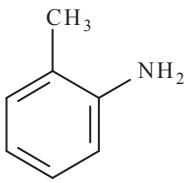
ortho-TOLUIDINE

ortho-Toluidine was considered by previous IARC Working Groups in 1977, 1981, 1987, 2000, and 2008 (IARC, 1978, 1982, 1987, 2000, 2010). Since that time new data have become available, which have been incorporated in this *Monograph,* and taken into consideration in the present evaluation.

1. Exposure Data

1.1 Identification of the agent

From IARC (2010), unless indicated otherwise
Chem. Abstr. Serv. Reg. No.: 95-53-4
Chem. Abstr. Serv. Name:
2-Methylbenzenamine



C_7H_9N
Relative molecular mass: 107.15
Description: Light yellow liquid becoming reddish brown on exposure to air and light
Boiling-point: 200–202 °C (O'Neil, 2006)
Solubility: Slightly soluble in water; soluble in alcohol, ether, and dilute acids

1.2 Uses

ortho-Toluidine is used as an intermediate in the synthesis of the large-volume herbicides, metolachlor and acetochlor, in the manufacture of more than 90 dyes and pigments (e.g. acid-fast dyestuffs, azo pigment dyes, triarylmethane dyes, sulfur dyes, and indigo compounds), and as an intermediate for synthetic rubber and rubber-vulcanizing chemicals, pharmaceuticals, pesticides, and other chemicals. *ortho*-Toluidine is also used in the clinical laboratory as an ingredient in a reagent for glucose analysis, and for tissue staining (IARC, 2010; NTP, 2004).

1.3 Human exposure

1.3.1 Occupational exposure

Occupational exposure to *ortho*-toluidine can occur by inhalation or skin contact during its production, or during the production of dyes, pigments and rubber chemicals manufactured from this chemical. Laboratory and medical personnel may be exposed when using *ortho*-toluidine for staining tissues (IARC, 2010).

From the US National Occupational Exposure Survey (1981–83) it was estimated that 30000 workers, including approximately 15500 women, were potentially exposed to *ortho*-toluidine (NIOSH, 1990). No estimates of the number of exposed workers in the European Union have been reported.

At a chemical plant in the former Soviet Union where *ortho*-toluidine was produced via reduction of *ortho*-nitrotoluene, workers were exposed to concentrations of *ortho*-toluidine in the air that generally exceeded the maximum permissible concentration [of 3 mg/m^3, IARC (1982)] by 2–7-fold. In a total of 215 air samples, the highest exposure levels were observed during distillation and extraction processes (25–28.6 mg/m^3). Dermal exposures also were documented (Khlebnikova *et al.*, 1970). Measurements in the 1940s in a US dye-production plant indicated that the concentration of *ortho*-toluidine was < 0.5 ppm [2 mg/m^3] in the workroom air and in the breathing zone of the workers, and < 0.3–1.7 mg/L in the urine of workers engaged in the production of thioindigo (Ott & Langner, 1983). Exposure to *ortho*-toluidine was also reported to occur in plants involved in dye-production in Italy (Rubino *et al.*, 1982), Germany (Stasik, 1988), and the USA (New Jersey) (Delzell *et al.*, 1989), but no data on exposure levels were provided.

Concentrations of *ortho*-toluidine in indoor air in plants producing rubber antioxidants or vulcanising rubber articles ranged up to several hundred µg/m^3 and *ortho*-toluidine concentrations in post-shift urine samples were around 100 µg/L (Ward *et al.*, 1991; Teass *et al.*, 1993; Ward *et al.*, 1996; Korinth *et al.*, 2006).

Medical and laboratory personnel also are potentially exposed to *ortho*-toluidine, although air concentrations are reportedly low (EPA, 1984; Kauppinen *et al.*, 2003).

