

Absence of Health Hazards Associated with RDX Manufacture and Use

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A cross-sectional epidemiologic study was conducted to investigate a cluster of three cases of systemic lupus erythematosus at one munitions plant. The study demonstrated no excess of autoimmune disease and also failed to identify any abnormalities of the hematologic, hepatic, or renal systems in employees with 8 hour time-weighted exposures, to RDX of up to 1.57 mg/m³ (average exposure was 0.28 mg/m³).

Cyclotrimethylene trinitramine (RDX) is a commonly used explosive. In 1972, production in U.S. Army plants was estimated at over 80,000 tons.¹ Work experience with RDX during World War II was considerably more favorable than with another explosive trinitrotoluene (TNT). No fatalities were experienced in RDX facilities as opposed to 22 fatalities from TNT.²⁻³ Reported toxicity effects of RDX in man have been limited to the central nervous system and have been manifested as epileptic type seizures.⁴⁻⁵ Toxic effects in animals in addition to central nervous system damage have included degeneration of renal tubular epithelium, fatty degeneration of the liver, and hyaline degeneration in heart muscle.⁶

These toxic effects in animals were produced by acute or chronic feeding studies using large doses of RDX. There appears to be no animal studies of inhalation toxicity and no low dosage studies that would be comparable to RDX levels in the workplace. Also, since methodology to measure airborne concentrations of

RDX in the workplace has only recently been developed, older studies of RDX induced seizures were unable to correlate toxic effects to levels of RDX. The threshold limit value (TLV[®]) for RDX is 1.5 mg/m³. This level appears to have been arbitrarily selected and based on the dubious assumption that toxic effect levels of RDX might be analogous to TNT, another cyclic, nitrated compound.⁷

The data presented include a separate analysis of medical tests performed on employees from U.S. Army ammunition plants who were originally part of a larger study looking at health effects of both TNT and RDX. Medical test results are compared to RDX levels expressed as 8 hour time-weighted average exposures to airborne RDX dust. Our findings provide support that the TLV of 1.5 mg/m³ may indeed be a safe exposure level for RDX.⁸

Background

Between 1972 and 1974, three cases of systemic lupus erythematosus (SLE) were noted in the employee population at one U.S. Army ammunition plant. The plant physician observed that this incidence greatly exceeded the incidence in the local community and the U.S. Army Environmental Hygiene Agency (USA-EHA) was asked to conduct an evaluation. Based on the structural similarity between RDX and various drugs known to provoke drug-induced SLE, 64 workers considered to have highest RDX exposures were screened. The fluorescent antinuclear antibody test (FANA) was used in an attempt to identify new cases or demonstrate evidence of autoimmune disease.⁹ No new cases were identified; however, because of the small number of persons tested, lack of knowledge concerning prevalence of positive FANA results in the normal population and limited understanding of the toxic effects of RDX, additional studies were deemed necessary. The methods and results of a subsequent study are discussed below.

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Methods

Five different U.S. Army ammunition plants were asked to provide lists of employees by job title. Based upon knowledge of the different jobs, 4,973 employees were separated into two categories (controls and exposed to RDX and/or TNT). Using random number tables 2022 employees (1017 exposed, 1005 controls) were selected and asked to voluntarily participate in the study. Control and exposed categories were later evaluated based on industrial hygiene evaluations and a number of individuals initially selected as exposed were reassigned to the control group. The response rates for initial groups were: exposed 76.3%, controls 71.1%; white 73.8%, nonwhite 73.5%; and male 73.7%, female 73.8%. Statistical comparisons were made of age distribution, sex, and race and an excellent match of exposed and control groups was verified. Reclassification of certain workers from the exposed to control group did not affect the closeness of the match. Details of the method of selection have been previously discussed.⁸ The plants were selected based on the number of employees engaged in manufacture or load assemble, pack (LAP) operations utilizing TNT, RDX, or cyclotetramethylenetetranitramine (HMX) or their mixtures.

