2,4,6-TRINITROTOLUENE

1. Exposure Data

1.1 Chemical and physical data

1.1.1 *Nomenclature*

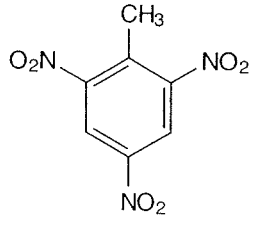
Chem. Abstr. Serv. Reg. No.: 118-96-7

Chem. Abstr. Name: 2-Methyl-1,3,5-trinitrobenzene

IUPAC Systematic Name: 2,4,6-Trinitrotoluene

Synonyms: Methyltrinitrobenzene; 1-methyl-2,4,6-trinitrobenzene; TNT; α-TNT; trinitrotoluene; α-trinitrotoluol; s-trinitrotoluene; s-trinitrotoluol; *sym*-trinitrotoluene; *sym*-trinitrotoluol

1.1.2 *Structural and molecular formulae and relative molecular mass*



$C_7H_5N_3O_6$ Relative molecular mass: 227.13

1.1.3 *Chemical and physical properties of the pure substance*

(*a*) *Description*: Yellow monoclinic needles or orthorhombic crystals from alcohol (Lewis, 1993; Lide, 1993)

(*b*) *Boiling-point*: 240 °C (explodes) (Lide, 1993)

(*c*) *Melting-point*: 82 °C (Lide, 1993)

(*e*) *Spectroscopy data*: Infrared (prism [21886], grating [32803]), nuclear magnetic resonance (C-13 [18215, V486]) and mass spectral data have been reported (Sadtler Research Laboratories, 1980)

(*e*) *Solubility*: Slightly soluble in water (0.01% (0.10 g/L) at 25 °C); soluble in acetone, benzene, oils and greases, and diethyl ether (McConnell & Flinn, 1946; Budavari, 1989; Lide, 1993)

(*f*) *Volatility*: Vapour pressure, 0.0002 mm Hg [0.027 Pa] at 20 °C; relative vapour density (air = 1), 7.85 (Verschueren, 1983; Boublík *et al.*, 1984)

(*g*) *Stability*: Moderate explosion risk; the pure chemical will detonate only if vigorously shocked or heated to > 200 °C (Lewis, 1993). Reacts with nitric acid and metals (e.g. lead or iron) to form explosive products more sensitive to shock or friction. Bases (e.g. sodium hydroxide, potassium iodide, tetramethyl ammonium octahydrotriborate) induce deflagration in molten trinitrotoluene. Can react vigorously with reducing materials (Sax & Lewis, 1989).

(*h*) *Octanol/water partition coefficient (P)*: log P, 1.60 (Hansch *et al.*, 1995)

(*i*) *Conversion factor*: $mg/m^3 = 9.29 \times ppm$[1]

1.1.4 *Technical products and impurities*

2,4,6-Trinitrotoluene is available commercially in the following forms: dry or wetted with < 10%, < 30% or > 30% water by weight. Military-grade flaked trinitrotoluene is available with the following specifications: setting-point, 80.2 °C; water, 0.10% max.; acidity (as H_2SO_4), 0.02% max.; alkalinity, none; materials insoluble in benzene, 0.05% max.; and sodium, 0.001% max. Commercial-grade trinitrotoluene (Nitropel) is available with the following specifications: setting-point, 80.1 °C; and water, 1.2% max. (United States National Library of Medicine, 1995; ICI Explosives Canada, undated).

Trade names for 2,4,6-trinitrotoluene include Entsufon, Gradetol, Nitropel, Tolit, Tolite, Trilit, Tritol, Trotyl and Trotyl oil.

1.1.5 *Analysis*

Selected methods for the analysis of 2,4,6-trinitrotoluene in various media are presented in Table 1.

Table 1. Methods for the analysis of 2,4,6-trinitrotoluene

Sample matrix	Sample preparation	Assay procedure	Limit of detection	Reference
Air	Draw air through modified Tenax-GC tube; desorb with acetone	GC/TEA	21 µg/m³	US Occupational Safety and Health Administration (1990) [Method 44]
	Draw air through glass wool–charcoal; desorb with benzene	GC/ECD	< 0.05 ppb [< 5 µg/m³]	Pella (1976)
	Direct incorporation of sample into glow discharge chamber	GDMS	~1.4 ppt [13 ng/m³]	McLuckey *et al.* (1988)
	Direct incorporation of sample into reaction chamber	IMS	0.01 ppb	Spangler *et al.* (1983)

[1]Calculated from: mg/m^3 = (relative molecular mass/24.45) × ppm, assuming temperature (25 °C) and pressure (101 kPa)

Table 1 (contd)

Sample matrix	Sample preparation	Assay procedure	Limit of detection	Reference
Incinerator emission	Draw air through Amberlite XAD-2; desorb with toluene	GC/ECD	0.025 µg/mL	Van Slyke *et al.* (1985)
Water	Collect sample on SEP-PAK cartridges and elute with methanol; concentrate; elute from reverse-phase column with methanol/water	HPLC/UV	0.5–1.0 µg/L	Kaplan & Kaplan (1981)
	Extract sample with dichloromethane or adsorb on Amberlite XAD resin and elute with dichloromethane	GC/ECD	NR	Feltes *et al.* (1990)
	Extract sample with toluene	GC/ECD	0.06 µg/L	Hable *et al.* (1991)
	Solid-phase extraction	HPLC	0.1 µg/L	Roberts (1986)
	Collect sample on Amberlite XAD-2/4/8; dry; desorb with dichloromethane; dry over anhydrous Na_2SO_4; exchange solvent to methanol; concentrate; elute from reverse-phase column with methanol/water	HPLC/UV	50 ng/L	Feltes & Levsen (1989)
	Collect sample on Hayesep-R; elute with acetone; concentrate; add internal standard; exchange solvent to methanol/water	HPLC/UV/PC	1 µg/L	US Army (1989)
Wastewater, groundwater	Dilute sample with methanol/acetonitrile; filter; elute from reverse-phase column with methanol/acetonitrile/water	HPLC/UV	14 µg/L	Jenkins *et al.* (1984)
Soil	Air dry, grind, homogenize sample; extract with acetonitrile in ultrasonic bath; dilute with aqueous $CaCl_2$; filter; elute from reverse-phase column with methanol/water	HPLC/UV	0.08 µg/g	Jenkins *et al.* (1989); Bauer *et al.* (1990)
	Extract with methanol; filter extract; add $CaCl_2$ and refilter; pump through indicator tube	Indicator tube	0.5 µg/g	Jenkins & Schumacher (1990)
	Extract with acetone; react supernatant with potassium hydroxide/sodium sulfite; read absorbance at 540 nm	Colorimetry	1 µg/g	Jenkins & Walsh (1992)
Urine	Acidify sample to hydrolyse; neutralize and extract with toluene; add Na_2SO_4 and filter; evaporate and redissolve in acetone or acetonitrile	HPLC/MS	0.1 µg/L	Yinon & Hwang (1985, 1986a)