1.3.2 Non-occupational exposure

Significant non-occupational exposures to *ortho*-toluidine may result from the use of some hair dyes, the local anaesthetic prilocaine, or tobacco smoke. In a study from Turkey (Akyüz & Ata, 2008), *ortho*-toluidine was found in 34 of the 54 hair dyes tested, at levels up to 1547 µg/g. Prilocaine, a widely used anaesthetic, is metabolized to *ortho*-toluidine. In 25 patients who received local anaesthesia, the average amount of *ortho*-toluidine adducts to haemoglobin (Hb) increased 6–360-fold, from 0.54 ± 0.95 ng/g Hb before treatment to 22 ± 13.2 ng/g Hb at 24 hours after surgery (Gaber *et al.*, 2007). *ortho*-Toluidine has been measured in mainstream cigarette smoke at 9–144 ng per cigarette (Stabbert *et al.*, 2003), and concentrations in urine of smokers are higher than in non-smokers (Riffelmann *et al.*, 1995; Riedel *et al.*, 2006). *ortho*-Toluidine has also been detected in surface waters and industrial effluents (Shackelford & Keith, 1976; Neurath *et al.*, 1977; EPA, 1984; NTP, 2004), in vegetables such as kale, celery and carrots, in the volatile aroma of black tea (Vitzthum *et al.*, 1975; Neurath *et al.*, 1977), and in breast milk (DeBruin *et al.*, 1999), but levels are generally very low.

2. Cancer in Humans

Several cohort studies have been conducted among workers potentially exposed to *ortho*-toluidine (Table 2.1 available at http://monographs.iarc.fr/ENG/Monographs/vol100F/100F-06-Table2.1.pdf). Rubino *et al.* (1982) reported excess bladder-cancer risks in relation to *ortho*-toluidine exposure, however, other exposure to potential bladder carcinogens also occurred in this work environment. Ward *et al.* (1991) reported an excess in bladder cancer in 1749 US workers employed in the production of rubber additives from *ortho*-toluidine and aniline. Risks were greatest for workers with the strongest likelihood of exposure and for those with long-term exposure (> 10 years). Further cases of bladder cancer in this facility were reported by Markowitz & Levin (2004), but rates were not calculated. Exposure to low-level 4-aminobiphenyl was suspected, so a protein-adduct biomarker study was carried out (Ward *et al.*, 1996), which supported the conclusion that

ortho-toluidine was the most likely cause of the bladder-cancer excess, because 4-aminobiphenyl adducts to haemoglobin were unrelated to work in the facility. Using revised exposure categories, Carreón *et al.* (2010) conducted a re-analysis of the data and confirmed that workers in this plant have an increased risk for bladder cancer.

Sorahan *et al.* (2000) and Sorahan (2008) reported an excess in bladder-cancer risk in workers exposed to *ortho*-toluidine in the United Kingdom. Sorahan (2008) found increased risks with longer duration of employment in departments where *ortho*-toluidine was processed ($P < 0.05$), after adjusting for exposure to other bladder carcinogens in the factory.

Overall, the epidemiological studies show consistent associations between exposure to *ortho*-toluidine and bladder cancer. Although exposure to other bladder carcinogens occurred for several of the cohorts, the overall evidence is consistent with an association of exposure to *ortho*-toluidine and bladder cancer.

3. Cancer in Experimental Animals

Studies on the carcinogenicity of *ortho*-toluidine in the mouse, rat and hamster after oral administration or subcutaneous injection were reviewed in previous *IARC Monographs* (IARC, 2000, 2010). There have been no additional carcinogenicity studies in animals reported since the most recent evaluation (IARC, 2010).

ortho-Toluidine was tested for carcinogenicity as its hydrochloride salt by oral administration in the feed in two experiments in mice and in three experiments in rats, and as the free base in one limited subcutaneous-injection experiment in hamsters. Results of adequately conducted carcinogenicity studies are summarized in Table 3.1.

Oral administration of *ortho*-toluidine to male and female mice caused an increased incidence of haemangiomas and haemangiosarcomas (combined) in both sexes in one study (Weisburger *et al.*, 1978). The same result was found in male rats in another study, but the separate incidence for haemangiosarcomas was also increased (NTP, 1979). The incidences of hepatocellular carcinomas and of hepatocellular adenomas and carcinomas combined were increased in females in the latter study (NTP, 1979).

