical analysis, and Messrs. Paul Jacobs and James McWayne for feeding and caring for the animals during the 14-day holding period.

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THE ACUTE TOXICITY OF POLYETHYLENE GLYCOL 200 IN LABORATORY ANIMALS

1. INTRODUCTION

One of the missions of the Toxicology Branch, Research Division, is to develop a toxicological data base of chemical compounds. This data base is compiled from studies conducted with laboratory animals to aid in predicting the possible hazardous effects in man. Acute inhalation studies are conducted to determine what risks are incident to single exposures and to provide appropriate safety guidelines.

Polyethylene glycol is a dihydroxy derivative of the paraffins. Polyethylene glycol formula weights range from 200 to 10,000. The physical state ranges from water-white liquids (PEG 200) to waxy solids (Carbowax^{R}). The physical properties of polyethylene glycol 200 are:

(a) Molecular weight: 190-210
(b) Specific gravity: 1.125 (25°C)
(c) Freezing range : Supercools
(d) Water solubility: Soluble in all proportions

Polyethylene glycols are used extensively in industry as lubricants, plasticizers, binders, and for other similar applications. In the pharmaceutical industry, they are widely used as components of water-soluble ointment bases, soluble dressings for wounds, carriers for penicillin, sulfa drugs, and peroxides, and in suppositories, where they serve as the base and the carrier. In cosmetics, they are used in skin conditioner creams, aqueous hair dressing, and as solvents for dyes used in lipsticks.

Literature searches and preliminary and acute toxicity studies conducted in Chemical Systems Laboratory indicate PEG 200 to be nontoxic. In a preliminary toxicity test,[1] the oral toxicity for rats was greater than 5 ml/kg. This dose produced no deaths in 10 rats during 14 days of observation. In percutaneous toxicity tests using rabbits, no deaths (0/10) occurred within 14 days after a dose of 2.0 ml/kg.[1] PEG 200 was classed as a nonirritant following administration of a dose of 0.1 ml/eye in the eye irritation test on rabbits.[1] In skin irritation tests on rabbits (abraded and unabraded), PEG 200 was considered not to be a primary skin irritant following application of 0.5 ml.* The Ames assay (microbiological mutagen) indicated that PEG 200 had no mutagenic potential.[1] The intravenous mouse LD50 after 14 days observation was 8.45 (7.53-9.48) ml/kg.* In an acute inhalation toxicity test using 10 rats, no deaths occurred over a 2-week observation period after a 1-hour exposure to PEG 200 at a concentration of 23.1 mg/l.[1] No sensitization was evident in guinea pigs receiving eight injections of PEG 200 intracutaneously according to the method of Draize.[1] A 0.1% suspension in water was injected three times weekly for 3 weeks, the first dose being 0.05 ml and the other seven doses 0.1 ml. Three weeks were allowed for the development of sensitization.[2] In a meeting on 28 June 1979, a Chemical Selection Working Group of the National Cancer Institute in Bethesda, MD, decided that PEG 200 was not a potential carcinogen. This group also

* Manthei, J. H. Research Division, Chemical Systems Laboratory. Personal communication, March 1980.

stated in the minutes of the meeting that a "wide range of polyethylene glycols (e.g., 200, 400, 1540, 4000) have been tested and generally found to be non-suspicious." There are, however, no available data on the inhalation hazards of PEG 200 aerosols except for the preliminary 1-hour rat test previously mentioned.

PEG 200 is a prime candidate for use as a safe training smoke with unmasked personnel and also as a screening smoke to replace fog oil which may contain possible carcinogens.

PEG 200 was selected as a fill for the UK Simulator, Projectile, Airburst, Liquid (SPAL) training system which has been adopted by the USA. The Army Surgeon General approved this usage provided that protective clothing and masks are worn throughout the test periods by personnel subject to repeated exposures, and that protective clothing and masks at "ready" position are used by all other personnel. Approval was also granted for the use of aerial spray tanks in chemical defense training exercises.