Table 1 (contd)

Sample matrix	Sample preparation	Assay procedure	Limit of detection	Reference
Urine (contd)	Acidify and heat sample; neutralize and extract with diethyl ether; evaporate and redissolve in acetone; develop silica gel plate with benzene/diethyl ether/methanol	TLC/ if possible densito-metry	100 ng/spot	Liu *et al.* (1991)
Blood	Centrifuge sample; dilute serum with water; extract with dichloromethane; centrifuge and add Na_2SO_4; filter and evaporate; redissolve in dichloromethane; evaporate and redissolve in acetonitrile	HPLC/MS	NR	Yinon & Hwang (1986b)
Plasma, kidney	Add NaCl/acetic acid solution to sample; extract with toluene; add water and evaporate organic phase; add acetonitrile containing internal standard; filter	HPLC/UV	248 µg/L (plasma) 211 ng/g (kidney)	Lakings & Gan (1981)
Muscle, fat	Homogenize sample; extract with acetonitrile; concentrate; add internal standard and water; filter	HPLC/UV	66 ng/g	Lakings & Gan (1981)
Liver	Homogenize sample; add NaCl/acetic acid solution; extract with toluene; evaporate and redissolve in acetonitrile containing internal standard; filter	HPLC/UV	50 ng/g	Lakings & Gan (1981)
Handswabs	Wipe hand with swab soaked in acetone; squeeze out acetone and concentrate	HPLC/TEA	10 pg	Fine *et al.* (1984)
	Wipe hand with swab soaked in MTBE and extract with MTBE in pentane; centrifuge to remove debris; clean-up on Amberlite XAD-7 and elute with ethyl acetate	GC/ECD	< 2 ng/swab	Douse (1985, 1987); Douse & Smith (1986)
	Wipe hand with swab soaked in ethanol; extract in water/buffer solution with vortexing; add aliquots to antibody-coated microtitre plates	ELISA	15 ng/swab	Fetteroff *et al.* (1991)

GC, gas chromatography; TEA, thermal energy analysers; ECD, electron capture detection; GDMS, glow-discharge mass spectrometry; IMS, ion-mobilization spectrometry; HPLC, high-performance liquid chromatography; UV, ultraviolet detection; NR, not reported; PC, photoconductivity detection; MS, mass spectrometry; TLC, thin-layer chromatography; MTBE, methyl *tert*-butyl ether; ELISA, enzyme-linked immunosorbent assay

1.2 Production and use

1.2.1 *Production*

2,4,6-Trinitrotoluene has been produced by nitration of toluene with 'mixed acid' (HNO_3 and H_2SO_4) either in three steps or by continuous flow according to the Schmid-Meissner and Biazi processes. Small amounts of the 2,3,4- and 2,4,5-isomers are produced, which can be removed by washing with aqueous sodium sulfite solution. The Bofors-Norell process includes both continuous nitration of toluene or mononitrotoluene to trinitrotoluene, and continuous crystallization from dilute nitric acid (Ryon, 1987; Budavari, 1989; Lewis, 1993).

Typically, the production process begins with continuous nitration of toluene and the subsequent crystallization of 2,4,6-trinitrotoluene. The product is then washed and neutralized and then dried in a tank at up to 100 °C. Dry 2,4,6-trinitrotoluene is crushed and flaked and packed in cloth or containers. A small fraction of total trinitrotoluene production is further distilled, washed, dried and packed (ICI Explosives Canada, undated).

2,4,6-Trinitrotoluene is produced by two companies in Japan, and one company each in Argentina, Brazil, Canada, China, Egypt, Finland, Portugal, Taiwan, Turkey and the United Kingdom (Chemical Information Services, 1994).

1.2.2 *Use*

2,4,6-Trinitrotoluene is used as a high explosive in military and industrial applications. It has been widely used for filling shells, grenades and airborne demolition bombs, as it is sufficiently insensitive to the shock of ejection from a gun barrel but can be exploded on impact by a detonator mechanism. It has been used either as the pure explosive or in binary mixtures. The most common binary mixtures of 2,4,6-trinitrotoluene are cyclotols (mixtures with RDX (cyclotrimethylenetrinitramine or 1,3,5-trinitrohexahydro-1,3,5-triazine)), octols (mixtures with HMX (cyclotetramethylenetetranitramine or 1,3,5,7-tetranitro-1,3,5,7-tetraazocyclooctane)), amatols (mixtures with ammonium nitrate) and tritonals (mixtures with aluminium). In addition to military use, small amounts of 2,4,6-trinitrotoluene have been used for industrial explosive applications, such as deep-well and underwater blasting. It has also been used as a chemical intermediate in dyestuffs and photographic chemicals (Gibbs & Popolato, 1980; Budavari, 1989; Kline, 1990; Lewis, 1993).

1.3 Occurrence

1.3.1 *Natural occurrence*

2,4,6-Trinitrotoluene is not known to occur as a natural product.

1.3.2 *Occupational exposure*

Exposures to 2,4,6-trinitrotoluene may occur during its primary production, in munitions manufacture and loading, and during blasting operations. 2,4,6-Trinitrotoluene is

readily absorbed through the skin, so measurements of personal airborne concentrations will underestimate exposures when the opportunity for dermal uptake is present. Exposures to airborne 2,4,6-trinitrotoluene may occur when 2,4,6-trinitrotoluene as a dust is mixed with other ingredients or as 2,4,6-trinitrotoluene vapour.

(*a*) *Manufacture of trinitrotoluene*

El Ghawabi *et al.* (1974) described exposures to 2,4,6-trinitrotoluene during its manufacture. Mean summer concentrations of trinitrotoluene in mg/m^3 (range) for the following operations are: nitration, 0.62 (0.15–1.2); crystallization, 0.5 (0.25–0.7); filtration, 0.75 (0.4–0.9); washing, 0.5 (0.25–0.75); crushing, 7.5 (6–10); and distillation, 0.5 (0.4–0.6). Mean winter concentrations of 2,4,6-trinitrotoluene were slightly lower. The highest exposures occurred during crushing operations, which were intermittent.

