



## The Report on Carcinogens

### What is the Report on Carcinogens?

The Report on Carcinogens is a scientific and public health document that identifies substances that pose a cancer hazard for people in the United States. It is intended to help people make informed decisions about their own health. It is a congressionally mandated document prepared by the National Toxicology Program (NTP) for the Secretary of the U.S. Department of Health and Human Services.

The Report on Carcinogens identifies many different types of chemicals; infectious agents, such as viruses; physical agents, such as X-rays and ultraviolet radiation; mixtures; and exposure scenarios, collectively called substances. All substances pose a potential cancer hazard. Having this information may help prevent some cancers.

### How are substances listed?

A substance can be listed in the Report on Carcinogens either as known to be a human carcinogen or as reasonably anticipated to be a human carcinogen. See <https://ntp.niehs.nih.gov/go/15209> for specific listing criteria.

#### *Known to be a human carcinogen*

This category is used primarily when there is sufficient evidence from human studies showing a cause-and-effect relationship between exposure to the substance and human cancer. Occasionally, substances are listed in this category based on human studies showing that the substance causes biological effects known to lead to the development of cancer.

### Key Points

- Scientific, public health document identifying substances that pose a cancer hazard.
- Lists a substance as either known to be a human carcinogen or reasonably anticipated to be a human carcinogen.
- Includes information on 256 listings, including eight newly reviewed listings.
- Prepared by the National Toxicology Program for the Secretary of the U.S. Department of Health and Human Services.



#### *Reasonably anticipated to be a human carcinogen*

This category includes substances where there is limited evidence of cancer in humans or sufficient evidence in experimental animals showing a cause-and-effect relationship between exposure to the substance and cancer. Additionally, a substance can be listed in this category if there is evidence that it is the member of a class of substances already listed in the Report on Carcinogens, or that it causes biological effects known to lead to the development of cancer.

### Newly reviewed substances

Substance	Listing Status	Description
Chronic infection with <i>H. pylori</i>	Known to be a human carcinogen	Bacterium
Antimony trioxide	Reasonably anticipated to be a human carcinogen	Chemical compound
Bromochloroacetic acid (BCA)	Reasonably anticipated to be a human carcinogen	Water disinfection byproduct
Bromodichloroacetic acid (BDCA)	Reasonably anticipated to be a human carcinogen	Water disinfection byproduct
Chlorodibromoacetic acid (CDBA)	Reasonably anticipated to be a human carcinogen	Water disinfection byproduct
Dibromoacetic acid (DBA)	Reasonably anticipated to be a human carcinogen	Water disinfection byproduct
Dichloroacetic acid (DCA)	Reasonably anticipated to be a human carcinogen	Water disinfection byproduct
Tribromoacetic acid (TBA)	Reasonably anticipated to be a human carcinogen	Water disinfection byproduct



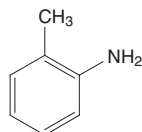
## *o*-Toluidine

### CAS No. 95-53-4

Known to be a human carcinogen

*o*-Toluidine was first listed in the *Third Annual Report on Carcinogens* (1982), and its hydrochloride was first listed in the *Second Annual Report on Carcinogens* (1981)

Also known as 2-methylbenzenamine



### Carcinogenicity

*o*-Toluidine is known to be a human carcinogen based on sufficient evidence of carcinogenicity from studies showing that it causes urinary-bladder cancer in humans, together with studies showing that it causes cancer in experimental animals at several tissue sites, including the urinary bladder in rats (indicating tumor-site concordance between humans and experimental animals), and studies demonstrating the biological plausibility of mechanisms of its carcinogenicity in humans. *o*-Toluidine was first listed in the *Third Annual Report on Carcinogens* as reasonably anticipated to be a human carcinogen based on sufficient evidence from studies in experimental animals. Since that time, additional cancer studies in humans have been published, and the listing was changed to known to be a human carcinogen in the *Thirteenth Report on Carcinogens* (2014).

#### Cancer Studies in Humans

Epidemiological studies have demonstrated a causal relationship between exposure to *o*-toluidine and urinary-bladder cancer in humans. This conclusion is based on an evaluation of three cohort studies of dye workers (Case and Pearson 1954, Ott and Langner 1983, Pira *et al.* 2010), two cohort studies of rubber-chemical workers (Sorahan 2008, Carreón *et al.* 2014), and a population-based case-control study (Richardson *et al.* 2007). The most informative study is the National Institute for Occupational Safety and Health (NIOSH) cohort study of U.S. rubber-chemical workers, because it provided the best assessment of *o*-toluidine exposure and co-exposures (Carreón *et al.* 2014).

