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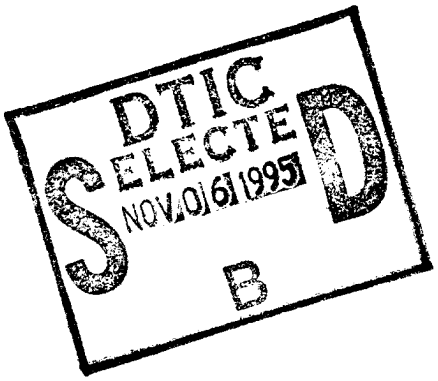
ACUTE AND REPEATED DOSE INHALATION TOXICITY EFFECTS OF PYROTECHNICALLY DISSEMINATED TEREPHTHALIC ACID SMOKE (XM83 GRENADE)



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13. ABSTRACT *(Maximum 200 words)*
The XM83 grenade, containing terephthalic acid (TPA) is the training smoke to replace the U.S Army's hexachloroethane (HC) smoke grenade. Inhalation studies (acute and repeated dose) were conducted to assess the health hazard potential of pyrotechnically generated TPA and its combustion products. Acute exposure levels ranged from 150 - 1,900 mg/m^3 for 30 min; repeated dose exposures ranged from 128 - 1,965 mg/m^3 for 30 min/day for 5 days. Exposed and control Fisher 344 rats were evaluated for toxic signs, bronchoalveolar lavage (BAL), cellular chemiluminescence (CL), and histopathologic changes. During exposure, rats exhibited slight to moderate lacrimation, rhinorrhea, lethargy, and dyspnea, which reversed within 1-hr post-exposure. No deaths occurred, even at highest smoke concentrations. Other than a temporary increase in white blood cell count, all BAL and CL parameters were within normal limits. Histopathological changes were confined to dose-related nasal necrosis and inflammation in both the acute and repeated dose exposures at levels above 900 mg/m^3. The main pyrotechnic combustion products formed were formaldehyde, benzene, and carbon monoxide. These by-products were above their respective threshold limit values at various dose levels but should not be of toxicological concern if the smoke is deployed in an open area. Overall, TPA is a safer training smoke than HC.

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PREFACE

The work described in this report was authorized under Project No. 1-88-09-7380, Smoke and Obscurants. This work was started in March 1993 and completed in January 1994. The experimental data are recorded in laboratory notebooks 90-0094, 91-0044, 91-0081, 93-0057, and 93-0070.

In conducting the research described in this report, the investigators adhered to the *Guide for the Care and Use of Laboratory Animals*, National Institute of Health Publication No. 85-23, 1985, as promulgated by the Committee on Revision of Institute of Laboratory Animal Resources, Commission of Life Sciences, National Research Council (Washington, DC). These investigations were also performed in accordance with the requirements of AR 70-18, *Laboratory Animals, Procurement, Transportation, Use, Care, and Public Affairs*, and the Laboratory Animal Use and Review Committee (LAURC), U.S. Army Edgewood Research, Development and Engineering Center (ERDEC), which oversees the use of laboratory animals by reviewing all ERDEC research protocols requiring laboratory animals for approval. This project, assigned LAURC Protocol No. 21093000A281, was approved on 22 June 1993. This study was conducted in accordance with QC/QA standards.

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Acknowledgments

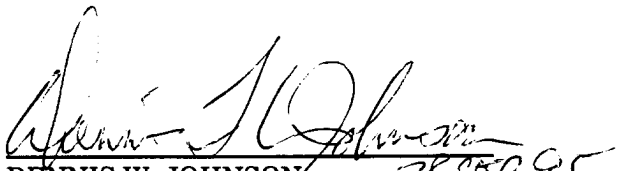
The authors would like to thank Joseph Affleck and Joseph Hill of the Life Sciences Department, U.S. Army Chemical and Biological Defense Agency, for their help in caring for and transporting animals for this study.

QUALITY ASSURANCE

This study, conducted as described by Protocol 21093000A281, was examined for compliance with Good Laboratory Practices as published by the U. S. Environmental Protection Agency in 40 CFR Part 792 (effective 17 Aug 1989). The dates of all inspections and the dates the results of those inspections were reported to the Study Director and management were as follows:

Phase inspected	Date	Date reported
Exposure	3 Aug 92	6 Aug 92
Lavage, toxic signs, chemistry, particle sizing	4 Aug 92	6 Aug 92
Data & Final Report	27 Sep 95	28 Sep 95

To the best of my knowledge, the methods described were the methods followed during the study. The report was determined to be an accurate reflection of the raw data obtained.



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ACUTE AND REPEATED DOSE INHALATION TOXICITY EFFECTS OF PYROTECHNICALLY DISSEMINATED TEREPHTHALIC ACID SMOKE (XM83 GRENADE)

1. INTRODUCTION

The XM83 grenade, containing terephthalic acid (TPA) is the prime candidate to replace the U.S. Army's hexachloroethane (HC) smoke grenade (AN-M8). The HC grenade is used for training purposes and for combat. It's currently being considered for replacement because (1) HC is a suspect human carcinogen, (2) a number of human deaths have occurred from over-exposure in the past, and (3) HC produces toxic combustion products (i.e., zinc chloride, chlorinated organics, and phosgene).[1] The XM83 grenade is considered a safer smoke because TPA is noncarcinogenic, and its' combustion products should be less toxic. However, the XM83 grenade would be used for training purposes only since its burn time is approximately 1/3 to 1/5 the burn time of the HC smoke.[2]

The primary component (TPA) of the XM83 grenade has been widely used in the chemical industry to produce polyesters. Numerous toxicology studies conducted by private industry have found TPA to be relatively nontoxic. It is a mild irritant to skin and mucous membranes, does not accumulate in tissues and is excreted unchanged.[3] It is nonmutagenic. However, at high dose levels, there is a high probability for the induction of bladder calculi and bladder hyperplasia in rats.[3] A previous inhalation study on rats exposed to pyrotechnically disseminated TPA smoke showed mild irritation to the mucous membranes, rhinorrhea, and minimal tracheal and lung inflammation.[4]

The U.S. Environmental Protection Agency (EPA) has determined from available data that commercial TPA does not cause significant adverse human health or environmental effects. As a result, the EPA has issued a proposed rule to delete TPA from the list of toxic chemicals under Section 313 of the Emergency Planning and Community Right-to-Know Act (EPCRA).[5] Thus, TPA appears to be an excellent candidate for a "safe" training smoke; however, there is little data on the toxicity of pyrotechnically generated TPA and its combustion products. The purpose of this study was to evaluate the acute and repeated dose inhalation toxicity of the XM83 grenade and its combustion products.

