N,N-DIMETHYL-*P*-TOLUIDINE

1. Exposure Data

1.1 Identification of the agent

1.1.1 Nomenclature

Chem. Abstr. Serv. Reg. No.: 99-97-8

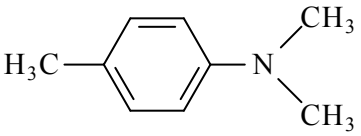
Chen. Abstr. Serv. Name: *N,N*-Dimethyl-*para*-toluidine

IUPAC Systematic Name: *N,N*,4-Trimethyl-aniline

Synonyms: 4-Dimethylaminotoluene, *N,N*-dimethyl-4-methylaniline, *p,N,N*-trimethylaniline, *N,N*,4-trimethylbenzen-amine

Acronyms: DMPT

1.1.2 Structure and molecular formula, and relative molecular mass



Molecular formula: $C_9H_{13}N$
Relative molecular mass: 135.21

1.1.3 Physical and chemical properties

Description: Light yellow to brown, oily fluid with a characteristic amine-like odour (IFA, 2015)

Density (at 20 °C): 0.94 g/cm³ (IFA, 2015)

Octanol/water partition coefficient (P): log K_{ow}, 2.81 (HSDB, 2015)

Melting point: –15 °C (IFA, 2015)

Boiling point: 211 °C (HSDB, 2015)

Volatility: Vapour pressure, 0.01 kPa [0.178 mm Hg], at 20 °C (IFA, 2015)

Vapour density: 4.66 (air = 1) at 20 °C (IFA, 2015)

Solubility: Insoluble to moderately soluble in water (650 mg/L at 37 °C) (ECHA, 2015)

Stability: Lower explosion limit, 1.2 vol. %; upper explosion limit, 7.0 vol. % (IFA, 2015)

Flash point: 83 °C (IFA, 2015)

Ignition temperature: 425 °C (IFA, 2015)

Conversion factor (at 101 kPa, 20 °C): 1 ppm = 5.62 mg/m³ (IFA, 2015)

1.2 Production and use

1.2.1 Production

(a) Production methods

Multiple methods exist for the manufacture of *N*-alkyltoluidines, including *N,N*-dimethyl-*p*-toluidine, such as acid-catalysed alkylation of unalkylated toluidines with lower unbranched alcohols or ether. Another method involves reductive alkylation with lower aldehydes or ketones using metal catalysts under hydrogen pressure (Bowers, 1996).

(b) Production volume

N,*N*-Dimethyl-*p*-toluidine was listed as a high production volume chemical in the USA, indicating that > 1 million pounds [approximately 454 tonnes] were produced or imported between 1990 and 1994 annually (HSDB, 2015). Annual United States production volumes of *N*,*N*-dimethyl-*p*-toluidine from 1986 to 2014 are given in Table 1.1. With annual production reported to be 1–10 million pounds [approximately 454–4536 tonnes] in 2014, it remains a high production volume chemical in the USA (HSDB, 2015). The total tonnage band per annum is estimated to be between 10 and 100 tonnes in the European Union (ECHA, 2015). Globally, more than 130 suppliers of *N*,*N*-dimethyl-*p*-toluidine could be identified in 2016 with about two thirds (> 80) located in Asia (ChemicalBook Inc., 2016).

Table 1.1 Annual production volume of *N*,*N*-dimethyl-*p*-toluidine in the USA, 1986–2014

Year	Production range (pounds)
1986	10 000–500 000 [~4.5–227 tonnes]
1990	10 000–500 000 [~4.5–227 tonnes]
1994	> 1 million–10 million [~ > 454–4536 tonnes]
1998	> 1 million–10 million [~ > 454–4536 tonnes]
2002	> 500 000–1 million [~ > 227–454 tonnes]
2006	> 1 million- 10 million [~ > 454–4536 tonnes]
2014	> 1 million–10 million [~ > 454–4536 tonnes]

Compiled by the Working Group from non-confidential Chemical Data Reporting information (EPA, 2011, 2015; HSDB, 2015)

1.2.2 Use

N,*N*-Dimethyl-*p*-toluidine is used as an accelerator in the preparation of dental materials and bone cements to activate the polymerization reaction or when curing methyl methacrylate monomers. The concentrations in these preparations are usually between 0.5% and 3% (NTP, 2012). It has also been used for the preparation of acrylic denture material for the past 50 years (HSDB, 2015). In addition, *N*,*N*-dimethyl-*p*-toluidine is an important ingredient of industrial glues and artificial fingernail preparations, when short setting times are needed, and is also used as an intermediate in the manufacture of dyes and pesticides (NTP, 2012).

1.3 Measurement and analysis

N,*N*-Dimethyl-*p*-toluidine in dental material was analysed by high-performance liquid chromatography with ultraviolet detection (Shintani et al. 1993; Stea et al. 1997). Sample preparation was carried out by solid-phase extraction.

Air monitoring of *N*,*N*-dimethyl-*p*-toluidine has been described as part of NIOSH Method 2002 (aromatic amines) using gas chromatography and flame ionization detection (NIOSH, 1994). Sample preparation includes sorption on silica gel at a sampling rate of 1 L/minute or less, and the estimated limit of detection is 0.01 mg per sample.

No analytical procedures were found for the determination of *N*,*N*-dimethyl-*p*-toluidine specifically in the environment (air, water), food, urine or blood, with the exception of the determination of its *N*-oxides in enzyme reaction mixtures (i.e. liver microsomes) using high-performance liquid chromatography with ultraviolet detection (Seto & Guengerich, 1993). *N*,*N*-Dimethyl-*p*-toluidine may be determined by current methods for the determination of monocyclic aromatic amines in blood or urine (Richter & Branner, 2002; Weiss & Angerer, 2002; Lamani et al., 2015).

1.4 Occurrence and exposure

1.4.1 Natural occurrence

N,*N*-Dimethyl-*p*-toluidine does not occur naturally.

1.4.2 Environmental occurrence

In the environment, *N*,*N*-dimethyl-*p*-toluidine is broken down rapidly in air. It travels through soil and may volatilize from moist soil and water surfaces (HSDB, 2015).

1.4.3 Occupational exposure

Potential widespread human exposure to *N*,*N*-dimethyl-*p*-toluidine can occur in occupational settings related to its use in bone cements, dental prostheses, industrial glues, and artificial fingernails. Surgeons, surgical staff, dentists, dental technicians, nail salon operators, and users of industrial glues may receive significant exposure to *N*,*N*-dimethyl-*p*-toluidine by inhalation or through the skin (NTP, 1999).

The National Occupational Exposure Survey, which was conducted by the National Institute for Occupational Safety and Health (NIOSH) between 1981 and 1983, estimated that 62 720 workers (among whom 27 118 were women) were potentially exposed to *N*,*N*-dimethyl-*p*-toluidine in the workplace (NIOSH, 1990). In 2014, three companies in the USA manufactured *N*,*N*-dimethyl-*p*-toluidine (HSDB, 2015).