In a Finnish 2,4,6-trinitrotoluene production plant, the mean 2,4,6-trinitrotoluene air concentrations were 0.35 mg/m^3 (range, 0.31–0.39 mg/m^3) in the synthesis process room and 0.1 mg/m^3 (range, 0.02–0.19 mg/m^3) in the packing room (Savolainen *et al.*, 1985).

(*b*) *Munitions production*

Munitions production begins with the mixing of 2,4,6-trinitrotoluene with other ingredients, where 2,4,6-trinitrotoluene may be 30% of the bulk weight (Woollen *et al.*, 1986). After milling or mixing, the mixture is transported to a filling area or shed where it is transferred into metal containers or cardboard tubes that, when filled, are crimped closed. The contents of the containers are then fused or 'melted' by heating or dipping into hot wax. The final step is packaging.

Early reports of 2,4,6-trinitrotoluene exposures during munitions production were usually associated with reports of adverse health effects, and described air concentrations of 0.5–3.5 mg/m^3 2,4,6-trinitrotoluene (Cone, 1944; Eddy, 1944; Stewart *et al.*, 1945; Ermakov *et al*, 1969). Stewart *et al.* (1945) reported 2,4,6-trinitrotoluene exposures of 0.3–0.6 mg/m^3 for filling area workers in a munitions loading plant and 0.3–1.3 mg/m^3 for workers who worked in the melt houses; these workers wore overalls and caps but no gloves or masks.

Air sampling for 2,4,6-trinitrotoluene was conducted in 1952 at an ammunition plant in the United States during a variety of operations (Goodwin, 1972). Air concentrations (in mg/m^3) for the following operations (personal samples) were: mixing 2,4,6-trinitrotoluene, 0.8–1.4; melting 2,4,6-trinitrotoluene, 0.9–2.9; screening 2,4,6-trinitrotoluene, 0.2–1.3; assembling grenades, 0.5–9.5; pouring 2,4,6-trinitrotoluene, 0.5–3.1; and pellet insertion, 1.6–4.7. Workers wore respirators in 'dusty areas' and wore overalls, disposable head coverings, socks and gloves. They were required to bathe with potassium sulfite soap, which turned red when in contact with 2,4,6-trinitrotoluene, until the red colour disappeared.

Exposures during intermittent 2,4,6-trinitrotoluene bagging operations ranged from 0.62 to 4.00 mg/m^3 in a study at a United States military munitions washout plant (Friedlander *et al.*, 1974). After engineering controls were introduced at this plant in

1974, personal 8-h time-weighted average (TWA) exposures ranged from 0.08 to 0.59 mg/m^3 (Hathaway, 1977).

Exposures at a shell-loading plant in the United States ranged from 0.3 to 0.8 mg/m^3 (8-h TWA) and increased as production rate increased (Morton *et al.*, 1976). Engineering controls were instituted after air concentrations higher than 1.5 mg/m^3 were found at some operations.

In a study of 533 2,4,6-trinitrotoluene-exposed munitions workers, 8-h TWA personal exposures ranged from not detected to 1.84 mg/m^3, with 12% of workers exposed to more than 0.5 mg/m^3 (Buck & Wilson, 1975).

In a series of Czech studies of a plant manufacturing ammunition, mean workroom air concentrations of 2,4,6-trinitrotoluene were 0.22–9.6 mg/m^3 in the 1950s, 0.03–4.2 mg/m^3 in the 1960s and 0.04–0.76 mg/m^3 in the 1970s. The highest air concentrations were found in pressing and filling operations. In another plant producing powdered explosives for mines and quarries, mean workroom air concentrations of 2,4,6-trinitrotoluene ranged from 0.05 to 6.3 mg/m^3 in the 1960s and 1970s. The highest air concentrations were found during cartridge- and sack-filling operations (Hassman, 1979).

A study of explosives production in the United Kingdom compared air concentrations of 2,4,6-trinitrotoluene with post-shift urinary dinitroaminotoluene metabolites (Woollen *et al.*, 1986). Personal exposure (mg/m^3) for the following operations were: milling, 0.2 (range, < 0.01–0.71); filling, 0.04 (range, < 0.01–0.22); crimping, 0.39; and packing, 0.05. This study showed substantial interindividual variability in post-shift concentrations of dinitroaminotoluene from day to day. An important finding of this study was that personal inhalation exposures of 2,4,6-trinitrotoluene did not account for observed excretion of dinitroaminotoluene, thus, dermal uptake must have been an important exposure route.

In a Finnish study of both trinitrotoluene production and munitions assembly, the highest concentrations of 2,4,6-trinitrotoluene vapour were in casting and cooling and those of 2,4,6-trinitrotoluene dust in the sieve house (Ahlborg *et al.*, 1988a). Workers wore respirators and protective clothing during operations with higher exposure potential. Personal air concentrations of 2,4,6-trinitrotoluene for the following departments in mg/m^3 in 1983 were: trotyl (2,4,6-trinitrotoluene) foundry, 0.2–0.5; sieve house, 0.5; test foundry, 0.2–0.3; octol-hexotol (mixture of explosives including 2,4,6-trinitrotoluene) foundry, 0.1–0.2; and grenade assembly, 0.1. Based on urine concentrations of 2,4,6-trinitrotoluene metabolites, the authors concluded that dermal absorption contributed significantly to 2,4,6-trinitrotoluene uptake. Dermal uptake most probably occurs among the workers exposed to high dust concentrations such as, for example, those in the sieve house.

In a munitions plant in the United States, 2,4,6-trinitrotoluene and RDX were monitored in several areas (Bishop *et al.*, 1988). In the kettle area, where 2,4,6-trinitrotoluene was transferred from boxes to kettles, air concentrations averaged 0.02 mg/m^3. In the incorporation area where 2,4,6-trinitrotoluene was melted and transferred to kettles for combination with RDX, 2,4,6-trinitrotoluene air concentrations averaged 0.207 mg/m^3. In

a bagging area where the final product was packaged, air concentrations averaged 0.006 mg/m^3.

(*c*) *Blasting operations*

During explosive blasting operations in Ukrainian pit mines, exposures as high as 12.5 ± 3.31 mg/m^3 2,4,6-trinitrotoluene were measured in the breathing zone of workers filling dry drill holes with explosives containing 21% trinitrotoluene. Contamination of the hands and uncovered parts of the body was greater in the pit mine blasters than in the warehouse loaders. It occurred through contact with the contaminated surface of the bags, shaking them out and collecting explosive material which had spilled (Melnichenko, 1976).

