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September 23, 2013
BY E-MAIL

Dr. Lori White
Office of Liaison, Policy and Review
DNTP, NIEHS
P.O. Box 12233
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Research Triangle Park, NC 27709

Re: Federal Register Notice: August 21, 2013
Request for Public Comment on Peer-Review Draft, Report on Carcinogens, Monograph on Ortho-Toluidine

Dear Dr. White:

On March 20, 1999, I wrote to Dr. C. W. Jameson, who was the head of the Report on Carcinogens group at the National Toxicology Program, and requested that ortho-toluidine be listed as "known to be a human carcinogen" in the 10th Report on Carcinogens. While the process has taken longer than I anticipated, I fully endorse your agency's proposal to list ortho-toluidine as "known to be a human carcinogen" in the next Report on Carcinogens (RoC).

The draft ortho-toluidine monograph is the most comprehensive summary of the evidence of ortho-toluidine's carcinogenicity that has ever been compiled. I commend the staff of the National Toxicology Program for their outstanding efforts in developing this report.

From 1969 to 1981, I was a staff representative for the Oil, Chemical and Atomic Workers International Union (OCAW) and was assigned to assisting its local unions on health and safety issues. The OCAW represented thousands of workers in the dye manufacturing industry and I inspected a number of these plants during that time period.

I am now an attorney in private practice. Since 1987, I have represented chemical workers in personal injury, product liability claims who have developed bladder cancer as a result of their occupational exposure to ortho-toluidine. In addition, I have represented hundreds of ortho-toluidine exposed workers in two successful class actions which provides them with free, lifetime medical monitoring for the early detection of bladder cancer.

In addition, since 1989, I have acted as an attorney adviser to the authorized employee representative of the hourly workers at The Goodyear Tire & Rubber Company plant in Niagara Falls, New York. This local union, formerly known as OCAW Local 8-277, obtained a health hazard evaluation of the Goodyear plant in 1988 from the National Institute for Occupational Safety and Health (NIOSH). The findings of the NIOSH investigation of this rubber chemicals plant have been published in studies by Ward (1991 and 1996), Carreón (2010), and Hanley (2012), which are extensively cited in the draft monograph.

According to the 12th Report, "the purpose of the RoC is to identify hazards to human health posed by carcinogenic substances." 12th RoC at 3. The ultimate purpose of this effort must be the prevention of disease. My comments are focused on potential occupational exposure to this substance. In addition, the published profile for ortho-toluidine should advise that both the mandatory and recommended occupational exposure limits for ortho-toluidine in the United States were not set to protect workers against cancer.

The Freeman Report

In the record of this proceeding is a report by Professor Harold S. Freeman of North Carolina State University entitled "Use of o-Toluidine in the Manufacture of Dyes and on the Potential for Exposure to other Chemicals in the Processes involving o-Toluidine." Apparently, this report was obtained by Integrated Laboratory Systems, Inc., a contractor to the NTP.

In this report, Prof. Freeman makes several statements regarding past and current occupational exposure to ortho-toluidine which are at complete variance with my experience. Prof. Freeman does not provide any citation to any authority for these statements.

On page 9 of his report, Prof. Freeman states:

> Clearly, the types of possible exposures would depend on whether protective measures were employed. Since the adoption of OSHA regulations in the mid-1970s, lab coats and gloves have been used, to guard against dermal exposures. Where these regulations were followed, dermal exposures would not be an issue. In addition, standards pertaining to air-flow (ventilation) in the work place were adopted, to control air-borne exposures. Most domestic plants provided disposable air masks to their workers as well.

The Occupational Safety and Health Administration (OSHA) of the U. S. Department of Labor has never promulgated a workplace standard which would require the use of any

specific engineering controls, work practices, or personal protective equipment for workers handling ortho-toluidine.

OSHA's only regulation of ortho-toluidine occurred in 1971. At the time, OSHA adopted a 5 parts per million (ppm) permissible exposure limit (PEL) which had originally been developed by the American Conference of Governmental Industrial Hygienists (ACGIH). This ACGIH threshold limit value (TLV) had last been updated in 1963. A review of the ACGIH documentation for this TLV demonstrates that it was set to only protect workers against the immediate toxic effects of exposure. No epidemiological studies were considered when setting this TLV. See ACGIH 1971 documentation at Exhibit A.

As initially demonstrated by Ward (1996) at page 1052, "even at airborne exposure levels significantly below the OSHA time-weighted average permissible exposure limit, substantial absorption and accumulation" of ortho-toluidine can occur due to skin absorption.

For example, Goodyear determined that the time weighted average exposure to ortho-toluidine during 1976-1979 in its rubber chemicals department was 0.10 parts per million, or just one-fiftieth of the legal limit in the United States. Subsequent exposure levels were even lower. See Hanley (2012) at page 481. Yet, I have documented 10 confirmed cases of bladder cancer among the Goodyear workers whose first exposure in the rubber chemicals department began in 1976 or later.

