Excess Hepatobiliary Cancer Mortality among Munitions Workers Exposed to Dinitrotoluene

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An analysis of the mortality experience of workers exposed to dinitrotoluene (DNT) was conducted to test the hypothesis that DNT exposure is associated with an increased risk of cancers of the liver and biliary tract. A total of 4,989 workers exposed to DNT and 7,436 unexposed workers who had worked for at least 5 months at the study facility between January 1, 1949 and January 21, 1980, were included in this investigation. Workers were considered exposed if they had worked at least 1 day on a job with probable exposure to DNT. The vital status as of December 31, 1982, was successfully ascertained for approximately 97% of these workers. Standardized mortality ratios (SMRs) were estimated based upon comparisons with the US population using a modified life-table program. In addition, standardized rate ratios (SRRs) were computed based upon direct comparisons between the DNT and the internal unexposed cohort. An excess of hepatobiliary cancer was observed among workers exposed to DNT in this study. The rate ratio for hepatobiliary cancer was 2.67 (six cases observed) based upon comparison with the US population (SMR = 2.67, 95% CI = 0.98, 5.83), and 3.88 based upon comparison using the internal unexposed referent group (SRR = 3.88, 95% CI = 1.04, 14.41). This study failed to demonstrate an exposure-response relationship between duration of DNT exposure and hepatobiliary cancer mortality. Our study was limited by the small number of workers with long duration of exposure to DNT, and by the lack of quantitative information on exposure to DNT and other chemicals. Nonetheless, the excess in hepatobiliary cancer mortality observed among DNT-exposed workers in this study is similar to the findings from experimental studies of DNT-exposed animals. On balance, we believe that our findings add some support for the hypothesis that occupational exposure to DNT may be carcinogenic.

Dinitrotoluene (DNT) is used in the production of dyes, propellants, explosives, and as an intermediate in the synthesis of toluenediamine. Chronic feeding studies in rats using technical grade DNT have demonstrated a statistically significant increase in the incidence of hepatocarcinomas, bile duct carcinomas, and subcutaneous fibrosarcomas.[1] A significant excess of hepatocellular carcinomas has been reported in rats fed the purified 2,6-DNT isomer,[2] whereas similarly designed studies using the purified 2,4-DNT isomer resulted in a statistically significant excess of liver cancer in one study,[3] and no significant excess of liver cancer in two other studies.[4,5] Technical grade DNT consists of approximately 76% 2,4-DNT isomer, 19% 2,6-DNT isomer and 5% of the remaining four isomers.[6] Thus, the 2,6-DNT isomer appears to be a potent hepatocarcinogen in rodents, whereas the evidence for the hepatocarcinogenicity of the 2,4-DNT isomer is weak.

Only one epidemiologic study of DNT-exposed workers, which was designed to examine the association between hepatobiliary cancer and DNT exposure, has been reported to date. Levine and co-workers at the Chemical Industry Institute of Toxicology (CIIT) conducted a retrospective cohort mortality study of workers exposed to DNT at two plants that produced munitions for the US Army.[7] One of the facilities included in the CIIT study was the subject of our investigation. Although the CIIT study failed to detect an excess at any cancer site, a statistically significant excess in mortality from ischemic heart disease was unexpectedly observed.

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Following is a report of a retrospective cohort mortality study of workers exposed to DNT at a munitions facility. This cohort was identified in an earlier study designed primarily to examine the relationship between ischemic heart disease and exposure to nitroglycerin and DNT, the results of which have been previously reported.[8]

Materials and Methods

The study population was identified from current and former white male workers who were employed at the US Army munitions facility in Radford, Virginia. The study facility was constructed in 1940 for the production of munitions and rocket motors. The work force and production has varied greatly, reaching a peak during World War II and shutting down between 1946 and 1948. The plant has been in continual operation since the start of the Korean conflict in 1949. There are three basic production lines at this facility which produce: 1) single base propellants containing nitrocellulose, and DNT, 2) double-base propellants containing nitrocellulose, and nitroglycerine, and 3) triple-base propellants containing nitrocellulose, nitroglycerine, and nitroguanidine. Trinitrotoluene (TNT) was also produced in a separate building between 1968 and 1974, and was not used in the production of propellants.