Oral administration of *ortho*-toluidine to male rats caused an increased incidence of subcutaneous fibromas and fibrosarcomas (combined) in one study (Weisburger *et al.*, 1978), and of skin and spleen fibromas, mammary gland fibroadenomas and peritoneal sarcomas in another (Hecht *et al.*, 1982). In a third study in male and female rats, *ortho*-toluidine increased the incidence of subcutaneous fibromas and of mesotheliomas of multiple organs or the *tunica vaginalis* in males, and of mammary gland fibroadenomas and urinary bladder transitional-cell carcinomas in females. An increased incidence of fibrosarcomas, angiosarcomas, osteosarcomas or sarcomas (not otherwise specified) (combined) of multiple organs (mainly subcutis and spleen or bone) was also observed in both sexes; and a significant increase in the incidence of fibrosarcomas and sarcomas of multiple organs in males, and of spleen angiosarcomas and osteosarcomas of multiple organs in females (NTP, 1979).

When administered as the free base by subcutaneous injection to male and female Syrian golden hamsters, *ortho*-toluidine produced no increase in tumour incidence compared with controls (Hecht *et al.*, 1983).

Table 3.1 Carcinogenicity studies in experimental animals fed *ortho*-toluidine

Species, strain (sex) Duration Reference	Route Dosing regimen, Animals/group at start	Incidence of tumours	Significance	Comments
Mouse, Swiss CD-1 (M, F) 21 mo Weisburger *et al.* (1978)	Groups of 25 M and 25 F mice were fed a diet containing 0, 16000 or 32000 ppm *ortho*-toluidine hydrochloride. After 3 mo, due to toxicity, doses were lowered to 8000 or 16000 ppm for a further 15 mo. Treated animals were then kept without treatment for an additional 3 mo.	Haemangiomas and Haemangiosarcomas (combined): M–0/14 (concurrent control), 5/99 (pooled control), 5/14*, 9/11* F–0/15, 9/102, 5/18**, 9/21*	*$P < 0.025$ (vs all controls **$P < 0.05$ (vs all controls)	Purity, 97–99% Pooled controls: additional controls used for the other compounds tested in the study. Tumour incidence of concurrent and pooled controls were compared statistically (both separately and together) with those of treated groups. Separate incidence for haemangiomas and haemangiosarcomas NR.
Mouse, B6C3F$_1$ (M, F) 103 wk NTP (1979)	Groups of 50 M and 50 F mice, were fed a diet containing 1000 or 3000-ppm *ortho*-toluidine hydrochloride for 103 wk. A group of 20 M and 20 F mice served as untreated controls.	*Males* Haemangiomas and Haemangiosarcomas (combined): 1/19, 2/50, 12/50* Haemangiosarcomas: 1/19, 1/50, 10/50* *Females* Hepatocellular adenomas and carcinomas (combined): 0/20, 4/49, 13/50** Hepatocellular carcinomas: 0/20, 2/49, 7/50***	*$P < 0.005$ (trend test) **$P < 0.007$ (Fisher's exact test), $P < 0.001$ (trend test) ***$P = 0.015$ (trend test)	Purity > 99%
Rat, Sprague-Dawley CD (M) 24 mo Weisburger *et al.* (1978)	Groups of 25 M rats were fed a diet containing 0, 8000 or 16000-ppm *ortho*-toluidine hydrochloride. After 3 mo, due to toxicity, doses were lowered to 4000 or 8000 ppm for a further 15 mo. Treated animals were then kept without treatment for an additional 6 mo.	Subcutaneous fibromas and fibrosarcomas (combined): M–0/16 (concurrent control), 18/111 (pooled control), 18/23*, 21/24* Urinary bladder transitional-cell carcinomas: M–0/16, 5/111, 3/23, 4/24	*$P < 0.025$ (vs all controls)	Purity, 97–99% Pooled controls: additional controls used for the other compounds tested in the study. Tumour incidences of concurrent and pooled controls were compared statistically (both separately and together) with those of treated groups
Rat, Fischer F344 (M) 93 wk Hecht *et al.* (1982)	Groups of 30 M rats were fed a diet containing 0 or 4000 ppm *ortho*-toluidine hydrochloride for 72 wk. Total dose of *ortho*-toluidine hydrochloride ingested was 31.3 g/rat.	Skin fibromas: 1/27, 25/30* Spleen fibromas: 0/27, 10/30* Mammary gland fibroadenomas: 0/27, 11/30* Peritoneal sarcomas: 0/27, 9/30**	*$P < 0.001$ (Fisher's exact test) **$P < 0.01$ (Fisher's exact test)	Purity NR