A USAEHA team visited each plant over a six week period. Blood samples were collected, processed and shipped by air (at least daily) to a commercial laboratory. Essentially, all samples were processed by the laboratory within 24 hours of collection. Blood samples were analyzed for serum glutamic pyruvic transaminase (SGPT), serum glutamic oxaloacetic transaminase (SGOT), lactic dehydrogenase (LDH), alkaline phosphatase (ALK PHOS), Bilirubin (total and direct), albumin, glucose, cholesterol, blood urea nitrogen (BUN), total protein, hemoglobin (Hb), hematocrit (Hct), reticulocyte count, and fluorescent antinuclear antibodies (FANA).

FANA determinations were made using the indirect immunofluorescent technique. Frozen mouse liver was used as the substrate. Test results were considered positive if any pattern of nuclear staining was present. Titrations were performed by doubling dilutions of human sera starting at a 1:20 dilution. Both negative and positive controls were employed to validate the reactivity of the mouse liver substrate.

Atmospheric sampling of all types of operations involving exposure to open explosives was conducted at each plant. Because of the intermittent nature of many operations (e.g., pouring explosives), attempts were made to sample over as long a period as possible and generally averaged several hours. Paired samples were collected in the breathing zone of workers with 37-mm, type A, glass fiber filters. The calibrated air samplers were battery-operated MSA Model 6 or Bendix Model C115, belt-mounted pumps operating within a flow range of 1.5 to 2.5 liters per minute.

The filter cassettes were processed for analysis after sampling by extraction of each filter with 5 ml of chromatographic quality benzene. The resulting solutions were analyzed for RDX contents by use of gas chromatography. RDX was analyzed by taking the benzene solutions to dryness and redissolving the residue in 1 ml of chromatographic quality acetone. One microliter injections of the acetone solutions were made on a Tracor model 550 gas chromatograph equipped with an electron capture detector. Injection port temperature was maintained at 200°C, detector temperature at 240°C and column temperature at 210°C. The single column was an all glass system, 6-ft. by 1/8-in. packed with 3% OV-11 on 100-120 mesh GasChrome Q.† Carrier gas flow rate was maintained at 75 ml/minute and detector flow at 72 ml/minute.

Results and Analysis of Data

Of the 2,022 employees selected for the study, 1,491 participated for an overall response rate of 73.7%. Of these, 558 were exposed to RDX alone or in combination with TNT and/or HMX, 863 were unexposed to explosives and the remaining were exposed to TNT only. A total of 69 were exposed to RDX only and 24 were exposed to RDX and HMX.

Table 1 shows the results of FANA tests by race and sex. There were no significant differences between positive results and exposure to explosives. In fact, prevalence of positive FANA tests was higher (3.5%) in nonexposed than RDX exposed employees (2.2%). Most FANA titers were low (either 1:20 or 1:40). There were four titers of 1:160 and one of 1:80. Of these five individuals, one was exposed only to HMX, one was exposed to RDX and TNT, and three had no exposure to explosives. No cases of SLE were found by followup tests on either exposed or unexposed employees conducted by the individual plants.

Because TNT exposure is known to have the potential for causing both hematologic and liver function abnormalities, employees having TNT exposure in addition to RDX are excluded from further analyses. Employees having mixed RDX and HMX exposures are included even though analysis of HMX air levels was not performed. Employees having RDX exposure are placed into two categories, those whose exposure was below detectable limits and those with exposures of 0.01 mg/m³ or greater. Exposures ranged from undetectable to 1.57 mg/m³. The mean exposure of those 70 employees with detectable exposure was 0.28 mg/m³. Exposure to RDX alone or in combination with HMX was limited to two plants and involved only white employees. For this reason, a nonexposed control population was selected among white employees at these two plants only. The demographic distribution is shown in Table 2.

The results of blood chemistry determinations and hematological findings are presented in Table 3. Standard deviations were calculated and used in data analysis. They were omitted from the table to improve readability. There were no statistically significant differences between results from exposed and non-exposed workers.

Table 1. — Prevalence (%) of Positive FANA by Race Sex Group and Exposure Category.