Overall, there is credible evidence of an association between increased urinary-bladder cancer risk and exposure to *o*-toluidine based on consistent findings across studies, the relationship of cancer risk to exposure level and duration, and large magnitudes of effect across studies. An increased risk of urinary-bladder cancer (incidence or mortality) was observed in all four studies with adequate latency (time since first exposure) that used statistical or other methods capable of detecting an association (Case and Pearson 1954, Sorahan 2008, Pira *et al.* 2010, Carreón *et al.* 2014). Two studies did not find an excess of urinary-bladder cancer among *o*-toluidine-exposed workers; however, the statistical power to detect an effect was very low in the U.S. dye-workers study (Ott and Langner 1983), and misclassification of exposure was a serious concern for both the U.S. dye-workers cohort study and the Canadian case-control study (Richardson *et al.* 2007).

Risk of urinary-bladder cancer increased with increasing level or duration of exposure to *o*-toluidine and time since first exposure, which supports a causal relationship. Among U.S. rubber-chemical workers definitely exposed to *o*-toluidine, a statistically significant exposure-response relationship between cumulative exposure rank and urinary bladder cancer incidence was observed ( $P_{\text{trend}} < 0.001$  for analysis based on a 10-year latency period); workers in the high-

est exposure category had an over seven-fold higher risk than workers in the lowest exposure category (Carreón *et al.* 2014). Risk also increased significantly with time since first exposure among U.S. rubber-chemical workers ( $P_{\text{trend}} < 0.001$ ) and with increasing exposure duration in both studies of rubber-chemical workers ( $P_{\text{trend}} < 0.001$  for U.S. workers [Carreón *et al.* 2014] and  $P_{\text{trend}} < 0.005$  for U.K. workers [Sorahan 2008]). (In the study of U.K. rubber-chemical workers, employment duration was used as a surrogate for *o*-toluidine exposure [Sorahan 2008].) The graph below shows the risk estimates from five of the six studies considered in the assessment (no urinary bladder cancer deaths were observed in the U.S. dye-workers study [Ott and Langner 1983]).

#### Cohort studies:

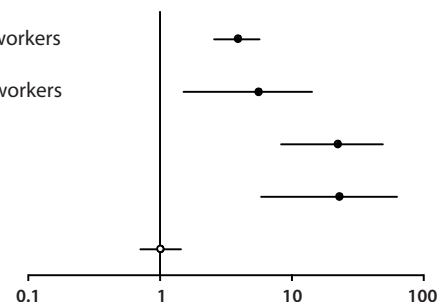
U.S. rubber-chemical workers

U.K. rubber-chemical workers

Italian dye workers

U.K. dye workers

#### Case-control study



#### Risk estimates for urinary-bladder cancer, with 95% confidence intervals

Rubber-chemical-worker cohorts: standardized incidence ratio.

Dye-worker cohorts: standardized mortality ratio.

Case-control study: odds ratio (for incidence cases).

The cohort study of U.S. rubber-chemical workers was the most informative study for evaluation of potential confounding from occupational co-exposures, because it had good occupational hygiene data on exposure to *o*-toluidine and other chemicals (Carreón *et al.* 2014). This study provided substantial evidence that *o*-toluidine was the agent causally related to the observed increase in urinary bladder cancer risk among *o*-toluidine-exposed workers. These findings are supported by the study of U.K. rubber-chemical workers (Sorahan 2008), which found an increased risk of urinary-bladder cancer in analyses adjusting for several occupational co-exposures. Occupational co-exposures, including exposures to animal carcinogens, were of greater concern for the two cohort studies of workers manufacturing magenta dyes (Case and Pearson 1954, Pira *et al.* 2010); possible positive interactions among exposures might help to explain the large risk estimates observed. Although information on cigarette smoking was limited in these studies, potential confounding from smoking could reasonably be ruled out in the cohort study of U.S. rubber-chemical workers, based on analysis of a subset of workers for whom smoking information was available (Carreón *et al.* 2014), and it is unlikely to explain the large risk estimates found in the smaller studies. The finding of increased urinary bladder cancer risk in different cohorts with different exposure conditions and different co-exposures strongly supports the conclusion that *o*-toluidine is the common causal risk factor.