Polyethylene glycol 200 is one of the candidates selected for acute toxicology evaluation in the Smoke Toxicology Program. This study was undertaken to aid in the development of safety guidelines for PEG 200 based on its toxicological, pathological, and physiological effects in rats and mice exposed to acute airborne concentrations for short periods.

2. INVESTIGATIONAL MATERIALS AND PROCEDURES

2.1 Materials and equipment. Polyethylene glycol 200 (PEG 200) was purchased from Union Carbide Corporation, Chemicals and Plastics Division, 270 Park Avenue, New York, New York, 10017. It was stored at room temperature in the original can until ready for use.

2.1.1 Animals. All mammals were selected, quarantined, and examined before issue by personnel of the Veterinary Resources Branch, Veterinary Medicine Division, Biomedical Laboratory.

2.1.1.1 Rats. Rattus norvegicus, Fischer 344 Strain, white, 150 to 200 grams, males and females for inhalation testing.

2.1.1.2 Rats. Rattus norvegicus, Sprague-Dawley Strain, white, 200 to 300 grams, males and females, for iv and oral toxicity tests.

2.1.1.3 Mice. $B_6C_3F_1$ mice, brown, 30 to 40 grams, male and female for inhalation testing.

2.1.1.4 Drosophila melanogaster. Fruit flies for mutagenesis tests.

2.2 Procedures.

2.2.1 Chamber operation and sample analysis. Exposures of rats and mice to airborne concentrations of PEG 200 were conducted in a 1000-liter dynamic flow stainless-steel chamber, constructed to provide laminar airflow and insure uniform exposure to the test compound. The chamber flow ranged from 168 to 182 liters per minute. This flow rate was used to

calculate the nominal PEG 200 concentration. A second method of analysis (gravimetric) was to weigh the two filter pads before and after the sample was taken from the chamber. The net weight gain divided by the number of liters of chamber air drawn gave the concentration of PEG 200 in milligrams per liter. A third method of analysis was by gas chromatography.

A PEG 200 aerosol was generated using 16- and 18-gauge, air-operated, opposed, jet-fed Laskin generators. Air pressure through the generators was adjusted to achieve the desired test concentration of PEG 200.

Approximately 90% of the particles generated were less than 2 microns using this dispersion apparatus. The cascade impactor particle size sample was obtained from the chamber at the half-way point of the 6-hour exposure.

Rodents were exposed in compartmented stainless-steel wire mesh cages. Each compartment measured 7 X 3-3/4 X 3-1/4 inches.

2.2.2 Inhalation toxicity evaluation. Groups of male and female Fischer 344 rats and $B_6C_3F_1$ mice were to be exposed for 6 hours to PEG 200 at a concentration of 2510 mg/m^3. Each group exposed would be observed for death and toxic signs over a 14-day observation period. If after this period no deaths had occurred, no further exposures would be conducted on the test material.

2.2.3 Blood studies. After the 2-week observation period, all rats, exclusive of those used for physiological evaluation, were anesthetized with pentobarbital sodium, and blood samples were taken by cardiac puncture. The following blood parameters were evaluated: triglycerides, cholesterol, glucose, blood urea, nitrogen, creatinine, uric acid, sodium, potassium, chloride, carbon dioxide, alkaline phosphatase, serum glutamic pyruvic transaminase, serum glutamic oxalacetic transaminase, albumin, globulin, total protein, lactic dehydrogenase, total bilirubin, calcium, phosphorus, red blood cells, white blood cells, differential white count, hemoglobin, and hematocrit. Blood testing in mice was confined to the latter five parameters.

2.2.4 Physiological evaluation of respiration. The measurement of pulmonary resistance in the unaesthetized rat included using a body plethysmograph from which respiratory flow, pressure changes in the plethysmograph during the respiratory cycle, and airway pressure were monitored. Values obtained from these measurements were used in the computation of pulmonary resistance.

The pressure changes within the plethysmograph, the respiratory flows and the airway pressures, were measured with a Hewlett-Packard Model 270 pressure transducer. The signals from the transducers were amplified using Hewlett-Packard 8805B carrier amplifiers.