Exposure Category	Males		Females		Total (n)
	White	Nonwhite	White	Nonwhite	
TNT alone	0.0	0.0	16.6*	0.0†	1.8 (57)
All Other Exposed‡	1.6	0.0	2.9	5.5	2.2 (558)
Nonexposed	3.3	1.7	4.3	4.1	3.5 (863)
Total	2.5	0.8	4.0	4.7	2.9

*One of six exposed.

†None exposed.

‡Includes all exposures to RDX, HMX either alone or in combination with other explosives (including TNT).

Table 2. — Demographic Distribution of RDX Exposed Employees and Unexposed Controls.

Exposure	White Female	White Male
RDX only	26	43
RDX and HMX	0	24
Nonexposed	101	237

Table 3. — Mean Laboratory Values for RDX Exposed and Nonexposed Employees.

Laboratory Determination	Male			Female		
	Nonexposed	RDX Exposure		Nonexposed	RDX Exposure	
		Undetected*	0.01 mg/m ³ or Over		Undetected*	0.01 mg/m ³ or Over
No. of individuals	217	22	45	101	1	25
LDH	173	191	174	184	167	184
ALK PHOS	82	78	80	70	88	67
SGOT	22	25	21	21	10	20
SGPT	21	25	18	13	10	12
Bilirubin	0.5	0.4	0.4	0.4	0.4	0.4
Hb	15.2	14.7	15.2	13.8	13.9	13.8
Hct	47	45.6	47	41.7	43.3	41.4
Reticulocyte Count	0.7	0.9	0.7	1	0.3	1.1
Total Protein	7.2	7.2	7.3	7.3	7.6	7.2
BUN	15.5	15.6	16.4	13.2	8	12.6
Glucose	94	91	93	92	67	92
Cholesterol	212	202	208	212	206	227

*Some exposure was felt to exist based on professional judgment but no RDX was detected by breathing zone sampling.

The results were also analyzed to determine if an excess of abnormal laboratory determinations might exist among exposed workers. The results of such a comparison for Hb levels is shown in Table 4.

Similar tables were also constructed for hematocrit, reticulocyte count, LDH, ALK PHOS, SGOT, SGPT, and bilirubin. There were no statistically significant differences between exposed and unexposed groups. Summaries of these results are shown in Tables 5 and 6.

Discussion

The results of medical tests failed to reveal any abnormalities that could be related to RDX work exposure. This is in contrast to dose-related effects on hematologic function with TNT exposure.⁹ Because of the state of the economy, voluntary turnover of workers had been low and since the end of the Vietnam War, many workers have been involuntarily released leaving the more senior employees to participate in this study. Thus, these apparent nonhealth related variables have biased the study group towards chronically exposed workers. This bias would be expected to enhance the likelihood of identifying a chronic adverse health effect of RDX if it in fact existed. Although the average work exposure to RDX was only 0.28 mg/m³, many workers were exposed to levels of RDX between 0.5 and 1.5 mg/m³. While these results do not prove that 1.5 mg/m³ of RDX is a safe exposure, they do suggest that it may be a safe level. The results of the industrial hygiene sampling also indicates that it is quite feasible to maintain workplace levels of RDX below 1.5 mg/m³ in these plants.

This study also failed to reveal any evidence that RDX work ex-

posure might be responsible for induction of SLE. The FANA screening test used in this study has been reported to be positive preceding the development of chemically-induced SLD.^{10, 11} An excess prevalence of positive FANA titers would have been expected in RDX exposed workers compared to controls if they were responsible for the development of SLE. This did not occur; in fact, the prevalence of positive FANA titers was actually found to be lower in exposed workers. Significant FANA titers have been reported to include those which are positive at dilutions of 1:160 or greater with a prevalence of 1/134 in normal blood donors.¹² The prevalence of significant titers in known or suspected cases of SLE was 19/24. Prevalence of significant FANA titers found by this study was 2/558 for RDX or HMX exposed employees and 2/863 for controls. This compares very closely to that found for normal blood donors.