#### Cancer Studies in Experimental Animals

Evidence for the carcinogenicity of *o*-toluidine from studies in experimental animals is based on the statistically significant increased incidences of malignant tumors or benign and malignant tumors combined at several different tissue sites in rats and mice. This conclusion is based on four studies in two different strains of rats (Weisburger *et al.* 1978, NCI 1979, Hecht *et al.* 1982, NTP 1996) and two studies in two different strains of mice (Weisburger *et al.* 1978, NCI 1979). All of these studies were two-year carcinogenicity studies ex-

cept for one high-dose subchronic exposure study in which the animals were exposed to *o*-toluidine for 13 or 26 weeks (NTP 1996).

Dietary exposure to *o*-toluidine caused tumors of the urinary bladder and connective tissue (sarcoma) in rats of both sexes, subcutaneous tissue and mesothelium in male rats, blood vessels in male and female mice, and liver in female mice. Importantly, rats developed tumors at the same tissue site (urinary bladder) as observed in humans. The urinary bladder cancer findings in female rats are considered to be robust because of the relatively high, statistically significant increased tumor incidences, the rarity of the tumor in this species, the exposure-response relationship, and the shorter time to first observed tumor in the high-dose females than in the low-dose females (NCI 1979). Although the incidences of urinary-bladder cancer were lower and not significantly increased in male rats, these tumors are considered to be exposure-related because of their rarity and their occurrence in all three carcinogenicity studies (Weisburger *et al.* 1978, NCI 1979, Hecht *et al.* 1982). Furthermore, the incidence of transitional-cell hyperplasia of the urinary bladder (a precancerous lesion) was significantly increased in male rats exposed to *o*-toluidine for 13 or 26 weeks in the subchronic exposure study (NTP 1996).

Observations of tumors at tissue sites in addition to the urinary bladder support the conclusion that *o*-toluidine is a carcinogen. The incidences of sarcoma in the spleen and other tissue sites were significantly increased in rats of both sexes (NCI 1979) and in male rats in two different studies (NCI 1979, Hecht *et al.* 1982). Several types of sarcoma in different organs were combined in the statistical analyses, because the histologic appearance of the various types of sarcoma, which were of mesenchymal origin, was similar, and many sarcomas had invaded adjacent organs and soft tissue (NCI 1979). All three carcinogenicity studies in rats, including studies in two different strains (Weisburger *et al.* 1978, NCI 1979, Hecht *et al.* 1982), reported benign or malignant tumors of the subcutaneous tissues (fibroma or fibrosarcoma) in male rats. In one study, the incidence of mesothelioma (of the tunica vaginalis or abdominal cavity and organs) was significantly increased in male rats (NCI 1979). This finding is supported by observations of malignant mesothelioma and mesothelial hyperplasia of the epididymides in male rats after dietary exposure to *o*-toluidine for 13 weeks followed by 13 weeks of observation. In mice, the combined incidence of benign and malignant tumors of the blood vessels (hemangioma and hemangiosarcoma) was increased in two different strains (Weisburger *et al.* 1978, NCI 1979) and in both sexes of one strain (NCI 1979). One study also found a statistically significant dose-related increase in the combined incidence of benign and malignant liver tumors (hepatocellular adenoma and carcinoma) in female mice (NCI 1979).

In rats, dietary exposure to *o*-toluidine also caused statistically significant increased incidences of benign tumors (fibroadenoma) of the mammary gland in males (Hecht *et al.* 1982) and females (NCI 1979), supporting the evidence for carcinogenicity of *o*-toluidine in experimental animals. Although these tumors usually are noncancerous, they occasionally progress to malignancy (adenocarcinoma) (Boorman *et al.* 1990).

In two studies of exposure to *o*-toluidine by subcutaneous injection, one in Syrian golden hamsters (Hecht *et al.* 1982) and one in rats (Pliss 2004), no exposure-related effects were observed. However, these studies had methodological limitations.

