STEVEN H. WODKA

Member of Bar
New Jersey
District of Columbia

ATTORNEY AT LAW
577 LITTLE SILVER POINT ROAD
P.O. BOX 66
LITTLE SILVER, NEW JERSEY 07739-0066
(732) 530-2815

Fax (732) 530-3627
stevewodka@verizon.net

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BY U.S. MAIL and E-MAIL

Dr. Ruth Lunn, Director
Office of the Report on Carcinogens
DNTP, NIEHS
P.O. Box 12233
MD K2-14
Research Triangle Park, NC 27709

Re: Federal Register Notice: January 19, 2012
Request for Public Comment on Nomination of Ortho-Toluidine to Report on Carcinogens

Dear Dr. Lunn:

I am an attorney in private practice. Since 1987, I have represented workers in personal injury, product liability claims who have developed bladder cancer as a result of their occupational exposure to ortho-toluidine. Currently, I represent four such claimants in litigation pending in the Superior Court of New Jersey and in the United States District Court for the Western District of New York. In addition, I have represented hundreds of ortho-toluidine exposed workers in two successful class actions which provided them with free medical monitoring programs for the early detection of bladder cancer.

Ortho-toluidine has been listed in every Report on Carcinogens (RoC) since the Third Annual report in 1983. In the current Twelfth (2011) RoC, ortho-toluidine is classified as "reasonably anticipated to be a human carcinogen." That classification, however, is not consistent with the current published scientific literature. I write to request that the National Toxicology Program (NTP) reclassify ortho-toluidine to "known to be a human carcinogen."

The Twelfth RoC acknowledges the International Agency for Research on Cancer's 2008 reclassification of ortho-toluidine into Group 1, "carcinogenic to humans." The IARC has now published the full monograph on ortho-toluidine in Volume 99, IARC Monographs on the Evaluation of Carcinogenic Risks to Humans, "Some Aromatic Amines, Organic Dyes, and Related Exposures." IARC's Group 1 classification and its conclusion that ortho-toluidine can cause cancer of the urinary bladder was recently reconfirmed in monograph Volume 100F (2012), "A Review of Human Carcinogens: Chemical Agents and Related Occupations."

The NTP classifies a substance as "known to be human carcinogen" when "there is sufficient evidence of carcinogenicity from studies in humans, which indicates a causal relationship between exposure to the agent, substance, or mixture, and human cancer." Sections 2.2 and 5.2 from the ortho-toluidine chapter in IARC Volume 99 provide more than enough data to satisfy this RoC classification criteria. The IARC concluded that the "epidemiological data provide strong evidence that ortho-toluidine causes bladder cancer." Id. at 450.

In addition to IARC monograph volumes 99 and 100F, there are two significant studies which were not published in time for consideration by the IARC.

In Pira et al. (2010), the SMR for bladder cancer among workers engaged in fuchsin or ortho-toluidine manufacture was 22.5 (95% CI = 8.3 to 49.00) where 6 bladder cancer deaths were observed and 0.3 were expected. Id. at 1098. The authors observed that "[o]ur study provides additional evidence for the carcinogenicity of o-toluidine on the human bladder" since "[w]orkers included in this category were primarily exposed to o-toluidine" and because "workers who were exposed to both o-toluidine and benzidine and/or naphthylamine were excluded from this group." Id.

In Richter et al. (2006), the first proof of ortho-toluidine DNA adducts in the human bladder was obtained by analyzing DNA from urinary sediments. In a further study by Böhm et al. (2010), samples of bladder tissue were obtained from 46 sudden death victims at the time of autopsy and from 12 samples of human bladder tumors. DNA adducts of ortho-toluidine well above background levels were detected in 11 of 12 tumor samples. In 46 samples of bladder tissue from the sudden death victims, ortho-toluidine DNA adduct levels were significantly lower compared to tumor samples but were still detectable in 13 samples from the epithelial and 10 samples from the submucosal layer, respectively. These results further demonstrate that ortho-toluidine is a human bladder carcinogen.

The NTP RoC is one of the most respected authoritative sources of information on the potential carcinogenicity of chemicals. By reclassifying ortho-toluidine as "known to be a human carcinogen," not only will the NTP make its classification of ortho-toluidine consistent with the scientific literature, but several advances in the protection of the public health may also result.

