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Letter to the Editor

Author's Response to Letters to the Editor regarding "Risk Assessment for Toluene Diisocyanate and Respiratory Disease Human Studies"

To the editor,

In response to the comments of **[letter by Osman-Sypher]** the *healthy worker survivor effect* (HWSE) is now recognized as an important potential source of bias in occupational disease epidemiology [1,2]. It is particularly troublesome in etiologic studies and when estimating the exposure response relationship in worker populations exposed to irritants or experiencing acute adverse health effects. It occurs when some workers leave employment (or exposure) sooner than others due to health problems but similar effects (such as attenuation of exposure response with increasing cumulative exposure) could result if full ascertainment and recording of exposure-attributable effects depended on exposure levels, if there were development of tolerance, or if personal protective equipment (PPE) had been utilized by some employees but not accounted for in analyses. Toluene diisocyanate (TDI) is just one of numerous reactive entities that occur in composite polymerization systems in manufacturing (e.g., cyanoacrylates, ABS, epoxy resins). The literature reveals complaint-initiated investigations of such materials which subsequently report no apparent association of respiratory problems with duration and other exposure measures at current exposure levels, but without accounting for HWSE or other violations of the assumed model [e.g., Goodman et al. [3]].

To adequately understand and account for the role of HWSE in a specific study population would require detailed work and exposure history, pre-and post-employment information, classification on other risk factors for the outcome, and sufficient statistical power that are rarely available. The Occupational Safety and Health Act of 1970 requires that the U.S. Occupational Health and Safety Administration (OSHA) set standards for limiting chemical exposures at work using the "best available evidence" (BAE) [4]. For analysis of TDI and sensitization with HWSE selection or confounding bias, the BAE is clearly far from ideal. There is no appropriate, "validated model," particularly for meta-analyses where the impact of HWSE (or PPE) could vary widely across the TDI employers (or in similar analyses reported previously for worker populations exposed to metalworking fluids [5]). On the other hand there is extensive reporting of what investigators concluded to be cases of sensitization or new onset asthma *that are attributable to TDI* based on individual exposure history and clinical evaluation. Those were the outcomes on which this risk assessment [1] was based; attributability was not based on statistical inference in a meta-analysis. The statistical model that was utilized here summarizes the apparent decline in the observed exposure response in workplaces with higher average exposures. The underlying assumption was that, with correction for HWSE and other intervening factors, a linear relation exists for attributable outcomes and the summary estimate of current (and recent) TDI exposure reported for each workforce. How well the facility average exposure adequately represents the relevant hazard arising from serial peak or cumulative inhalation exposures, and/or dermal contact, in a linear relationship, is a matter for interpretation and further research. As for possible PPE use, when reported at all, there is almost never quantitative information on prevalence of PPE use across jobs and protection factors assuming appropriate fit-testing and cartridge maintenance. Not accounting for PPE use would overestimate exposures and underestimate exposure-response. Thus PPE use in the TDI studies is a possible contributor to the observed decrease in estimates of exposure response with increasing facility average TDI exposure levels. This was another reason to attempt to estimate exposure response at low TDI concentrations in this risk assessment. The PPE issue should have been discussed explicitly in the published article [1] although few of the studies used mentioned PPE use.

All studies from the literature search which 1) identified attributable cases of new onset asthma or sensitization (on varying criteria, as explained [1]) and 2) reported basic information on workforce size, period of observation (case-finding) and average TDI exposure were included in the risk assessment. Some studies reported relatively small numbers of cases and some reported *only* the attributable cases. The confusion here arises from the definition of cases (new onset asthma or sensitization). This risk assessment deals only with *a prior TDI-attributable* cases—identified by investigators—of which there should be none if the TDI environment is not causative. The true incidence rate should increase in some manner over some range of increasing measures of exposure but the observed rate does not consistently do so except possibly at TDI levels below 10 ppb (Fig. 1 [1]). The model specified to address this problem poses a simple exponential decline in an effort to estimate the exposure response at low levels (minimal HWSE, PPE). Other plausible specifications for the decline would produce roughly comparable estimates of the intercept, all in the range of the observed exposure response below 5 ppb average exposures. In the model, XR = b*exp(-c*(X)), the exposure response (XR) approaches *b* as average exposure (X) approaches 0. A "hyperbolic" exposure response would occur only in the absence of attributable cases and with inclusion of background (non-attributable case) events.