2. MATERIALS AND METHODS

2.1 Materials.

The XM83 grenade contains 300 g of material of which TPA is the primary component. The complete formulation of the TPA mixture and starter mixture used in the XM83 grenade is listed in Table 1.

2.2 Animal Use/Husbandry.

Male Fisher 344 rats were obtained from the Charles River Laboratories (Wilmington, MA). Only male rats were used because female rats are less susceptible to urinary calculi formation from TPA.[3] On arrival, the rats were housed in individual, suspended stainless steel cages in the Life Sciences Department's animal care facility.

Housing conditions were 12-hr light/dark cycle with 22 $\pm$ 4 °C temperature and 40-70% relative humidity (RH). Certified commercial rodent chow and water were available *ad libitum*. Rodent management, handling, and use were in accordance with the National Institute of Health Publication 85-23, *Guide for the Care and Use of Laboratory Animals*.[6]

The animals were quarantined for 7 days prior to exposure. During that time, the animals were certified healthy by the Chief, Veterinary Support Team, Life Sciences Department, then weighed, tattooed and randomly placed into groups. On the day of exposure, a climate-controlled vehicle was used to transport the rats to and from the animal facility and the exposure chamber.

2.3 Acute Inhalation Exposure.

Groups of male Fischer 344 rats were exposed by whole body inhalation to five concentrations (150 mg/m^3 to 1,880 mg/m^3) of pyrotechnically disseminated TPA for 30 min to determine a dose response. Air exposed rats served as the control group. All animals were observed for toxic signs during and after exposure. Exposed and control rats were submitted for lavage and pathological evaluation at 24 hr and 14 days post-exposure (PE) according to the schedule listed in Table 2.

2.4 Repeated Dose Inhalation Exposure.

Groups of male Fischer 344 rats were exposed by whole-body inhalation to three concentration levels (128 mg/m^3, 946 mg/m^3, and 1,960 mg/m^3) of the XM83 disseminated TPA smoke for 30 min/day, every other day for 5 days. Air-exposed rats served as controls. All animals were observed for toxic signs during and after exposure. Exposed and control rats were submitted for lavage and pathological evaluation at 24 hr, 14 days, and 3 months PE according to the schedule listed in Table 3.

2.5 Chamber Exposure System.

The rats were placed into compartmentalized cages and exposed whole body in a 300-L Hinners inhalation chamber connected to a 20-m^3 chamber. The TPA was pyrotechnically disseminated from an XM83 grenade actuated in the 20-m^3 chamber. Immediately after grenade ignition, smoke from the large chamber was diverted via a 4-in. diameter duct to the exposure chamber, along with an appropriate amount of dilution air. The concentration in the exposure chamber was maintained by periodically adjusting a bleeder valve between the two chambers to vary the amount of smoke from the large chamber with dilution air. Chamber environmental parameters monitored during exposure included airflow, temperature, and RH. Following the 30-min exposure, the chamber was purged, and the rats were returned to the animal holding facility for the PE period.

2.6 Chamber Sample Collection and Analysis.

Aerosol concentrations of the XM83 smoke were determined gravimetrically by drawing chamber air through 25 mm glass fiber filter pads. Filter pad samples were drawn from the 300-L exposure chamber at 5-, 15-, and 25-min intervals after the animal exposure began.

Inorganic combustion gases monitored were carbon monoxide (CO), carbon dioxide (CO_2), sulfur dioxide (SO_2), ammonia (NH_3), formaldehyde (H_2CO), and nitrous

oxide (NOx). Chamber air samples (2 L) were drawn from the chamber using a 2-L syringe (Hamilton, Reno, NV). The sampled gas was transferred to a Teflon gas sample bag (Alltech, Avondale, PA) from which the gas detector tubes (Matheson-Kitagawa, East Rutherford, NJ) were attached and the sample analyzed. In addition, an electro-chemical gas sensor (AIM Gas Detector, Houston, TX) was used to monitor for O_2 and CO.

Formaldehyde was also measured during exposure using an absorption tube-gas chromatographic method (NIOSH Method No. 2502).[7] Formaldehyde samples were collected at the rate of 50 mL/min with absorption tube ORBO-22® (Supelco, Bellefonte, PA) behind a dust prefilter. After sampling, the absorption tubes were desorbed with isooctane, sonicated for 45 min in an ultrasonic bath, and analyzed for the H_2CO derivative (3-benzyloxazolidine) formed in the absorption tube. Formaldehyde samples were analyzed by capilliary column (30 m, 0.25 mm i.d., 0.25 μm Stabilwax® Restek, Bellefonte, Pa), gas chromatography (GC) with flame ionization detection. Formaldehyde samples were quantitated by comparing the peak area of 3-benzyloxazolidine present in the absorption tubes to a calibration curve (linear regression) established from daily injections of 3-benzyloxazolidine standards (Equation 1). The 3-benzyloxazolidine standards were obtained from Supelco, Incorporated (Bellefonte, PA).

$$\text{Formaldehyde } (mg/m^3) = \frac{\mu g/mL \text{ (calib curve)} \times \text{(mL dil)} \times 0.184 \text{ (Conv factor)}}{\text{L sampled}} \quad (1)$$

Volatile organic combustion products were sampled from the 300-L chamber onto tenax tubes at a 2-5 L/min flowrate. After sampling, the organic vapor was thermally desorbed from the tenax tube, separated by GC, and identified by mass spectral analysis. A background check of potential contaminants in the chamber was performed prior to grenade dissemination.

