Petition for a Permanent Standard to Protect Workers Against the Carcinogenic Effects of Occupational Exposure to Ortho-Toluidine

Now come Steven H. Wodka[1], an attorney, Steven B. Markowitz[2], a medical doctor, Ronald L. Melnick[3], a toxicologist, and Elizabeth M. Ward[4], an epidemiologist, pursuant to Section 6(b) of the Occupational Safety and Health Act of 1970, 29 U.S.C. § 655, and petition the Occupational Safety and Health Administration of the U. S. Department of Labor to issue a permanent standard to protect workers against the carcinogenic effects of occupational exposure to the chemical substance ortho-toluidine (CAS No. 95-53-4).

A new permanent standard is required because the current OSHA permissible exposure limit of 5 parts per million of ortho-toluidine in the air, as an 8-hour time weighted average with a skin designation, at 29 CFR 1910.1000 Table Z-1 Limits for Air Contaminants: (a) fails to protect exposed workers, "to the extent feasible, on the basis of the best available evidence, that no employee will suffer material impairment of health or functional capacity even if such employee has regular exposure to the hazard dealt with by such standard for the period of his working life" (s*ee* 29 U.S.C. § 655(b)(5)), and (b) presents a significant risk to exposed workers that is far in excess of

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[1] Steven H. Wodka has represented more than 30 claimants who have developed urothelial carcinomas as a result of occupational exposure to ortho-toluidine at industrial facilities in New York and New Jersey since 1987. Attorney Wodka is also Class Counsel for two certified and settled class actions for medical monitoring for the early detection of bladder cancer at these plants.

[2] Steven B. Markowitz is Professor and Director of the Barry Commoner Center for Health and the Environment of the City University of New York and is also Adjunct Professor of Environmental Medicine and Public Health at the Icahn School of Medicine at Mount Sinai. Dr. Markowitz is a co-author of a 1991 study published in the J Natl Cancer Inst. "Excess number of bladder cancers in workers exposed to ortho-toluidine and aniline" (Ward, 1991). Dr. Markowitz has testified in support of claimants who have developed bladder cancer as a result of occupational exposure to ortho-toluidine.

[3] Ronald L. Melnick was a senior toxicologist, National Toxicology Program, National Institute of Environmental Health Sciences for twenty-eight years, retiring in 2009. Dr. Melnick has testified in support of claimants who have developed bladder cancer as a result of occupational exposure to ortho-toluidine.

[4] Elizabeth M. Ward was an epidemiologist with the United States Public Health Service (retired) and the American Cancer Society (retired). Dr. Ward is lead author of two studies published in the J Natl Cancer Inst., "Excess number of bladder cancers in workers exposed to ortho-toluidine and aniline" (Ward, 1991) and "Monitoring of aromatic amine exposures in workers at a chemical plant with a known bladder cancer excess" (Ward, 1996).

the benchmark risk of one death or one case of serious injury/illness per thousand workers (s*ee Industrial Union Department v. American Petroleum Institute*, 448 U.S. 607, 655 (1980)).

Ortho-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." National Toxicology Program (NTP), *The Report on Carcinogens*, Thirteenth Edition, U.S. Department of Health and Human Services (2014).

The International Agency for Research on Cancer (IARC) has classified ortho-toluidine into its highest category, Group 1, because it "is carcinogenic to humans." According to the IARC, "ortho-toluidine causes cancer of the urinary bladder." *IARC Monographs on the Evaluation of Carcinogenic Risks to Humans*, Volume 99 (2010).

A. History of the current OSHA permissible exposure limit.

OSHA's current 5 parts per million (ppm) permissible exposure limit (PEL) for ortho-toluidine was adopted by the agency in 1971 from a threshold limit value (TLV) set by the American Conference of Governmental Industrial Hygienists (ACGIH). The ACGIH 5 ppm TLV was based on research that was last conducted in 1963. The potential carcinogenicity of ortho-toluidine was never considered by the ACGIH. *See* ACGIH, 1971.

On July 14, 1978, OSHA listed ortho-toluidine as a Category I "Confirmed Carcinogen" as part of its proposed Cancer Policy rulemaking. On January 19, 1989, OSHA proposed to retain the 5 ppm PEL with a skin designation following a risk assessment based solely on animal studies. Court challenges to both rulemakings instituted by employers doomed these proposed rules. Thus, the current federal OSHA PEL rests on an ACGIH TLV that was set in the 1960's without any consideration for carcinogenicity.

B. Animal carcinogenicity.

The finding that a chemical causes tumors in experimental animals indicates that the interaction of that chemical or its metabolites with tissues of the exposed organism are sufficient to create biological changes that initiate and/or promote the cancer process.

Ortho-toluidine is carcinogenic to the urinary bladder of rats (Weisburger et al.,1978; NCI, 1979; Hecht et al., 1982); in addition, it induces bladder tumors in dogs (Pliss, 2004; NTP, 2014a). While the agent tested by the NCI for carcinogenicity was the hydrochloride salt of ortho-toluidine, it is referred to as ortho-toluidine because in body fluids the salt dissolves and separates into ortho-toluidine and chloride ions.