1.3.3 *Environmental occurrence*

(*a*) *Water*

Although for many years waste munitions were discarded at sea, 2,4,6-trinitrotoluene has not been detected (< 2 ng/L) in ocean waters or sediment near several dump sites off the coasts of South Carolina, Florida, California or Washington, United States (Hoffsommer & Rosen, 1972; Hoffsommer *et al.*, 1972).

2,4,6-Trinitrotoluene has been detected in surface-water and groundwater samples collected in several monitoring studies in the vicinity of munitions facilities. It was detected in contaminated groundwater both beneath and originating from the disposal beds of a demilitarization facility in Nevada, United States, at a maximum concentration of 620 µg/L in 1976; in 1977, it was detected in groundwater samples collected at the same place at concentrations of 320 µg/L 200 ft [61 m] away from the facility and 1 µg/L at 1070 ft [326 m] away (Goerlitz & Franks, 1989). 2,4,6-Trinitrotoluene concentrations of 12.0 and 19.0 µg/L were detected in surface-water samples collected from two brooks near Hirschagen/Waldhof, Germany, in the vicinity of what was a munitions manufacturing plant during the Second World War; the river into which the brooks fed (River Losse) had a concentration of 0.7 µg/L. Two ponds in the Clausthal-Zellerfeld region of Germany, again near a former munitions manufacturing plant, had levels of 0.5 µg/L; the ponds feed into the River Oder, which had a level of < 0.01 µg/L (Feltes *et al.*, 1990). Concentrations of 2,4,6-trinitrotoluene ranged from 690 to 1370 µg/L in groundwater samples collected near a former explosives factory in Elsnig, Germany (Steuckart *et al.*, 1994).

In samples of wastewaters generated in the manufacture of 2,4,6-trinitrotoluene over a 12-month period in the United States, 2,4,6-trinitrotoluene was detected in 20% (11/54 samples) at a concentration range of 0.1–3.4 mg/L (Spanggord *et al.*, 1982a). It was also detected in the effluent water from a 2,4,6-trinitrotoluene manufacturing plant in Virginia, United States, at concentrations ranging from 101 to 143 ppm (mg/L) (Nay *et al.*, 1972). 2,4,6-Trinitrotoluene has also been found in 'pink-water effluents' (wastewater from one of the purification steps in the manufacture of 2,4,6-trinitrotoluene) at concentrations of 774–998 µg/L in lagoon water and 2900–6400 µg/L in groundwater

(Triegel *et al.*, 1983) and at 1–178 mg/L in effluents from loading, assembling and packaging plants in the United States (Patterson *et al.*, 1977).

(*b*) *Soil and sediments*

At a waste-disposal site in Missouri, United States, where 2,4,6-trinitrotoluene explosives were burned in the 1940s, 2,4,6-trinitrotoluene has been detected in surface-soil samples at an average concentration of 13 g/kg (Haroun *et al.*, 1990). In West Virginia, United States, at burning sites at a munitions plant, 2,4,6-trinitrotoluene and other nitroaromatics were detected in surface soils at concentrations of up to 4% (40 g/kg). Nitroaromatics, principally 2,4,6-trinitrotoluene, were detected at up to 20 g/kg within 5–10 m of the foundations of processing and refining facilities (Kraus *et al.*, 1985). Concentrations of 2,4,6-trinitrotoluene ranged from 0.1 to 38.6 g/kg in soil samples collected from an army depot in Oregon, United States (Jenkins & Walsh, 1992). A soil sample collected near a former ammunition plant in Brandenburg, Germany, had a 2,4,6-trinitrotoluene level of 234 µg/kg (Steuckart *et al.*, 1994). At a munitions plant located in Texarkana, TX, United States, 2,4,6-trinitrotoluene has been detected at a concentration of about 15% in samples of sludge taken from ponds used as solids-settling areas for pink-water effluent; 2,4,6-trinitrotoluene concentrations were highest in surface-soil samples (e.g. 18.8 mg/kg at a depth of 0.2–0.6 m), and decreased with depth (e.g. < 3 mg/kg below 4.5 m) (Phung & Bulot, 1981). 2,4,6-Trinitrotoluene concentrations of 200–56 700 ppm (mg/kg) were found in sludge samples from pink-water lagoons and at 18.9–158 ppm [mg/kg] in surface-soil samples collected from directly beneath the lagoon in United States (Triegel *et al.*, 1983).

1.4 Regulations and guidelines

Occupational exposure limits and guidelines in several countries are given in Table 2.

Table 2. Occupational exposure limits and guidelines for 2,4,6-trinitrotoluene

Country	Year	Concentration (mg/m^3)	Interpretation
Argentina	1991	0.5 (Sk)	TWA
Australia	1993	0.5 (Sk)	TWA
Belgium	1993	0.5 (Sk)	TWA
Bulgaria[a]	1995	0.5 (Sk)	TWA
Canada	1991	0.5 (Sk)	TWA
Colombia[a]	1995	0.5 (Sk)	TWA
Czech Republic	1993	0.5 (Sk)	TWA
		2.5	STEL
Denmark	1993	0.5 (Sk)	STEL
Egypt	1993	0.5	TWA
Finland	1993	0.5 (Sk)	TWA
		3	STEL
France	1993	0.5 (Sk)	TWA

Table 2 (contd)

Country	Year	Concentration (mg/m^3)	Interpretation
Germany	1995	0.1 (Sk, II1, IIIB)	MAK
Hungary	1993	0.3 (Sk)	TWA
		0.5	STEL
Jordan[a]	1995	0.5 (Sk)	TWA
Mexico	1991	0.5	TWA
		3	STEL (15 min)
Netherlands	1994	0.1 (Sk)	TWA
New Zealand[a]	1995	0.5 (Sk)	TWA
Philippines	1993	1.5 (Sk)	TWA
Republic of Korea[a]	1995	0.5 (Sk)	TWA
Russia	1993	0.1 (Sk)	TWA
		0.5	STEL
Singapore[a]	1995	0.5 (Sk)	TWA
Switzerland	1993	0.1 (Sk)	TWA
		0.2	STEL
Turkey	1993	1.5 (Sk)	TWA
United Kingdom	1995	0.5 (Sk)	TWA
USA			
ACGIH (TLV)	1995	0.5 (Sk)[b]	TWA
OSHA (PEL)	1994	1.5 (Sk)	TWA
NIOSH (REL)	1994	0.5 (Sk)	TWA
Viet Nam[a]	1995	0.5 (Sk)	TWA