#### Other Relevant Data

*o*-Toluidine can be absorbed following inhalation, dermal, or oral exposure. Its distribution, metabolism, and excretion have been studied primarily in rodents, where *o*-toluidine was detected in blood, spleen, liver, kidneys, urinary bladder, and other tissues. In rats, the

majority of the administered dose of *o*-toluidine was excreted as metabolites in the urine following exposure by all routes; much smaller amounts were eliminated in exhaled air and feces. Although the data on human metabolism of *o*-toluidine are limited, the rat metabolite *N*-acetyl-*o*-toluidine is a likely human metabolite. As discussed below, there is indirect evidence that rats and humans share common metabolic activation pathways (Son *et al.* 1980, Ward *et al.* 1996, English *et al.* 2012).

#### Studies on Mechanisms of Carcinogenesis

Although the mechanisms of carcinogenicity of *o*-toluidine are not completely understood, the available evidence suggests that they are complex and involve several key modes of action, including metabolic activation that results in binding of reactive metabolites to DNA and proteins, mutagenicity, oxidative DNA damage, chromosomal damage, and cytotoxicity (Skipper *et al.* 2010). The key metabolic activation steps and genotoxic effects occur in both experimental animals and humans.

Metabolism of monocyclic aromatic amines, including *o*-toluidine, involves many competing activating and deactivating pathways, including *N*-acetylation, *N*-oxidation and *N*-hydroxylation, and ring oxidation. Cytochrome P450-mediated *N*-hydroxylation to *N*-hydroxy-*o*-toluidine, a carcinogenic metabolite, occurs in the liver. *N*-hydroxy-*o*-toluidine can be either metabolized to *o*-nitrosotoluene or conjugated with glucuronic acid or sulfate and transported to the urinary bladder via the circulation. Once in the urinary bladder, *N*-hydroxy-*o*-toluidine can be released from the conjugates in an acidic urine environment to either react directly with DNA or be bioactivated via sulfation or acetylation by cytosolic sulfotransferases or *N*-acetyltransferases (presumably NAT1). The postulated activated form (based on comparison with other aromatic amines), *N*-acetoxy-*o*-toluidine, is a reactive ester that forms electrophilic arylnitrenium ions that can bind to DNA (Kadlubar and Badawi 1995, Riedel *et al.* 2006, English *et al.* 2012).

Studies of other aromatic amines that cause urinary-bladder cancer have shown that during transport of the *N*-hydroxyarylamines to the urinary bladder, bioreactive metabolites (nitroso compounds) can form and bind to hemoglobin in the blood (Skipper and Tannenbaum 1994). Evidence suggesting that this pathway is relevant to humans comes from numerous studies that detected *o*-toluidine hemoglobin adducts in humans (following both occupational and nonoccupational exposures), consistent with observations in experimental animals. Hemoglobin adducts are thought to be formed from the *o*-toluidine metabolite *o*-nitrosotoluene (Eyer 1983, English *et al.* 2012), which also causes urinary-bladder cancer in rats (Hecht *et al.* 1982). (*o*-Nitrosotoluene is formed via metabolism of *o*-toluidine to *N*-hydroxy-*o*-toluidine.)

Other activation pathways (ring-oxidation pathways) for aromatic amines include peroxidase-catalyzed reactions that form reactive metabolites (quinone imines formed from nonconjugated phenolic metabolites) in the urinary bladder. These metabolites can produce reactive oxygen species, resulting in oxidative cellular damage and compensatory cell proliferation (Skipper *et al.* 2010, English *et al.* 2012). Support for this mechanism comes from studies of oxidative DNA damage induced by *o*-toluidine metabolites in cultured human cells (HL-60), calf thymus DNA, and DNA fragments from key genes thought to be involved in carcinogenesis (the *c-Ha-ras* oncogene and the *p53* tumor-suppressor gene) (Ohkuma *et al.* 1999, Watanabe *et al.* 2010). Also supporting this mechanism are observations of *o*-toluidine-induced DNA damage (strand breaks) in cultured human urinary-bladder cells (Watanabe *et al.* 2010) and urinary-bladder

cells from rats and mice exposed *in vivo* to *o*-toluidine (Robbiano *et al.* 2002, Sekihashi *et al.* 2002).