A NIOSH investigation of air sampling from a nail salon measured only trace amounts of *N*,*N*-dimethyl-*p*-toluidine (Kronoveter, 1977). No other measurements of occupational exposure were identified.

1.4.4 Exposure of the general population

Sniffing glues, some of which contain 1–7% of the compound (Misiak & Scheffler, 2003; 3M Company, 2004), could possibly result in exposure to *N*,*N*-dimethyl-*p*-toluidine (Neumark et al., 1998; Wu et al., 2008; Marsolek et al., 2010).

Due to its use as polymerization accelerator for the manufacture of bone cement and dental materials, *N*,*N*-dimethyl-*p*-toluidine has been identified in a variety of commonly used bone cements at concentrations of about 10–30 g/kg (~1–3%) (Haddad et al., 1996; Stea et al., 1997). Exposure from bone cement is thought to have been responsible for sensitization in some patients (Haddad et al., 1996).

Two cases of the accidental ingestion of artificial fingernail solutions containing unspecified concentrations of *N*,*N*-dimethyl-*p*-toluidine have been reported. In the first case, a child aged 16 months drank 15 mL of solution (estimated to contain about 60 mg of *N*,*N*-dimethyl-*p*-toluidine or 6 mg/kg body weight [bw]) and on admission to hospital, methaemoglobin was 43% (normal value, < 2%) (Potter et al., 1988). In the second case, a baby aged 5 months ingested 30 mL of solution and after 1 hour, methaemoglobin was 11%. The children recovered after the administration of methylene blue and oxygen (Kao et al., 1997).

1.4.5 Exposure assessment and biological markers

No studies to assess exposure in humans by measuring *N*,*N*-dimethyl-*p*-toluidine or its metabolites in the blood or urine were available to the Working Group.

1.5 Regulations and guidelines

No specific occupational exposure limit has been reported for *N*,*N*-dimethyl-*p*-toluidine, but this chemical can cause methaemoglobinaemia. The German Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area established guidance values for methaemoglobin-forming amino and nitro compounds in terms of an umbrella regulation. Methaemoglobin values > 1.5% indicate that workers are exposed to aromatic amino and nitro compounds, and the Commission has recommended a level of 5% as a "ceiling" (Leng & Bolt, 2006). [The magnitude of exposure to *N*,*N*-dimethyl-*p*-toluidine leading to this level has not yet been specified.]

According to the risk phrases of the Globally Harmonized System of Classification and Labelling of Chemicals of the United Nations, *N*,*N*-dimethyl-*p*-toluidine is harmful if is swallowed (H301), is in contact with skin (H311), or is inhaled (H331). *N*,*N*-Dimethyl-*p*-toluidine may also cause damage to organs through prolonged and repeated exposure (reproductive organs after oral exposure) (H373) and is harmful to aquatic life, with long-lasting effects (H412) (ECHA, 2015).

2. Cancer in Humans

No data were available to the Working Group.

3. Cancer in Experimental Animals

See Table 3.1

3.1 Mouse

Groups of 50 male and 50 female B6C3F$_1$/N mice (age, 5–6 weeks) were given *N*,*N*-dimethyl-*p*-toluidine (purity, > 99%) by gavage in corn oil at doses of 0 (control), 6, 20, or 60 mg/kg bw on 5 days per week for 105 weeks. Survival of females at 60 mg/kg bw was significantly lower than that of the group receiving the vehicle control. The mean body weights of males and females at 60 mg/kg bw were > 10% lower than those of the vehicle controls after week 89 and week 65, respectively. The decreased survival of females at 60 mg/kg bw, and the decrease in body-weight gain in males and females at 60 mg/kg bw were attributed to the development of treatment-related tumours (NTP, 2012; Dunnick et al., 2014).

In males, treatment-related increases in hepatocellular tumours were observed in males, including increases in the incidence of hepatocellular adenoma (multiple): 17/50 controls, 19/50 at 6 mg/kg bw, 27/50 at 20 mg/kg bw ($P \leq 0.05$) and 26/50 at 60 mg/kg bw ($P \leq 0.05$); hepatocellular carcinoma (multiple): 7/50 controls, 7/50 at 6 mg/kg bw, 16/50 at 20 mg/kg bw ($P \leq 0.05$) and 22/50 at 60 mg/kg bw ($P \leq 0.01$); hepatocellular carcinoma (including multiple): 22/50 controls (*P* for trend, 0.002), 25/50 at 6 mg/kg bw, 30/50 at 20 g/kg bw and 36/50 at 60 mg/kg bw ($P = 0.005$); hepatocellular adenoma or carcinoma (combined): 38/50 controls (*P* for trend, 0.005), 44/50 at 6 mg/kg bw, 47/50 at 20 mg/kg bw ($P = 0.010$), and 48/50 at 60 mg/kg bw ($P = 0.006$); and hepatoblastoma: 1/50 controls, 5/50 at 6 mg/kg bw, 10/50 at 20 mg/kg bw ($P = 0.005$) and 8/50 at 60 mg/kg bw ($P = 0.021$). The incidence of hepatocellular adenoma, hepatocellular carcinoma or hepatoblastoma (combined) was 38/50 controls (*P* for trend, 0.006), 45/50 at 6 mg/kg bw, 48/50 at 20 mg/kg bw ($P = 0.004$), and 48/50 at 60 mg/kg bw ($P = 0.006$). The historical incidence for hepatoblastoma in studies by gavage in corn oil was 14/350 (4.0% ± 2.8%; range, 0–8%) and for all routes was 61/1149 (5.3% ± 7.1%; range, 0–34%) and that for hepatocellular adenoma, hepatocellular carcinoma or hepatoblastoma (combined) in studies by gavage in corn oil was 242/350 (69.1% ± 8.0%; range, 58–78%) and for all routes was 852/1149 (74.2% ± 11.5%; range, 52–92%).

In females, treatment-related increases in the incidence of hepatocellular tumours were observed, including that of hepatocellular adenoma (multiple): 2/50 controls, 6/50 at 6 mg/kg bw, 29/50 at 20 mg/kg bw ($P \leq 0.01$) and 35/50 at 60 mg/kg bw ($P \leq 0.01$); hepatocellular adenoma (including multiple): 17/50 controls (*P* for trend, < 0.001), 19/50 at 6 mg/kg bw, 37/50 at 20 mg/kg bw ($P < 0.001$), and 44/50 at 60 mg/kg bw ($P < 0.001$); hepatocellular carcinoma (multiple): 1/50 controls, 3/50 at 6 mg/kg bw, 5/50 at 20 mg/kg bw, and 19/50 at 60 mg/kg bw ($P \leq 0.01$); hepatocellular carcinoma (including multiple): 6/50 controls (*P* for trend, < 0.001), 13/50 at 6 mg/kg bw ($P = 0.049$), 18/50 at 20 mg/kg bw ($P = 0.002$),

Table 3.1 Studies of carcinogenicity in experimental animals treated with *N,N*-dimethyl-*p*-toluidine by gavage in corn oil

