## 2, 4, 6-Trinitrotoluene (TNT)

This is a compilation of all positive and null cancer epidemiology studies and animal cancer bioassays identified during the preliminary toxicological evaluation of 2,4,6-trinitrotoluene (TNT), as well as some genotoxicity studies and reviews. TNT is used as a high explosive in military and industrial applications. Exposure to TNT may occur during its production, in munitions manufacture and loading, and during blasting operations. Exposure to water or soil contaminated by discarded munitions or manufacturing waste may also occur.

## **Epidemiological data**

Residential exposure in an area with severe soil and water contamination by TNT due to manufacture of explosives

- Case-control study of leukemia: Kilian et al. (2001)
- Descriptive study of leukemia: Kolb et al. (1993)

## Occupational exposure of male ordnance factory workers

• Case-control study of hematological abnormalities: West and Stafford (1997)

#### Animal carcinogenicity data

### Two-year animal bioassays of TNT in diet

- Fischer 344 rats: Army (1984a)
- B6C3F<sub>1</sub> mice: Army (1984b)

## **Other relevant data**

- Genotoxicity evidence, a review and some examples:
  - o IARC (1996) genetic toxicity summary table
  - o Frameshift mutagen in *Salmonella* strain TA-98 & TA100 (Won *et al.*, 1976; Tan et al., 1992)
  - o Mouse lymphoma gene mutation assay (Styles and Cross, 1983)
  - o Chinese hamster ovary cell mutation assay (Kennel et al., 2000).
  - o Chromosomal aberrations in exposed workers carrying the *NAT1* rapid aceylator genotype (Sabbioni et al., 2007)
- Hemoglobin adducts
  - o Health effects in exposed workers (Sabbioni et al., 2005)
  - o Biomarkers of exposure (Liu et al., 1995; Sabbioni et al., 2006)
- Reviews
  - o Bolt et al. (2006)
  - o IARC (1996) [IARC's review did not include the animal bioassays of Army (1984a, 1984b) or the case control studies of West and Stafford (1997) and Kilian et al. (2001).]

# References<sup>1</sup>

Army (1984a). Determination of the chronic mammalian toxicological effects of TNT: Twenty-four month chronic toxicity/carcinogenicity study of trinitrotoluene (TNT) in the Fischer 344 rat. Final report: Phase III. Contract no. DAMD17-79-C-9120. Frederick MD: U.S. Army Medical Research and Development Command, Fort Detrick. Document no. AD-A168 637.

Army (1984b). Determination of the chronic mammalian toxicological effects of TNT: Twenty-four month chronic toxicity/carcinogenicity study of trinitrotoluene (TNT) in the B6C3F1 hybrid mouse. Final report: Phase IV. Contract no. DAMD17-79-C-9120. Frederick MD: U.S. Army Medical Research and Development Command, Fort Detrick. Document no. AD-A168 754.

Bolt HM, Degen GH, Dorn SB, Plöttner S, Harth V (2006) Genotoxicity and potential carcinogenicity of 2,4,6-TNT trinitrotoluene: structural and toxicological considerations. Reviews on environmental health. Oct-Dec; 21(4):217-28.

International Agency for Research on Cancer (IARC, 1996). IARC Monographs on the evaluation of carcinogenic risks to humans. Vol 65: Printing processes and printing inks, carbon black and some nitro compounds. Pp. 449-475,

Kennel SJ, Foote LJ, Morris M, Vass AA, Griest WH (2000). Mutation analyses of a series of TNT-related compounds using the CHO-hprt assay. J Appl Toxicol 20(6):441-8

Kilian PH, Skrzypek S, Becker N, Havemann K (2001). Exposure to armament wastes and leukemia: a case-control study within a cluster of AML and CML in Germany. Leuk Res. Oct;25(10):839-45.

Kolb G, Becker N, Scheller S, Zugmaier G, Pralle H, Wahrendorf J, Havemann K (1993). Increased risk of acute myelogenous leukemia (AML) and chronic myelogenous leukemia (CML) in a county of Hesse, Germany. Soz Praventivmed 38(4):190-5.

Liu YY, Yao M, Fang JL, Wang YW (1995). Monitoring human risk and exposure to trinitrotoluene (TNT) using haemoglobin adducts as biomarkers. Toxicol Lett., May; 77(1-3):281-7.

Sabbioni G, Jones CR, Sepai O, Hirvonen A, Norppa H, Järventaus H, Glatt H, Pomplun D, Yan H, Brooks LR, Warren SH, Demarini DM, Liu YY (2006). Biomarkers of exposure, effect, and susceptibility in workers exposed to nitrotoluenes. Cancer Epidemiol Biomarkers Prev. Mar;15(3):559-66.

<sup>&</sup>lt;sup>1</sup> Copies of these listed references, as either the abstract or the complete publication, have been provided to members of the Carcinogen Identification Committee. The abstracts or papers have been provided in the order in which they are discussed in this document; they have not been ordered alphabetically.

Sabbioni G, Liu YY, Yan H, Sepai O. (2005). Hemoglobin adducts, urinary metabolites and health effects in 2,4,6-trinitrotoluene exposed workers. Carcinogenesis. 2005 Jul;26(7):1272-9. Epub 2005 Apr 7.

Sabbioni G, Sepai O, Norppa H, Yan H, Hirvonen A, Zheng Y, Järventaus H, Bäck B, Brooks LR, Warren SH, Demarini DM, Liu YY (2007). Comparison of biomarkers in workers exposed to 2,4,6-trinitrotoluene. Biomarkers. Jan-Feb;12(1):21-37.

Styles JA, Cross MF (1983). Activity of 2,4,6-trinitrotoluene in an in vivo mammalian gene mutation assay. Cancer Lett 20(1):103-8.

Tan EL, Ho CH, Griest WH, Tyndall RL (1992). Mutagenicity of trinitrotoluene and its metabolites formed during composting. J Toxicol Environ Health 36: 165-175.

Won WD, DiSalvo LH, Ng J (1976). Toxicity and mutagenicity of 2,4,6-trinitrotoluene and its microbial metabolites.