Because bladder tumors occur rarely in untreated male Sprague-Dawley rats (approximately 3 per thousand rats, or 0.3%) (Giknis and Clifford et al., 2004), the increased incidences observed in the study by Weisburger et al.,1978 (13% and 17%) were likely due to the exposures to ortho-toluidine. Bladder tumor incidences were increased significantly in the NCI study in female F344 rats (NCI, 1979); the increases in bladder tumor incidence in male F344 rats (6% in NCI, 1979; and 13% by Hecht et al., 1982) were not statistically significant but were much greater than the spontaneous rate (0.3%) of this tumor in unexposed male F344 rats (Haseman et al., 1998). A metabolite of ortho-toluidine, o-nitrosotoluene, is also carcinogenic to the urinary bladder of rats (Hecht et al., 1982). In addition, hyperplasia of the bladder epithelium was increased in rats exposed to ortho-toluidine. The latter lesion is part of the continuum of induced proliferative lesions leading to papillomas and malignant carcinomas. *See* Table 1, below.

Table 1. Carcinogenicity of *o*-toluidine and its metabolite *o*-nitrosotoluene in the urinary bladder of rats

Strain, sex	Average % in feed	Hyperplasia	Papilloma or Carcinoma	Reference
o-Toluidine		Incidence[a] (%)		
Sprague-Dawley, male	0 0.47 0.93		0/16 (0) 3/23 (13) 4/24 (22)	Weisburger et al., 1978
F344, male	0 0.3 0.6	0/20 9/50* 7/44	0/20 (0) 3/50 (6) 1/44 (2)	NCI, 1979
F344, female	0 0.3 0.6	0/20 21/45* 13/47*	0/20 (0) 10/45* (22) 22/47* (47)	NCI, 1979
F344, male	0 0.4		0/27 (0) 4/30 (13)	Hecht et al., 1982
o-Nitrosotoluene				
F344, male	0 0.34		0/27 (0) 15/29* (52)	Hecht et al., 1982

[a] Incidence is the number of animals with a lesion/number of animals examined
*Significantly different from concurrent controls, $P \leq 0.05$

The animal cancer data together with epidemiological data demonstrate that the urinary bladder is a common site of tumor induction by ortho-toluidine in humans and animals. Tumor site concordance between animals and humans has been frequently observed for human carcinogens (Wilbourn et al., 1986; Huff, 1999).

C. Mechanistic evidence.

Mechanistic data demonstrates how exposure to ortho-toluidine leads to tumor formation and supports the causal relationship between exposure to this aromatic amine and increased bladder cancer risk in humans.

1. Metabolism of ortho-toluidine.

"N-oxidation catalyzed by cytochrome P450 [forming N-hydroxy-o-toluidine] appears to be a necessary if not sufficient step in the activation of o-toluidine to a bladder and liver carcinogen" (English et al., 2012). In rats given a single dose of ortho-toluidine, the metabolite N-hydroxy-o-toluidine was detected in the urine at 6 hours after treatment (Kulkarni et al., 1983). Nitrosoarenes are oxidation products of N-hydroxylarylamines (Son et al., 1980; Birner et al., 1988; Sabbioni et al., 1994). o-Nitrosotoluene, the nitrosoarene metabolite of ortho-toluidine, has also been detected in the urine of rats dosed with ortho-toluidine (Son et al. 1980); this chemical also induces bladder tumors in rats (Hecht et al., 1982). Thus, similar to carcinogenic polycyclic aromatic amines (e.g., 4-aminobiphenyl and 2-naphthylamine), ortho-toluidine undergoes activation by N-oxidation.

2. Formation of hemoglobin adducts.

Ortho-toluidine, as well as other carcinogenic polycyclic aromatic amines, undergo N-hydroxylation and form hemoglobin adducts (IARC, 2010). The formation of hemoglobin adducts results from systemically available N-hydroxyarylamines in the blood undergoing oxidation in red blood cells generating methemoglobin and forming nitrosoarenes; the latter chemicals bind to a cysteine sulfur group in hemoglobin to form the adducts (Skipper and Tannenbaum, 1994).

Because oxidation of aromatic amines to N-hydroxylamines in the liver is a key step in the genotoxicity of this class of chemicals, and because N-hydroxylamines can form adducts with DNA and hemoglobin, the formation of hemoglobin adducts is a surrogate biomarker of aromatic amine exposure, bioactivation, and potential reactivity with DNA (Skipper and Tannenbaum, 1994; Gaber et al., 2007; Talaska and Al-Zoughool, 2003). Occupational exposures to several aromatic amines, including 2-naphthylamine, 4-aminobiphenyl, and benzidine, have long been known to be causal of human bladder cancer, and hemoglobin adducts have been used as biomarkers of human exposure to these compounds (IARC, 2012). Numerous studies have also demonstrated the formation of hemoglobin adducts in humans and rats exposed to ortho-toluidine. Levels of hemoglobin adducts of ortho-toluidine were significantly higher (~10-fold) in workers exposed to ortho-toluidine at a chemical manufacturing facility in Niagara Falls, New York (The Goodyear Tire & Rubber Company plant) compared to unexposed workers at that facility (Ward, 1996). Thus, hemoglobin

adducts of ortho-toluidine are clearly formed in humans exposed to this aromatic amine (Sabbioni and Beyerbach, 1995; Ward, 1996).

3. Formation of DNA adducts.

In a study of the binding of the N-acetoxy metabolites of monocyclic aromatic amines (including ortho-toluidine) with deoxyguanosine or isolated DNA, the predominant DNA adduct was formed by a covalent bond between the arylamine nitrogen and the C8 atom of deoxyguanosine (Marques et al., 1996; 1997). The authors concluded that reactive metabolites of single ring aromatic amines “react with DNA to yield covalent adducts structurally identical to those derived from carcinogenic polyarylamines”.