The experimental procedure was to place a rat in a restraining device that isolated the animal's head from its trunk, using a heavy rubber collar around the neck. This restrainer was placed in a larger plastic box that was sealed from the outside. Respiratory flow was measured using a

pneumotachometer attached to the head portion of the restrainer. Airway pressure was also measured from this point when the pneumotachometer opening was obstructed. Plethysmographic pressures were taken from the larger sealed container. The animal remained in this apparatus from 3 to 5 minutes while measurements were being recorded.

Respiratory resistance was calculated in the following manner:

$$\text{Resistance (cm } H_2O/\ell/\text{sec)} = \frac{P_1 \times P_2}{F \times P_3}$$

where

P_1 = airway pressure (cm H_2O)

P_2 = plethysmographic pressure (cm H_2O)

P_3 = plethysmographic pressure during airway construction (cm H_2O)

F = respiratory flow (ℓ/sec)

Pulmonary resistance (EPR) was estimated and respiratory rate (f_R) values were obtained 1 day and 14 days following a 6-hour exposure. Control values were obtained from a different group of animals (three males and three females) at the same time.

Statistical comparisons of the data were based on the "t" test, comparing the exposed animals to their own controls and age group.

2.2.5 Pathology. Necropsies were performed on selected rodents. Included were external examination and fixation of tissues from the following:

Gross lesions	Tissue masses/suspect tumors
Turbinates	Trachea
Lungs	Heart
Esophagus	Stomach
Small intestine	Pancreas
Large intestine	Liver
Adrenal	Kidney
Bladder	Gonads
Spleen	Brain
Eyes	Thyroid

Pathological evaluation was performed by Dr. James D. Conroy and Dr. Billy C. Ward, Veterinary Pathologists of DVM Pathology Associates, PO Box 5204, Mississippi State, MS 39762.

2.2.6 Acute intravenous toxicity (LD50). Adult male and female rats in equal numbers (three of each sex) were randomly selected for intravenous injection of neat (undiluted) PEG 200. Injections were made into the femoral vein following its surgical exposure for ease in injecting. One group was tested with 10.0 ml/kg and one with 5.0 ml/kg. The 10.0 ml/kg dose was the highest dose that could be safely injected using this route of

administration. Rats were marked on the tail with indelible black ink, making positive identification possible during the 14-day observation. They were observed for toxic signs and deaths continuously during the day of dosing, and at least twice daily thereafter.

2.2.7 Acute oral toxicity test (LD50). Randomly selected rats, of equal number by sex and in groups of six, were dosed orally by intubation. The tube used was a large-bore (16-gauge) stainless-steel feeding tube with a bulbular tip. Rats were dosed at levels of 15.8 ml/kg (17.78 gm) to 32.0 ml/kg (36.0 gm). By this route of administration, 5.0 ml is considered to be the maximum dose for a 200-gram rat; this would be equivalent to 25.0 ml/kg. Our dose of 32.0 ml/kg exceeded this, but was used in order to develop an LD50 in the rat by this route.

The rats were fasted overnight prior to dosing (free access to water). Food and water were withheld for approximately 6 hours following dosing. Rats were identified by a series of tail markings using indelible black ink and were observed for toxic signs and death for 14 days.

2.2.8 Mutation test of PEG-200 using the fruit fly sex-linked recessive lethal test. Exposures were made via a feeding technique in which the liquid polyethylene glycol-200 (PEG 200) was diluted in distilled water and added to the dry food medium (Caroline Biological Formula 4-24). Plastic culture vials containing 5.0 grams of food and 15 ml of test solution were used for exposure. Wild Oregon-K strain Drosophila melanogaster red-eyed males, 1-2 days old, were added to the exposure vials and kept in an incubator with controlled light, temperature, and humidity. The food test solution was changed each 24 hours during the 72-hour exposure. The flies were held an additional 24 hours for mortality determinations. A negative control of distilled water and a positive control of methylmethanesulfonate (MMS), a known mutagen, were used.