Species, strain (sex) Age at start Duration Reference	Purity Dose regimen No. of animals at start No. of surviving animals	Incidence of tumours	Significance	Comments
Mouse, B6C3F$_1$/N (M) 5–6 wks 105 wks NTP (2012)	Purity, > 99% 0, 6, 20, 60 mg/kg bw 5 days/wk for 105 wks 50/group 34, 36, 31, 36	*Liver*		GLP study
		Hepatocellular adenoma (multiple): 17/50, 19/50, 27/50*, 26/50*	Trend: NR *$P \leq 0.05$	
		Hepatocellular adenoma (including multiple): 29/50, 34/50, 37/50, 36/50	NS	
		Hepatocellular carcinoma (multiple): 7/50, 7/50, 16/50*, 22/50**	Trend: NR *$P \leq 0.05$ **$P \leq 0.01$	
		Hepatocellular carcinoma (including multiple): 22/50, 25/50, 30/50, 36/50*	Trend: $P = 0.002$ *$P = 0.005$	
		Hepatocellular adenoma or carcinoma (combined): 38/50, 44/50, 47/50*, 48/50**	Trend: $P = 0.005$ *$P = 0.010$ **$P = 0.006$	
		Hepatoblastoma: 1/50, 5/50, 10/50*, 8/50**	*$P = 0.005$ **$P = 0.021$	
		Hepatocellular adenoma, hepatocellular carcinoma or hepatoblastoma (combined): 38/50, 45/50, 48/50*, 48/50**	Trend: $P = 0.006$ *$P = 0.004$ **$P = 0.006$	
Mouse, B6C3F$_1$/N (F) 5–6 wks 105 wks NTP (2012)	Purity, > 99% 0, 6, 20, 60 mg/kg bw 5 days/wk for 105 wks 50/group 43, 40, 39, 32	*Liver*		GLP study
		Hepatocellular adenoma (multiple): 2/50, 6/50, 29/50*, 35/50*	Trend: NR *$P \leq 0.01$	
		Hepatocellular adenoma (including multiple): 17/50, 19/50, 37/50*, 44/50*	Trend: $P < 0.001$ *$P < 0.001$	
		Hepatocellular carcinoma (multiple): 1/50, 3/50, 5/50, 19/50*	Trend: NR *$P \leq 0.01$	
		Hepatocellular carcinoma (including multiple): 6/50, 13/50*, 18/50**, 31/50***	Trend: $P < 0.001$ *$P = 0.049$ **$P = 0.002$ ***$P < 0.001$	
		Hepatocellular adenoma or carcinoma (combined): 20/50, 25/50, 42/50*, 45/50*	Trend: $P < 0.001$ *$P < 0.001$	
		Hepatoblastoma: 0/50, 1/50, 0/50, 4/50*	Trend: $P = 0.007$ *$P = 0.044$	

Table 3.1 (continued)

Species, strain (sex) Age at start Duration Reference	Purity Dose regimen No. of animals at start No. of surviving animals	Incidence of tumours	Significance	Comments
Mouse, B6C3F$_1$/N (F) 5–6 wks 105 wks NTP (2012) (cont.)		Hepatocellular adenoma, hepatocellular carcinoma, or hepatoblastoma (combined): 20/50, 26/50, 42/50*, 45/50*	Trend: $P < 0.001$ *$P < 0.001$	
		Lung		
		Alveolar/bronchiolar adenoma: 2/50, 4/50, 8/50*, 12/50**	Trend: $P < 0.001$ *$P = 0.039$ **$P < 0.001$	
		Alveolar/bronchiolar carcinoma: 0/50, 1/50, 2/50, 1/50	NS	
		Alveolar/bronchiolar adenoma or carcinoma (combined): 2/50, 5/50, 9/50*, 13/50**	Trend: $P < 0.001$ *$P = 0.021$ **$P < 0.001$	
		Forestomach		
		Squamous cell papilloma: 1/50, 5/50, 6/50*, 7/50**	Trend: $P = 0.037$ *$P = 0.049$ **$P = 0.017$	
		Squamous cell carcinoma: 0/50, 1/50, 0/50, 0/50	NS	
		Squamous cell papilloma or carcinoma (combined): 1/50, 6/50, 6/50*, 7/50**	*$P = 0.049$ **$P = 0.017$	
Rat, F344 (M) 6–7 wks 104 wks NTP (2012)	Purity, > 99% 0, 6, 20, 60 mg/kg bw 5 days/wk for 104 wks 50/group 37, 37, 31, 21	*Liver*		GLP study The incidence of thyroid follicular cell adenoma or carcinoma (combined) at 60 mg/kg bw was outside that of the range for this tumour in historical controls (all routes, 0–6%)
		Hepatocellular adenoma: 0/50, 0/50, 1/50, 1/50	NS	
		Hepatocellular carcinoma: 0/50, 0/50, 1/50, 6/50*	Trend: $P < 0.001$ *$P = 0.009$	
		Hepatocellular adenoma or carcinoma (combined): 0/50, 0/50, 2/50, 6/50*	Trend: $P < 0.001$ *$P = 0.009$	
		Nasal cavity		
		Transitional epithelium adenoma: 0/50, 3/49, 2/50, 11/49*	Trend: $P < 0.001$ *$P < 0.001$	
		Transitional epithelium carcinoma: 0/50, 0/49, 0/50, 2/49	Trend: $P = 0.033$	
		Transitional epithelium adenoma or carcinoma (combined): 0/50, 3/49, 2/50, 13/49*	Trend: $P < 0.001$ *$P < 0.001$	

Table 3.1 (continued)

Species, strain (sex) Age at start Duration Reference	Purity Dose regimen No. of animals at start No. of surviving animals	Incidence of tumours	Significance	Comments
Rat, F344 (M) 6–7 wks 104 wks NTP (2012) (cont.)		*Thyroid* Follicular cell adenoma: 1/50, 0/49, 1/50, 3/49 Follicular cell carcinoma: 0/50, 2/49, 1/50, 2/49 Follicular cell adenoma or carcinoma (combined): 1/50, 2/49, 2/50, 4/49	 NS NS NS	
Rat, F344 (F) 6–7 wks 105 wks NTP (2012)	Purity, > 99% 0, 6, 20, 60 mg/kg bw 5 days/wk for 105 wks 50/group 33, 42, 33, 23	*Liver* Hepatocellular adenoma: 0/50, 1/50, 1/50, 3/49 Hepatocellular carcinoma (multiple): 0/50, 0/50, 0/50, 1/49 Hepatocellular carcinoma (including multiple): 0/50, 0/50, 0/50, 4/49* Hepatocellular adenoma or carcinoma (combined): 0/50, 1/50, 1/50, 7/49* *Nasal cavity* Transitional epithelium adenoma: 0/50, 1/49, 0/50, 2/49	 Trend: $P = 0.044$ NS Trend: $P < 0.001$ *$P = 0.041$ Trend: $P < 0.001$ *$P = 0.003$ NS	GLP study The incidence of transitional epithelium adenoma of the nasal cavity at 60 mg/kg bw was outside that of the range for this tumour in historical controls (corn oil gavage studies, 0%; all routes, 0–2%)