Quantitative information on the past or present levels of DNT exposure was unfortunately not available for this facility. Greater weight was given towards documenting exposures to nitroglycerin exposures in this investigation, inasmuch as this was the primary exposure of concern when this study was initiated. Furthermore, evaluation of DNT exposure would be problematic given the potential for dermal as well as respiratory absorption, and changes in work practices and the production process over time at the study facility. Therefore, it was not possible to quantitatively estimate DNT exposures for this analysis. Instead, we developed a qualitative system for evaluating the potential for exposure to DNT as described below.

A listing of all unique jobs that occurred more than once in the study computer file was created. This listing was reviewed by National Institute of Occupational Safety and Health industrial hygienists with the assistance of company and union representatives. Each job was rated concerning the probability of exposure (probably exposed, possibly exposed, or definitely unexposed) to DNT. Jobs classified as probably exposed were clearly located in a production area that processed materials containing DNT. Some job titles were clearly unique to the areas that processed DNT-containing materials, whereas for others knowledge of the production line was needed to make an exposure determination. (Any job located on the single base line was considered to be probably exposed to DNT.) Jobs which could not be clearly determined to be in an area that did or did not use DNT were classified as possibly exposed to DNT. All other jobs were classified as definitely unexposed to DNT.

All white male workers who had been employed for at least 5 months at the facility from January 1, 1949 to January 21, 1980 were identified from the company personnel records for inclusion in the study. Women and nonwhites represented a small percentage of the work force at this facility, and were thus excluded from the study to avoid unstable rates. Based upon the exposure classification system described above, the following two subcohorts were identified: 1) workers who had been employed for at least 1 day in a job with probable exposure to DNT, and 2) workers who had never been employed in a job with either possible or probable DNT exposure (unexposed). Workers who had been employed in jobs with possible exposure to DNT (and had not worked in a job with probable exposure) were excluded from the analysis, because of their ambiguous exposure history.

A computer master file was created for these cohorts containing demographic and work history information. Detailed work histories were coded only for individuals in the DNT subcohort (probable exposure) which included dates, propellant lines (single, double, or triple) when applicable, and job codes for all position changes at the facility. Only general work histories (first and last date of employment) were coded for the unexposed cohort. Work histories, which occurred before the study begin date (1/1/49), were used in the calculation of duration of exposure to DNT, although person-years were not counted before this date. Separate analyses were performed in which jobs with "possible" exposure to DNT were either included or not included in the calculation of the total duration of exposure to DNT.

The vital status of the cohort members was ascertained through linkage with records from the following sources: Social Security Administration, Internal Revenue Service, local post offices, and state motor vehicle departments. Through these sources, the vital status of the study population was ascertained up to December 31, 1982. Death certificates were obtained for deceased individuals from state vital statistics bureaus, and coded by a trained nosologist using the International Classification of Diseases (ICD) revision in effect at the time of death. A personal location service was also used to locate some of the more difficult cases to obtain death certificates.

Indirect comparisons between the mortality experience of the study population and the US population were made using a life-table program developed by the National Institute of Occupational Safety and Health.[9] This program computes expected numbers of deaths by multiplying cause, 5-year age group, and 5-year calendar time-specific mortality rates for white males in the US population by the corresponding person-years distribution of the study population. Person-years for the DNT cohort was calculated from the study begin date (1/1/49) or from the time an individual had been employed for at least 5 months at the facility and had worked at least 1 day in an exposed operation, whichever occurred later. Person-years for the nonexposed cohort were calculated from the study begin date (1/1/49) or from the time an individual had been employed for 5 months at the facility, whichever occurred

later. Person-years for both cohorts were calculated until the end of the study (12/31/82) for survivors, or until the individual was lost to follow-up for those not successfully traced through 1982, or until the date of death for those who died before the end of the study, whichever came first. SMRs were calculated by dividing the observed number of deaths by the number expected. Exact statistical tests (two-sided) and associated 95% confidence intervals (CI) were estimated based upon the Poisson distribution.[10]