N-hydroxy metabolites of ortho-toluidine form DNA adducts primarily at the C8 position of deoxyguanosine; this site of DNA adduct formation is consistent with what has been observed with carcinogenic polycyclic aromatic amines when their N-hydroxy metabolites were incubated with calf thymus DNA (Beland et al., 1983; Beland et al., 1997). In addition, 4-aminobiphenyl and benzidine form adducts at the C8 position of deoxyguanosine in bladder DNA of treated dogs (IARC, 2010). While adducts to deoxyguanosine were the most prevalent after the in vitro reaction of calf thymus DNA with the N-acetoxyarylamine of ortho-toluidine, adducts with the other three bases (deoxycytosine, deoxythymidine, and deoxyadenosine) were also detected (Jones and Sabbioni et al., 2003). Thus, metabolites of ortho-toluidine form DNA adducts similar to those of carcinogenic polycyclic aromatic amines.

DNA adducts formed from ortho-toluidine have also been detected in human bladder tissue samples (Böhm et al., 2011). DNA adduct levels were higher in tumor samples than in normal bladder tissue. Although the sources of individual exposures to ortho-toluidine were not known, the authors concluded: “the presence of DNA adducts releasing o-toluidine in human bladder tissue clearly show that o-toluidine is genotoxic to humans and further support the classification of o-toluidine as a human carcinogen.”

4. DNA strand breaks.

The induction of DNA single strand breaks by ortho-toluidine has been reported in several studies (Danford, 1991). Improperly repaired DNA strand breaks can lead to genomic instability, which can enhance the rate of cancer development. Genomic instability is a characteristic of cancers in which mutations and chromosomal rearrangements occur at a high frequency.

In a comparative study of chemicals that have been shown to induce bladder tumors in rats, ortho-toluidine and 2-naphthylamine induced DNA strand breaks (measured by the Comet assay) in primary cultures of human and rat urinary bladder

epithelial cells (Robbiano et al., 2002). In addition, DNA strand breaks were induced in the urinary bladder mucosa of rats given single oral doses of each of these aromatic amines. Neither compound induced DNA strand breaks in the liver or kidney of treated rats. Thus, both ortho-toluidine and 2-naphthylamine are genotoxic bladder carcinogens.

5. Cytogenetic assays.

"Results from several cytogenetic studies have demonstrated clastogenic [chromosome damaging] activity of o-toluidine in mammalian cells in vitro" (English, 2012). Mixed results (positive and negative) have been reported in in vitro cytogenetic studies of ortho-toluidine (Danford, 1991). In mice given single intraperitoneal injections of ortho-toluidine, there were no significant increases of chromosomal aberrations in bone marrow cells, but there was an increase in the number of sister chromatid exchanges (SCEs) per bone marrow cell (McFee et al., 1989). A slight increase in micronucleated erythrocytes was detected in bone marrow cells when ortho-toluidine was administered in saline but not when administered in dimethylsulfoxide. In mice dosed up to 4 times with ortho-toluidine, there was no significant increase in the frequency of micronuclei in bone marrow cells (Nakai et al., 1994). An increase in chromosome aberrations was detected in Chinese hamster lung cells treated with ortho-toluidine (Nakai et al., 1994).

6. Cell transformation.

In several cellular assay systems conducted at multiple laboratories, ortho-toluidine was positive for the induction of morphologically transformed colonies of cells (Tanaka et al., 2012; Maire et al., 2012). Based on available genotoxicity data, English et al., 2012 concluded that, "o-toluidine is genotoxic in vitro and in vivo."

D. Epidemiological and industrial hygiene studies performed by NIOSH.

The Goodyear Tire & Rubber Company plant in Niagara Falls, New York manufactures raw materials that are used in the manufacturing of tires called rubber chemicals. Since 1957, this plant has manufactured an antioxidant used in tires known as "Nailax" that has the trade name of "Wingstay." Nailax manufacturing takes place in Department 245 of the Niagara Falls plant. One of the main raw materials used in the plant to make Nailax is ortho-toluidine.

Since 1957, this Goodyear plant has been one of the largest US users of ortho-toluidine. The two former US manufacturers of ortho-toluidine, E. I. du Pont de Nemours and Company and First Chemical Corporation, considered the Goodyear plant as one of their "top ten" customers in terms of volume. Based on available data, annual ortho-toluidine consumption at this plant ranged from 3.3 million pounds in 1960 to 8.0

million pounds in 1993, with an average of 6.7 million pounds being consumed annually between 1960 and 1998. *See* The Goodyear Tire & Rubber Company, 1999, "Raw Material Purchased and Production Volumes." The manufacture of Nailax at the Goodyear plant using ortho-toluidine continues through to the date of the filing of this petition.

In 1988, in response to a request from the Oil, Chemical and Atomic Workers (OCAW) International Union, the National Institute for Occupational Safety and Health (NIOSH) began a health hazard evaluation of the Goodyear plant in Niagara Falls. The union requested this evaluation because eight cases of bladder cancer had been reported to the union between 1973 and 1988 among current and former employees of the plant. All eight workers had worked in Department 245 and all had exposure to ortho-toluidine.