From Arbeidsinspectie (1994); US National Institute for Occupational Safety and Health (NIOSH) (1994a,b); US Occupational Safety and Health Administration (OSHA) (1994); American Conference of Governmental Industrial Hygienists (ACGIH) (1995); Deutsche Forschungsgemeinschaft (1995); Health and Safety Executive (1995); United Nations Environment Programme (1995)

Sk, absorption through the skin may be a significant source of exposure; TWA, time-weighted average; STEL, short-term exposure limit; II1, substances with systemic effects (half-life < 2h); IIIB, suspected of having carcinogenic potential; TLV, threshold limit values; PEL, permissible exposure limit; REL, recommended exposure limit

[a] Follows ACGIH TLVs

[b] Substance identified by other sources as a suspected or confirmed human carcinogen

2. Studies of Cancer in Humans

2.1 Case report

Garfinkel *et al.* (1988) reported a case of liver cancer in a 61-year-old engineer who had been exposed daily to 2,4,6-trinitrotoluene for 35 years. He had no past history of infectious hepatitis or alcohol abuse, which are known risk factors for liver cancer.

2.2 Descriptive study

Kolb *et al.* (1993) conducted an ecological study in which comparisons were made between the incidence of acute and chronic myelogenous leukaemias in two counties in Central Hesse, Germany. Contamination of the soil with 2,4,6-trinitrotoluene had been documented in one of the counties (Marburg-Biedenkopf) resulting from an underground plant in the city of Stadtallendorf that had produced 2,4,6-trinitrotoluene during the Second World War: this study was initiated following the observation of what was believed to be an unusually high number of leukaemias in the city of Stadtallendorf. The incidence of leukaemia in Marburg-Biedenkopf during 1983–89 was compared with that of the neighbouring county of Giessen which was not contaminated with 2,4,6-trinitrotoluene. Cases of leukaemia among individuals over the age of 18 were identified in the medical centres covering the two counties, and the population at risk was identified through residential registries. A statistically significant excess of acute and chronic myelogenous leukaemia was observed among male and female residents of Marburg-Biedenkopf. Stratification of the analysis by age revealed that excess risk was predominantly among residents over 65 years of age.

3. Studies of Cancer in Experimental Animals

No adequate data were available to the Working Group.

4. Other Data Relevant for an Evaluation of Carcinogenicity and its Mechanisms

4.1 Absorption, distribution, metabolism and excretion

4.1.1 *Humans*

The toxicology of 2,4,6-trinitrotoluene has been reviewed (Zakhari *et al.*, 1978; Rickert, 1987).

2,4,6-Trinitrotoluene is absorbed through the skin in exposed workers (Voegtlin *et al.*, 1921; Neal *et al.*, 1944).

In humans exposed orally to 2,4,6-trinitrotoluene, dinitroaminotoluenes (2,4-dinitro-6-aminotoluene and 2,6-dinitro-4-aminotoluene) were found in the urine (Horecker & Snyder, 1944; Lemberg & Callaghan, 1945).

Hassman (1971a,b) carried out two surveys of 2,4,6-trinitrotoluene-exposed workers. Air concentrations of 2,4,6-trinitrotoluene was found to range from 0.6 to 4.0 mg/m^3. The urinary excretion of 2,6-dinitro-4-aminotoluene was 2.5 and 6.5 mg/L, respectively.

Absorption and excretion of 2,4,6-trinitrotoluene was assessed in groups of workers in two explosives factories. 2,6-Dinitroaminotoluene (and 2,4-dinitro-6-aminotoluene) were found in most post-shift urine samples (mean level, 9.7 mg/L; range, 0.1–44 mg/L). (In unhydrolysed samples, much lower levels were detected, indicating that only a small fraction is present as free amine, and that the remainder is bound, probably as a *N*-glucuronide conjugate). There was a decrease in concentrations over night and an increase over shift, and the highest levels were usually found a few hours after the end of exposure; thus, relatively fast absorption and excretion occur. However, dinitroaminotoluenes were still present after 36 h and even after 17 days, indicating a fraction with slow metabolism. No association was found between levels of urinary dinitroaminotoluenes and air levels of 2,4,6-trinitrotoluene (< 0.01–0.29 mg/m^3 and 0.05–0.71 mg/m^3 by personal sampling in the two factories), and the urinary levels varied considerably between days. Calculations showed that inhalation did not account for the urinary dinitroaminotoluenes and that dermal uptake must have been considerable (Woollen *et al.*, 1986).

In urinary samples from a group of 2,4,6-trinitrotoluene workers, 2,6-dinitro-4-aminotoluene was the main metabolite (at 0.24–9.65 mg/L), followed by 4,6-dinitro-2-aminotoluene. Unchanged 2,4,6-trinitrotoluene, 2,6-diamino-4-nitrotoluene and 2,4-diamino-6-nitrotoluene were present at lower concentrations (Yinon & Hwang, 1986a).

Ahlborg *et al.* (1988b) analysed diazo-positive metabolites in hydrolysed urine from 2,4,6-trinitrotoluene workers. In workers with low, medium and high exposure, the levels after a holiday were lower (means, 0.36–0.49 μmol/mol creatinine in the three groups) than post-shift levels (0.56, 0.84 and 1.06 μmol/mol creatinine, respectively; the corresponding air levels were undetectable, < 0.3 and up to 0.5–0.6 mg/m^3, respectively). After the holiday, there was no difference in urinary excretion between workers with varying intensity of exposure.

4.1.2 *Experimental systems*

Rabbits administered oral doses of about 100–300 mg/kg bw 2,4,6-trinitrotoluene excreted the following in the urine: 2,6-dinitro-4-hydroxylaminotoluene, 2,6-dinitro-4-aminotoluene and 2,4-dinitro-6-aminotoluene (Channon *et al.*, 1944). The blood of male rabbits given 100 mg 2,4,6-trinitrotoluene by gavage contained 2,6-dinitro-4-aminotoluene and 2,4-dinitro-6-aminotoluene, as well as the parent compound (Yinon & Hwang, 1987). The urine of male SPD rats given 20 mg 2,4,6-trinitrotoluene by gavage contained the parent compound, 2,4-diamino-6-nitrotoluene, 2,6-dinitro-4-aminotoluene and 2,4-dinitro-6-aminotoluene (Yinon & Hwang, 1985). In male SPD rats receiving a

skin application of 20 mg 2,4,6-trinitrotoluene for 2 h, 2,4-diamino-6-aminotoluene and 2,6-dinitro-4-aminotoluene were seen in urine (Yinon & Hwang, 1987).