The aerodynamic particle size of each exposure concentration was measured using a 10-stage cascade impactor (model 2210-K, Graseby-Andersen, Atlanta, GA). Chamber air samples were drawn through the impactor at 7 L/min and collected onto glass fiber substrates beneath each stage. The substrates were subsequently weighed to determine mass collected at each size range. Particle size sample data was analyzed by log-normal regression (least squares method) of particle size versus cumulative relative mass to determine mass median aerodynamic diameter (MMAD) and geometric standard deviation (σg).

2.7 Bronchoalveolar Lavage (BAL).

At each PE interval, rats due for BAL were anesthetized (i.p.) with pentabarbitol, and a tracheal catheter was inserted for pulmonary lavage. The lung washing technique consisted of instilling a calculated volume of normal saline (0.015 mL/g body weight) into the lungs and immediately withdrawing the saline until a slight pressure was felt on the syringe plunger. Two lavage washes were done in quick succession. The recovered lavage fluid from both washes was pooled and centrifuged at 3500 rpm (300 g) for 10 min at 4 °C.

Following centrifugation, the supernatant fluid was separated from the pellet. The pellet was resuspended in 1 mL of 50% bovine serum albumin, and total cell counts were taken on a ZBI (Hialeah, FL) Coulter Counter®. A differential cell count was made using a Wright-Giemsa stain. The cell pellet was resuspended in Hank's balanced salts solution; the macrophage concentration was determined in a hemocytometer, and cell viability was determined via the trypan blue exclusion test.

The supernatant lavage fluid was assayed for total protein with the Bio Rad® Protein Assay and for enzymatic activity of lactate dehydrogenase (LDH), alkaline phosphatase (ALKP), and β-glucuronidase (β-Glu). The LDH and ALKP were determined on an Abbott VP Series II using Sigma Chemical Company (St. Louis, MO) diagnostic kits. The β-Glu was assayed manually using a Sigma diagnostic kit.

2.8 Chemiluminescence Bioassay.

Six rats from a satellite group were used for the chemiluminescence bioassay. Lung washing from three rats provided cells for exposure to neat TPA. Likewise, lung washings from the other three rats provided cells for exposure to pyrotechnically disseminated TPA. The rat cells were exposed to a TPA concentration gradient that corresponded to the acute inhalation exposure levels (150 - 1,888 mg/m^3).

2.8.1 Cell Harvest.

Rat alveolar macrophages were obtained by bronchotracheal lavage. Male Fischer 344 rats were anesthetized with sodium pentobarbital (65 mg/Kg body weight) via i.p. injection. After the rats were fully anesthetized, the abdominal cavity was opened, a renal blood vessel was exposed and severed, exsanguinating the animal.

The rats lungs were infused through the trachea with 10 mL of iced phosphate buffered saline (PBS) (pH 7.0-7.4) augmented with 5% dextrose (w/v). The fluid was gently instilled and withdrawn until 60-80 mL of fluid had been collected. All fluid was pooled and maintained at 4 °C.

2.8.2 Cell Preparation.

Following lavage, the recovered fluid was centrifuged at 1500 rpm, 4 °C for 15 min. The supernatant was pipetted off the cells, which were gently resuspended in 1.0 mL ice-cold PBS with dextrose by repeated aspirations with a pipette. The cells were pooled and washed three times with 10 mL of PBS and resuspended in 10 mL of M199 containing 10% fetal calf serum. Aliquots of the cell suspension were removed from the centrifuge tube and adjusted to yield 2-3 x 10^6 macrophages per mm^3, the number of macrophages needed for chemiluminescence assay. A 1-mL aliquot of the macrophage suspension was dispensed into a vial with 2 mL of M199 plus 10% fetal calf serum. All vials were pre-incubated for 2 hr at 37 °C, 5 L/min CO_2 tension, moist incubator.

2.8.3 Chemiluminescence

After 2 hr, the vials were removed from the incubator and inoculated with the test substance (neat TPA or pyrotechnically disseminated TPA) and incubated for 20 hr. After incubation, all vials were centrifuged for 15 min at 1500 rpm and 4 °C. The cells were washed once with augmented M199 (37 °C), and resuspended in same to a final

volume of 4 mL. An aliquot cell suspension was removed from each test and control vial, and PE cell viability was ascertained using trypan blue exclusion.

After 1 hr, scintillation counts on the vials were conducted on a Packard Tri-Carb Model TR 1900 liquid scintillation counter (Packard Tri-Carb Rack and Instrument Company, Meriden, CT) housed in a dark room (red light only) at ambient temperature and humidity. Non-optimized Zymosan was added to all tubes at timed intervals to stimulate macrophages. Counting continued until 28-32 cycles were completed.

2.9 Carboxyhemoglobin (COHb).

In the repeated study, five rats from each dose level had their blood analyzed for COHb. Blood was drawn by tail snip of 20 rats at 0-5 min PE. Blood COHb concentrations were determined with a model IL 282 CO-Oximeter (Instrumentation Laboratory, Lexington, MA).

2.10 Animal Necropsy/Histopathology.

At the appropriate PE intervals, all rats scheduled for pathological evaluation were euthanized with CO_2 and necropsied. During necropsies, in accordance with Contract No. DAAA15-92-D-0009, Pathology Associates, Incorporated (Frederick, MD) performed a full gross examination of all tissues. In addition, the animals' total body weights (acute and repeated dose studies) and organ weights (repeated dose only) consisting of adrenals, brain, heart, kidneys, liver, lungs, and testes were recorded. All tissues were fixed, transported to the contractor's site, and evaluated for any histopathological changes.