Direct comparisons were made between the mortality rates of the DNT-exposed and the unexposed cohorts for cancers of the liver and biliary passages. Directly SRRs were computed using the age and calendar time distribution of the person-years of the entire study population as the factor for weighing the stratum-specific rates. A modification of the Mantel-Haenszel procedure was used for computing χ^2 test statistics and associated two-sided P-values based upon the assumption of a binomial distribution for the observed number of deaths.[11] Test-based 95% CI were computed for the SRRs.[12]

Results

A total of 4,989 and 7,436 workers met our criteria for inclusion in the DNT and nonexposed cohorts, respectively. The results from follow-up of these cohorts are presented in Table 1. We were able to successfully identify the vital status of approximately 97% of the workers in both cohorts. Despite an intensive search, death certificates could not be obtained for 10 out of 747 deaths (1.3%) from the DNT cohort, and 28 out of 1,602 deaths (1.7%) from the unexposed cohort. The percentage of deaths was somewhat larger among the unexposed cohort (21.5%) than among the DNT cohort (15.0%). This difference may be explained by the older age distribution of the unexposed cohort relative to the DNT cohort. On average, the unexposed cohort was approximately 3 years older at the time of hire and at the end of the study (date last observed), although these differences were not statistically significant based on a Student's t-test ($P > .05$).

The results from comparing the mortality rates of the DNT cohort to that of the US population for all causes and for malignant causes of death are presented in Table 2. Overall cancer mortality was observed to be less than expected for both the DNT (SMR = 0.84, 95% CI = 0.70, 1.00) and nonexposed (SMR = 0.78, 95% CI = 0.69, 0.88) cohorts. A borderline significant (P = .052, two-tailed) excess of cancer of the "biliary passages, liver and gall bladder" (henceforth referred to as hepatobiliary cancer) was observed among the DNT cohort (SMR = 2.67, 95% CI = 0.98, 5.83). Using the unexposed group as the referent, the directly SRR for hepatobiliary cancer among DNT-exposed workers was 3.88 (95% CI = 1.04, 14.41) and statistically significant (P = .04). One case of liver cancer for which the primary site was unspecified was observed among the DNT (1.07 expected) and unexposed (0.40 expected) cohorts. Deaths of this type are coded separately from hepatobiliary cancers, because they may be metastatic tumors from another site. An additional case of biliary cancer was known to have occurred after the study end date in a DNT-exposed worker.

The results from the life-table analysis for hepatobiliary cancer among DNT-exposed workers stratified by age and calendar year at risk are presented in Table 3. Hepatobili-

TABLE 1
Cohort Vital Status as of December 31, 1982

Vital Status	DNT Cohort		Nonexposed Cohort	
	n	%	n	%
Alive	4,102	82.2	5,610	75.4
Deceased	747	15.0	1,602	21.5
Unknown	140	2.8	224	3.0
Total	4,989	100.0	7,436	100.0

TABLE 2
SMRs and 95% CI for All Causes and Selected Cancer Sites among the DNT and Unexposed Cohorts

Cause of Death (ICD9*)	DNT Cohort		Unexposed Cohort	
	Observed	SMR (95% CI)	Observed	SMR (95% CI)
All causes	747	1.02 (0.97–1.09)	1602	1.04 (0.99–1.10)
All malignancies	128	0.84 (0.70–1.00)	249	0.78† (0.69–0.88)
Mn buccal and pharynx (140–140)	2	0.40 (0.05–1.47)	12	1.18 (0.61–2.08)
Mn biliary, liver, and gall bladder (155, 156)	6	2.67† (0.98–5.83)	4	0.81 (0.22–2.09)
Mn liver primary unspecified (197.8)	1	0.93 (0.02–5.21)	1	0.40 (0.01–2.26)
Mn respiratory system (160–163.9)	48	0.85 (0.63–1.14)	104	0.91 (0.75–1.11)
Mn male genital organs (185–187, 172.5, 173.5)	7	(0.42–2.14)	15	(0.41–1.21)
Mn urinary organs (188, 189.0–189.3, 189.9)	7	0.93 (0.37–1.93)	11	0.65 (0.43–1.18)
Mn lymphopoietic (200–207)	19	1.19 (0.72–1.87)	26	0.82 (0.54–1.21)
Mn all other sites	38	0.67 (0.48–0.92)	76	0.64 (0.50–0.80)

$P < 0.05$ (two-tailed)

* Deaths codes from the International Classification of Diseases (ICD) 9th Revision are presented in parenthesis under the specific death categories.
† P = .052 (two-tailed).