2,6-Dinitro-4-aminotoluene and 2,6-dinitro-4-hydroxylaminotoluene were found in the urine of dogs given 2,4,6-trinitrotoluene orally (Snyder, 1946).

In the above studies, no data exist to assess the percentage of the dose that was eliminated as each metabolite. 2,4,6-Trinitrotoluene undergoes both oxidative and reductive metabolism in animals. The nitro groups are reduced through intermediate hydroxylamines to amines. The methyl group can be oxidized to an alcohol and an acid, both of which can be conjugated with glucuronic acid and excreted in the urine.

Zwirner-Baier *et al.* (1994) treated female Wistar rats by oral gavage with 0.5 mmol [114 mg]/kg bw 2,4,6-trinitrotoluene and found that, 24 h after dosing, 2,4,6-trinitrotoluene was bound to haemoglobin.

4.2 Toxic effects

4.2.1 *Humans*

The toxicity of 2,4,6-trinitrotoluene to humans has been reviewed (Hathaway, 1977; Zakhari *et al.*, 1978; Ryon & Ross, 1990).

2,4,6-Trinitrotoluene has several types of effect on the haematological system. Exposure to 2,4,6-trinitrotoluene may cause methaemoglobinaemia, with cyanosis. In the bone marrow, hypercellularity and hypocellularity have been reported, the latter resulting in a reduction of circulating red and white blood cells and platelets and, in severe cases, aplastic anaemia (24 cases in the United Kingdom, 14 in the United States), which has symptoms such as pallor, fatigue, bleeding and infection (Sievers *et al.*, 1946).

Djerassi and Vitany (1975) reported three cases of acute haemolytic disease in glucose-6-phosphate dehydrogenase-deficient workers filling shells with a 2,4,6-trinitrotoluene mixture. The onset of the disease was within two to four days after the start of exposure. The air concentration was not known, but had earlier been 1.8–2.95 mg/m^3.

Nine workers in a factory producing 2,6,6-trinitrotoluene had somewhat lower activities than 25 unexposed controls of the enzymes δ-aminolevulinic acid synthase (EC 2.3.1.37) and haeme synthase (EC 4.99.1.1) in red blood cells (presumably in reticulocytes). The 2,4,6-trinitrotoluene concentration in the process room air was 0.35 (range, 0.31–0.39) mg/m^3 and that in the packing department was 0.10 (0.02–0.19) mg/m^3 (Savolainen *et al.*, 1985).

Liver damage is the second main toxic effect of exposure to 2,4,6-trinitrotoluene. Initial symptoms in acute poisoning include jaundice, excretion of bile pigments in urine, epigastric pain, nausea and, in some cases, eventual coma and death. In 10 acute fatal cases, pathological examination revealed reduced liver weight, destruction of parenchymal cells, haemorrhagic areas, perivascular infiltration of lymphocytes and polymorphonuclear lymphocytes, and fat-infiltration of cells (McConnel & Flinn, 1946). A single case of macronodular liver cirrhosis (and hepatocellular carcinoma) was diagnosed in an engineer who had been exposed to 2,4,6-trinitrotoluene daily for 35 years and had had no history of viral hepatitis or alcohol abuse (Garfinkel *et al.*, 1988).

Stewart *et al.* (1945) studied students who worked in a munitions loading plant in which both inhalation and skin exposure occurred. For 52 students who worked in filling areas during the four-to-11-week study period, the air levels of 2,4,6-trinitrotoluene ranged from 0.3 to 0.6 mg/m^3 for an average of 33 days. These students also had significant skin exposure and 27 of them developed skin rashes. Ten students working in both filling areas (average, 18 days) and melt houses (average, 15 days) had exposures ranging from 0.3 to 1.3 mg/m^3 and probably had only minimal skin exposure. Compared to pre-employment values, over 80% of the students had decreases in their blood haemoglobin levels. Only minimal changes in reticulocyte counts occurred during exposure, but there was an increase 48 h after termination of 2,4,6-trinitrotoluene exposure. In addition, students in both filling areas and melt houses had significant increases in blood bilirubin levels.

El Ghawabi *et al.* (1974) examined 38 (three were excluded because of previous diseases) workers in a 2,4,6-trinitrotoluene production and shell-loading plant and 20 unexposed control workers. The 2,4,6-trinitrotoluene exposure ranged from 0.1 to 1.2 mg/m^3, with peaks of up to 10 mg/m^3. The 2,4,6-trinitrotoluene workers had higher prevalences of respiratory (sneezing, sore throat and cough) and gastrointestinal (stomach ache, anorexia, constipation, flatulence, nausea and vomiting) complaints than the controls. Further, they had lower average blood haemoglobin levels: 85% (100% is 15 g/100 mL) versus 96% in controls. However, there were no significant differences in liver tests and no case of cataract was recorded.

In a shell-loading plant, 43 workers were examined before employment and then followed monthly for five months. During this period, the time-weighted exposure increased from 0.3 to 0.8 mg/m^3 2,4,6-trinitrotoluene as a result of increased production. At the end of the five months, there were statistically significant increases in serum lactate dehydrogenase and SGOT (serum glutamic oxalacetic transaminase). Further, blood haemoglobin levels decreased, although not statistically significantly (Morton *et al.*, 1976).

Cataracts have been reported in 2,4,6-trinitrotoluene workers, even at low exposure levels. Opacities are bilateral, symmetric and typical. They are initially noted only in the peripheral parts of the lens, where they do not interfere with the visual fields. Six cases of cataract were recorded in 12 munitions factory workers (mean age, 39.5 years) exposed to air levels of 2,4,6-trinitrotoluene ranging from 0.14 to 0.58 mg/m^3 (Härkönen *et al.*, 1983). Of 413 workers (mean age, 38 years) exposed to 2,4,6-trinitrotoluene (for three months to 29 years; air levels stated to have been below 1 mg/m^3), cataracts were found in 34.6%; among workers exposed to more than 20 years, the figure rose to 88.7%. There was said to be no association between cataracts and liver tests (Anshou, 1990). The changes in the lens may be virtually irreversible.

Allergic contact dermatitis has been reported in skin areas exposed to 2,4,6-trinitrotoluene (Goh & Rajan, 1983; Goh, 1984).

4.2.2 *Experimental systems*

(*a*) *Single-dose studies*

The acute toxicity of 2,4,6-trinitrotoluene has been reported in laboratory animals including rats, mice and dogs (Dilley *et al.*, 1982). The reported oral LD_{50} values for 2,4,6-trinitrotoluene in male and female Sprague-Dawley rats were 1320 mg/kg bw and 795 mg/kg bw, respectively. The oral LD_{50} in both male and female Swiss-Webster mice was 660 mg/kg bw.