2.11 Data Analysis Plan.

Data analysis was conducted according to a statistical "decision tree" described by Gad and Weil.[8] First, Bartletts's Test for homogeneity of variance was used as a check of the assumption of equivalent variances and was followed by the use of analysis of variances (ANOVA). Nonparametric, heterogeneous data was analyzed by the Kruskal-Wallis nonparametric ANOVA. Finally, Dunnett's Test was used on parametric homogeneous data to identify significantly different groups.

3. RESULTS

3.1 Chamber Aerosol Concentration and Particle Size Analysis.

The XM83 grenade produced a very dense white cloud in the 20-m^3 chamber. The XM83 aerosol concentrations (5 exposure levels-acute, 3 exposure levels-repeated) and concurrent particle size data from the exposure chamber are summarized in Table 4. The MMAD of the particles ranged from 1.3-1.7 μm for both studies, well within the respirable range for particle deposition in the lung. Chamber environmental parameters monitored during exposure included air flow (15 air changes/hour minimum), temperature (22 $\pm$ 4 °C), and RH (40-70%).

3.2 Gas and Vapor Concentrations.

Dissemination of the XM83 smoke grenade generated combustion gases and organic vapors in addition to the TPA smoke. We found measurable levels of CO, SO_2, NOx, benzene, toluene, H_2CO, and CO_2 (above ambient). The concentrations of these combustion products for the acute study are listed in Tables 5 and 6. Results of the repeated dose are listed in Tables 7 and 8. Oxygen levels were monitored in the chamber during the repeated dose study and were greater than 20.5% at all dose levels. Ammonia and nitrogen dioxide gases were below the detectable limits.

3.3 Toxic Sign Observations.

Rats exposed to both the acute and repeated dose levels of pyrotechnically disseminated TPA exhibited a small number of minor toxic signs. At low dose levels (128-150 mg/m^3), the rats exhibited slight lacrimation, lethargy, and rhinorrhea. At medium dose levels (500-1,000 mg/m^3), the rats exhibited slight-to-moderate lacrimation, rhinorrhea, lethargy, and dyspnea; and at the high dose levels (1,200-2,000 mg/m^3), the animals exhibited moderate lacrimation, rhinorrhea, lethargy, and moderate-to-severe dyspnea. Smoke particles were observed on the rats nares during exposures at the medium and above dose levels. Almost all signs were reversed within 1 hr PE.

3.4 BAL, Chemiluminescence, and COHb.

The results of the BAL evaluations are presented in Tables 9-12. There were no statistically significant differences in biochemical (β-Glu, LDH, ALKP, total protein) analysis of lavage fluid from rats exposed to grenade-disseminated TPA. There was one significant difference in the white blood count (WBC) for the high dose level exposures (24-hr PE, acute study). The WBC count for the 14-day PE was also positive; however, this was probably due to a bacterial infection. All other cytological parameters (total nucleated cells, macrophages, lymphocytes, and polymorphonuclear neutrophils) were normal. Blood COHb measurements taken during the repeated dose study showed that rats exposed at the high dose level had a statistically significant increase in COHb levels over controls (Table 13).

3.5 Pathological Evaluations.

Gross pathology evaluation found no exposure-related gross lesions in the rats necropsied at either 24 hr, 14 days, or 3 months PE for either the acute or repeated dose study.

Microscopic examination of the necropsied tissues showed dose-related lesions present in the rats necropsied at 24 hr PE. These lesions were limited to the nasal cavity of rats in the mid 1, mid 2, high 1, and high 2 dose groups in the acute study and the high dose group in the repeated study. The lesions consisted of necrosis of the epithelium lining the nasal cavity and acute inflammation extending below the epithelium and also into the nasal cavity. The most extensive and severe lesions were found in rats from the high 2 dose group in the acute study.

No necrosis or inflammation was observed in rats from any dose group after 14 days PE. However, hyperplasia of the goblet cells of the nasal cavity was observed in three of six rats in the high 1 dose group and six of six animals in the high 2 dose group

for the acute study. This response was also observed in three of six rats in the high dose group of the repeated study and was considered to be part of the resolution process of the necrosis and inflammation present in the animals immediately after exposure. At 3 months PE of the repeated study, no exposure-related lesions were observed in any animals.

4. DISCUSSION

Acute and repeated dose inhalation studies were conducted to assess the health hazard potential of the XM83 TPA smoke grenade. Accordingly, Fisher 344 rats were exposed by acute inhalation to a wide range of smoke concentrations to determine a no effect and effect level for various toxicological endpoints (toxic signs, BAL, chemiluminescence, and histopathological changes). One major area of concern was the effect of high concentrations of smoke on the respiratory system since smoke levels in the range of 1,000-2,000 mg/m^3 could occur for short periods of time (1-5 min) under battlefield or training conditions. Rats were also exposed via repeated dose to assess the above effects from a repeated inhalation exposure. Inhalation exposures were conducted every other day for 5 days to mimic field training.

The absence of lesions below 511 mg/m^3 concurs with a previous acute inhalation study on pyrotechnically disseminated TPA from anti-dim cans, which found no compound related histopathology from exposure levels ranging from 100 to 400 mg/m^3.[4] In the repeated study, nasal lesions were found only at the highest dose level (1,965 mg/m^3). However, in the acute study, lesions were found at both mid-dose levels (511-927 mg/m^3). The absence of lesions at the mid-dose level for the repeated study may have been due to the allowed recovery time between dose levels. The epithelium lining within the nasal cavity can heal very rapidly. In addition, newly formed epithelial cells may not have the same susceptibility to injury following an initial exposure to the XM83 smoke. Examination of the epithelium layer in the rat turbinates for the high dose, repeated study showed less necrosis than found in rats exposed in the high dose, acute study. Goblet cell hyperplasia was present only in the highest dose levels at 14 day PE for both studies, indicating repair of the nasal area. There were no treatment related lesions at 3 months PE.