bw, body weight; F, female; GLP, good laboratory practice; M, male; NR, not reported; NS, not significant; wk, week

and 31/50 at 60 mg/kg bw ($P < 0.001$); hepatocellular adenoma or carcinoma (combined): 20/50 controls (P for trend, < 0.001), 25/50 at 6 mg/kg bw, 42/50 at 20 mg/kg bw ($P < 0.001$), and 45/50 at 60 mg/kg bw ($P < 0.001$); and hepatoblastoma: 0/50 controls (P for trend, 0.007), 1/50 at 6 mg/kg bw, 0/50 at 20 mg/kg bw, and 4/50 at 60 mg/kg bw ($P = 0.044$). The incidence of hepatocellular adenoma, hepatocellular carcinoma or hepatoblastoma (combined) was 20/50 controls (P for trend, < 0.001), 26/50 at 6 mg/kg bw, 42/50 ($P < 0.001$) at 20 mg/kg bw, and 45/50 at 60 mg/kg bw ($P < 0.001$). The historical incidence for hepatoblastoma in studies on gavage in corn oil was 1/347 (0.3% ± 0.8%; range, 0–2%) and for all routes was 4/1195 (0.3% ± 0.8%; range, 0–2%) and that for hepatocellular adenoma, hepatocellular carcinoma or hepatoblastoma (combined) in studies on gavage in corn oil was 91/347 (26.2% ± 12.7%; range, 8–40%) and for all routes was 444/1195 (37.2% ± 22.9%; range, 6–82%). In addition, an increase was observed in the incidence of lung alveolar/bronchiolar adenoma: 2/50 controls (P for trend, < 0.001), 4/50 at 6 mg/kg bw, 8/50 at 20 mg/kg bw ($P = 0.039$), and 12/50 at 60 mg/kg bw ($P < 0.001$); and alveolar/bronchiolar adenoma or carcinoma (combined): 2/50 controls (P for trend, < 0.001), 5/50 at 6 mg/kg bw, 9/50 at 20 mg/kg bw ($P = 0.021$), and 13/50 at 60 mg/kg bw ($P < 0.001$). The historical incidence for alveolar/bronchiolar adenoma or carcinoma (combined) in studies on gavage in corn oil was 23/346 (6.7% ± 3.2%; range, 2–12%) and for all routes was 100/1196 (8.4% ± 4.3%; range, 2–22%). A few alveolar/bronchiolar carcinomas were found in treated groups (0/50 controls, 1/50 at 6 mg/kg bw, 2/50 at 20 mg/kg bw and 1/50 at 60 mg/kg bw). The incidence for this tumour was not significant and was within the historical control range, which was 7/346 (2.0% ± 2.0%; range, 0–4%) in studies on gavage in corn oil and 44/1196 (3.7% ± 3.3%; range, 0–14%) for all studies. Significant increases were also observed in the incidence of forestomach squamous cell papilloma: 1/50 controls (P for trend, 0.037), 5/50 at 6 mg/kg bw, 6/50 at 20 mg/kg ($P = 0.049$), and 7/50 at 60 mg/kg bw ($P = 0.017$); and forestomach squamous cell papilloma or carcinoma (combined): 1/50 controls, 6/50 at 6 mg/kg bw, 6/50 at 20 mg/kg bw ($P = 0.049$) and 7/50 at 60 mg/kg bw ($P = 0.017$). The historical incidence of forestomach squamous cell papilloma in studies of gavage in corn oil was 12/348 (3.5% ± 1.5%; range, 2–6%) and for all routes was 22/1198 (1.8% ± 1.7%; range, 0–6%) and that of forestomach squamous cell papilloma or carcinoma (combined) in studies of gavage in corn oil was 12/348 (3.5% ± 1.5%; range, 2–6%) and for all routes was 23/1198 (1.9% ± 1.6%; range, 0–6%). One female mouse given 6 mg/kg bw had a forestomach squamous cell carcinoma (0/50 controls, 1/50 at 6 mg/kg bw, 0/50 at 20 mg/kg bw, and 0/50 at 60 mg/kg bw). The historical incidence for forestomach squamous cell carcinoma in studies on gavage in corn oil was 0/348 and that for all routes was 1/1198 (0.1% ± 0.4%; range, 0–2%).

Treatment-related non-neoplastic lesions were seen in the liver, nose, lung, olfactory lobe and spleen in males and females. In females, increases in non-neoplastic lesions of the forestomach, bone marrow and mesenteric lymph node were also observed (NTP, 2012). [The strength of this study was that it was a 2-year cancer bioassay in males and females with a large number of animals per group, multiple doses, and in compliance with good laboratory practice.]

3.2 Rat

Groups of 50 male and 50 female Fischer 344/N rats (age, 6–7 weeks) were given *N*,*N*-dimethyl-*p*-toluidine (purity, > 99%) by gavage in corn oil at doses of 0 (control), 6, 20, or 60 mg/kg bw on 5 days per week for 104 weeks (males) or 105 weeks (females). At termination after 2 years, survival in male rats at 60 mg/kg bw was significantly lower than that in controls, which was attributed to the development of

treatment-related tumours. Mean body weights of males and females at 60 mg/kg bw were > 10% lower than those in the vehicle-control group after weeks 61 and 33, respectively (NTP, 2012; Dunnick et al., 2014).

In males, treatment-related increases in the incidence of hepatocellular tumours included those of hepatocellular carcinoma: 0/50 controls (*P* for trend, < 0.001), 0/50 at 6 mg/kg bw, 1/50 at 20 mg/kg bw, and 6/50 at 60 mg/kg bw (*P* = 0.009); and hepatocellular adenoma or carcinoma (combined): 0/50 controls (*P* for trend, < 0.001), 0/50 at 6 mg/kg bw, 2/50 at 20 mg/kg bw, and 6/50 at 60 mg/kg bw (*P* = 0.009). The incidence of hepatocellular adenoma was 0/50 controls, 0/50 at 6 mg/kg bw, 1/50 at 20 mg/kg bw, and 1/50 at 60 mg/kg bw. The historical incidence of hepatocellular carcinoma was 0/299 in studies of gavage in corn oil and 5/1249 (0.4% ± 1.0%; range, 0–4%) for all routes. Increases were also observed in the incidence of nasal cavity transitional epithelium adenoma: 0/50 controls (*P* for trend, < 0.001), 3/49 at 6 mg/kg bw, 2/50 at 20 mg/kg bw, and 11/49 at 60 mg/kg bw (*P* < 0.001); and nasal cavity transitional epithelium adenoma or carcinoma (combined): 0/50 controls (*P* for trend, < 0.001), 3/49 at 6 mg/kg bw, 2/50 at 20 mg/kg bw, and 13/49 at 60 mg//kg bw (*P* < 0.001). The historical incidence for nasal cavity transitional epithelium adenoma indicated that they have not previously been observed in historical controls (studies of gavage in corn oil: 0/299; all routes: 0/1248). The incidence of nasal cavity transitional epithelium carcinoma was not significantly increased by pairwise comparison, although 2 males given 60 mg/kg bw had these tumours (0/50 controls, 0/49 at 6 mg/kg bw, 0/50 at 20 mg/kg bw, and 2/49 at 60 mg/kg bw; *P* for trend, 0.033); no historical control data were available for this tumour type. There was a non-significant increase in thyroid gland follicular cell adenoma or carcinoma (combined) (1/50 controls, 2/49 at 6 mg/kg bw, 2/50 at 20 mg/kg bw, and 4/49 at 60 mg/kg bw), although the incidence at 60 mg/kg bw was outside of the incidence range for this tumour in historical controls. The incidence for thyroid gland follicular cell adenoma or carcinoma (combined) in the historical controls was 9/299 (3.0% ± 2.1%; range, 0–6%) in studies on gavage in corn oil and 23/1239 (1.9% ± 2.2%; range, 0–6%) for all routes. A non-significant increase in the incidence of thyroid gland follicular cell carcinoma was observed (0/50 controls, 2/49 at 6 mg/kg bw, 1/50 at 20 mg/kg bw, and 2/49 at 60 mg/kg bw), for which the historical control incidence was 3/299 (1.0% ± 1.7%; range, 0–4%) in studies on gavage in corn oil and 10/1239 (0.8% ± 1.5%; range, 0–4%) for all routes.