(*b*) *Repeated-dose studies*

Levine *et al.* (1984) investigated the subchronic toxicity of 2,4,6-trinitrotoluene in male and female Fischer 344 rats treated with 1, 5, 25, 125 or 300 mg/kg bw per day for 13 weeks by administration in the diet. Anaemia was observed in all treated rats, the severity of which was dose-dependent. Splenomegaly, hepatomegaly/hepatocytomegaly and testicular atrophy were seen at doses of 125 and 300 mg/kg per day.

Dilley *et al.* (1982) administered gelatin capsules containing 0, 0.2, 2.0 and 20 mg/kg bw 2,4,6-trinitrotoluene to beagle dogs daily for up to 13 weeks. In the same study, Sprague-Dawley rats received 0, 0.002, 0.01, 0.05 or 0.25% and Swiss-Webster mice 0, 0.001, 0.005, 0.025 or 0.125% 2,4,6-trinitrotoluene in their diets over the same period. At the highest doses, all species exhibited anaemia. Additionally, the authors reported enlarged spleens and livers and depressed body weight and/or depressed body-weight gain (temporary in dogs and mice) for all species. 2,4,6-Trinitrotoluene induced elevated cholesterol and depressed serum glutamic pyruvic transaminase (SGPT) activity in dogs and rats. SGPT depression in rats appeared after 13 weeks. Reduced testes size was observed in rats at the highest dose. Most of the toxic effects were reversible; however, in rats, testicular atrophy did not reverse within a four-week recovery period after treatment.

Levine *et al.* (1990) evaluated the oral toxicity of 2,4,6-trinitrotoluene in male and female beagle dogs administered 0, 0.5, 2, 8 or 32 mg/kg bw daily for 26 weeks. Dose-dependent anaemia was observed in treated dogs. Dose-dependent decreases in SGPT were seen in both males and females. In dogs receiving 8 or 32 mg/kg per day, hepatomegaly was observed and hepatocytomegaly increased in severity as a function of dose. Spleen enlargement was also observed. The major toxic effects, therefore, included haemolytic anaemia, methaemoglobinaemia, liver injury, splenomegaly and death (only at 32 mg/kg bw per day).

(*c*) *Biochemical alterations*

Tenhunen *et al.* (1984) injected male Wistar rats intraperitoneally with 100 mg/kg bw 2,4,6-trinitrotoluene in olive oil and the animals were killed 48 h after injection. δ-Aminolevulinic acid synthase activity in reticulocytes was approximately 70% that of control values, and red blood cell coproporphyrin was marginally below that of control values. Liver haeme synthase activity was approximately 60% that of control values and no effect was noted on δ-aminolevulinic acid synthase or biliverdin reductase activity in livers.

Jiang *et al.* (1991) treated male Wistar rats by oral gavage with 200 mg/kg bw 2,4,6-trinitrotoluene per day on six days per week for six weeks. Blood, testes and liver were obtained from animals killed after two, four and six weeks of treatment. At six weeks of treatment, copper concentrations in testes were decreased by 30% compared to controls and remained so for two weeks after the end of the six-week treatment regimen. Zinc concentrations in testes were significantly depressed throughout, and two weeks beyond the six-week treatment period.

Lingyuan *et al.* (1989) treated Chinese rhesus monkeys with 60 and 120 mg/kg bw 2,4,6-trinitrotoluene orally once a day, four times a week for three months. Forty-eight hours after the last treatment, the monkeys were killed and mitochondria and microsomes were prepared for measurement of superoxide anion and hydrogen peroxide. Hydrogen peroxide was quantified by measuring the conversion of methanol to formaldehyde. The results revealed that 2,4,6-trinitrotoluene increased the formation of hydrogen peroxide.

In studies by Short and Lee (1980) to assess whether 2,4,6-trinitrotoluene could modify the biotransformation of model xenobiotics, male CD rats were administered orally 0.4 mmol [91 mg]/kg bw 2,4,6-trinitrotoluene twice a day for three days and once on the fourth day. The results indicated that 2,4,6-trinitrotoluene was not effective in inducing in-vivo biotransformation of xenobiotics (as measured by zoxazolamine paralysis or hexobarbital sleeping time).

4.3 Reproductive and developmental effects

No data were available to the Working Group.

4.4 Genetic and related effects

4.4.1 *Humans*

Urine concentrates from workers exposed to 2,4,6-trinitrotoluene showed, compared to urine concentrates from unexposed controls, an increased mutagenic activity in *Salmonella typhimurium* strain TA98 in the absence of rat-liver S9. The same strain responded only weakly when the S9 mix was used, while, with *Escherichia coli* WP2 *uvrA* in the presence of S9, no effect of worker exposure was observed (Ahlborg *et al.*, 1985). Since the response with *S. typhimurium* strains TA98 and TA98NR (deficient in nitroreductase activity) was about the same, bacterial nitroreductase activity is not significantly responsible for the mutagenicity of the urine samples (Ahlborg *et al.*, 1988a).

4.4.2 *Experimental systems* (see also Table 3 and Appendices 1 and 2)

2,4,6-Trinitrotoluene was mutagenic in *S. typhimurium* strains TA1538 and TA98 (with and without rat S9) as well as in TA98 and TA100, with and without human placenta S9 and with and without rat-liver S9. In addition, 2,4,6-trinitrotoluene was reported to be negative in strains TA1535 and TA100NR3 (nitroreductase-deficient) and positive in TA1537 (with and without rat S9). In the P388 mouse lymphoma gene mutation assay, 2,4,6-trinitrotoluene induced mutations in the absence, but not in the presence of S9-mix.