The OSHA Hazard Communication Standard requires a chemical manufacturer to review the NTP RoC when preparing its material safety data sheets. See 29 CFR §1910.1200 (d)(4)(i) and (g)(2)(vii). In my product liability practice, I have yet to see a manufacturer's ortho-toluidine material safety data sheet which clearly and unequivocally provides a warning that ortho-toluidine can cause bladder cancer in humans. Reclassification of ortho-toluidine should increase awareness of the potential risk from occupational exposure.

Equally troubling is that the OSHA permissible exposure limit for ortho-toluidine is 5 parts per million in the air, a level which was set in 1958 by the American Conference of Governmental Industrial Hygienists, without any consideration for the chemical's potential carcinogenicity. In Ward et al. (1991), workers definitely exposed to ortho-toluidine for at least 10 years experienced a bladder cancer standardized incidence ratio (SIR) of 27.2 (90% CI = 11.8 to 53.7). Ward studied the workers at The Goodyear Tire & Rubber Company plant in Niagara Falls, New York where ortho-toluidine is used to make an antioxidant for tire manufacturing. Goodyear's exposure records for ortho-toluidine, which began in 1976, reported that all air sampling results were below 2 ppm, and that the geometric mean of the results for the earliest (and highest) period of measured exposure, 1976 to 1979, was just .10 ppm. It can only be concluded that the OSHA permissible exposure limit of 5 ppm is a lethal level of exposure, i.e., exposure at 5 ppm will cause cancer. If a "safe" level of exposure exists, it must be less than .10 ppm. In the past, the RoC clearly advised its readers that the OSHA permissible exposure limit for ortho-toluidine was set only to control "toxic effects other than cancer." See, e.g. Ninth RoC (2000) at page III-208. This cautionary statement should be included in the future RoCs until the OSHA standard is made protective against cancer.

Finally, the current Twelfth RoC correctly states that "o-toluidine is a metabolite of prilocaine, a topical anesthetic." See Gaber et al. (2007). However, the FDA required warnings do not provide any information as to the potential carcinogenic risk from the use of prilocaine. Reclassification of ortho-toluidine should cause the FDA to consider requiring an explicit cancer warning, if not an out-right ban on the use of prilocaine, especially on children.

Please let me know if you need any further information.

Sincerely yours,

[Redacted]

Steven H. Wodka

References

Böhm F, Schmid D, Denzinger S, Wieland WF, Richer E. 2011. DNA adducts of ortho-toluidine in human bladder. Biomarkers 16(2): 120-128.

Gaber K, Harréus UA, Matthias C, Kleinsasser NH, Richter, E. 2007. Hemoglobin adducts of the human bladder carcinogen o-toluidine after treatment with the local anesthetic prilocaine. Toxicology 229: 157-164.

IARC. 2010. ortho-Toluidine. In: Some Aromatic Amines, Organic Dyes, and Related Exposures. IARC Monographs on the Evaluation of Carcinogenic Risks to Humans, vol. 99. Lyon, France: International Agency for Research on Cancer. pp. 407-469.

IARC. 2012. ortho-Toluidine. In: A Review of Human Carcinogens: Chemical Agents and Related Occupations. IARC Monographs on the Evaluation of Carcinogenic Risks to Humans, vol. 100F. Lyon, France: International Agency for Research on Cancer. pp. 1-8.

Pira E, Piolatto G, Negri E, Romano C, Boffetta P, Lipworth L, McLaughlin JK, La Vecchia C. 2010. Bladder cancer mortality of workers exposed to aromatic amines: a 58-year follow-up. J. Natl. Cancer Inst. 102: 1096-1099.

Richter E, Gaber K, Harréus UA, Matthias C, Kleinsasser NH. 2006. O-Toluidine adducts in human bladder DNA and hemoglobin by the local anesthetic prilocaine. Toxicol. Lett. 164: S255.

Ward E, Carpenter A, Markowitz S, Roberts D, Halperin W. 1991. Excess number of bladder cancers in workers exposed to ortho-toluidine and aniline. J Natl Cancer Inst. 83: 501-506.