TABLE 3
SMRs, Observed and Expected, and Person-Years from the DNT Cohort for Cancers of the Liver, Biliary Passages, and Gall Bladder Stratified by Age and Calendar Year at Risk*

Variable	Observed	Expected	Person-Years	SMR
Age at risk				
<50	1	0.40	72,663	2.48
50 to 59	2	0.76	17,924	2.63
60 to 69	1	0.75	6,606	1.34
≥70	2	0.33	1,479	6.33
Year at risk				
<1960	0	0.12	16,012	0
1960 to 1969	3	0.48	26,897	6.25*
1970 to 1979	0	1.14	43,480	0
1980 to 1982	3	0.51	12,283	5.93*

* $P < .05$ (two-tailed).

ary cancer mortality was greatest among workers over 70 years of age (SMR = 6.33, 95% CI = 0.73, 21.89). Statistically significant elevations in hepatobiliary cancer mortality were observed among exposed workers at risk during the 1960s (SMR = 6.25, 95% CI = 1.29, 18.26), and during the most recent (1980 or later) study time period (SMR = 5.93, 95% CI = 1.21, 17.19).

The results from stratifying the life-table analysis by duration of exposure and time since first exposure are presented in Table 4. Hepatobiliary cancer mortality was greatest among DNT-exposed workers 10 to 19 years after their first exposure (SMR = 4.19, 95%CI = 0.87, 12.35), and lowest among workers 20 years after their first exposure (SMR = 1.75, 95% CI = 0.21, 6.34). There was no evidence of an increasing trend in hepatobiliary cancer mortality with duration of exposure. In fact, a significantly elevated SMR was observed for workers in the shortest duration (<1 year) of exposure group (SMR = 4.01, 95% CI = 1.09, 10.24). It is noteworthy that only 7% (6,430/98,673) of the cohort person-years were in the 5 or more years of DNT-exposure category. Only jobs with probable exposure to DNT were counted for estimating duration of exposure for the analysis presented in Table 4. However, an alternative analysis was performed in which jobs with "possible" exposure as well as jobs with "probable" exposure to DNT were counted for estimating duration of exposure. The results from this alternative analysis (data not shown) also demonstrated significantly increased risk among short duration (< 1 year) of exposure workers, and were otherwise similar to the results from the analysis presented in Table 4.

TABLE 4
SMRs, Observed and Expected Deaths by Duration of Exposure and Time since First Exposure

Time since First Exposure (years)	Duration of Exposure to DNT (years)			Total
	<1	1-<5	>5	
0-<10				
Observed	1	0	0	1
Expected	0.19	0.18	0.02	0.38
SMR	5.31	0	0	2.56
10-<20				
Observed	1	1	1	3
Expected	0.32	0.32	0.07	0.71
SMR	3.13	3.11	13.42	4.19?*
≥20				
Observed	2	0	0	2
Expected	0.49	0.52	0.13	1.14
SMR	4.07	0	0	1.75
Total				
Observed	4	1	1	6
Expected	1.00	1.02	0.23	2.24
SMR	4.01*	0.98	4.37	2.67†

* $P < .05$ (two-tailed).
† $P = .052$ (two-tailed).

The primary cancer site and other characteristics of the six hepatobiliary cancer cases are summarized in Table 5. We were able to obtain hospital pathology and other records for five of the six hepatobiliary cancer cases exposed to DNT. Based on a review of these records, the primary cancer site appeared to be the liver in two cases, hepatic bile duct in two cases, and gall bladder with direct extension to the hepatic bile duct in one case. According to the death certificate, the sixth case was a cancer of the common hepatic bile duct. According to hospital records, one of the liver cancer cases had previously developed cirrhosis of the liver and posttransfusion hepatitis. It is noteworthy that five of the six hepatobiliary cases were first exposed to DNT during the early 1950s.