In its first report issued in December, 1989, NIOSH found that 14 cases of bladder cancer had occurred among the 1749 individuals ever employed at the plant, while only 3.54 cases were expected based on New York State incidence rates. The ratio of observed to expected cases (also known as the Standardized Incidence Ratio or SIR) of 3.95 was found to be highly statistically significant (p=0.00002), indicating that this risk was very unlikely to have occurred by chance. The highest risk was observed among workers who had ever been employed in Department 245 "where workers were definitely exposed to ortho-toluidine." Workers in Department 245 had a SIR of 6.64 (p=0.00004) which signified that they were 6.64 times more likely than New York State residents of similar age and sex to develop bladder cancer during the same time period. (NIOSH, 1989).

NIOSH also reported that "worker exposure monitoring data that Goodyear industrial hygiene staff have collected since 1982 show that air concentrations of all chemicals present in Department 245 have been consistently less than one part per million (ppm)." (NIOSH, 1989).

During the period of February 27 to March 9, 1990, NIOSH conducted an industrial hygiene study of ortho-toluidine exposure at the Goodyear plant. The results of the study were issued in a 114-page report entitled "Interim Report No. 2" in March, 1992 (NIOSH, 1992).

In this study, NIOSH conducted both air and urine sampling of the workers exposed to ortho-toluidine. "Because. . .o-toluidine. . .[has the] potential for absorption through the skin, a sampling strategy was developed to measure exposure through the air and indicate potential exposure from liquid chemical to the skin." (NIOSH, 1992).

With respect to air sampling, NIOSH reported personal air sampling results for ortho-toluidine that ranged from 87.4 to 1,630 micrograms per cubic meter (μg/m^3) (.020

to .373 ppm) as an 8-hour time-weighted average (TWA) and area air sample results that ranged from 36.8 to 2,460 µg/m³ (.008 to .563 ppm) as an 8-hour TWA. Significantly, both sets of results were substantially less than the OSHA permissible exposure limit of 22,000 µg/m³ (equivalent to 5 parts per million). In fact, the highest peak sample (non-TWA) obtained by NIOSH during the entire study was 7,170 micrograms per cubic meter of air (1.64 ppm) in a production operator utility who was cleaning the Sparkler filter. (NIOSH, 1992).

NIOSH also conducted pre-shift and post-shift urine sampling for ortho-toluidine. The workers were divided into two groups, one with exposure to ortho-toluidine in Department 245 and one without exposure, and their results were compared. For the unexposed control workers, the mean of the post-shift urine samples for ortho-toluidine was 2.8 µg/L and 1.2 µg/L for the pre-shift samples. However, in the exposed Department 245 workers, the mean of the post-shift urine samples for ortho-toluidine was 98.7 µg/L and 15.4 µg/L for the pre-shift samples. (Ward, 1996, Table 1). For ortho-toluidine, the pre-shift mean in the exposed group was 12.8 times higher than in the unexposed, while the post-shift mean in the exposed was 35.3 times that in the unexposed. (Ward, 1996). There was no overlap of urine levels between exposed and unexposed workers. Even though the highest airborne exposure results were less than one-third of the allowable OSHA PEL, NIOSH concluded that the urine sampling data "provides unequivocal evidence that Department 245 workers were absorbing o-toluidine. . .into their bodies during the workshift." (NIOSH, 1992).

NIOSH also reported that the highest post-shift urinary ortho-toluidine level in the Goodyear workers was 527 µg/L (.53 mg/liter). (NIOSH, 1992).

By 1993, DuPont scientists, as a result of their work to develop a new urinary biomonitoring method, had determined that exposure to ortho-toluidine at the OSHA permissible exposure limit (PEL) of 5 ppm for an 8 hour day would result in an ortho-toluidine concentration in the urine of 20 milligrams per liter. (DuPont, 1993, Estimates of Exposure to Aniline, Benzidine, Beta-naphthylamine and o-Toluidine).

Thus, worker exposure at the OSHA permissible exposure limit of 5 ppm for an 8-hour day would produce a urinary concentration of 20 milligrams per liter, which was 37 times higher than the highest level found in the Goodyear workers.

In her deposition, DuPont corporate representative Barbara Dawson confirmed that DuPont had obtained this finding in 1993:

> Q. In Dawson Exhibit 13, Nelson had reported that NIOSH had found ortho-toluidine levels in the urine of the Goodyear workers in a range of .014 to .53 milligrams per liter; correct?

MR. WISHNOFF: Object to form.

A. That's what it says.

Q. So if I do the math correctly, a 5 part per million exposure for 8 hours a day would produce a urinary concentration some 37 times higher than what was found in the Goodyear workers. Correct?

MR. WISHNOFF: Object to the form.

Q. In other words, the difference between .53 milligrams versus 20 milligrams.

A. That's what it says.

Barbara Dawson deposition, 2016.

DuPont never notified OSHA, NIOSH or the US Environmental Protection Agency of this finding in 1993 or at any later time. Section 8(e) of the Toxic Substances Control Act (TSCA) requires a chemical manufacturer to report to the EPA if it finds out something new about a chemical that might pose a substantial risk to human health. In a February 2, 1995 submission to US Environmental Protection Agency under TSCA Section 8(e), DuPont failed to report the results of its 1993 study of urinary concentrations at the 5 ppm OSHA PEL. Instead, DuPont falsely reported that: "Based on all available toxicity data, including the new findings, the existing worker exposure limit (Acceptable Exposure Limit, AEL[5]) was reviewed and its validity at 5 ppm, 8- and 12 hr. time weighted average, confirmed." (DuPont, 1995).