In females, the incidence of hepatocellular adenoma was significantly increased according to trend statistics (*P* = 0.044): 0/50 controls, 1/50 at 6 mg/kg bw, 1/50 at 20 mg/kg bw, and 3/49 at 60 mg/kg bw; and that of hepatocellular carcinoma was significantly increased at the highest dose: 0/50 controls, 0/50 at 6 mg/kg bw, 0/50 at 20 mg/kg bw, and 4/49 at 60 mg/kg bw (*P* = 0.041). A significant increase in the incidence of hepatocellular adenoma or carcinoma (combined) was also observed: 0/50 controls (*P* for trend, < 0.001), 1/50 at 6 mg/kg bw, 1/50 at 20 mg/kg bw, and 7/49 at 60 mg/kg bw (*P* = 0.003). The historical incidence of these tumours was 1/300 (0.3% ± 0.8%; range, 0–2%) in studies with administration by gavage in corn oil, and 12/1200 (1.0% ± 1.6%; range, 0–4%) for all routes. A non-significant increase in the incidence of nasal cavity transitional epithelium adenoma was also observed (0/50 controls, 1/49 at 6 mg/kg bw, 0/50 at 20 mg/kg bw, and 2/49 at 60 mg/kg bw), although the incidence in females given the highest dose was outside the historical range for this tumour, which was 0/299 in studies on gavage in corn oil, and 1/1196 (0.1% ± 0.4%; range, 0–2%) for all routes.

Treatment-related non-neoplastic lesions were seen in the liver and nose of males and females; non-neoplastic lesions also occurred in the spleen, kidney, and bone marrow of males

and females. In addition, significant increases in forestomach and mesenteric lymph node non-neoplastic lesions were found in male rats (NTP, 2012). [The strength of this study was that it was a 2-year cancer bioassay in males and females, with a large number of animals per group, multiple doses, and in compliance with good laboratory practice.]

4. Mechanistic and Other Relevant Data

4.1 Absorption, distribution, metabolism, excretion

4.1.1 Absorption, distribution, and excretion

(a) Humans

No data were available to the Working Group.

(b) Experimental systems

[U-^{14}C]-Labelled *N*,*N*-dimethyl-*p*-toluidine was rapidly absorbed after a single oral administration of 2.5, 25 or 250 mg/kg bw to male and female Fischer 344 rats and B6C3F$_1$ mice (four animals/treatment group) (Dix et al., 2007). Absorption of the dose was nearly complete based on the data on excretion and their similarity to those obtained from groups of rats and mice injected intravenously. Cumulative excretion amounted to about 90% in the urine and 4% in the faeces 24 hours after gavage. *N*,*N*-Dimethyl-*p*-toluidine-derived radioactivity appeared to have been widely distributed to the tissues. At the terminal 24-hour time-point, the assayed tissues, including blood, liver, kidney, skin, muscle and adipose tissue, contained 2–5% of the total dose. In rats, the highest concentration of radioactivity was detected in the liver, followed by the kidney and urinary bladder. The lung and liver contained the highest concentrations in mice. The tissue-to-blood ratio of *N*,*N*-dimethyl-*p*-toluidine-derived radioactivity at these sites was > 1. Male rats excreted about 60% of the total dose in urine within 6 hours of receiving a dose of 2.5 mg/kg bw, whereas male and female rats receiving 25 mg/kg bw excreted about half as much (i.e. about 30%). However, cumulative excretion in the urine was similar for both doses at the 24-hour time-point. These results indicated initial saturation of absorption and/or elimination of the higher dose. The data on urinary excretion for 2.5 and 25 mg/kg bw were similar over time for male mice. Female mice appeared to excrete less of the higher dose in the urine than males; however, this difference was probably due to poor recovery of radiolabel in the urine of one or more individuals. All of the other data on disposition in female mice were similar to those of males. [The Working Group noted that the data from groups of male rats and mice that received 250 mg/kg bw by gavage were compromised by acute toxicity.] Cumulative excretion of the dose in the high-dose rats amounted to only ~70%, possibly as a result of the initial acute toxicity. Most of the unexcreted radiolabel was present in the gastrointestinal tract at 24 hours. In a supplemental experiment reported to the National Toxicology Program, the absorption and excretion of a high dose were nearly complete at 72 hours after treatment, with about 2% of the total dose detected in tissues and the gastrointestinal tract (NTP, 2012). The data for male mice receiving 250 mg/kg bw in this study were not reported here due to death or unresolved morbidity associated with all individuals in the treatment group.