Overall, the extensive data on genetic and related effects of *o*-toluidine indicate that it can cause mutations, DNA and chromosomal damage, and cell transformation (Danford 1991, IARC 2000, 2010). Although *o*-toluidine is a weak mutagen in bacteria, it causes mutations in human lymphocytes, and two *o*-toluidine metabolites (*N*-hydroxy-*o*-toluidine and *o*-nitrosotoluene) are potent mutagens in bacteria with mammalian metabolic activation. In rats exposed to *o*-toluidine *in vivo*, DNA adducts have been detected in liver (as with other aromatic amines) and nasal but not urinary-bladder tissue. *In vivo* exposure to *o*-toluidine also caused DNA strand breaks in rat kidney, colon, and stomach and mouse liver, lung, stomach, and brain. There is evidence that *o*-toluidine causes large-scale chromosomal damage in yeast and mammalian cells (e.g., deletions, insertions, translocations, and aneuploidy), micronucleus formation in cultured cells and reticulocytes from exposed rats, and sister chromatid exchange in cultured human and rodent cells and cells from rodents exposed *in vivo*. Exposure to aromatic amines has been shown to induce chromosomal instability in genetically stable urinary bladder cancer cells. Chromosomal instability is associated with aneuploidy and loss of heterozygosity. Aneuploidy is a common feature of urinary-bladder cancer in humans, and loss of heterozygosity is an important mechanism for inactivation of tumor-suppressor genes (Höglund *et al.* 2001, Sandberg 2002, Phillips and Richardson 2006).

## Properties

*o*-Toluidine is a synthetic chemical that may be classified as a monocyclic aromatic amine, arylamine, or alkyylaniline (Yu *et al.* 2002, IARC 2010, Skipper *et al.* 2010). It exists at room temperature as a light-yellow liquid that darkens rapidly on exposure to air and light, and is described as having an aromatic odor (IPCS 1998). It is soluble in water, soluble in dilute acids, and miscible with ethanol, diethyl ether, and carbon tetrachloride (ChemIDplus 2012, HSDB 2012). *o*-Toluidine hydrochloride (HCl) is the solid salt form of *o*-toluidine, which exists at room temperature as a green or white crystalline solid that is slightly soluble in water (Akron 2012, ChemIDplus 2012). Physical and chemical properties of *o*-toluidine and its hydrochloride are listed in the following table.

Property	<i>o</i> -Toluidine	<i>o</i> -Toluidine HCl
Molecular weight	107.2 <sup>a</sup>	143.6 <sup>b</sup>
Density	0.998 g/cm <sup>3</sup> at 20°C <sup>a</sup>	1.228 g/cm <sup>3</sup> at 20°C <sup>a</sup>
Melting point	< -15°C <sup>a</sup>	215°C <sup>c</sup>
Boiling point	198°C to 201°C <sup>a</sup>	242.2°C <sup>c</sup>
Log <i>K</i> <sub>ow</sub>	1.32 <sup>c</sup>	1.62 <sup>c</sup>
Water solubility	16.6 g/L at 25°C <sup>d</sup>	8290 mg/L at 25°C <sup>d,e</sup>
Vapor pressure	0.33 mm Hg at 25°C <sup>a</sup>	0.293 mm Hg at 25°C <sup>d</sup>
Vapor density relative to air	3.69 <sup>a</sup>	NR

Sources: <sup>a</sup>Akron 2012, <sup>b</sup>NTP 1996, <sup>c</sup>HSDB 2012, <sup>d</sup>ChemIDplus 2012, <sup>e</sup>Estimated value. NR = not reported.

## Use

Major uses for *o*-toluidine have included manufacture of (1) rubber chemicals (Hanley *et al.* 2012), (2) pesticide intermediates such as 4-chloro-*o*-toluidine and 6-ethyl-*o*-toluidine (2-ethyl-6-methylaniline), which is used to manufacture the widely used herbicides metolachlor and acetochlor, and (3) more than 90 dyes and pigments, including acid-fast dyestuffs, azo dyes and pigments, triarylmethane dyes, sulfur dyes, and indigo compounds, either directly or via dye intermediates; four major intermediates are acetoacet-*o*-toluidine, 3-hydroxy-2-naphthoyl-*o*-toluidine, 2-toluidine-5-sulfonic acid, and *o*-aminoazotoluene (Bowers 2011). Data submitted to the U.S. En-

vironmental Protection Agency's (EPA's) Toxics Release Inventory (TRI) and Chemical Data Reporting Rule programs provide evidence for the continuing use of *o*-toluidine for all of these manufacturing uses except dye production and manufacture of the pesticide intermediate 4-chloro-*o*-toluidine. Other, minor uses of *o*-toluidine are as an intermediate in the synthesis of pharmaceuticals (e.g., prilocaine) (Vardanyan and Hruba 2006) and in the clinical laboratory as an ingredient in a reagent for glucose analysis and for tissue staining (IARC 2012).