Table 3.1 (continued)

Species, strain (sex) Duration Reference	Route Dosing regimen, Animals/group at start	Incidence of tumours	Significance	Comments
Rat, Fischer F344 (M, F) 104 wk NTP (1979)	Groups of 50 M and 50 F rats, were fed a diet containing 3000 or 6000-ppm *ortho*-toluidine hydrochloride for 101–104 wk. A group of 20 M and 20 F rats served as untreated controls.	*Males* Sarcomas NOS, fibrosarcomas, angiosarcomas or osteosarcomas (combined) of multiple organs (mainly subcutis and spleen or bone): 0/20, 15/50**, 37/49* Sarcomas NOS of multiple organs: 0/20, 3/50, 11/49*** Fibrosarcomas of multiple organs: 0/20, 8/50, 20/49* Subcutaneous integumentary fibromas: 0/20, 28/50*, 27/49* Mesotheliomas of multiple organs or *tunica vaginalis*: 0/20, 17/50*, 9/49*** *Females* Sarcomas NOS, fibrosarcomas, osteosarcomas or angiosarcomas (combined) of multiple organs (mainly subcutis and spleen or bone): 0/20, 3/50, 21/49* Osteosarcomas of multiple organs: 0/20, 0/50, 18/49**** Spleen angiosarcomas: 0/20, 7/49, 9/49*** Urinary bladder transitional-cell carcinomas: 0/20, 9/45***, 22/47* Mammary gland fibroadenomas: 6/20, 20/50, 35/49*****	*$P < 0.001$ **$P = 0.003$ ***$P < 0.05$ ****$P = 0.001$ *****$P = 0.002$	Purity > 99% Mortality of male and female rats was significantly increased by treatment ($P < 0.001$).

F, female; M, male; mo, month or months; NOS, not otherwise specified; NR, not reported; vs, versus; wk, week or weeks

4. Other Relevant Data

A general Section on "Aromatic amines: metabolism, genotoxicity, and cancer susceptibility" appears as Section 4.1 in the *Monograph* on 4-aminobiphenyl in this volume.

ortho-Toluidine is a constituent of tobacco smoke and it is excreted in larger amounts in the urine of smokers than of non-smokers (Riedel *et al.*, 2006). *ortho*-Toluidine induced urinary bladder and mammary gland tumours in rats and liver tumours and haemangiosarcomas in mice. The risk for cancer of the urinary bladder was elevated in workers exposed to *ortho*-toluidine. This substance has been evaluated in a large number of genetic toxicology studies (IARC, 2010); however, there has been much inconsistency in the results reported.

The metabolism of *ortho*-toluidine has not yet been fully characterized, but the available data indicate a preferential ring-oxidation or *N*-acetylation rather than *N*-oxidation (Son *et al.*, 1980). Similarly, cancers of the urinary bladder associated with occupational exposure to *ortho*-toluidine may result from peroxidative activation of the chemical, catalysed by prostaglandin H synthase in the epithelium of the urinary bladder (Zenser *et al.*, 2002). *ortho*-Toluidine-haemoglobin adduct levels were increased in patients treated with the anaesthetic prilocaine (Gaber *et al.*, 2007) and in workers employed in the rubber chemicals manufacturing area of a chemical plant (Ward *et al.*, 1996). Metabolites are excreted primarily as sulfate or glucuronide conjugates, since *ortho*-toluidine is not a substrate for human NAT1-mediated acetylation (Zhang *et al.*, 2006).