4.1.2 Metabolism

(a) Humans

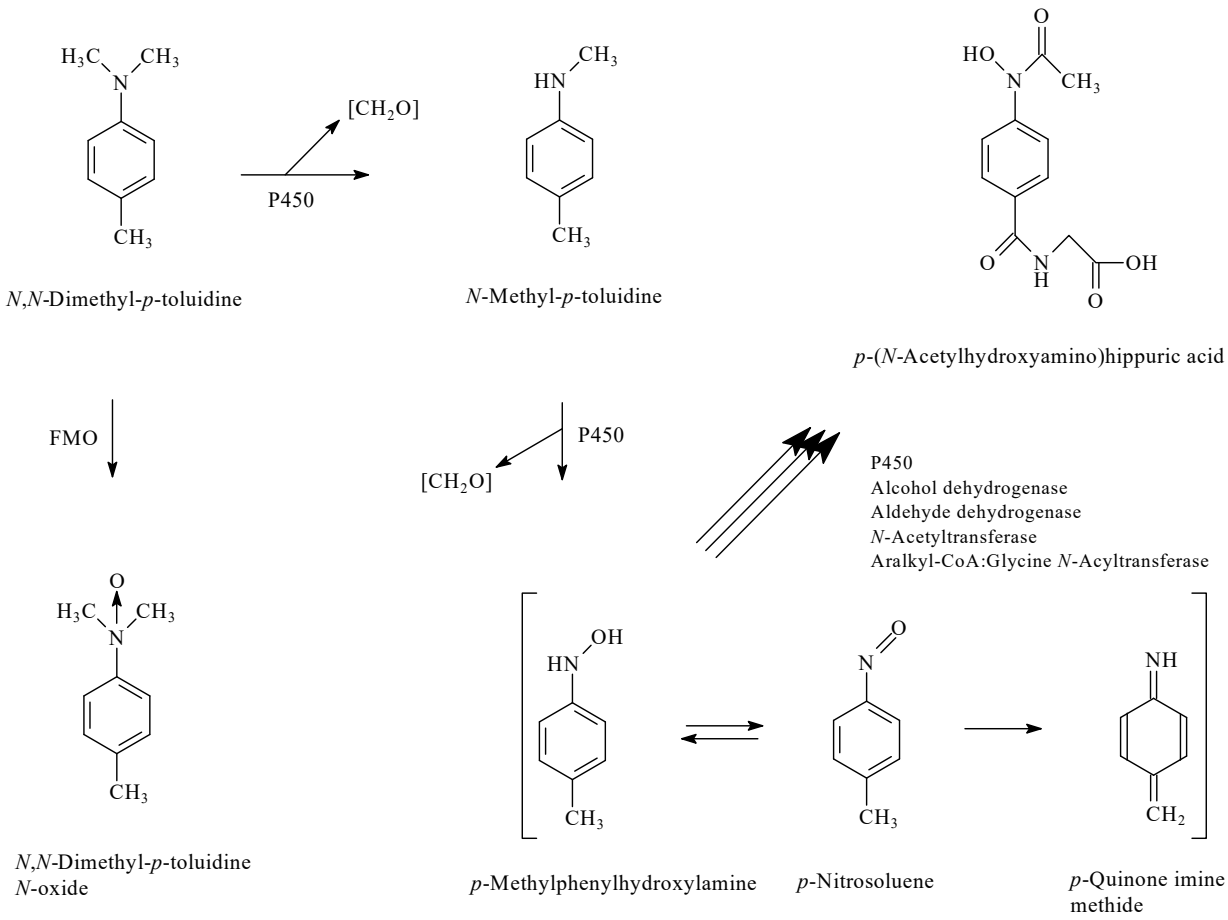
No data were available to the Working Group.

(b) Experimental systems

See Figure 4.1

As reported by Kim et al. (2007), the metabolism of *N*,*N*-dimethyl-*p*-toluidine was rapid and

Fig. 4.1 Known and postulated metabolites of *N,N*-dimethyl-*p*-toluidine in rats



Adapted from Kim et al. (2007) and Dunnick et al. (2014)
FMO, flavin-containing monooxygenase; P450, cytochrome P450; coA, coenzyme A

extensive in rats in a study conducted by Dix et al. (2007). The major radiolabelled metabolite in rat urine was identified as *p*-(*N*-acetylhydroxyamino)hippuric acid that was catalysed by cytochrome P450, alcohol and aldehyde dehydrogenases, *N*-acetyl transferase and aralkyl-coenzyme A:glycine-*N*-acyltransferase. The urine also contained *N*-methyl-*p*-toluidine, an oxidative product of *N,N*-dimethyl-*p*-toluidine, and a precursor of the glycine conjugate.

Intermediates in this pathway are postulated to include *p*-methylphenylhydroxylamine and an electrophilic *p*-quinone imine methide (4-methylene-2,5-cyclohexadiene-1-imine) (Kim et al., 2007; Dunnick et al., 2014). The formation of *p*-methylphenylhydroxylamine may lead to the oxidation of haemoglobin (Potter et al., 1988) or DNA binding (Marques et al., 1997). *N,N*-Dimethyl-*p*-toluidine *N*-oxide, considered to be catalysed primarily by flavin-containing monooxygenases, was also excreted in urine, as was a small amount of parent *N,N*-dimethyl-*p*-toluidine (Kim et al., 2007).

Table 4.1 Genetic and related effects of *N,N*-dimethyl-*p*-toluidine in non-human mammals in vivo

Species, strain (sex)	Tissue	End-point/test	Results	Dose (LED/HID)	Reference
Rat, Sprague-Dawley (M)	Liver	DNA damage/ DNA strand breaks	±	4 mg/kg bw, gavage and i.p.	Taningher et al. (1993)
Rat, Sprague-Dawley (M)	Liver	DNA damage/ DNA strand breaks	+	60 mg/kg bw, gavage, 4 days	NTP (2012)
Mouse, Balb/C (M)	Liver	DNA damage/ DNA strand breaks	±	1 mg/kg bw, gavage and i.p.	Taningher et al. (1993)
Mouse, B6C3F$_1$ (M)	Blood leukocytes, liver	DNA damage/ DNA strand breaks	–	75 mg/kg bw × 4 days, gavage	NTP (2012)
Mouse, B6C3F$_1$ (M & F)	Peripheral blood	Chromosomal damage/ micronucleus formation	–	125 mg/kg bw per day for 3 mo; gavage	NTP (2012)
Mouse, B6C3F$_1$ (M)	Peripheral blood	Chromosomal damage/ micronucleus formation	–	75 mg/kg bw × 4 days, gavage	NTP (2012)

+, positive; –, negative; ±, equivocal (variable responses in several experiments within an adequate study); bw, body weight; F, female; HID, highest ineffective dose; i.p., intraperitoneal; LED, lowest effective dose; M, male; mo, month

4.2 Mechanisms of carcinogenesis

The evidence on the key characteristics of carcinogens (Smith et al., 2016), concerning whether *N,N*-dimethyl-*p*-toluidine is genotoxic and alters cell proliferation, cell death, and nutrient supply, is summarized below.

4.2.1 Genetic and related effects

(a) Humans

No data in exposed humans were available to the Working Group. In cultured human lymphocytes, the bone cement polymethyl methacrylate, containing *N,N*-dimethyl-*p*-toluidine (2.6% w/w) and hydroquinone (75 ± 15 ppm), significantly increased the frequency of micronucleus formation. However, the components of the mixture were not tested individually (Bigatti et al., 1994).

(b) Experimental systems

See Table 4.1, Table 4.2, and Table 4.3

(i) In vivo

In the livers of male BALB/c mice and male Sprague-Dawley rats given *N,N*-dimethyl-*p*-toluidine by gavage or intraperitoneal injection, DNA fragmentation was modestly increased by the alkaline elution test (Taningher et al., 1993).

The alkaline comet assay gave negative results in liver cells or blood leukocytes of male B6C3F$_1$ mice treated by gavage once daily for 4 days at 30–75 mg/kg bw. In contrast, male Sprague-Dawley rats given daily doses of 60 mg/kg bw for 4 days had a small but statistically significant (P = 0.024) increased percentage of tail DNA in the liver cells compared with the group administered the corn-oil vehicle only (NTP, 2012).