The actual excess risk for bladder cancer in the Goodyear workers with first exposure in 1976 or later is now known to NIOSH and should be reported in the agency's forthcoming update of the bladder cancer incidence study of this plant. Hanley (2012) concluded at page 489:

> Despite these low exposures, an elevated risk of bladder cancer has been reported in the cohort. This suggests that the OELs [occupational exposure limits] may not be sufficiently protective or that skin absorption of these chemicals presents an important contribution to the observed morbidity, or both.

In short, the permissible "legal" level for occupational exposure to ortho-toluidine in the United States is high enough to cause cancer in exposed workers.

Thus, it is overly simplistic for Prof. Freeman to suggest that "standards pertaining to air-flow (ventilation)," and "lab coats and gloves" protected workers against both air-borne and dermal exposures beginning in "the mid-1970s." As shown above, airborne exposure to ortho-toluidine in the Goodyear plant was a tiny fraction of the permissible limit. The Goodyear workers were provided with uniforms, but cotton clothing does not provide a barrier against skin absorption of ortho-toluidine. The substance is absorbed

by the cloth and brings the chemical into direct contact with the skin. Equally unprotective is the use of any type of glove. Even as late as 2005, NIOSH found that Goodyear was still permitting the use of polyvinyl chloride and nitrile gloves which do not prevent ortho-toluidine permeation. See February 3, 2006 NIOSH letter to the Medical Director of The Goodyear Tire & Rubber Company.

DuPont, until recently the leading U.S. manufacturer of ortho-toluidine, specified only certain types of protective gloves for use with ortho-toluidine because commonly used materials, such as polyvinyl chloride and latex, are easily permeated by ortho-toluidine, a fact which DuPont had established by 1954. For example, from 1977 to 1982, DuPont specified only butyl rubber gloves, and from 1983 to 2010, DuPont specified only butyl rubber or neoprene gloves, depending on the type of exposure. See DuPont material safety data sheets for ortho-toluidine.

I represented Patrick Fung, who manufactured dyes from ortho-toluidine at Passaic Color & Chemical Company in Paterson, New Jersey from 1987 to 2002. This plant was precisely the industry which was the subject of Prof. Freeman's report. Patrick Fung was never provided with a white lab coat. Rather, his employer provided him with used scrap clothing which the workers called "rags" which would be thrown out at the end of the day because they became so stained with chemicals. Fung deposition at 194-195. His gloves were the type used for washing dishes and were marked for household use only. Id. at 299-305. Mr. Fung was diagnosed with bladder cancer in 2002.

In his report summary (p.15), Prof. Freeman states:

> Following the recognition of its carcinogenicity in laboratory animals and its potential for causing cancer in humans, o-toluidine manufacture and its use in dye manufacturing has been largely banned in the western world and in many parts of the east, and the number of dyes based on this compound has dropped dramatically.

While the number of dyes based on ortho-toluidine may have declined, it is erroneous to believe that ortho-toluidine "manufacture and its use in dye manufacturing has been largely banned in the western world and in many parts of the east." No country has banned the manufacture of or industrial use of ortho-toluidine. Most ortho-toluidine used today in the United States is supplied by Germany, India, and China.

Recommendation for the published profile

In the profile at the "Regulations" section for the Occupational Safety and Health Administration (OSHA) and the "Guidelines" section for the American Conference of Governmental Industrial Hygienists (ACGIH), the profile should state that the existing

OSHA permissible exposure limit of 5 parts per million and the ACGIH threshold limit value time-weighted average of 2 ppm are "based on toxic effects other than cancer." This language previously appeared in the 3rd through 10th Report on Carcinogens with respect to OSHA. See, e.g. Tenth RoC (2002) at page III-243.

The Report on Carcinogens is a standard reference document for chemical manufacturers, employers, health and safety professionals, and worker representatives, not only in the United States, but throughout the world. Because of its widespread availability, well-organized format, and authoritativeness, the RoC is often the only document reviewed in order to determine a chemical's carcinogenicity.

Even if the reader also takes the time to check the tables of the OSHA PELs in the Federal regulations and the TLVs-TWAs in the ACGIH TLV booklet, no information is provided to warn the reader that these limits were not intended to protect against cancer.

As shown above, the OSHA PEL of 5 ppm was set to only guard against the immediate toxic effects of exposure.

In 2001, the ACGIH revised their documentation for ortho-toluidine. Even though it was well aware of the epidemiological studies, including the Goodyear study, and the animal evidence of carcinogenicity, the ACGIH inexplicably pushed carcinogenicity aside and recommended a TLV-TWA of 2 ppm, which it admitted would only protect against the immediate toxic effects of exposure. See ACGIH 2001 documentation.

Accordingly, it is incumbent that the NTP warn its readers that these occupational exposure limits were set without regard to protecting workers against developing cancer.