It is important to note that beyond the nasal cavity, no other lesions were present in the respiratory system. Lung lavage fluid analysis and cytological assays correlate well with the histopathologic examination. Other than an increase in WBCs for the 24 hr PE, there were no significant changes in the lung BAL and chemiluminescence parameters between exposed and control rats. Jernigan et al. found some pathology beyond the nasal cavity with pure TPA. They reported minimal degeneration of tracheal epithelium in rats exposed to 3.31 mg/m^3 TPA (6 hr/day, 5 days/week for 4 weeks).[9] Observation of the grenade-disseminated particles during chamber exposure and particle sizing showed that the particles were sticky and tended to cling together. The combination of the particles sticking together as well as exudate secretions from the rats nose may have confined the particles to the nasal cavity. Since obligate nose-breathing rodents exhibit lower pulmonary and higher nasal and tracheobronchial deposition than humans,[10] it is reasonable to assume that, given the 1-2 μm particle size, some lung deposition would have occurred for human exposure.

The presence of other combustion products in the XM83 smoke were of toxicological concern. Therefore, gas and vapor samples were collected during the

exposures to monitor these by-products. Inorganic gases detected above the threshold limit values (TLV) were CO and SO_2. Organic gas and vapors above the TLV levels were benzene and H_2CO. It should be noted that these combustion products occurred within a dynamic inhalation chamber that maintained a stable concentration of smoke for 30 min. Actual field disseminations of the grenade would probably show a negligible amount of these gases and vapors due to the effects of wind and dilution by the atmosphere.

The inorganic gas of most toxicological concern was CO. One possible mechanism for its formation would be the reaction of potassium chlorate with sucrose in the TPA mix (Equation 2). Carbon monoxide was above the time-weighted average (TWA) level of 25 ppm at smoke concentrations above 511 mg/m^3. The highest concentration of CO measured was 213 ppm at the high dose level (1,965 mg/m^3 smoke) of the repeated study. However, this level was not high enough to adversely affect the rats in this study as shown by the modest increase in blood COHb level at the high dose level. A nose-only exposure study of rats to CO (1 hr/day, 14 days) by Ayres et al. found it would take CO levels approaching 1,000-1,800 ppm to adversely affect the rats respiratory rate and erythrocyte parameters and cause inflammation of the cardiac muscle.[11] Sulfur dioxide was also detected above the TLV-short-term exposure limit (STEL) (2 ppm SO_2) and TLV-TWA (5 ppm SO_2) at smoke concentrations above 1,268 mg/m^3. However, the SO_2 detected in the gas detector tubes may have been caused by other interferences.

$$4\ KClO_3 + C_{12}H_{22}O_{11} \longrightarrow 4\ KCl + 12\ CO + 11\ H_2O \qquad (2)$$

Benzene and H_2CO were both above TLV levels. Benzene levels ranged from 19-38 ppm at the high dose levels (TLV-TWA 10 ppm), but were below the TLV at the medium and low dose exposures. The formation of benzene probably occurred during the pyrolysis of TPA. Formaldehyde was above the TLV-TWA of 0.3 ppm at all dose levels and reached a peak concentration of 11-21 ppm at the high dose exposures. Formaldehyde was probably formed during organic combustion.

A comparison of the combustion products present in the disseminated TPA versus the HC smokes shows that the HC smoke is more toxic. The most toxic combustion products identified from the TPA in this study included H_2CO, benzene, and CO. The significance of these compounds has been discussed above. For the HC smoke, a greater number of potentially harmful compounds have been identified. These compounds include toxic inorganic compounds (zinc chloride, hydrogen chloride, arsenic, and cadmium chloride salts) found in the particle phase of the smoke and chlorinated hydrocarbons (hexachlorobenzene, hexachloroethane, perchloroethylene, carbon tetrachloride, and trichloroethylene) found in the vapor phase of the smoke.[12] Most of the chlorinated hydrocarbons present are potential carcinogens. When comparing the inhalation toxicities of the HC and TPA smokes, it is important to keep in mind that any pyrotechnic smoke device will disseminate some components or combustion products that are not desirable. Neither smoke system should be employed in an enclosed environment, due to the high build-up of the smoke and its associated combustion products, which could prove injurious or fatal to unprotected personnel. Therefore, during any type of smoke dissemination, personnel must wear protective respiratory equipment.

A comparison of the inhalation effects of TPA versus the HC smoke shows that the HC smoke is more toxic. In this study, rats were exposed via acute and repeated dose inhalations to high concentrations (2,000 mg/m^3) of TPA smoke. No deaths occurred, and toxic signs were reversed within 1 hr after exposure. There were also no long-term effects from the repeated TPA inhalation at 3 months PE. A number of inhalation studies on the effects of HC smoke on animals, which show considerable lung pathology,[13-16] have been conducted. On the basis of concentration alone, zinc chloride and hydrogen chloride are the two components that appear to pose the greatest acute inhalation threat from the HC smoke.[12] Common effects include inflammatory changes in the lung such as edema, emphysema, fibrosis, and macrophage infiltration.[12] Both the zinc chloride and hydrogen chloride can cause acute respiratory distress and have been fatal in both animal and human exposures, depending upon the concentration and exposure time. A comprehensive review on the health effects of HC smoke has been conducted by Eaton et al.[12] The long-term effects from potential carcinogens in the HC smoke are uncertain at this time.

5. CONCLUSIONS

The XM83 grenade, containing terephthalic acid (TPA) is the prime training smoke candidate to replace the U.S. Army's hexachloroethane (HC) smoke grenade.

There were dose-related necrosis and inflammation of the nasal cavity in the rats from the medium and high dose levels of the acute study and the high dose level of the repeated dose study. These were resolved by 14 days after exposure. No other compound-related lesions were present.