Table 3. Genetic and related effects of 2,4,6-trinitrotoluene

Test system	Result[a]		Dose[b] (LED/HID)	Reference
	Without exogenous metabolic system	With exogenous metabolic system		
SA0, *Salmonella typhimurium* TA100, reverse mutation	+	+	50	Spanggord *et al.* (1982b)
SA0, *Salmonella typhimurium* TA100, reverse mutation	+	0	25	Whong & Edwards (1984)
SA0, *Salmonella typhimurium* TA100, reverse mutation	+	+	10	Tan *et al.* (1992)
SA0, *Salmonella typhimurium* TA100, reverse mutation	+	+	0.5	Karamova *et al.* (1994)
SA5, *Salmonella typhimurium* TA1535, reverse mutation	–	–	2500	Spanggord *et al.* (1982b)
SA5, *Salmonella typhimurium* TA1535, reverse mutation	–	0	100	Whong & Edwards (1984)
SA7, *Salmonella typhimurium* TA1537, reverse mutation	+	+	NR	Spanggord *et al.* (1982b)
SA7, *Salmonella typhimurium* TA1537, reverse mutation	+	0	25	Whong & Edwards (1984)
SA8, *Salmonella typhimurium* TA1538, reverse mutation	+	+	25	Kaplan & Kaplan (1982)
SA8, *Salmonella typhimurium* TA1538, reverse mutation	+	+	NR	Spanggord *et al.* (1982b)
SA8, *Salmonella typhimurium* TA1538, reverse mutation	+	0	12.5	Whong & Edwards (1984)
SA9, *Salmonella typhimurium* TA98, reverse mutation	+	0	2.5	Won *et al.* (1976)
SA9, *Salmonella typhimurium* TA98, reverse mutation	+	0	250	Kaplan & Kaplan (1982)
SA9, *Salmonella typhimurium* TA98, reverse mutation	+	+	NR	Spanggord *et al.* (1982b)

Table 3 (contd)

Test system	Result[a]		Dose[b] (LED/HID)	Reference
	Without exogenous metabolic system	With exogenous metabolic system		
SA9, *Salmonella typhimurium* TA98, reverse mutation	+	0	12.5	Whong & Edwards (1984)
SA9, *Salmonella typhimurium* TA98, reverse mutation	+	(+)	10	Tan *et al.* (1992)
SA9, *Salmonella typhimurium* TA98, reverse mutation	+	+	0.5	Karamova *et al.* (1994)
SAS, *Salmonella typhimurium* TA100NR3, reverse mutation	–	–	250	Spanggord *et al.* (1982b)
SAS, *Salmonella typhimurium* TA100NR (nitroreductase deficient), reverse mutation	–	–	50	Karamova *et al.* (1994)
SAS, *Salmonella typhimurium* TA100/1,8-DNP (o-acetyltransferase deficient), reverse mutation	–	–	50	Karamova *et al.* (1994)
GML, Gene mutation, mouse lymphoma cells P388, *tk* locus *in vitro*	+	–	40	Styles & Cross (1983)
UPR, Unscheduled DNA synthesis, male rat hepatocytes *in vivo*	–		1000 po × 1	Ashby *et al.* (1985)
MVM, Micronucleus test, male mouse bone marrow cells *in vivo*	–		80 ip × 1	Ashby *et al.* (1985)

[a] +, positive; (+), weak positive; –, negative; 0, not tested; ?, inconclusive (variable response within several experiments within an adequate study)

[b] LED, lowest effective dose; HID, highest ineffective dose. In-vitro tests, µg/mL; in-vivo tests, mg/kg bw; NR, dose not reported

2,4,6-Trinitrotoluene was negative in the mouse bone-marrow micronucleus assay and in an in-vivo/in-vitro rat liver assay for unscheduled DNA synthesis.

The mutagenicity of urine of rats exposed to 2,4,6-trinitrotoluene by intraperitoneal injection was studied in the *S. typhimurium* assay. In the absence of rat-liver S9, only a weakly positive response was observed in strain TA98, but a strong response was seen with strains YG1021 (nitroreductase-overproducing) and YG1024 (*O*-acetyltransferase-overproducing). The strains TA98NR and TA98/1,8-DNP_6 (*O*-acetyltransferase-deficient) showed no effect. In the presence of S9, strains YG1021 and YG1024 gave a weak effect. Thus, high levels of both nitroreductase and *O*-acetyltransferase significantly increase the sensitivity of the indicator strain to the mutagenicity of urine caused by 2,4,6-trinitrotoluene exposure (Einistö, 1991).

5. Summary of Data Reported and Evaluation

5.1 Exposure data

2,4,6-Trinitrotoluene is produced commercially by the nitration of toluene. It is used mainly as a high explosive in military and industrial applications. Exposures to 2,4,6-trinitrotoluene both through inhalation and skin absorption can occur during its production, during munitions manufacturing and loading, and during blasting operations. 2,4,6-Trinitrotoluene has been detected in wastewater, surface and groundwater, and in soils and sediments near plants manufacturing 2,4,6-trinitrotoluene and explosives.

5.2 Human carcinogenicity data

One ecological study was available that noted an association between leukaemia and residence in an area contaminated with 2,4,6-trinitrotoluene.

5.3 Animal carcinogenicity data

No adequate study on the carcinogenicity of 2,4,6-trinitrotoluene in experimental animals was available to the Working Group.

5.4 Other relevant data

In humans, absorption of 2,4,6-trinitrotoluene both through the skin and the gastrointestinal route had been demonstrated. 2,4,6-Trinitrotoluene is also probably absorbed in the respiratory tract. However, the dermal route is the commonest in occupational settings.

In humans exposed to 2,4,6-trinitrotoluene, mainly dinitroaminotoluenes and also diaminonitrotoluenes, probably mainly as conjugates, as well as unchanged 2,4,6-trinitrotoluene were found in the urine.

In humans, exposure to 2,4,6-trinitrotoluene has been found to cause haematological disorders, including aplastic anaemia, haematolytic anaemia and methaemoglobinaemia. 2,4,6-Trinitrotoluene may cause toxic hepatitis. Moreover, allergic contact dermatitis and cataracts may occur, as well as gastritis and respiratory mucous membrane and conjunctival irritation.

2,4,6-Trinitrotoluene undergoes both oxidative and reductive metabolism in animals. It causes anaemia and hepatotoxicity in rats and dogs. Testicular atrophy occurs in rats following exposure to 2,4,6-trinitrotoluene.

In workers exposed to 2,4,6-trinitrotoluene, increased bacterial mutagenic activity was found in the urine.

2,4,6-Trinitrotoluene is mutagenic in bacteria with and without a metabolic activation system. In cultured mammalian cells, it is mutagenic only in the absence of a metabolic activation system. Although 2,4,6-trinitrotoluene was negative in mammals *in vivo* for unscheduled DNA synthesis in the liver and micronuclei induction in bone marrow, the urine of rats is mutagenic after intraperitoneal injection of 2,4,6-trinitrotoluene.

5.5 Evaluation[1]

There is *inadequate evidence* in humans for the carcinogenicity of 2,4,6-trinitrotoluene.

There is *inadequate evidence* in experimental animals for the carcinogenicity of 2,4,6-trinitrotoluene.

Overall evaluation

2,4,6-Trinitrotoluene is *not classifiable as to its carcinogenicity to humans (Group 3).*

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