Please let me know if you need any further information on the points raised above. The comments above are solely my own. Thank you for the opportunity to participate in this important proceeding.

Sincerely yours,

/s/

Steven H. Wodka

enc.

References

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DOCUMENTATION

OF THE

THRESHOLD LIMIT VALUES

for

Substances

in

Workroom Air

WITH
SUPPLEMENTS FOR THOSE SUBSTANCES
ADDED OR CHANGED
SINCE 1971

AMERICAN CONFERENCE OF GOVERNMENTAL INDUSTRIAL HYGIENISTS

Third Edition 1971

3RD PRINTING 1976

Ex. A

proximated 12 ppm, according to Duncan et al.(2). The animals died of pulmonary edema and hemorrhage. Effects on the liver, kidneys and gastrointestinal tract were also noted, and dermal effects occurred. Repeated daily six-hour exposures at 0.1 ppm were reported to cause chronic inflammation of the tracheo-bronchial mucosa with fibrosa obliterans as the terminal lesion(3). A fever reaction in animals following intravenous injection of 0.02 mg/kg was reported by Scheel et al.(4).

The capacity of TDI to produce allergic sensitization of the respiratory tract in man is its most serious toxicologic action and the one which determines the magnitude of the threshold limit value. A survey of plant experience made in 1960 by Elkins(5) showed cases of respiratory involvement from repeated exposure to TDI not only at or around 0.1 ppm(6,7) but considerably below 0.1 ppm. Threshold limits for minimizing respiratory effects suggested by the participants in the survey were from 0.01 to 0.03 ppm.

According to Thompson and Scheel(8), studies with rats support the probability that lung reactivity to TDI is due to chemical damage and not antibody reactions. Williamson(9) and Markham and Fishburn(10) reported that workers were affected by concentrations generally below 0.02 ppm. Bruckner et al.(11) described a study of clinical and immunological factors which tends to support the TLV of 0.02 ppm.

Peters and co-workers(12) reported studies of workers exposed at concentrations for the most part below 0.01 ppm. Slight changes in vital capacity were noted at the end of the work shift. In a follow-up study after six months, additional decreases in ventilating capacity were found.

A threshold limit of 0.02 ppm is recommended. This figure should be sufficiently low to prevent substantially all sensitization and to minimize recurrent allergic attacks. In the opinion of the TLV Committee, the changes noted by Peters' group(12,13) are not of sufficient importance to invalidate this limit.

Other recommendations: Elkins (1959) 0.05 ppm; U.S.S.R. (1967) 0.07 ppm.

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o-TOLUIDINE - Skin

$CH_3C_6H_4NH_2$

5 ppm (Approximately 22 mg/m^3)

Smyth(1) found that rats were not killed by eight hours' inhalation of saturated vapors of o-toluidine. Henderson and Haggard(2) stated that its vapor toxicity was much like that of aniline (slight symptoms after several hours at 6 to 23 ppm and 7 to 53 ppm respectively). Fairhall(3) also noted that symptoms were similar to those of aniline intoxication.

Von Oettingen(4) in a review of the literature, stated that with repeated administration there was a reduction of the red blood cells, hematuria, anuria, and icterus. The effect on the central nervous system was reportedly less, and that on the vascular system more marked with toluidine than with aniline. Patty(5) also noted that transient hematuria may result from absorption of o-toluidine.

A TLV of 5 ppm, the same as that for aniline, is recommended to prevent systemic toxicity.

Other recommendations: Cook (1945), Smyth (1956), Elkins (1959) 5 ppm; U.S.S.R. (1967) 0.7 ppm; Czechoslovakia (1969) 1.1 ppm.

References:

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TOXAPHENE

(See Chlorinated Camphene)

TREMOLITE

(See Talc)

TRIBUTYL PHOSPHATE

$(C_4H_9)_3PO_4$

5 mg/m^3

Tri-n-butyl phosphate is encountered in industrial operations where it is used as an anti-foaming agent, plasticizer, and complexing agent in the extraction of heavy metals from their ores(1). Workers exposed to it have complained of nausea and headache(2). There is little information on tributyl phosphate. The majority of the phosphate esters which are used industrially are liquids with very high boiling points. Few of them have received intensive toxicologic investigation. The diesters are more acidic and hydrolyze more readily than the triesters(3).

Tributyl phosphate is a clear, colorless liquid having a boiling point of 289°C (with decomposition). It has a weak cholinesterase inhibiting property(4). Fassett(3), writing in Patty's textbook, noted that tributyl phosphate possessed a definite central nervous sytem excitatory action with production of terminal pulmonary edema in experimental animals. Vapors of tributyl phosphate, particularly if heated, can be very irritating if inhaled.

It is difficult to assign a TLV for tributyl phosphate in the absence of more data. A limit of 5 mg/m^3 should be sufficient to prevent complaints of nausea and headache associated with its use.

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