Male flies surviving the exposure tests were allocated for mutagenicity testing employing the Muller-5 technique. The males flies were mated with virgin Muller-5 bar-eyed females in pairs (P_1) in 7-ml test tubes. After 7 days the mating adults were discarded. The emerging offspring (F_1) were back-crossed in pairs in test tubes and discarded after 7 days. The emerging F_2 generation flies were examined for the absence of wild red-eyed males, indicating a mutation.

Mutation scoring was done as follows:

(a) The tubes containing any wild red-eyed males were scored as a negative mutation.

(b) The tubes containing no wild red-eyed males and containing 20 or more flies were scored as a positive mutation.

(c) The tubes containing no wild red-eyed males and less than 20 flies were scored as questionably positive and checked by back-crossing to the next generation.

3. RESULTS

3.1 Chamber conditions and sample analysis. The nominal 6-hour chamber concentration was determined to be 3,310 mg/m^3. This calculation did not take into account any disposition of PEG 200 on the walls of the mixing bowl, chamber, or caged animals. The concentrations for six chamber samples analyzed by the gravimetric method were 2600, 2950, 2830, 2690, 2570, and 2190 mg/m^3. The mean concentration and standard deviation was 2638 mg/m^3 $\pm$ 262. This method is not recommended since it includes moisture in the air as part of the weight and water uptake by the PEG 200 aerosols. Six samples obtained from the chamber during exposure and analyzed by gas chromatography gave the following concentrations: 2560, 2790, 2670, 2570, 2410, 2100 mg/m^3. The mean concentration and standard deviation was 2516 mg/m^3 $\pm$ 240. This was the concentration for the acute PEG 200 study. The Ct was 905,760 mg min/m^3. The particle size of the PEG 200 aerosol was determined using a 220 cyclone cascade impactor. The mass median diameter was 0.78μ as analyzed by gas chromatography. Chamber samples were collected using two filter pads at a rate of 8.5 l/min and the volume collected was 21 liters. The dense aerosol in the chamber produced almost complete obscuration. The room temperature was 75^{o}F, and relative humidity was 60%.

3.2 Inhalation toxicity evaluation. Twelve rats and 12 mice were exposed to 2516 mg/m^3 of PEG 200 for 6 hours. No toxic signs were noted, and all rats and mice survived.

LCt50 values for the rats and mice were not established due to the low acute toxicity of the PEG 200, but they are obviously greater than 905,670 mg min/m^3.

Surviving rats and mice received food and water ad libitum and appeared normal during the 14-day postexposure period.

3.3 Blood chemistry and hematology.

3.3.1 Blood chemistry. The means of the 20 blood chemistry parameters measured were analyzed using the "t" test for significance. Evaluations were made according to sex as well as for total animals. The level for testing significance was set at 0.05.

Intraperitoneal administration of pentobarbital sodium was selected as the anesthetic in this study due to possible effects of alternative anesthetics on the evaluation of lung pathology. The effect of pentobarbital sodium on the various blood parameters tested in the rat is unknown.

No consistently significant difference is apparent between the blood chemistries of the control and exposed rats.

3.3.2 Hematology. One of the three male rats exposed (0005) had a significant difference in hematocrit value (71.9%) as compared to the mean of the three control rats, 35.5 ± (33.4 to 37.5%). All other hematological parameters for this rat appeared to be within normal limits.

Although there is a significant difference in the percentages of the means and standard deviations of differential lymphocytes for the three female control rats (63.3 ± 4.62) and the three female exposed rats (70.0 ± 3.46), these percentages are within the limits for Fischer 344 rats (43.0 to 79.5).[3] Other hematological parameters appear to be in the normal range. No effects could be attributed to the PEG 200 exposure.

The $B_6C_3F_1$ male and female control and exposed mice showed normal hematological values.