Neither the frequencies of micronucleated erythrocytes nor the percentage of circulating reticulocytes were altered in the peripheral blood of male or female B6C3F$_1$/N mice treated by gavage with *N,N*-dimethyl-*p*-toluidine, suggesting that neither chromosomal damage nor bone marrow toxicity were induced in mice within the dose range and time periods tested (NTP, 2012).

(ii) In vitro

N,N-Dimethyl-*p*-toluidine showed both aneugenic and clastogenic activity in a concentration–related manner in the absence of metabolic activation in Chinese hamster V79 cells (Taningher et al., 1993).

Table 4.2 Genetic and related effects of *N*,*N*-dimethyl-*p*-toluidine in non-human mammalian cells in vitro

Test system, tissue	End-point/ test	Results	Agent, concentration (LEC/HIC)	Comments	Reference
Chinese hamster, CHO-K1 ovary cell line	Chromosomal damage/ micronucleus formation	+	Camphorquinone/DMPT (equimolar), 0–1 mM	DMPT alone was not tested; antioxidants had preventive effects	Li et al. (2007)
Chinese hamster, CHO-K1 ovary cell line	Chromosomal damage/ micronucleus formation	+	9-Fluorenone/DMPT (equimolar), 0–0.5 mM	DMPT alone was not tested; antioxidants had preventive effects	Li et al. (2008)
Chinese hamster lung, V79 cells	Chromosomal damage/ micronucleus formation	+	DMPT, 0.3 mM	Dose-dependent response (0.3–1.2 mM)	Taningher et al. (1993)

+, positive; DMPT, *N*,*N*-dimethyl-*p*-toluidine; HIC, highest ineffective concentration; LEC, lowest effective concentration

A concentration-related increase in micronuclei was observed in the CHO-K1 ovary cell line exposed to camphorquinone and *N*,*N*-dimethyl-*p*-toluidine or 9-fluorenone and *N*,*N*-dimethyl-*p*-toluidine ($P < 0.05$), with or without visible light irradiation (Li et al., 2007, 2008) [*N*,*N*-dimethyl-*p*-toluidine was not tested alone].

N,*N*-Dimethyl-*p*-toluidine was marginally positive in *Salmonella typhimurium* strain TA100 in the presence and absence of metabolic activation, and in strain TA104 in the presence of metabolic activation, but not in TA98 with or without metabolic activation. The compound was not mutagenic in plate incorporation tests (Miller et al., 1986).

Negative results were reported with or without metabolic activation in *Salmonella typhimurium* strains TA97, TA98, TA100 and TA1535 and in *Escherichia coli* WP2 *uvrA*/pKM101 (Taningher et al., 1993; NTP, 2012).

When tested in a bioluminescent test for bacterial genotoxicity using dark mutants of a marine luminous bacterium (*Vibrio fischeri* M169) and a 24-hour exposure period, *N*,*N*-dimethyl-*p*-toluidine showed considerable genotoxic activity at 4 mM [the half maximal inhibitory concentration value was also approximately 4 mM] (Nomura et al., 2006).

Exposure to camphorquinone in association with *N*,*N*-dimethyl-*p*-toluidine induced DNA strand breaks in PhiX-174 RF double-stranded plasmid DNA (Pagoria et al., 2005; Winter et al., 2005; Lee et al., 2007) [*N*,*N*-dimethyl-*p*-toluidine was not tested alone].

4.2.2 Altered cell proliferation or death

(a) Humans

No data in exposed humans were available to the Working Group.

N,*N*-Dimethyl-*p*-toluidine did not induce cytotoxicity in cultured human oral keratinocytes (OKF6/TERT 2), and simultaneous treatment with camphorquinone and *N*,*N*-dimethyl-*p*-toluidine did not affect apoptosis (Volk et al., 2014).

When assessed in human gingival fibroblasts in vitro, *N*,*N*-dimethyl-*p*-toluidine (500 µM) induced a significant and sustained accumulation of cells in the G0/G1 stage of the cell cycle compared with controls at 24 hours, implying that the growth inhibitory effect resulted from the arrest of DNA replication. The pattern of cell

Table 4.3 Genetic and related effects of *N,N*-dimethyl-*p*-toluidine in bacterial mutation tests

Species	Strain	End-point/ test	Results		Concentration (LEC/HIC)	Comments	Reference
			Without metabolic activation	With metabolic activation			
Salmonella typhimurium	TA98 TA100 TA104	Mutation/ reverse mutation (spot test)	– ± –	– ± ±	10 µL (of 300 µg/µL)/ plate	Negative in plate incorporation tests	Miller et al. (1986)
Salmonella typhimurium	TA97, TA98, TA100	Mutation/ reverse mutation	–	–	70 µg/plate		Taningher et al. (1993)
Salmonella typhimurium	TA97, TA98, TA100, TA1535	Mutation/ reverse mutation	–	–	1000 µg/plate		NTP (2012)
Salmonella typhimurium	TA98, TA100	Mutation/ reverse mutation	–	–	1500 µg/plate		NTP (2012)
Escherichia coli	WP2 *uvrA*/ pKM101	Mutation/ reverse mutation	–	–	1500 µg/plate		NTP (2012)
Vibrio fischeri	M169	Mutation/ other	+	NT	4 mM	Bioluminescence assay	Nomura et al. (2006)

+, positive; –, negative; ±, equivocal (variable responses in several experiments within an adequate study); DMPT, *N,N*-dimethyl-*p*-toluidine; HIC, highest ineffective concentration; LEC, lowest effective concentration; NT, not tested

death was consistent with necrosis (Masuki et al., 2007).

In human osteoblastic cells exposed to different bone-cement extracts, a significant correlation was found between the concentration of *N,N*-dimethyl-*p*-toluidine present in the extracts (up to 1 µg/100 mL) and a delay in cell-replication cycle (Stea et al., 1997). [The Working Group noted that the extracts did not contain *N,N*-dimethyl-*p*-toluidine only.]

(b) Experimental systems

In rat polymorphonuclear leukocytes, *N,N*-dimethyl-*p*-toluidine increased cytotoxicity in a concentration-dependent manner (Liso et al., 1997).

4.3 Data relevant to comparisons across agents and end-points

N,N-Dimethyl-*p*-toluidine was not tested by the Tox21 and ToxCast™ research programmes of the government of the USA (Kavlock et al., 2012; Tice et al., 2013). Analyses of other compounds evaluated in this volume with high-throughput screening data are presented in the *Monograph* on 1-bromopropane in the present volume.

4.4 Susceptibility to cancer

No data were available to the Working Group.

4.5. Other adverse effects

4.5.1 Humans

Methaemoglobinaemia, which is consistent with metabolism of *N*,*N*-dimethyl-*p*-toluidine to *p*-methylphenylhydroxylamine, was described in two poisoning cases of children who had ingested artificial fingernail solutions containing acetone, ethyl methacrylate, and *N*,*N*-dimethyl-*p*-toluidine (Potter et al., 1988) or acrylic ester monomers and *N*,*N*-dimethyl-*p*-toluidine (Kao et al., 1997).