The most important combustion products formed from the grenade-disseminated TPA included formaldehyde, benzene, and carbon monoxide. All were found above their respective TLVs at various dose levels. Actual field disseminations of the grenade would probably show a negligible amount of these gases and vapors due to the effects of wind and dilution by the atmosphere.

The short-term effects of a repeated inhalation exposure to the XM83 smoke were not significantly different from the acute inhalation exposure. There were also no long-term effects from the repeated TPA inhalation at 3 months PE.

Terephthalic acid is a safer smoke than HC. No deaths occurred, and toxic signs were reversed within 1 hr after animal exposures to high TPA smoke concentrations (2,000 mg/m^3). There were no pathological changes in the lung, and both bronchoalveolar lavage and chemiluminescence parameters where normal.

Table 1. TPA Formulation for the XM83 Grenade (Formula 103)

TPA Mix (98%)		Starter Mix (2%)	
Material	%	Material	%
Terephthalic acid	56.4	Silicon	16.12
Sugar (sucrose)	13.9	Potassium Nitrate	51.87
Magnesium Carbonate	3.0	Charcoal	17.03
Potassium Chlorate	22.8	Stearic Acid	10.71
Stearic Acid	3.0	Nitrocellulose	4.28
Polyvinyl Alcohol (PVA) (binder)	1.0*		

*Dissolved in water to form a 4.0% nominal solution. The PVA content of the completed mixture is approximately 1.0% on a dry weight basis.

Table 2. Schedule of Animal Usage (Acute Inhalation)

	Pathology		Lavage	
	24 hr	14 days	24 hr	14 days
CONTROLS (air exposed)	6	6	6	6
EXPOSED (TPA, mg/m^3)				
Low conc (150)	6	6	6	6
Med (1) conc (511)	6	6	6	6
Med (2) conc (927)	6	6	6	6
High (1) conc (1,268)	6	6	6	6
High (2) conc (1,888)	6	6	6	6

Table 3. Schedule of Animal Usage (Repeated Dose Inhalation)

	Pathology			Lavage		
	24 hr	14 days	3 months	24 hr	14 days	3 months
CONTROLS (air exposed)	6	6	6	6	6	6
EXPOSED (TPA, mg/m^3)						
Low conc (128)	6	6	6	6	6	6
Medium conc (946)	6	6	6	6	6	6
High conc (1,965)	6	6	6	6	6	6

Table 4. Chamber Aerosol Concentrations and Particle Size Data

Acute Inhalation Study		
Chamber Conc Total Aerosol[a]	Particle Size Data[b]	
(mg/m^3)	(MMAD) (μ)	(σg)
150 ± 33	1.50	2.81
511 ± 57	1.49	2.57
927 ± 35	1.40	2.16
1,268 ± 110	1.40	2.86
1,888 ± 310	1.33	2.85

Repeated Inhalation Study		
Chamber Conc Total Aerosol[c]	Particle Size Data[c]	
(mg/m^3)	(MMAD) (μ)	σg
128 ± 10	1.61	2.75
946 ± 43	1.75	2.62
1,965 ± 56	1.39	3.04

[a] n = 3, mean conc of 3 samples (5, 15, and 25 min)
[b] n = 1
[c] n = 5, mean conc (days 1-5)

Table 5. Inorganic Gas Concentrations from Grenade-Disseminated TPA (Acute Inhalation)

XM83 Conc (mg/m^3)	CO (ppm)	CO_2 (ppm)	NH_3 (ppm)	SO_2 (ppm)	NOx (ppm)
Controls	<0.5	500	<0.5	<1	<0.5
Low Dose (150)	15.0	500	<0.5	<1	<0.5
Med Dose 1 (511)	**45.0**	766	<0.5	<1	0.3
Med Dose 2 (927)	**78.0**	900	<0.5	1	0.5
High Dose 1 (1,268)	**128.0**	1,066	<0.5	**6**	0.7
High Dose 2 (1,888)	**148.0**	1,233	<0.5	**12**	0.8
TWA	**25.0**	**5,000**	**25.0**	**2**	**50.0**
STEL	--	**30,000**	**35.0**	**5**	--

Values are the mean of 5-, 15-, and 25-min readings. **Values above the TLV (TWA-STEL) are in bold.**

Table 6. Organic Gas and Vapor Concentrations from Grenade-Disseminated TPA (Acute Inhalation)

XM83 Conc Total Aerosol (mg/m^3)	Benzene GC-MS (ppm)	Toluene GC-MS (ppm)	Formaldehyde Gas Detector Tube (ppm)	Formaldehyde GC Method (ppm)
Controls	--	--	<0.5	<0.3
Low Dose (150)	3	0.3	**1.5**	<0.3
Med Dose 1 (511)	7	0.4	**5.0**	**2.4**
Med Dose 2 (927)	8	0.4	**7.0**	**6.4**
High Dose 1 (1,268)	**38**	1.4	**11.0**	**17.1**
High Dose 2 (1,888)	**37**	1.6	**21.0**	**18.1**
TWA	**10**	**50.0**	**0.3**	**0.3**
STEL	--	--	--	--

Values are the mean of 5-, 15-, and 25-min readings. **Values above the TLV (TWA-STEL) are in bold.**

Table 7. Inorganic Gas Concentrations from Grenade-Disseminated TPA (Repeated Dose Inhalation)