In 1991, NIOSH investigators led by Dr. Elizabeth M. Ward published the findings of their 1988-1989 epidemiological study of bladder cancer incidence at Goodyear. (*See* Ward E, Carpenter A, Markowitz S, et al. 1991. Excess number of bladder cancers in workers exposed to ortho-toluidine and aniline. *J Natl Cancer Inst* 83(7): 501–6.) Ward reported excess bladder cancer risk among the Goodyear workers that was statistically significant. The highest SIR [=16.4; 90% CI= 7.13-32.3] was found in the category 20+ years since first employment in Department 245. (Ward, 1991).

[5] An "AEL" is an in-house DuPont term for an "acceptable exposure limit." Henry Trochimowicz, ScD, a staff toxicologist at the Haskell Laboratory and chairman of DuPont's AEL Committee, defined an AEL as "a level of exposure believed to be safe for an individual to, let's say, breathe a chemical for eight hours a day, five days a week for his working lifetime without experiencing any serious adverse effect -- or any adverse effect." Henry Trochimowicz deposition (2007).

In 1996, NIOSH investigators again led by Dr. Ward published the findings of their 1990 industrial hygiene monitoring at the Goodyear plant. (*See* Ward EM, Sabbioni G, DeBord DG, Teass AW, Brown KK, Talaska GG, Roberts DR, Ruder AM, Streicher RP. 1996. Monitoring of aromatic amine exposures in workers at a chemical plant with a known bladder cancer excess. *J Natl Cancer Inst* 88(15): 1046-1052.) Dr. Ward reported that the mean air concentrations for ortho-toluidine ranged between 412 to 516 micrograms per cubic meter of air (.094 to .118 ppm). Ward further reported that

> [b]oth pre-shift and post-shift levels of o-toluidine. . .in the urine samples were significantly elevated among all worker groups in the rubber chemicals department compared with those among unexposed control workers. . . .post-shift concentrations of o-toluidine among exposed workers were 35 times higher than those among unexposed workers. Thus, the urine data provide substantial evidence that. . .o-toluidine [is] absorbed by workers in the rubber chemicals department.

(Ward, 1996). The NIOSH investigators concluded that "occupational exposure to o-toluidine is the most likely causal agent of the bladder cancer excess observed among workers in the rubber chemicals department of the plant." (Ward, 1996).

In 2012, NIOSH investigators led by Kevin W. Hanley performed an exposure assessment revision to the prior studies of the Goodyear plant by assigning "[a]n approximate rank of 'relative' exposure level for each department-job-year combination" "using a ranking scale of 0 to 10." (*See* Hanley KW, Viet SM, Hein MJ, Carreón T, Ruder AM. 2012. Exposure to o-toluidine, aniline, and nitrobenzene in a rubber chemical manufacturing plant: a retrospective exposure assessment update. *J Occup Environ Hyg* 9(8): 478-490.) Hanley reported "that appreciable absorption and systemic distribution will occur from direct skin contact with" ortho-toluidine. "Hence, air exposure measurements do not reflect total exposure dose for those workers with substantial skin contact to o-toluidine." Hanley further wrote that frequent skin contact with chemicals and process intermediates and inconsistent use of personal protective equipment was reported by workers at this facility, especially prior to 1989, even though the company reported that personal protective equipment policies were established about a decade earlier. (Hanley, 2012).

Most importantly, Hanley reported air sampling data conducted by Goodyear for the period of 1976 to 2004. For ortho-toluidine, the geometric mean exposures in Department 245 were 0.10, 0.015, and 0.0028 ppm for the time periods of 1976–1979, 1980–1994, and 1995–2004, respectively. (Hanley, 2012).

In 2014, NIOSH investigators led by Dr. Tania Carreon published the findings of a follow-up epidemiological study of bladder cancer incidence at the Goodyear plant. (*See* Carreón T, Hein MJ, Hanley KW, Viet SM, Ruder AM. 2014. Bladder cancer

incidence among workers exposed to o-toluidine, aniline and nitrobenzene at a rubber chemical manufacturing plant. *Occup Environ Med* 71(3): 175-182.) This study both "expanded" the 1988 cohort and updated its bladder cancer incidence through 2007. By this date (12/31/2007), fifty cases of bladder cancer had been identified. Carreon estimated bladder cancer risk for the cumulative relative exposure ranks developed by Hanley.

Carreon reported that:

- "Bladder cancer incidence was elevated among all workers, except those considered not exposed."

- "Excess bladder cancer was observed compared to the New York State population (SIR=2.87, 95% CI 2.02 to 3.96), with higher elevations among workers definitely exposed (moderate/high) (SIR=3.90, 95% CI 2.57 to 5.68)."

- "[W]e consider o-toluidine most likely responsible for the bladder cancer incidence elevation."

For the entire group of 50 bladder cancer cases identified by Carreon in the Goodyear workforce, the lower end of the range of the unit-day calculation (based on the relative exposure ranks) began at 292 unit-days (0.8 unit-year x 365 days). *See* Table 1, Carreon, 2014. Thus, less than one year of exposure produced excess cancer risk. Carreon concluded that "increased bladder cancer incidence was observed even at the lower cumulative rank."