Allergic responses to dental materials containing *N*,*N*-dimethyl-*p*-toluidine has been reported (Tosti et al., 1990; Verschueren & Bruynzeel, 1991). Positive reactions to *N*,*N*-dimethyl-*p*-toluidine were found in seven cases, all of whom showed rapid onset of aseptic loosening of total hip replacements, out of 70 patients (Haddad et al., 1996).

4.5.2 Experimental systems

In a chronic study, *N*,*N*-dimethyl-*p*-toluidine caused methaemoglobinaemia in F344/N rats after administration by gavage (NTP, 2012; Dunnick et al., 2014). Metabolic activation to *p*-methylphenylhydroxylamine was inferred from the presence of *p*-(*N*-acetylhydroxyamino) hippuric acid in the urine of rats given the compound (Kim et al., 2007; see Section 4.1.2). Macrocytic regenerative anaemia, methaemoglobinaemia, and increased Heinz body production was seen in rats (and to a lesser extent in mice) in a subchronic gavage study. Bone marrow hyperplasia occurred in exposed rats, but not in mice (NTP, 2012; Dunnick et al., 2014).

5. Summary of Data Reported

5.1 Exposure data

N,*N*-Dimethyl-*p*-toluidine is a chemical with a high production volume that is used worldwide as an accelerator in the preparation of dental materials, bone cements, industrial glues and artificial-fingernail preparations, and also as an intermediate in the production of dyes and pesticides. Chemical-production workers, surgeons, surgical staff, dentists, dental technicians, nail-salon operators, and users of industrial glues may be exposed to *N*,*N*-dimethyl-*p*-toluidine by inhalation and through the skin. Exposure among the general population may occur from dental material, bone cement, sniffing glue and fingernail solutions. No quantitative data on exposure or occupational exposure limits were identified.

5.2 Human carcinogenicity data

No data were available to the Working Group.

5.3 Animal carcinogenicity data

N,*N*-Dimethyl-*p*-toluidine was tested for carcinogenicity by oral administration (gavage) in one good laboratory practice (GLP) study in male and female mice and one GLP study in male and female rats.

In mice, *N*,*N*-dimethyl-*p*-toluidine caused a significantly increased incidence (with a significant positive trend, except for hepatoblastoma in males) of hepatocellular carcinoma, hepatoblastoma, hepatocellular adenoma or carcinoma (combined), and hepatocellular adenoma, hepatocellular carcinoma or hepatoblastoma (combined) in males, and hepatocellular adenoma, hepatocellular carcinoma, hepatoblastoma, hepatocellular adenoma or carcinoma (combined), and hepatocellular adenoma,

hepatocellular carcinoma or hepatoblastoma (combined) in females. It also caused a significantly increased incidence of alveolar/bronchiolar adenoma of the lung (with a significant positive trend), alveolar/bronchiolar adenoma or carcinoma (combined) of the lung (with a significant positive trend), forestomach squamous cell papilloma (with a significant positive trend) and forestomach squamous cell papilloma or carcinoma (combined) in female mice.

In rats, *N,N*-dimethyl-*p*-toluidine caused a significantly increased incidence (with a significant positive trend) of hepatocellular carcinoma, hepatocellular adenoma or carcinoma (combined), adenoma of the transitional epithelium of the nasal cavity and adenoma or carcinoma (combined) of the transitional epithelium of the nasal cavity in males. A significant positive trend was observed in the incidence of carcinoma of the transitional epithelium of the nasal cavity in males. Increases in the incidence of follicular cell adenoma or carcinoma (combined) of the thyroid gland in males were not significant by the pairwise or trend tests, although the incidence of these tumours at the highest dose exceeded the range for historical controls for these tumours. A significant positive trend was observed in the incidence of hepatocellular adenoma, hepatocellular carcinoma and hepatocellular adenoma or carcinoma (combined) in females. The incidences of hepatocellular carcinoma and hepatocellular adenoma or carcinoma (combined) in females given the highest dose were significantly increased compared with controls. The incidence of adenoma of the transitional epithelium of the nasal cavity in females given the highest dose exceeded the range for historical controls for this tumour.

5.4 Mechanistic and other relevant data

In rats and mice, *N,N*-dimethyl-*p*-toluidine is rapidly absorbed after oral administration. *N,N*-Dimethyl-*p*-toluidine and/or its metabolites are distributed widely to the tissues and the highest concentrations are detected in the liver and kidney of rats and lung and liver of mice. *N,N*-Dimethyl-*p*-toluidine is rapidly metabolized and excreted primarily in the urine. The major metabolic pathway leading to the formation of *p*-(*N*-acetylhydroxyamino)hippuric acid in rats includes putative reactive intermediates. The fate of *N,N*-dimethyl-*p*-toluidine has not been determined in humans.

With respect to the key characteristics of human carcinogens, there is *moderate* evidence that *N,N*-dimethyl-*p*-toluidine is electrophilic or can be metabolically activated, is genotoxic, or alters cell proliferation, cell death or nutrient supply.

A putative reactive intermediate of *N,N*-dimethyl-*p*-toluidine, *p*-methylphenylhydroxylamine, was implicated in the formation of methaemoglobinaemia in a case of unintentional (human) oral exposure to *N,N*-dimethyl-*p*-toluidine. *N*-Hydroxylated arylamines are capable of forming DNA adducts. The formation of an electrophilic *p*-quinone imine methide as a result of the metabolism of *N,N*-dimethyl-*p*-toluidine is plausible.

A significant increase in the frequency of micronucleus formation was observed in cultured human lymphocytes treated with the bone cement polymethyl methacrylate containing *N,N*-dimethyl-*p*-toluidine. *N,N*-Dimethyl-*p*-toluidine exhibited aneugenic and clastogenic activity in Chinese hamster V79 cells. *N,N*-Dimethyl-*p*-toluidine gave negative or marginally positive results in other assays, including mutation in *Salmonella* and DNA strand breaks in rats and mice.

The cell-replication cycle was delayed in human osteoblastic cells exposed to bone-cement extracts containing *N*,*N*-dimethyl-*p*-toluidine. *N*,*N*-Dimethyl-*p*-toluidine had a growth-inhibitory effect in human gingival fibroblasts in vitro and caused cytotoxicity in rat polymorphonuclear leukocytes, but not in cultured human oral keratinocytes.

There were few other data on other key characteristics of carcinogens (alters DNA repair or causes genomic instability, induces epigenetic alterations, induces oxidative stress, induces chronic inflammation, is immunosuppressive, modulates receptor-mediated effects, or causes immortalization).

6. Evaluation

6.1 Cancer in humans

There is *inadequate evidence* in humans for the carcinogenicity of *N*,*N*-dimethyl-*p*-toluidine.

6.2 Cancer in experimental animals

There is *sufficient evidence* in experimental animals for the carcinogenicity of *N*,*N*-dimethyl-*p*-toluidine.

6.3 Overall evaluation

N,*N*-Dimethyl-*p*-toluidine is *possibly carcinogenic to humans (Group 2B)*.

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