HHS Public Access

Author manuscript

Am J Ind Med. Author manuscript; available in PMC 2018 March 22.

Published in final edited form as:

Am J Ind Med. 2017 February ; 60(2): 223–225. doi:10.1002/ajim.22681.

Response to Goodman et al

Lynne E. Pinkerton, MD MPH, **James H. Yiin, PhD**, **Robert D. Daniels, PhD**, and **Kenneth W. Fent, PhD**

Industrywide Studies Branch, Division of Surveillance, Hazard Evaluations and Field Studies, National Institute for Occupational Safety and Health, Cincinnati, Ohio

We thank the Journal for providing us the opportunity to respond to the letter from Goodman et al. [2017] regarding the conclusions of our mortality study among toluene diisocyanate (TDI)-exposed workers [Pinkerton et al., 2016].

Goodman et al. [2017] point out that exposure measurement error can result in a bias towards the null or away from the null. We agree and did not assert otherwise. Rather, in our paper, we pointed out that exposure measurement error is among several possible explanations for the lack of an observed positive association of cumulative TDI exposure, based on inhalation, with lung and larynx cancer [Pinkerton et al., 2016].

Goodman et al. [2017] also raise the possibility of positive confounding by smoking because our risk estimate for other smoking-related cancers in the overall cohort is imprecise and chronic obstructive pulmonary disease (COPD) mortality, which is more strongly related to smoking, was elevated in the cohort compared to the general population. The standardized mortality ratio for other smoking-related cancers was 1.06 (95% confidence interval, 0.85–1.31), which is evidence against large differences in smoking patterns between the cohort and general population. Although Goodman et al. [2017] state that even slight differences could account for an elevated number of respiratory deaths, other data indicate that smoking is unlikely to fully explain our findings [Siemiatycki et al., 1988]. We caution against using the findings for COPD mortality to assess potential differences in smoking between the cohort and general population because other investigators have reported associations of TDI exposure with chronic bronchitis [Jones et al., 1992] and decline in pulmonary function [Diem et al., 1982].

*Correspondence to: Lynne E. Pinkerton, MD, MPH, Industrywide Studies Branch, Division of Surveillance, Hazard Evaluations, and Field Studies, National Institute for Occupational Safety and Health, 1090 Tusculum Ave, R-15, Cincinnati, OH 45226. lep5@cdc.gov.

AUTHORS' CONTRIBUTION

All authors meet the authorship criteria.

DISCLOSURE (AUTHORS)

The authors report no conflicts of interest.

DISCLOSURE BY AJIM EDITOR OF RECORD

Rodney Ehrlich declares that he has no competing or conflicts of interest in the review and publication decision regarding this article.

DISCLAIMER

The findings and conclusions in this report are those of the authors and do not necessarily represent the views of the National Institute for Occupational Safety and Health.

Institution at which the work was performed: National Institute for Occupational Safety and Health, Cincinnati, OH, USA.

Goodman et al. [2017] also raise the possibility of positive confounding by socioeconomic status because of elevated rates of death from violence and suicide. However, data exist suggesting that socioeconomic status results in relatively little bias (confounding bias factor <1.20) in lung cancer risk estimates [Siemiatycki et al., 1988]. Thus, it also seems unlikely that confounding by socioeconomic status fully explains the lung and laryngeal cancer results.

Goodman et al. [2017] question the biological plausibility of respiratory cancers from dermal exposure, especially when inhalation exposure does not appear to increase risk. The lack of an association with inhalational exposure could be related to differences in TDI metabolism by route of entry [Timchalk et al., 1994] or study limitations. Goodman et al. [2017] also claim that dermal absorption of TDI is likely to be very low due to its high reactivity. It is not clear what constitutes very low dermal absorption, especially with respect to a highly biologically active compound like TDI. Using radiolabeled 14C-TDI, Hoffmann et al. [2010] found that dermal absorption of TDI in rats was <1% of the applied dose. However, 6–17% (on average) of the applied dose could not be washed from skin at the application site and another 15–18% (on average) was found in the adjacent skin. This suggests that a significant portion of the applied dose of TDI penetrated the skin and/or was bound to macromolecules in the skin, due in part to its high reactivity.

However, the reactivity of TDI does not negate its toxicity. In fact, TDI-adducts are recognized by the human body as immunogenic haptens and may have an important role in the mechanism leading to respiratory sensitization [Karol, 1983; Botham et al., 1988; Nakashima et al., 2002]. Given their ability to interact with the respiratory system, TDI-adducts may also play a role in the development of lung cancer. In addition, skin absorption of TDI, even at <1%, may be toxicologically relevant. Yeh et al. (2008) found increasing urinary excretion of toluenediamine (TDA) in rats for up to 6 days following topical exposure to TDI, suggesting a sustained body burden. Austin [2007] found that workers who directly handled freshly produced foam had higher post-shift urinary TDA levels than those who did not have dermal contact with the foam, even though both sets of workers had similar inhalation exposures. This provides further evidence that handling freshly produced foam can contribute to the systemic dose of TDI. Residual TDI in foam could also react with moisture to form TDA, which is absorbed (24% penetration) by human skin [Marzulli et al., 1981] and is a known animal carcinogen [NTP, 2016]. We agree that specific mechanisms explaining lung cancer from dermal exposure to TDI remain unclear. Additional research is needed to elucidate these mechanisms, if they exist, or to provide compelling evidence against the carcinogenicity of dermal absorption.