ortho-Toluidine induces tumours in rodents and DNA lesions in multiple organs. Most studies reported that *ortho*-toluidine was not mutagenic in *S. typhimurium*, other studies showed positive responses in the same strains. The *N*-oxidized metabolite of *ortho*-toluidine, *N*-hydroxy-*ortho*-toluidine, was mutagenic in *S. typhimurium* strain TA100 (Gupta *et al.*, 1987). *ortho*-Toluidine induced intrachromosomal recombination in *Saccharomyces cerevisiae* in an assay that is responsive to the induction of DNA deletions (Carls & Schiestl, 1994); this response was reduced in the presence of an antioxidant. Other reported effects of *ortho*-toluidine (Danford, 1991) include the induction of sister chromatid exchange, aneuploidy, unscheduled DNA synthesis, DNA strand breaks, and cell transformation *in vitro*, and the induction of micronuclei in peripheral blood of rats treated *in vivo* (Suzuki *et al.*, 2005). The formation of 8-oxo-7,8-dihydro-2'-deoxyguanosine in calf thymus DNA incubated *in vitro* with 4-amino-3-methylphenol, a metabolite of *ortho*-toluidine, suggests a potential role of reactive oxygen species in the DNA-damaging effects of this aromatic amine (Ohkuma *et al.*, 1999). *ortho*-Toluidine induced DNA lesions – measured by means of the comet assay – in multiple organs of exposed rats and mice (Sekihashi *et al.*, 2002): increased DNA migration was observed in the liver, bladder, lung, and brain of mice, and in the liver, bladder, and stomach of rats.

5. Evaluation

There is *sufficient evidence* in humans for the carcinogenicity of *ortho*-toluidine. *ortho*-Toluidine causes cancer of the urinary bladder.

There is *sufficient evidence* in experimental animals for the carcinogenicity of *ortho*-toluidine.

There is moderate mechanistic evidence indicating that the carcinogenicity of *ortho*-toluidine involves metabolic activation, formation of DNA adducts, and induction of DNA-damaging effects.

ortho-Toluidine is *carcinogenic to humans (Group 1)*.

References

Akyüz M & Ata S (2008). Determination of aromatic amines in hair dye and henna samples by ion-pair extraction and gas chromatography-mass spectrometry. *Journal of Pharmaceutical and Biomedical Analysis*, 47: 68–80. doi:10.1016/j.jpba.2007.12.011 PMID:18280687

Carls N & Schiestl RH (1994). Evaluation of the yeast DEL assay with 10 compounds selected by the International Program on Chemical Safety for the evaluation of short-term tests for carcinogens. *Mutation Research*, 320: 293–303. doi:10.1016/0165-1218(94)90082-5 PMID:7508555

Carreón T, Hein MJ, Viet SM *et al.* (2010). Increased bladder cancer risk among workers exposed to o-toluidine and aniline: a reanalysis. *Occup Environ Med*, 67: 348–350. doi:10.1136/oem.2009.051136 PMID:19884651

Danford N (1991). The genetic toxicology of ortho-toluidine. *Mutat Res*, 258: 207–236. PMID:1719402

DeBruin LS, Pawliszyn JB, Josephy PD (1999). Detection of monocyclic aromatic amines, possible mammary carcinogens, in human milk. *Chem Res Toxicol*, 12: 78–82. doi:10.1021/tx980168m PMID:9894021

Delzell E, Macaluso M, Cole P (1989). A follow-up study of workers at a dye and resin manufacturing plant. *Journal of Occupational Medicine.*, 31: 273–278. doi:10.1097/00043764-198903000-00016 PMID:2918413

EPA (1984). *Chemical Hazard Information Profile (CHIP): ortho-Toluidine; ortho-Toluidine Hydrochloride*. Washington, DC: Office of Pesticide Programs and Toxic Substances.

Gaber K, Harréus UA, Matthias C *et al.* (2007). Hemoglobin adducts of the human bladder carcinogen o-toluidine after treatment with the local anesthetic prilocaine. *Toxicology*, 229: 157–164. doi:10.1016/j.tox.2006.10.012 PMID:17129655

Gupta RL, Gupta AK, Pathak DP, Juneja TR (1987). Mutagenic studies of ortho-toluidine and its potential metabolites. *Indian J Exp Biol*, 25: 618–622. PMID:3449450

Hecht SS, El-Bayoumy K, Rivenson A, Fiala E (1982). Comparative carcinogenicity of o-toluidine hydrochloride and o-nitrosotoluene in F-344 rats. *Cancer Letters*, 16: 103–108. doi:10.1016/0304-3835(82)90097-0 PMID:7116337

Hecht SS, El-Bayoumy K, Rivenson A, Fiala ES (1983). Bioassay for carcinogenicity of 3,2′-dimethyl-4-nitrosobiphenyl, O-nitrosotoluene, nitrosobenzene and the corresponding amines in Syrian golden hamsters. *Cancer Letters*, 20: 349–354. doi:10.1016/0304-3835(83)90034-4 PMID:6627231

IARC (1978). Some aromatic amines and related nitro compounds - hair dyes, colouring agents and miscellaneous industrial chemicals. *IARC Monogr Eval Carcinog Risk Chem Man*, 16: 1–400.