3.4 Respiratory physiology. The results of these tests are presented in table 1. There were no differences between the control and the exposed females at 1 and 14 days postexposure in either EPR or f_R. The lower f_R values observed in the exposed females are statistically different when compared to control f_R values; however, all values fall within the normal ranges of f_R for rats as determined by this method (f_R=110-75 respirations/min.) One exposed female (009) died during the 1-day postexposure pulmonary test. Pathological examination revealed a broken back. The only lesion observed was caused by minimal endometritis.

The exposed male rats had a significantly lower EPR when compared to controls. The estimated EPR of the male animals at 14 days postexposure showed a higher value than controls; however, they were not statistically different. The reason for the high value is that one animal in the group (003) had a large EPR compared to all other animals.

The f_R of the two groups of animals was not significantly different. The decrease in f_R in both the control and exposed animals from 1 day postexposure to 14 days postexposure is, in part, attributed to familiarity of the animals with the apparatus.

3.5 Pathology.

3.5.1 $B_6C_3F_1$ mice. One treated female mouse had mild adrenal cortical degeneration. Minimal to mild interstitial pneumonia characterized by focal to multifocal alveolar epithelial proliferation was observed in four mice (1MC, 2FC, 1FT). This lesion was noted frequently in treated and control mice in all groups and is probably a reflection of an endemic pneumonic viral (Sendai) infection in the colony. A moderate subacute arteritis was found in the lung of a treated female. Vacuolar changes of tubular epithelium occurred consistently in the renal cortex of male control and treated mice. Exposure to chloroform fumes is known to cause renal tubular degeneration in male mice, but the histologic changes of chloroform toxicity are generally more severe and progressive than the changes observed in these mice.

Table 1. Pulmonary Funtion Tests of Rats Exposed Acutely to 2516 mg/m^3 of PEG 200 for Six Hours

Condition	Sex	Estimated pulmonary resistance		Respiratory rate (f_R)	
		1 day postexposure	14 days postexposure	1 day postexposure	14 days postexposure
		$cmH_2O/l/sec$ (EPR) mean ± S.E. (n)		respirations/minute mean ± S.E. (n)	
Control	Female	52.6 ± 9.0 (3)	72.3 ± 9.0 (3)	146 ± 3.9 (3)	175 ± 1.0 (3)
Exposed	Female	87.4 ± 19.7 (2)	65.2 ± 5.4 (2)	108 ± 12.0 (2)	162 ± 2.8 (2)
Control	Male	75.7 ± 9.0 (3)	89.2 ± 8.8 (3)	147 ± 8.3 (3)	76 ± 7.5 (3)
Exposed	Male	42.5 ± 1.2 (3)	132.4 ± 37.2 (3)	154 ± 8.5 (3)	115 ± 23.9 (3)

Note: Numbers in ( ) are the number of animals in the group.

Endometrial cysts and cystic endometrial hyperplasia occurred in three control and four treated mice. The results of the histopathology of this group of mice exposed to acute inhalation of PEG 200 showed no significant agent-related lesions.

3.5.2 Fischer 344 rats. The histologic findings in rats were considered to be incidental. The lesions were graded minimal to mild and consisted of: fatty change of the adrenal cortex (1TF), protein casts in the kidney (2CF, 1TM, 1TF), renal hypoplasia (1CM), renal cortical cyst (1TF), and mild liver changes (1CM, 2TM).

One spontaneous death occurred approximately 24 hours after exposure in a female rat. This rat died while undergoing respiratory resistance measurements. The only lesion observed was minimal endometritis. Death was attributed to a broken back.

The results of the histopathology of this group of rats exposed to acute inhalation of PEG 200 showed no significant agent-related lesions.

3.6 Acute intravenous toxicity (LD50). No toxic signs or deaths were observed in rats given 5.0 ml/kg of PEG 200 intravenously. A dose of 10.0 ml/kg produced ataxia in all rats by 1 minute post-injection. One female rat died within 24 hours. All other rats in this group appeared normal after the first 24 hours and remained so during the 14-day observation. The 24-hour and 14-day LD50 for PEG 200 in the adult rat is therefore greater than 10.0 ml/kg.