Finally, Goodman et al. [2017] assert that, if dermal exposure to TDI increases lung cancer, a positive association of lung cancer with employment duration in finishing jobs involving cutting and similar activities would be expected because cumulative dermal exposure would increase with increasing employment duration in these jobs. However, we would expect cumulative dermal exposure to also depend on changes in personal protective equipment use and automation over time as well as dermal exposure from other finishing jobs. As a result, there may not be a clear relation between cumulative dermal exposure and employment duration in finishing jobs involving cutting and similar activities. Thus, we disagree with

Goodman et al.'s assertion that the observed negative association of lung cancer with employment duration in these jobs contradicts our conclusions.

Goodman et al. [2017] conclude that our study does not provide support for the carcinogenicity of TDI. We acknowledge that proof of a causal association between occupational exposure and cancer cannot be achieved by our study. Nonetheless, we contend that our findings add to a growing body of evidence of a causal association between TDI exposure and cancer and that dermal exposures could play an important role.

Acknowledgments

None.

FUNDING

This work was funded by the intramural research program of the National Institute for Occupational Safety and Health.

References

Austin S. Biological monitoring of TDI-derived amines in polyurethane foam production. Occup Med (Lond). 2007; 57(6):444–448. [PubMed: 17728315]

Botham PA, Hext PM, Rattray NJ, Walsh ST, Woodcock DR. Sensitisation of guinea pigs by inhalation exposure to low molecular weight chemicals. Toxicol Lett. 1988; 41:159–173. [PubMed: 2835830]

Diem JE, Jones RN, Hendrick DJ, Glindmeyer HW, Dharmarajan V, Butcher BT, Salvaggio JE, Weill H. Five-year longitudinal study of workers employed in a new toluene diisocyanate manufacturing plant. Am Rev Respir Dis. 1982; 126:420–428. [PubMed: 6289703]

Goodman J, Loftus C, Prueitt R, Zu K. Dermal TDI exposure is not associated with lung cancer risk. Am J Ind Med. 2017; 60(2):210–211.

Hoffmann HD, Leibold E, Ehnes C, Fabian E, Landsiedel R, Gamer A, Poole A. Dermal uptake and excretion of 14C-toluene diisocyanate (TDI) and 14C-methylene diphenyl diisocyanate (MDI) in male rats. Clinical signs and histopathology following dermal exposure of male rats to TDI. Toxicol Lett. 2010; 199(3):364–371. [PubMed: 20933064]

Jones RN, Rando RJ, Glindmeyer HW, Foster TA, Hughes JM, O'Neill CE, Weill H. Abnormal lung function in polyurethane foam producers: Weak relationship to toluene diisocyanate exposures. Am Rev Respir Dis. 1992; 146:871–877. [PubMed: 1329591]

Karol MH. Concentration dependent immunologic response to toluene diisocyanate (TDI) following inhalation exposure. Toxicol Appl Pharmacol. 1983; 68:229–241. [PubMed: 6304938]

Marzulli FN, Anjo DM, Maibach HI. In vivo skin penetration studies of 2,4-toluenediamine, 2,4-diaminoanisole, 2-nitro-p-phenylenediamine, p-dioxane and N-nitrosodiethanolamine in cosmetics. Food Cosmet Toxicol. 1981; 19(6):743–747. [PubMed: 7327475]

Nakashima K, Takeshita T, Morimoto K. Review of the occupational exposure to isocyanates: Mechanism of action. Environ Health Prev Med. 2002; 7:1–6. [PubMed: 21432282]

NTP (National Toxicology Program). Report on carcinogens. fourteenth edition. Research Triangle Park, NC: U.S. Department of Health and Human Services, Public Health Service; 2016. http://ntp.niehs.nih.gov/pubhealth/roc/index-1.html [Accessed 03 December, 2016]

Pinkerton LE, Yiin JH, Daniels RD, Fent KW. Mortality among workers exposed to toluene diisocyanate in the US polyurethane foam industry: Update and exposure-response analyses. Am J Ind Med. 2016; 59:630–643. [PubMed: 27346061]

Siemiatycki J, Wacholder W, Dewar R, Cardis E, Greenwood C, Richardson L. Degree of confounding bias related to smoking, ethnic group, and socioeconomic status in estimates of the associations between occupation and cancer. J Occup Med. 1988; 30:617–625. [PubMed: 3171718]

Timchalk C, Smith FA, Bartels MJ. Route-dependent comparative metabolism of [^{14}C]toluene 2,4-diisocyanate and [^{14}C] toluene 2,4-diamine in Fischer 344 rats. Toxicol Appl Pharmacol. 1994; 124:181–190. [PubMed: 8122263]

Yeh HJ, Lin WC, Shih TS, Tsai PJ, Wang ST, Chang HY. Urinary excretion of toluene diisocyanates in rats following dermal exposure. J Appl Toxicol. 2008; 28(2):189–195. [PubMed: 17582582]