IARC (1982). Some aromatic amines, anthraquinones and nitroso compounds, and inorganic fluorides used in drinking-water and dental preparations. *IARC Monogr Eval Carcinog Risk Chem Hum*, 27: 1–341. PMID:6955259

IARC (1987). Overall evaluations of carcinogenicity: an updating of IARC Monographs volumes 1 to 42. *IARC Monogr Eval Carcinog Risks Hum Suppl*, 7: 1–440. PMID:3482203

IARC (2000). Some industrial chemicals. *IARC Monogr Eval Carcinog Risks Hum*, 77: 1–529. PMID:11236796

IARC (2010). Some aromatic amines, organic dyes, and related exposures. *IARC Monogr Eval Carcinog Risks Hum*, 99: 1–678. PMID:21528837.

Kauppinen T, Pukkala E, Saalo A, Sasco AJ (2003). Exposure to chemical carcinogens and risk of cancer among Finnish laboratory workers. *Am J Ind Med*, 44: 343–350. doi:10.1002/ajim.10278 PMID:14502761

Khlebnikova MI, Gladkova EV, Kurenko LT *et al.* (1970). Problems of industrial hygiene and status of health of workers engaged in the production of O-toluidine *Gig Tr Prof Zabol*, 14: 7–10. PMID:5508062

Korinth G, Weiss T, Angerer J, Drexler H (2006). Dermal absorption of aromatic amines in workers with different skin lesions: a report on 4 cases. *Journal of Occupational Medicine and Toxicology (London, England)*, 1: 17–20. doi:10.1186/1745-6673-1-17 PMID:16854230

Markowitz SB & Levin K (2004). Continued epidemic of bladder cancer in workers exposed to ortho-toluidine in a chemical factory. *Journal of Occupational and Environmental Medicine*, 46: 154–160. doi:10.1097/01.jom.0000111602.76443.15 PMID:14767218

Neurath GB, Dünger M, Pein FG *et al.* (1977). Primary and secondary amines in the human environment. *Fd Cosmet Toxicol*, 15: 275–282. doi:10.1016/S0015-6264(77)80197-1 PMID:590888

NIOSH (1990). *National Occupational Exposure Survey (1981–83)*. Cincinnati, OH: National Institute for Occupational Safety and Health [http://www.cdc.gov/noes/noes2/73470occ.html]

NTP (1979). Bioassay of o-toluidine hydrochloride for possible carcinogenicity. *Natl Cancer Inst Carcinog Tech Rep Ser*, 153: 1–147. PMID:12799709

NTP (2004). o-Toluidine and o-toluidine hydrochloride *Rep Carcinog*, 11: 258–259. PMID:21089974.

Ohkuma Y, Hiraku Y, Oikawa S *et al.* (1999). Distinct mechanisms of oxidative DNA damage by two metabolites of carcinogenic o-toluidine. *Archives of Biochemistry and Biophysics*, 372: 97–106. doi:10.1006/abbi.1999.1461 PMID:10562421

O'Neil MJ, editor (2006). *The Merck Index*, 14th ed. Whitehouse Station, NJ: Merck & Co. Inc., p. 1639.

Ott MG & Langner RR (1983). A mortality survey of men engaged in the manufacture of organic

dyes. *Journal of Occupational Medicine.*, 25: 763–768. doi:10.1097/00043764-198310000-00018 PMID:6631562

Riedel K, Scherer G, Engl J *et al.* (2006). Determination of three carcinogenic aromatic amines in urine of smokers and nonsmokers. *J Anal Toxicol*, 30: 187–195. PMID:16803653

Riffelmann M, Müller G, Schmieding W *et al.* (1995). Biomonitoring of urinary aromatic amines and arylamine hemoglobin adducts in exposed workers and nonexposed control persons. *Int Arch Occup Environ Health*, 68: 36–43. doi:10.1007/BF01831631 PMID:8847111