Discussion

An excess of liver and biliary cancers was observed among DNT-exposed workers in this study. This excess was statistically significant when comparison was made with an internal referent group of workers and nearly statistically significant based upon comparisons with the US population. Greater weight should probably be given to the analysis based upon the internal referent group, inasmuch as this group is likely to be more similar to the DNT cohort in terms of other risk factors for hepatobiliary cancer than the US general population.

Our study has several limitations, some of which are related to the fact that this investigation was originally designed to evaluate the risks associated with nitroglycerin exposure rather than DNT exposure. The small number of hepatobiliary cancer cases and the small percentage of workers with long duration of exposure to DNT obviously limited the statistical power of our analyses. Of particular concern is the lack of quantification of DNT exposure levels experienced by workers in our study. DNT is absorbed through the skin, as well as through the respiratory tract, which makes the evaluation of exposure potential problematic. In 1942, a clinical cross-sectional study of DNT workers at our study facility revealed that 23%

TABLE 5
Summary of Characteristics of the DNT-Exposed Cases of Liver and Biliary Cancer

Year First Exposed	Duration of Exposure*	Time since First Exposure*	Primary Cancer Site
1970	1.5	31.1	Hepatic bile duct†
1952	0.1	29.6	Hepatocarcinoma‡
1953	0.2	9.9	Common bile duct‡
1954	0.3	15.5	Gall bladder‡
1953	0.2	28.8	Bile duct‡
1951	3.2	14.0	Hepatocarcinoma‡

* Units are years.
† Death certificate diagnosis.
‡ Hospital or pathology record diagnosis.

(36/154) of the workers suffered from anemia and two workers (1.4%) had acute toxic hepatitis, which are likely sequelae from overexposure to DNT.[13] Many of the jobs that were classified as "probably" exposed in this investigation were only known to involve contact with materials containing DNT, and the potential for DNT exposure for many of these jobs was probably minimal. The effect of including workers from these jobs in our study was to make it more difficult for the study to detect an excess risk (ie, bias towards the null hypothesis). Thus, the potential for inclusion of workers with minimal exposure to DNT is an unlikely explanation for the observed excess of liver cancer in our study.

Another limitation of our investigation is the fact that the DNT and unexposed cohorts may have been potentially exposed to a large number of other chemicals used at this facility. Of particular concern is exposure to tetranitromethane, a by-product in the production of TNT, and *N*-nitrosodiphenylamine, which is used in the production of single-based propellants containing DNT. The National Toxicology Program has recently reported an increased incidence of lung tumors in rodents fed tetranitromethane.[14] TNT was produced in a separate building at our study facility and was not used in the production of propellants containing DNT. Thus, it is unlikely that our DNT cohort was more exposed to tetranitromethane than the unexposed cohort, and therefore tetranitromethane was probably not a confounder in our study. An increased incidence of urinary bladder carcinomas has been reported in experimental studies of rats fed *N*-nitrosodi-phenylamine.[15] Although neither of these chemicals were associated with hepatobiliary cancer, it is possible that exposure to these or other chemicals used at this facility might have influenced our findings.

The biologic plausibility of our findings are supported by the excess of hepatobiliary carcinomas observed experimentally in rats exposed to DNT.[1,2] It should be noted that a purified form of DNT containing approximately 98% 2,4-DNT and 2% 2,6-DNT was used at the study facility. Inconsistent results have been obtained from rodent-feeding studies using the 2,4-DNT isomer. A statistically significant increased incidence of hepatocellular carcinoma was observed in a US Army-sponsored study in which rats were fed DNT containing 98% 2,4-DNT and 1.7% 2,6-DNT,[3] which is similar to the mixture used at the study facility. A statistically nonsignificant increase in hepatocellular carcinoma was observed in a study of male rats (but not female rats) fed purified (99%) 2,4-DNT.[4] Finally, hepatobiliary cancers were not observed in a study of rats fed highly purified (99.9%) 2,4-DNT.[2]