XM83 Conc Total Aerosol (mg/m^3)	CO[a] (ppm)	CO[b] (ppm)	CO_2[a] (ppm)	SO_2[a] (ppm)	NOx[a] (ppm)	O_2[b] (%)
Control Day (1-5)	<5	<1	733	<1	<0.5	20.8
Low Dose (128 mg/m^3)						
Day 1	10	11	800	<1	<0.5	20.7
Day 2	15	18	800	<1	<0.5	20.6
Day 3	--	15	700	<1	<0.5	20.5
Day 4	--	17	800	<1	<0.5	20.6
Day 5	13	19	800	<1	<0.5	20.9
Mean	13	16	780	<1	<0.5	20.7
Med Dose (946 mg/m^3)						
Day 1	**100**	**109**	1,000	<1	<0.5	20.5
Day 2	**100**	**111**	900	<1	<0.5	20.6
Day 3	--	**130**	1,000	<1	<0.5	20.7
Day 4	**95**	**127**	1,000	<1	<0.5	20.5
Day 5	--	**129**	--	<1	<0.5	20.6
Mean	**98**	**121**	975	<1	<0.5	20.6
High Dose (1,965 mg/m^3)						
Day 1	**200**	--	1,100	**10**	10	--
Day 2	**205**	**202**	1,250	**10**	10	20.8
Day 3	--	**258**	1,200	**10**	10	20.7
Day 4	**220**	**249**	1,200	**8**	10	20.6
Day 5	**225**	**242**	1,200	**12**	10	20.8
Mean	**213**	**238**	1,190	**10**	10	20.7
TWA	25	25	5,000	2	50	--
STEL	--	--	30,000	5	--	--

[a]Analysis by Kitagawa Gas Detector Tubes
[b]Analysis by AIM Electrochemical Detection
Values are the mean of 5-, 15-, and 25-min readings. **Values above the TLV (TWA-STEL) are in bold.**

Table 8. Organic Gas and Vapor Concentrations from Grenade-Disseminated TPA (Repeated Dose Inhalation)

XM83 Conc Total Aerosol (mg/m^3)	Benzene GC-MS (ppm)	Toluene GC-MS (ppm)	Formaldehyde Gas Detector Tube (ppm)	Formaldehyde GC Method (ppm)
Control Day (1-5)	--	--	<1	<0.3
Low Dose (128 mg/m^3)				
Day 1	1.9	0.4	**2.0**	**1.4**
Day 2	1.3	0.3	--	--
Day 3	3.4	0.4	**2.0**	**1.4**
Day 4	1.6	0.3	**2.0**	**1.7**
Day 5	3.0	0.4	--	**2.1**
Mean	2.3	0.4	**2.0**	**1.7**
Medium Dose (946 mg/m^3)				
Day 1	7.4	0.4	**5.0**	**2.8**
Day 2	--	0.3	**10.0**	**5.9**
Day 3	6.3	0.4	**10.0**	**6.0**
Day 4	7.0	0.4	**10.0**	**4.9**
Day 5	8.2	0.6	--	--
Mean	7.2	0.4	**9.0**	**4.9**
High Dose (1,965 mg/m^3)				
Day 1	**28.2**	1.3	**15.0**	**5.4**
Day 2	**17.7**	0.9	**22.0**	**10.4**
Day 3	**16.6**	0.7	**25.0**	**12.3**
Day 4	**11.8**	0.9	**22.0**	**33.5**
Day 5	**19.4**	1.4	--	**11.3**
Mean	**18.7**	1.0	**21.0**	**14.6**
TWA	**10.0**	**50.0**	**0.3**	**0.3**
STEL	--	--	--	--

Values are the mean of 5-, 15-, and 25-min readings. **Values above the TLV (TWA-STEL) are in bold.**

Table 9. Biochemical Analysis of Lavage Fluid from Rats Exposed to Grenade-Disseminated TPA (Acute Inhalation)

Groups	PE (Days)	B-Glu (Sigma U/mL)	LDH (IU/L)	ALKP (IU/L)	Protein (μg/mL)
Control	1	8.60 ± 3.87	32.06 ± 18.71	67.65 ± 3.58	44.01 ± 0.72
Low Dose	1	7.00 ± 2.21	29.66 ± 13.00	62.67 ± 8.17	47.67 ± 3.66
Med Dose 1	1	6.46 ± 1.46	31.06 ± 16.31	54.95 ± 17.52	47.13 ± 3.74
Med Dose 2	1	4.67 ± 0.54	38.48 ± 50.33	41.39 ± 17.78	45.13 ± 1.37
High Dose 1	1	5.42 ± 1.33	18.20 ± 3.55	53.20 ± 8.81	47.69 ± 6.36
High Dose 2	1	5.50 ± 1.31	23.38 ± 9.95	55.08 ± 8.39	44.97 ± 1.31
Control	14	--	18.54 ± 9.37	41.05 ± 17.14	17.65 ± 1.18
Low Dose	14	--	33.09 ± 20.66	54.62 ± 15.92	15.47 ± 1.52
Med Dose 1	14	--	45.93 ± 27.85	60.14 ± 9.25	18.42 ± 4.72
Med Dose 2	14	--	25.65 ± 36.42	58.20 ± 13.06	25.01 ± 5.65
High Dose 1	14	--	11.62 ± 10.78	52.76 ± 4.99	31.42 ± 32.51
High Dose 2	14	--	46.26 ± 18.53	61.70 ± 10.0	14.28 ± 2.76

Each value represents mean ± SD (n = 6), tested using Barlett's Test and ANOVA two-tailed @ $P \leq 0.05$.