Dr. Carreon made the following recommendation:

> Air monitoring data showed that exposure concentrations even among the highest exposed workers were very low relative to existing occupational exposure limits. Currently, the Occupational Safety and Health Administration Permissible Exposure Limit (PEL) for o-toluidine is 5 ppm as an 8-h time-weighted average. The geometric mean levels measured by NIOSH at the plant were at least an order of magnitude lower than the PEL and the American Conference of Governmental Industrial Hygienists' Threshold Limit Value of 2 ppm. The geometric mean levels of o-toluidine for samples collected by NIOSH were also lower than the most stringent exposure limit among European nations of 0.1 ppm set by Austria and Switzerland. The excess bladder cancer observed at the plant suggests that occupational exposure limits for o-toluidine may need to be re-examined, and that further measures, such as

dermal exposure control/reduction, may be required.

(Carreon, 2014).

E. NIOSH risk assessment for ortho-toluidine.

The final chapter in this outstanding effort by the National Institute for Occupational Safety and Health to identify the health hazards of occupational exposure to ortho-toluidine occurred in 2021 with the publication of its "Risk assessment for o-toluidine and bladder cancer incidence." (*See* Park RM, Carreón T, Hanley KW. 2021. Risk assessment for o-toluidine and bladder cancer incidence. *Am J Ind Med.* 64:758-770). This study was based on the previously published epidemiological studies of excess bladder cancer incidence at Goodyear's Niagara Falls plant (Ward, 1991 and Carreon, 2014), and on Goodyear's industrial hygiene air sampling for ortho-toluidine.

This NIOSH study determined that occupational exposure to ortho-toluidine at 1 part per billion in workplace air would cause an excess lifetime risk of developing bladder cancer of 1.2 to 7.1 cases per thousand, which equals or exceeds the US Supreme Court's definition of a significant risk of impairment of material health of one or greater in a thousand. *See Industrial Union Department* , *supra*, 448 U.S. at 655. NIOSH concluded that the "current ACGIH TLV and OSHA standards for OT are 2 and 5 ppm, respectively, 1000-fold higher than the exposure estimated here for 1–7 per thousand excess lifetime risk."

The key NIOSH findings appear in Table 5:

TABLE 5 Excess lifetime risk of incident bladder cancer in workers from a chemical manufacturing plant, attributable to *o*-toluidine airborne exposure (ppm) from model based on cumulative rank and assuming different dependencies on employment duration, and from model based on estimated *o*-toluidine concentrations

	Excess lifetime risk (per 1000) applying different model estimates			
o-toluidine (ppm)	OT ranks with unrestricted durations[a]	OT ranks with durations <5 years[a]	OT ranks with duration = 0[a]	OT concentration (no duration term)[a]
0.2	212	601	653	217
0.1	114	407	463	118
0.05	59	242	284	61
0.02	24	108	130	25
0.01	12	56	68	13
0.005	6.2	29	35	6.4
0.002	2.5	12	14	2.6
0.001 (1 ppb)	1.2	5.8	7.1	1.3
0.0005	0.6	2.9	3. 5	0.6
0.0002	0.2	1.2	1.4	0.3
0.0001	0.1	0.6	0.7	0.1

Note: OSHA PEL: 5 ppm; ACGIH TLV: 2 ppm.

Abbreviation: OT, *o*-toluidine.

[a]Based on OT exposure ranks with Rank 10 equivalent OT concentration = 0.36 ppm, and calculating lifetime risk with different treatments of duration (from Table 2, Model 5).

[b]Based on actual reported air concentrations of OT (from Table 3, Model 4).

F. The Goodyear workers remain at significant risk of developing bladder cancer.

The latest Goodyear air sampling for ortho-toluidine available to the Petitioners occurred between March 15 to May 30, 2019. Excluding the Professional Development Instructor, 22 samples were obtained. The results ranged from 0.05 parts per billion (ppb) to 111 ppb. The average of the results was 11.3 parts per billion. (The Goodyear Tire & Rubber Company, June 4, 2021, Bunce to White). Park, 2021 determined that at an exposure of 10 parts per billion, the excess lifetime risk of developing bladder cancer would be in the range of 12 to 68 per thousand, an exposure level that NIOSH identified during a tripartite review as "unequivocally above the level that protects for 1/1000 lifetime risk." Three job assignments at the Goodyear plant had exposures of 10 ppb or higher: tank farm operator, production operator, and lab technician.

The average exposure of 11.3 parts per billion is consistent with historical Goodyear data. In 2013, Goodyear corporate industrial hygienist Mike Porter issued a presentation entitled, "Niagara Falls Aryl Amine Exposures 1992-2012." At slide 6, Mr. Porter reported that the average exposure over that 20 year period was 11.2 parts per billion. (Goodyear, 2013).

Carreon, 2014 recorded 50 cases of bladder cancer through December 31, 2007. Since that date, an additional 27 cases of bladder cancer (including a urothelial carcinoma) have been diagnosed in current and former Goodyear Niagara Falls workers.

The Petitioners have also reviewed the results of pre- and post-shift urine monitoring data that were collected by Goodyear between December 15-29, 2020. (The Goodyear Tire & Rubber Company, June 4, 2021, Bunce to White). Excluding the Professional Development Instructor and Site Support, 24 pre- and post-shift samples were obtained. The post-shift results ranged from 1.5 to 50 nanograms per milliliter and the post-shift fold increase over the pre-shift amount ranged from 1.3 fold to 13.9 fold. (Nanograms per milliliter and micrograms per liter are equivalent measurements). These results provide conclusive evidence that the Niagara Falls workers are still absorbing ortho-toluidine into their bodies during the workshift.