These results would place PEG 200 into the relatively harmless class as judged by Hodge and Sterner[4] in their table of toxicity classes. There are indications in the literature[5] that intravenous doses of polyethylene glycols may cause clumping of blood cells and death from emboli. This, however, may be a characteristic of glycols of molecular weights of 1000 and greater.

Another investigator[6] injected dogs intravenously with up to 10.0 ml/kg of a 50% solution of PEG 200 and found no toxic effects. Venous CO_2 content, nonprotein nitrogen (NPN), and blood phosphate were normal. No gross or microscopic abnormalities were found in the kidneys, circulation, or various tissues.

3.7 Acute oral toxicity (LD50). All rats dosed orally with 32.0 ml/kg (36.0 gm/kg) exhibited ataxia and subsequently died (table 2). The 24-hour LD50 for males was 28.77 gm/kg, for females 27.56 gm/kg, and for the combined sexes 28.13 gm/kg.

The toxic signs in these rats were ataxia and convulsions, followed by prostration and death. We did not necropsy these animals; however, Smyth[7] has observed that the only gross pathological findings usually noted in rats dying from acute toxicity is congestion in the digestive tract.

Table 2. Oral Toxicity of PEG 200 in Adult Male and Female Rats

Doses		Onset of toxic signs observed in rats			
		Ataxia	Convulsions	Prostration	Death
ml/kg	gm/kg[a]	minutes			
32.0	36.00	Male - 3/3[b] (47.0, 49.0, 50.0)[c] Female - 3/3 (43.0, 44.0, 45.0)	Male - 1/3 (128.0) Female - 2/3 (61.0, 102.0)	Male - 3/3 (223.0, ON-[d](2)) Female - 3/3 56.0, 102.0,ON)	Male - 3/3 (ON) Female 3/3 (90.0, 188.0, ON)
25.0	28.13	Male - 1/3 (240.0) Female - 3/3 (60.0 (3))	Male - 0/3 Female - 0/3	Male - 1/3 (420.0) Female - 3/3 (420.0, ON(2))	Male - 1/3 (ON) Female - 2/3 Female - 2/3 ON
20.0	22.50	Male - 1/3 (56.0) Female - 0/3	Male - 0/3 Female - 0/3	Male - 0/3 Female - 0/3	Male - 0/3 Female - 0/3
15.8	17.78	Male - 0/3 Female - 0/3	Male - 0/3 Female - 0/3	Male - 0/3 Female - 0/3	Male - 0/3 Female - 0/3

a Specific gravity of PEG 200 at 25°C = 1.125.
b Response fraction - three out of three showed toxic signs.
c Time in minutes to onset of toxic signs.
d ON - response occurred overnight.

24 Hr LD50 (gm/kg)
Male = 28.77 (No CL), Female = 27.56 (No CL), Combined Sex = 28.13 (No CL)
CL = statistical confidence limits

3.8 Mutation test of PEG-200 using the fruit fly.

3.8.1 Sex-linked recessive lethal test. PEG 200 was toxic to fruit flies at and above the 10% concentration used in these tests (table 3). The mutation data are shown in table 4. A single mutation was noted at the lowest concentration of 0.01%, but was not statistically significant at the 0.05 or 0.01 level. The positive control of MMS did show a statistically significant mutation as tested. The computation of significance was done according to Kastenbaum and Bowman.[8]

4. DISCUSSION AND CONCLUSIONS

Inhalation exposure to a high airborne concentration of PEG 200 produced no remarkable acute toxic effects in rats and mice. A concentration of 2516 mg/m^3 for 6 hours failed to produce mortality. The LCt50 for PEG 200 is obviously greater than the 905,760 mg min/m^3 used in this study. In addition to the nonlethality of the acute PEG 200 exposure, no biologically significant alterations in blood chemistry, hematology, or pulmonary resistance were seen. No mutations or pathological abnormalities could be attributed to PEG 200. It is difficult to demonstrate any agent-related disorders or to predict safety to all individuals in a large population from the numbers of rodents used in this study. Sensitive or unhealthy individuals may experience ill effects at the concentration tested or even at lower concentrations or shorter durations of exposure.