Additional information on the three original cases of SLE at one plant also suggests that they are unrelated to exposure to RDX. Drug induced SLE is characterized by remission following discontinuation of the offending medication.¹¹ There was no remission of the disease in the three explosive workers who developed SLE following leave of absence from their jobs. If RDX had been responsible for the disease, clinical remission would have been expected. It appears that the three original cases of SLE were either coincidental or related to unknown factors other than RDX exposure at work.

Table 4. — Relationship Between Hemoglobin Values and RDX Exposure.

RDX Exposure	Mean Hb	Male		Female		
		No. Abnormal*	No. Normal	Mean Hb	No. Abnormal*	No. Normal
undetectable	14.7	3	19	13.9	0	1
0.01 mg/m ³ or over	15.2	4	41	13.8	0	25
not exposed	15.2	15	222	13.8	2	99

*Hb less than 14 gm/100 ml for males, less than 12 gm/100 ml for females.

Table 5. — Proportion of Abnormal Laboratory Determinations by RDX Exposure Category in Males.

Determination	Not Exposed	RDX EXPOSURE	
		Undetected	0.01 mg/m ³ or Over
Hb (< 14)*	15/237	3/22†	4/45
Hct (< 40)	1/237	1/22	1/45
Reticulocyte Count (> 1.5)	18/237	3/22	2/45
LDH (> 250)	2/237	1/22	0/45
ALK PHOS (> 105)	34/237	1/22	6/45
SGOT (> 35)	15/237	2/22	0/45
SGPT (> 35)	20/237	4/22	2/45
Bilirubin (> 1.0)	5/237	1/22	1/45

*Indicates abnormal range.

†Proportion of abnormal results to total number of individuals in exposure category.

Table 6. — Proportion of Abnormal Laboratory Determinations by RDX Exposure Category in Females.

Determination	Not Exposed	RDX EXPOSURE	
		Undetected	0.01 mg/m ³ or Over
Hb (< 12)*	2/101	0/1†	0/25
Hct (< 37)	4/101	0/1	0/25
Reticulocyte Count (> 1.5)	19/101	0/1	5/25
LDH (> 250)	11/101	0/1	1/25
ALK PHOS (> 105)	11/101	0/1	0/25
SGOT (> 35)	4/101	0/1	1/25
SGPT (> 35)	3/101	0/1	0/25
Bilirubin (> 1.0)	4/101	0/1	0/25

* Indicates abnormal range.

† Proportion of abnormal results to total number of individuals in exposure category.

Summary

Medical testing of RDX exposed workers failed to reveal any evidence of adverse health effects among workers with RDX exposures of up to 1.57 mg/m³ (0.28 mg/m³ average). This study particularly attempted to identify abnormalities of the hematologic, hepatic, and renal systems and the presence of autoimmune disease. No differences in the number of abnormalities of these systems between RDX exposed workers and unexposed controls were found, and unexposed controls had a higher (although not statistically significant) prevalence of positive tests for fluorescent antinuclear antibodies than exposed workers.

*Chromosorb Q is a registered trademark of Johns-Manville Products Corp., New York, N.Y.

†GasChrome Q is a registered trademark of Applied Science Laboratories, Inc., State College, Pa.

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Dysrhythmia — At the Base of Psychosomatic Ailments?

The study of metabolic rhythms and biological clocks is a fascinating field still in its infancy, but one with great potential to enhance our understanding of the biology of behavior — a subject with wide social ramifications. One possible though partial explanation for the current plague of psychosomatic ailments and stressful lives is that the culturally set pace of life in industrialized societies is frequently out of phase with its basic metabolic rhythms. The entire evolution of man took place while he was a hunter. The agricultural way of life accounts for less than one per cent of human history, and no biological changes seem to have occurred during the time. Thus, our bodies and the rhythms by which they oscillate are more or less the same as those of our remotest ancestors. But our societies and cultural determinants of behavior are quite obviously far from the same: hence the dysrhythmia.

— From "Medical Perspectives on Adulthood" by Herant A. Katchadourian in *The Journal of the American Academy of Arts and Sciences*, Spring, 1976.