In addition, the 2020 urine sampling identified a Chemical Operator Utility (COU) with a post-shift result of 50 nanograms per milliliter that was 13.9 times greater than his/her pre-shift amount. This worker's post-shift result was well within the range reported by NIOSH in Interim Report No. 2 in March 1992.

G. Components of a protective OSHA standard.

1. The permissible exposure limit should be based on both air and urine sampling.

Petitioners recommend that OSHA adopt a new permissible exposure limit for occupational exposure to ortho-toluidine that consists of limits in both the workplace air and in a worker's urine, and that a result exceeding either limit constitutes a violation of Section 9 of the statute. The airborne eight-hour, time-weighted permissible exposure limit should be reduced from 5 parts per million to 1 part per billion, and OSHA should also adopt a urine sampling limit of 0.2 micrograms of ortho-toluidine per liter of urine.

Park, 2021 demonstrates that the current permissible exposure limit of 5 parts per million poses a significant risk to workers. Park, 2021 also identifies the level at which occupational exposure no longer poses such a significant risk. However, air sampling for ortho-toluidine exposure does not provide reliable data on a worker's exposure from skin exposure because ortho-toluidine can make a "potential significant contribution to overall exposure via the cutaneous route, including mucous membranes and eyes, by contact with vapors, liquids, and solids." National Toxicology Program, Report on Carcinogens, Monograph on Ortho-Toluidine (2014). The inability of air sampling to measure skin absorption is heightened by ortho-toluidine's physical properties. Ortho-toluidine has a high boiling point (198-201ºC) and low volatility at ambient temperature (0.33 mm Hg at 25ºC). *Id*. Accordingly, unless the ortho-toluidine is heated, workplace surface contamination with ortho-toluidine can be readily absorbed through the skin, but it will not be adequately measured by airborne exposure sampling.

The two former US manufacturers of ortho-toluidine agree that air sampling is an unreliable indicator of worker exposure.

Barbara Dawson, DuPont's global industrial hygienist, testified that "[t]raditional industrial hygiene monitoring of the air is predictive only of the exposure potential from the inhalation route and does not take into account the dose which would be a result of skin absorption" and that DuPont has been aware of that fact since at least 1954. Barbara Dawson deposition, 2016, at 132:1-19.

Steven C. Dawson (not related to Barbara Dawson) was First Chemical Corporation's Manager of Industrial Hygiene and Health. Mr. Dawson testified that inhalation of ortho-toluidine, even within the so-called recommended limits, could allow for significant exposure to ortho-toluidine because the employee can still get a significant exposure through his skin. Steven Dawson deposition, 1991, at 51:12 to 53:4.

Their testimony is supported by an extensive history. In July 1974, Adrian L. Linch, of DuPont's Chambers Works Industrial Hygiene Laboratory, published an article "Biological Monitoring for Industrial Exposure to Cyanogenic Aromatic Nitro and Amino Compounds" in the *American Industrial Hygiene Association Journal*. (Linch, 1974). Ortho-toluidine was identified as one of the cyanogenic aromatic amino compounds that DuPont handled at the Chambers Works in New Jersey. Linch wrote (p. 426) that "[t]he primary control program is based on urine analysis to provide early warning of excessive exposure" because "[a]ir analysis based on fixed station or personnel monitor collection cannot provide by itself a surveillance program adequate for health conservation when significant absorption occurs through the skin."

By 1986, at the latest, DuPont's cyanosis control program at the Chambers Works enforced a zero tolerance for any amount of ortho-toluidine in an exposed worker's urine. DuPont's procedures required that urine samples for workers exposed to ortho-toluidine be chromatographed in order to confirm the presence of the substance. A urine sample with any confirmed amount of ortho-toluidine was considered "elevated." (DuPont, 1986, Cyanosis Control Program). Such results would cause the employee to be interviewed by the in-plant medical office in order to determine how the worker was exposed. Barbara Dawson testified that DuPont relied on this urine monitoring procedure in order "to protect people from exposure to ortho-toluidine." Barbara Dawson deposition, 2016, 91:19 to 93:11.

In 2017, the European Union adopted a recommended occupational exposure standard for ortho-toluidine. European Commission, SCOEL/REC/301, o-Toluidine, 2-methylaniline, Recommendation from the Scientific Committee on Occupational Exposure Limits, adopted February 8, 2017. It was based on a standard first adopted in Germany in 2012 utilizing data on the ortho-toluidine levels in the urine of the general

population. It set a BGV (biological guidance value) of 0.2 micrograms of ortho-toluidine per liter of urine. The European Union determined that because ortho-toluidine is a "genotoxic carcinogen, no health-based biological limit value can be set for it."

Thus, the European Union established a biological guidance value for workers' ortho-toluidine urinary concentrations based on the background level in the unexposed population, which is essentially the same recommendation made by NIOSH to Goodyear in 1992. "The eventual goal of such a program would be to control exposure to o-toluidine and aniline to such a degree that the urinary concentrations do not differ from those in the unexposed population." NIOSH Interim Report No. 2, 1992, at 47.

2. Engineering controls must be required as the primary means of protecting workers.

Engineering controls, which provide a complete physical and functional separation between the worker and any potential exposure, must be mandated by a new standard. This is not a new concept for the manufacture, use or handling of ortho-toluidine.