Table 10. Biochemical Analysis of Lavage Fluid from Rats Exposed to Grenade-Disseminated TPA (Repeated Dose Inhalation)

Groups	PE (Days)	B-Glu (Sigma U/mL)	LDH (IU/L)	ALKP (IU/L)	Protein (μg/mL)
Control	1	5.85 ± 0.78	42.30 ± 45.49	33.32 ± 4.79	--
Low Dose	1	5.75 ± 1.64	41.49 ± 29.11	29.91 ± 11.99	--
Med Dose	1	6.29 ± 1.59	65.10 ± 87.20	54.61 ± 61.74	--
High Dose	1	6.96 ± 2.01	81.13 ± 31.59	32.60 ± 13.46	--
Control	14	7.08 ± 0.38	27.72 ± 15.50	54.74 ± 6.31	26.33 ± 20.87
Low Dose	14	7.90 ± 1.92	43.92 ± 25.05	60.40 ± 5.77	10.5 ± 4.72
Med Dose	14	7.24 ± 1.38	27.56 ± 18.59	59.75 ± 8.46	12.0 ± 3.03
High Dose	14	6.54 ± 1.25	22.54 ± 8.45	52.41 ± 16.47	12.67 ± 3.50
Control	90	6.45 ± 1.46	34.74 ± 9.33	83.04 ± 11.77	5.26 ± 2.46
Low Dose	90	4.62 ± 1.77	35.59 ± 19.23	61.42 ± 29.72	4.98 ± 3.24
Med Dose	90	5.87 ± 2.45	31.88 ± 22.88	63.41 ± 25.52	6.70 ± 4.47
High Dose	90	6.42 ± 1.39	30.36 ± 9.83	80.34 ± 23.16	4.20 ± 3.27

Each value represents mean ± D (n = 6), tested using Barlett's Test and ANOVA two-tailed @ $P \leq 0.05$.

Table 11. Cytological Analysis of Lavage Fluid from Rats Exposed to Grenade-Disseminated TPA (Acute Inhalation)

				Nucleated Cell Differential		
Groups	PE (Days)	WBC ($x10^3$)	Total Nucleated Cells ($x10^4$)	MAC (%)	LYMPHS (%)	PMN (%)
Control	1	0.96 ± 0.29	3.75 ± 1.15	98 ± 1	1 ± 1	1 ± 1
Low Dose	1	0.86 ± 0.38	3.60 ± 0.68	98 ± 2	2 ± 1	0 ± 0
Med Dose 1	1	0.90 ± 0.30	3.77 ± 0.66	98 ± 2	1 ± 1	0 ± 1
Med Dose 2	1	3.84 ± 5.43	2.22 ± 2.68	97 ± 2	3 ± 2	0 ± 0
High Dose 1	1	**1.12 ± 0.47**	4.04 ± 2.01	96 ± 5	3 ± 5	1 ± 1
High Dose 2	1	**1.66 ± 0.56**	4.08 ± 1.74	95 ± 7	4 ± 2	1 ± 2
Control	14	0.57 ± 0.10	0.88 ± 0.84	98 ± 2	2 ± 1	0
Low Dose	14	0.67 ± 0.18	0.08 ± 0.02	97 ± 2	3 ± 2	0
Med Dose 1	14	0.62 ± 0.18	1.06 ± 0.80	97 ± 2	3 ± 2	0
Med Dose 2	14	**2.93 ± 1.59**	2.38 ± 1.95	95 ± 4	5 ± 4	0
High Dose 1	14	**5.92 ± 3.73**	--	97 ± 2	3 ± 2	0
High Dose 2	14	**5.32 ± 3.84**	1.62 ± 1.27	98 ± 2	2 ± 1	0

Each value represents mean ± SD (n = 6), tested using Barlett's Test and ANOVA two-tailed @ $P \leq 0.05$. **Values in bold are significant.**

Table 12. Cytological Analysis of Lavage Fluid from Rats Exposed to Grenade-Disseminated TPA (Repeated Dose Inhalation)

Groups	PE (Days)	WBC ($x10^3$)	Total Nucleated Cells ($x10^4$)	Nucleated Cell Differential MAC (%)	LYMPHS (%)	PMN (%)
Control	1	0.70 ± 0.20	2.41 ± 0.67	93 ± 3	6 ± 3	1 ± 1
Low Dose	1	0.77 ± 0.24	1.53 ± 0.42	96 ± 3	3 ± 2	1 ± 1
Med Dose	1	0.73 ± 0.15	2.92 ± 2.15	94 ± 5	5 ± 4	1 ± 2
High Dose	1	1.25 ± 1.13	1.91 ± 0.86	96 ± 4	3 ± 3	1 ± 1
Control	14	1.22 ± 0.45	5.19 ± 2.58	99 ± 1	1 ± 2	--
Low Dose	14	1.18 ± 0.32	4.07 ± 1.53	99 ± 1	1 ± 1	--
Med Dose	14	0.97 ± 0.43	3.35 ± 0.97	98 ± 2	2 ± 1	--
High Dose	14	1.32 ± 0.51	4.63 ± 1.01	98 ± 1	2 ± 1	--
Control	90	0.98 ± 0.29	5.05 ± 1.96	91 ± 4	5 ± 2	4 ± 3
Low Dose	90	0.58 ± 0.13	2.87 ± 0.99	88 ± 3	6 ± 3	6 ± 5
Med Dose	90	0.85 ± 0.34	4.93 ± 2.29	95 ± 4	3 ± 2	2 ± 1
High Dose	90	0.92 ± 0.29	3.65 ± 2.34	95 ± 5	3 ± 3	2 ± 3

Each value represents mean ± SD (n = 6), tested using Barlett's Test and ANOVA two-tailed @ $P \leq 0.05$.

Table 13. Blood COHb Levels of Rats Exposed to Grenade-Disseminated TPA (Repeated Dose Study)

Exposure Days Concentration	Day 1 (%)	Day 2 (%)	Day 3 (%)	Day 4 (%)
Control	2.36 ± 1.11	3.30 ± 0.38	3.74 ± 1.22	3.50 ± 0.2
Low	3.56 ± 1.74	3.58 ± 0.34	2.43 ± 0.92	3.54 ± 0.83
Medium	3.24 ± 1.43	--	3.84 ± 1.43	**4.85[a] ± 0.56**
High	**4.82[a] ± 0.36**	**5.40[a] ± 0.73**	**4.70[b] ± 0.33**	**5.22[a] ± 0.61**

[a]significant at $p < 0.01$; not significant at $p < 0.05$ (New-Keul test)
[b]significant at $p < 0.05$ (ANOVA two-tailed)
Values in bold are significant. Data from Exposure Day 5 not available.

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