## Production

*o*-Toluidine is considered to be a high-production-volume chemical, based on its combined U.S. production and import volume, which was in the range of 50 million to 100 million pounds in 2015 (EPA 2016). However, this range likely represents only imports, as no information was found on its U.S. production in 2018. *o*-Toluidine was produced in the United States in large quantities in the past; for example, annual production in the early 1970s exceeded 1 million pounds (HSDB 2012).

## Exposure

Several lines of evidence indicate that a significant number of people living in the United States are exposed to *o*-toluidine. This evidence includes the use of large amounts of imported *o*-toluidine and biological monitoring data demonstrating widespread exposure in both occupationally and nonoccupationally exposed individuals and in both smokers and nonsmokers.

The highest exposure to *o*-toluidine occurs in the workplace; urinary exposure levels were over 26-fold higher among workers exposed to *o*-toluidine than among unexposed workers (Ward *et al.* 1996). Occupational exposure to *o*-toluidine can occur by inhalation or dermal contact (IARC 2010) during its production or during its use in production of rubber chemicals, chemical intermediates for pesticides, or intermediates for dyes and pigments. Medical and laboratory personnel also are exposed to low concentrations of *o*-toluidine in air (IARC 2012).

The highest levels of occupational exposure to *o*-toluidine in air were reported from a study of *o*-toluidine production workers at a chemical plant in the former Soviet Union. Concentrations of *o*-toluidine in the air were 2 to 7 times the maximum permissible concentration of 3 mg/m<sup>3</sup> [0.7 ppm] for the Soviet Union (IARC 2012). Most of the air-monitoring data in the United States suggest that occupational exposure levels of *o*-toluidine are usually less than 1 ppm (e.g., up to 0.5 ppm in the dye and pigment industry), but may have been higher in the past. The most detailed occupational exposure data are air-monitoring data from a NIOSH assessment in 1990 and company data collected from 1976 to 2004 for workers at a rubber-chemical department in a U.S. chemical manufacturing plant involved in antioxidant production, accelerant production, recycling processing, and maintenance (Hanley *et al.* 2012). In the 1990 NIOSH assessment, *o*-toluidine exposure levels (geometric mean breathing-zone concentrations) were approximately 0.1 ppm for antioxidant production workers and maintenance personnel and approximately 0.5 ppm for accelerant production and recycling processing workers. The company data indicated that geometric mean *o*-toluidine exposure levels among rubber-chemical workers decreased from 0.1 ppm for 1976 to 1979 to less than 0.02 ppm for 1995 to 2004.

The presence of *o*-toluidine in urine and as hemoglobin adducts in individuals without known occupational exposure indicates more widespread population exposure. *o*-Toluidine was detected in breast milk (DeBruin *et al.* 1999) and after acid hydrolysis of urinary-bladder tissue and tumors from individuals with no known exposure

to *o*-toluidine (Böhm *et al.* 2011). Potential sources of exposure include tobacco smoking, dental products (e.g., prilocaine), consumer products (e.g., hair dyes, dyestuff in clothing and cosmetics), food, and the environment (El-Bayoumy *et al.* 1986, Riffelmann *et al.* 1995). Although nonoccupational exposure levels are lower than occupational exposure levels, these exposures are common, indicating that more people living in the United States are potentially exposed to *o*-toluidine from these sources than occupationally.

*o*-Toluidine has been measured in mainstream cigarette smoke at 9 to 144 ng per cigarette (Stabbert *et al.* 2003). *o*-Toluidine concentrations in second-hand smoke have been reported to be approximately 20 times the concentration in primary smoke (Patrianakos and Hoffmann 1979). In 2007–2008, approximately 88 million nonsmokers in the United States were exposed to second-hand smoke (CDC 2014). In the absence of occupational exposure, *o*-toluidine urinary concentrations and hemoglobin adducts have generally been reported to be somewhat higher in smokers than in nonsmokers (El-Bayoumy *et al.* 1986, Riffelmann *et al.* 1995, Riedel *et al.* 2006); however, no such difference was noted between occupationally exposed smokers and nonsmokers, because occupational exposure is so much greater than exposure from smoking (Riffelmann *et al.* 1995, Ward *et al.* 1996, Korinth *et al.* 2007).