James Medaris was the supervisor of the manufacturing unit that made ortho-toluidine at the DuPont Chambers Works in Deepwater, New Jersey from 1965 through 1995. In his 2012 deposition, Medaris testified that ortho-toluidine was manufactured in the hydrogen reduction building. From the beginning of his assignment in that building in 1965 through 1995, Medaris testified that the ortho-toluidine production facilities were designed to contain the product because "all vessels and piping systems are closed" and that any vents on any vessels were vented to the outside of the building. (pp. 53-54). For example, Medaris testified that 55 gallon drums of ortho-toluidine were filled by an operator working through a glove box and that the air was ventilated to outside the building. In addition, even though the operator filling the drums was completely separated from the ortho-toluidine because of the glove box arrangement, the operator was also wearing an air supplied face mask, a butyl rubber jacket, butyl rubber pants, butyl rubber gloves, and butyl rubber overshoes (pp. 86-87). Medaris testified that the locker room facilities were divided into a clean and dirty side separated by a shower. James Medaris deposition, 2012.

3. Personal protective equipment must be impermeable to ortho-toluidine.

Certain commonly used personal protective materials, such as nitrile rubber or polyvinyl chloride (PVC), allow for the permeation of ortho-toluidine contamination from the surface of the equipment, through the material, and onto the worker's skin. Only materials that bar ortho-toluidine permeation should be permitted, such as butyl rubber or neoprene. *See* DuPont MSDS, 2010. Whenever the possibility exists of uncontrolled

exposure to ortho-toluidine, as, for example, during repair of a pipe or pump containing ortho-toluidine, the worker should be required to wear an air-supplied, fully enclosed suit manufactured from a material that bars ortho-toluidine permeation, such as butyl rubber or neoprene. Again, such a requirement has been recognized for decades. *See Modern Occupational Medicine*, 1954, edited by A. J. Fleming, MD, Assistant Medical Director, DuPont; C. A. D'Alonzo, MD, Special Assistant, Medical Division, DuPont; and, J. A. Zapp, PhD, Director, DuPont's Haskell Laboratory for Toxicology and Industrial Medicine, in which DuPont reported on the first, full-scale field trial of the effectiveness of its "Chem-Proof Air Suit," which was conducted on June 17, 1953 in Chapter 8, "Protective Clothing for the Chemical Industry."

4. Warnings and information to workers.

Workers should be provided with clear and unequivocal warnings that **ortho-toluidine causes cancer**, not that it "may" cause cancer. Workers should not only be informed that ortho-toluidine exposure causes bladder cancer, but also that it can cause a malignancy anywhere along the human urothelium, from the renal pelvis in the kidneys, through the ureters, and in the bladder as well. As stated by DuPont's John A. Zapp, the Director of its Haskell Laboratory for Toxicology and Industrial Medicine from 1952 to 1976, on July 13, 1973 to the US Department of Labor Standards Advisory Committee on Carcinogens: "the really important thing is to get the message to the workman in such form that he fully understands what the hazards are, and the best means for avoiding them, what are his best and most scientific means of protection." *See* OSHA, 1973, Partial transcript from meeting of the Standards Advisory Committee on Carcinogens. Such warnings should be required whenever and wherever there is potential exposure, beginning at the tank car delivering the ortho-toluidine to the plant through to the final product, which may contain residual ortho-toluidine.

5. Medical surveillance.

Beginning in 1997, two industrial users of ortho-toluidine have been conducting medical monitoring programs for the early detection of bladder cancer. Screening tests permit the detection of bladder tumors at the earliest stage in their development when treatment by a urologist can be most effective before the tumor invades the muscle wall of the bladder. The Goodyear plant in Niagara Falls, New York and the former Morton Chemical plant in Paterson, New Jersey (now the responsibility of The Dow Chemical Company) conduct these programs. Their screening protocols have been effective in detecting bladder tumors in participants who are completely asymptomatic. The screening tests include: urinalysis, urine cytology, Hemastix (colorimetric indicator self-test strips to detect microscopic blood in the urine), NMP-22 (a biological marker, *BladderCheck*), and FISH (fluorescence in situ hybridization). Bladder cancer screening is rapidly evolving and advancing in its sensitivity and specificity. An OSHA standard

should include a combination of the most sensitive and specific tests for both current and former exposed workers.

Because the liver is the primary site for the initial metabolism of ortho-toluidine, medical surveillance should also monitor for liver toxicity.

Conclusion

Ortho-toluidine is considered to be a high-production-volume chemical, based on its importation into the United States in quantities of tens of millions of pounds per year. *See* https://chemview.epa.gov/chemview. The NIOSH National Occupational Exposure Survey (NOES) conducted between 1981 and 1983 estimated that about 30,000 workers were potentially exposed to ortho-toluidine at that time. *See* NTP Report on Carcinogens Monograph on Ortho-toluidine, (2014) at 9.

The current OSHA permissible exposure limit of 5 parts per million does not protect workers against the carcinogenic effects of ortho-toluidine. Research conducted by former ortho-toluidine manufacturer DuPont and studies performed by NIOSH unequivocally demonstrate that the currently permissible exposure level of 5 parts per million in the workplace is, in fact, a lethal level of exposure.

Please advise if the agency has any questions or needs any further information.

Respectfully submitted,

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