Rubino GF, Scansetti G, Piolatto G, Pira E (1982). The carcinogenic effect of aromatic amines: an epidemiological study on the role of o-toluidine and 4,4′-methylene bis (2-methylaniline) in inducing bladder cancer in man. *Environmental Research*, 27: 241–254. doi:10.1016/0013-9351(82)90079-2 PMID:7084156

Sekihashi K, Yamamoto A, Matsumura Y *et al.* (2002). Comparative investigation of multiple organs of mice and rats in the comet assay. *Mutat Res*, 517: 53–75. PMID:12034309

Shackelford WM, Keith LH (1976). *Frequency of Organic Compounds Identified in Water.* Athens, GA: Environmental Research Laboratory (EPA-600/4–76–062), pp. 35, 226

Son OS, Everett DW, Fiala ES (1980). Metabolism of o-[methyl-14C]toluidine in the F344 rat. *Xenobiotica*, 10: 457–468. doi:10.3109/00498258009033781 PMID:7445517

Sorahan T (2008). Bladder cancer risks in workers manufacturing chemicals for the rubber industry. *Occup Med (Lond)*, 58: 496–501. doi:10.1093/occmed/kqn104 PMID:18725381

Sorahan T, Hamilton L, Jackson JR (2000). A further cohort study of workers employed at a factory manufacturing chemicals for the rubber industry, with special reference to the chemicals 2-mercaptobenzothiazole (MBT), aniline, phenyl-beta-naphthylamine and o-toluidine. *Occupational and Environmental Medicine*, 57: 106–115. doi:10.1136/oem.57.2.106 PMID:10711278

Stabbert R, Schäfer K-H, Biefel C, Rustemeier K (2003). Analysis of aromatic amines in cigarette smoke. *Rapid Commun Mass Spectrom*, 17: 2125–2132. doi:10.1002/rcm.1161 PMID:12955743

Stasik MJ (1988). Carcinomas of the urinary bladder in a 4-chloro-o-toluidine cohort. *Int Arch Occup Environ Health*, 60: 21–24. doi:10.1007/BF00409374 PMID:3350600

Suzuki H, Ikeda N, Kobayashi K *et al.* (2005). Evaluation of liver and peripheral blood micronucleus assays with 9 chemicals using young rats. A study by the Collaborative Study Group for the Micronucleus Test (CSGMT)/Japanese Environmental Mutagen Society (JEMS)-Mammalian Mutagenicity Study Group (MMS). *Mutat Res*, 583: 133–145. PMID:15899588

Teass AW, DeBord DG, Brown KK *et al.* (1993). Biological monitoring for occupational exposures to o-toluidine and aniline. *Int Arch Occup Environ Health*, 65: :S115–S118. doi:10.1007/BF00381320 PMID:8406905

Vitzthum OG, Werkhoff P, Hubert P (1975). New volatile constituents of black tea aroma. *J Agric Food Chem*, 23: 999–1003. doi:10.1021/jf60201a032

Ward E, Carpenter A, Markowitz S *et al.* (1991). Excess number of bladder cancers in workers exposed to ortho-toluidine and aniline. *Journal of the National Cancer Institute*, 83: 501–506. doi:10.1093/jnci/83.7.501 PMID:2005633

Ward EM, Sabbioni G, DeBord DG *et al.* (1996). Monitoring of aromatic amine exposures in workers at a chemical plant with a known bladder cancer excess. *Journal of the National Cancer Institute*, 88: 1046–1052. doi:10.1093/jnci/88.15.1046 PMID:8683635

Weisburger EK, Russfield AB, Homburger F *et al.* (1978). Testing of twenty-one environmental aromatic amines or derivatives for long-term toxicity or carcinogenicity. *J Environ Pathol Toxicol*, 2: 325–356. PMID:84039

Zenser TV, Lakshmi VM, Hsu FF, Davis BB (2002). Metabolism of N-acetylbenzidine and initiation of bladder cancer. *Mutat Res*, 506–507: 29–40. doi:10.1016/S0027-5107(02)00149-5 PMID:12351142

Zhang N, Liu L, Liu F *et al.* (2006). NMR-based model reveals the structural determinants of mammalian arylamine N-acetyltransferase substrate specificity. *Journal of Molecular Biology*, 363: 188–200. doi:10.1016/j.jmb.2006.08.026 PMID:16959263