Intravenous and oral toxicity tests on rats place PEG 200 in the relatively harmless class.

Table 3. Toxicity of PEG 200 in 1- to 2-Day Old Male Fruit Flies

Test chemical	Concentration	Number exposed	% Mortality at 72 hours
PEG 200	50%	25	100
PEG 200	25%	25	100
PEG 200	10%	25	100
PEG 200	1%	135	1
PEG 200	0.1%	110	2
PEG 200	0.01%	110	0
Distilled water - negative control		110	3
MMS - positive control	0.5 mM	178	11
MMS - positive control	1.0 mM	222	98

Table 4. Induction of Lethal Mutations in 1- to 2-Day Old Male Fruit Flies

Test chemical	% Concentration	X chromosomes tested	No. of lethals	% lethals
PEG 200	1	104	0	0
PEG 200	0.1	108	0	0
PEG 200	0.01	102	1*	1
Water - negative Control		94	0	0
MMS - positive Control	0.5mM	145	40**	28
MMS - positive Control	1.0mM	24	9**	38

*No significant difference at the 0.05 or 0.01 levels of significance
**A significant difference at the 0.05 and 0.01 levels of significance

LITERATURE CITED

1. Draize, J.H., Woodward, G., and Calvery, H.O. Methods for the Study of Irritation and Toxicity of Substances Applied Topically to the Skin and Mucous Membranes. J. Pharmacol. Exp. Ther. 82, 377 (1944).

2. Smyth, H.F. Jr., Carpenter, C.P., and Weil, C.S. The Toxicology of Polyethylene Glycols. J. Am. Pharm. Assoc. (Sci. Ed.) 39, 349-354 (1950).

3. Mitruka, B.M., and Rawnsley, H.M. Biochemical and Hematological Reference Values in Normal Experimental Animals, p 77. Masson Publishing USA, Inc., New York, New York. 1977.

4. Hodge, H.C., and Sterner, J.H. Am. Ind. Hyg. Assoc. J., 10(4), 93 (1943).

5. Smyth, H.F. Jr., Carpenter, C.P., and Weil, C.S. The Toxicology of Polyethylene Glycols. J. Am. Pharm. Assoc. (Sci. Ed.) 39, 349-354 (1950).

6. Lee, Cheng-Chun, and Anderson, R.C. Toxicological Studies on Vancomycin and Polyethylene Glycol 200. Toxicol. Appl. Pharmacol. 4, 206-214 (1962).

7. Smyth, H.F., Carpenter, C.P., and Shaffer, C.B. The Subacute Toxicity and Irritation of Polyethylene Glycols of Approximate Molecular Weights of 200, 300, and 400. J. Am. Pharm. Assoc. 34, 172-174 (1975).

8. Kastenbaum, M.A., and Bowman, K.O. Tables for Determining the Statistical Significance of Mutation Frequencies. Mutat. Res. 9, 527-549 (1970).

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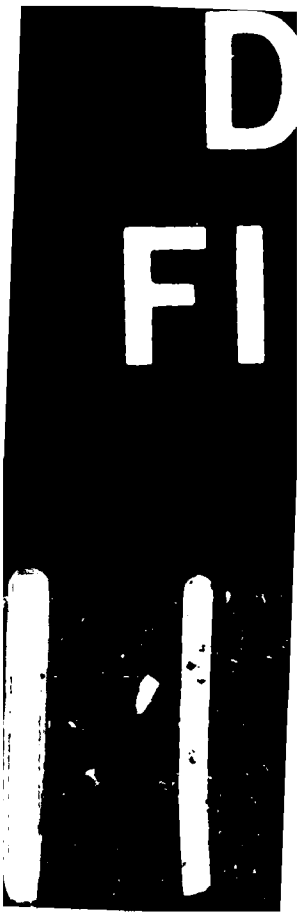
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