The lack of a dose-response relationship between duration of DNT exposure and hepatobiliary cancer mortality, may argue against a causal interpretation for our findings. However, approximately 93% of the DNT cohort person-years had less than 5 years of exposure to DNT. Thus, this study had limited statistical power to detect a dose-response trend. It is also conceivable that intensity, rather than duration, of DNT exposure is more etiologically relevant for the development of hepatobiliary cancers. If short-term workers at this facility experienced more intense exposures to DNT than long-term workers, then one might expect to see an inverse trend with duration of exposure as was seen in this study.

Our study findings are inconsistent with a previous study of workers exposed to DNT by Levine and coworkers at the CIIT.[7] The CIIT study failed to detect any cases of liver or biliary cancer, but did report an excess in mortality from ischemic heart disease. In our study, we observed an excess of hepatobiliary cancer, and as previously reported, we did not observe excess of ischemic heart disease among DNT-exposed workers.[8] This inconsistency is somewhat surprising given the fact that our study facility was one of the two facilities included in the CIIT study. However, our study and the CIIT study had different criteria for identifying DNT-exposed workers. The CIIT study only included "highly" exposed workers, whereas our study included all workers with exposure to DNT. Furthermore, the CIIT study included workers employed at the facility between 1940 and 1959, whereas our study included workers employed between 1949 and 1980. Based on these inclusion criteria, the CIIT study only identified 301 workers for inclusion in their study, whereas we identified 4,989 DNT-exposed workers for inclusion in our study. The fact that our study was larger, and hence more powerful statistically, might explain why our study was able, and the CIIT study was unable, to detect an excess of hepatobiliary cancer. However, to a large extent, the increase in sample size in our study was achieved by including workers with minimal exposures, which should have reduced rather than increased statistical power.

Hepatitis B virus is the major established risk factor for primary hepatocellular carcinoma, although cirrhosis and chronic hepatitis injury from aflatoxin, alcoholism, parasitic infections, and hormone ingestion have

also been associated.[16] There was no evidence of gallstones in the medical records of the biliary cancer cases exposed to DNT in this study. According to hospital reports, one of the exposed liver cancer cases had previously developed posttransfusion hepatitis and cirrhosis, which may have contributed to the development of liver cancer in this case. However, hepatitis was not described in the medical records of any of the other liver or biliary cancer cases observed among the DNT cohort, and is thus unlikely to explain our findings. A significant excess in mortality from alcoholism (ICD, 8th Revision, 303) was observed in both cohorts. This association was slightly stronger in the nonexposed cohort (SMR = 2.78, 95% CI = 1.65, 4.40) than in the DNT cohort (SMR = 2.40, 95% CI = 1.10, 4.56). Surprisingly, mortality from cirrhosis of the liver, a disease strongly associated with alcohol consumption and liver cancer, was less than expected and similar in the DNT (SMR = 0.81, 95% CI = 0.51, 1.28) and nonexposed (SMR = 0.82, 95% CI = 0.58, 1.28) cohorts. Given the similarity in the mortality rates for alcoholism and cirrhosis between the two cohorts, these factors are unlikely to have confounded our findings, although the possibility of an interaction between alcohol and DNT exposure cannot be excluded. There is also little evidence that other known risk factors for hepatic and biliary cancers could be responsible for the excess of hepatobiliary cancers observed in our study.

In conclusion, we have observed an excess of liver and biliary cancer among workers exposed to DNT in this study. This excess was nearly statistically significant based upon comparison with the US population, and statistically significant based upon a more relevant comparison with an internal referent group. Our study was limited by the small number of workers with long duration of exposure to DNT, and by the lack of quantitative information on exposure to DNT and other chemicals. Nonetheless, the excess in hepatobiliary cancer mortality observed among DNT exposed workers in this study is similar to the findings from experimental studies of DNT exposed animals. On balance, we believe that our findings add some support for the hypothesis that occupational exposure to DNT may be carcinogenic.

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