Exposure to *o*-toluidine can occur from prilocaine, a product used for dental anesthesia, which is metabolized to *o*-toluidine. Based on prilocaine's 6% share of the U.S. dental local anesthetic market, several million individuals would potentially be exposed to *o*-toluidine each year through prilocaine use in dental procedures (Gutenberg *et al.* 2013). In a study of patients who received prilocaine for local anesthesia, hemoglobin adducts had increased approximately 41-fold by 24 hours after surgery (Gaber *et al.* 2007, IARC 2012). *o*-Toluidine has also been found in hair dyes sold in Turkey (at levels of up to 1,547 µg/g) (IARC 2012), and *o*-toluidine-based dyes are found in many commercial products, including tattoo inks. Most of these dyes are manufactured outside the United States, but no U.S. import restrictions were found, and such products, including hair dyes, potentially may be sold on the Internet (Allbiz 2013, Alibaba 2014). A study of *o*-toluidine hemoglobin adducts in approximately 300 hairdressers in Sweden reported a significant increase in adduct concentrations with increasing number of hair-waving treatments performed per week and a trend toward increasing concentrations with increased use of light-color permanent hair dye treatments (Johansson *et al.* 2014).

*o*-Toluidine or toluidine (isomer not specified) was found in some food samples, primarily vegetables in German surveys from the 1970s; for example, levels in carrots ranged from less than 0.1 ppm to 7.2 ppm (HSDB 2012). *o*-Toluidine was also detected as a volatile in black tea (IARC 2012). No information on *o*-toluidine content was found in the U.S. Food and Drug Administration's Total Diet Study for market baskets collected between September 1991 and October 2003 (FDA 2006).

Evidence suggesting potential exposure to *o*-toluidine from the environment comes from EPA's TRI database. On- and off-site environmental releases of *o*-toluidine from 15 facilities in 2010 totaled slightly over 6,600 lb, of which 77.4% was released to air, 19.6% to underground injection, and 3.0% to water (TRI 2012). *o*-Toluidine has been detected in water and sediment worldwide. In addition, a biological monitoring study in Europe reported that *o*-toluidine hemoglobin adduct levels in children varied with geographical residence; levels were lower in a largely rural location than in urban locations, suggesting the importance of environmental sources of exposure.

## Regulations

### Coast Guard (Dept. of Homeland Security)

Minimum requirements have been established for safe transport of *o*-toluidine on ships and barges.

### Department of Transportation (DOT)

Toluidines are considered hazardous materials and marine pollutants, and special requirements have been set for marking, labeling, and transporting these materials.

### U.S. Environmental Protection Agency (EPA)

#### Clean Air Act

*National Emission Standards for Hazardous Air Pollutants*: Listed as a hazardous air pollutant.

#### Comprehensive Environmental Response, Compensation, and Liability Act

Reportable quantity (RQ) = 100 lb.

#### Resource Conservation and Recovery Act

*Listed Hazardous Waste*: Waste codes for which the listing is based wholly or partly on the presence of *o*-toluidine or *o*-toluidine hydrochloride = U222, U328, K112, K113, K114.

Listed as a hazardous constituent of waste.

### Occupational Safety and Health Administration (OSHA, Dept. of Labor)

This legally enforceable PEL was adopted from the 1968 ACGIH TLV-TWA shortly after OSHA was established. The PEL may not reflect the most recent scientific evidence and may not adequately protect worker health.

Permissible exposure limit (PEL) = 5 ppm.

Potential for dermal absorption.

## Guidelines

### American Conference of Governmental Industrial Hygienists (ACGIH)

Threshold limit value – time-weighted average (TLV-TWA) = 2 ppm.

Potential for dermal absorption.

### National Institute for Occupational Safety and Health (NIOSH, CDC, HHS)

Immediately dangerous to life and health (IDLH) limit = 50 ppm.

Potential for dermal absorption.

Listed as a potential occupational carcinogen.

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