Some studies based on pulmonary function tests (PFT) were excluded from the analysis of annual proportional loss because they exhibited improving PFT, interpreted by this investigator to

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be a consequence of survivor bias effect dominating the decline from TDI exposure expected *a priori* from prior investigations. From the several studies published by the Tulane group at a polyurethane manufacturer, this risk assessment used Weill et al., 1981 (asthma incidence [6]) and Jones et al., 1992 (pulmonary function [7]). A high incidence rate in the first year of employment indicates that some form of HWSE is operating (such as depletion of hyper-susceptible workers or those with other health issues), or exposure misclassification, but without individual exposure history cannot be explained. The Adams study [8] did indeed carefully follow new hires although one wonders how well the reasons for termination are known or reported (responses could have a bearing on subsequent employment opportunities). The time trend of exposures cited by **[the letter writers 1]** (percent above 20 ppb) does not pertain to average TDI levels and may represent relatively few high-exposed jobs assigned priorities for intervention. The studies by Collins et al. [9] and Middendorf et al. [10] (NIOSH collaborations) were not included in the risk assessment analysis because they appeared after the close of the literature search, however, the asthma incidence that they reported was examined in the same manner and found to be quite consistent with the main findings (and was presented in the Discussion [1]). As pointed out by [**letter writers 1**] variable (but unknown) exposure within workplace groups was not addressed and this would tend to diminish an observable HWSE. Dermal exposures are a major concern and difficult to quantify; it would be useful to assess how well air levels can be a surrogate for dermal exposures within specific production environments.

The following is in response to comments by **[letter by Chappelle]**. The contention in the published article [1] is that systematic differences across workplaces confound estimates of exposure response. Whether it concerns completeness of case-ascertainment, survival in employment of less susceptible workers, development of tolerance, exposure misclassification or variable PPE use, for example, it poses a challenge for risk assessment at low-exposures. The Adams article [8], pertaining to one workplace, does not by itself address this systematic difference. Quantitative exposure history was not available in the Adams study beyond duration of TDI exposure. Workers who remained in employment after year 1, could have been in job classifications with lower average TDI exposure than those held in year 1. Of course, worker removal improves the prognosis but an important question remains: in general, how often do symptomatic workers remove themselves without management involvement or their awareness of reasons.

The absence of even a monotonically increasing incidence (or prevalence) of *attributable* adverse effects over the range of the available exposure metric (as in figures [1]), strongly implies an inappropriate analytical model for investigating exposure response in those TDI environments. Abstracting information from published work (that was not originally intended for quantitative risk assessment) sometimes requires judgment; examples of apparent discrepancies identified by commentators should be presented for public review. The statistical model employed here, as explained above, was intended for smoothing of the systematically divergent exposure responses, not for testing causation.

A logistic regression model was not applied [1]. As explained above, the XR model predicts a very finite intercept in the limit of zero exposure. For asthma incidence, the slope at $X=0$ is $d(XR)/dX = d(b \times exp(-c\ X))/dX = -bc \times exp(0) = -bc$. If the cited meta-analysis (submitted for publication [11]) did not account for a heterogeneity in XR across workplaces related to survival or other violations of the underlying proposed model, then its conclusions are questionable. The Wang et al. article (2021) [12] appeared after the current work (literature search) was completed (and pertained to study conducted by Collins et al. [9] and Mittendorf et al. [10] cited above). The Bodner et al. (2001) article [13] was included in the present analysis of asthma incidence but not of PFT trends. The regression analyses of FEV_1 and FVC reported in Bodner included age and height in the model but also terms for asthma status and shortness of breath (very statistically significant) which would of course compete with estimates for PFT trends on cumulative TDI exposure (very insignificant: $p = 0.8$). Furthermore, age itself would be associated with cumulative TDI exposure; a regression using *percent predicted* PFT values would have addressed this potential confounding. The exposures for the two groups in the Omae et al. PFT analysis were reported in the 1992 publication [14] (reference 60 in [1]) not in Omae et al. (1984) [15].

It is true that TDI-associated adverse effects are potentially attributable to other exposures associated with TDI, such as to amines in some PU factories [16], but this would not explain the observation of sensitization across diverse manufacturing settings. As stated in the article, polyurethane production has additional possible TDI-related emissions originating in the polymerization process and when handling partially cured foam. Unexplained excess lung disease mortality was observed in Pinkerton et al. [17] but a strong HWSE bias was likely. It is appropriate from a precautionary perspective to estimate approximately what could be the attributable risk in association with TDI-related exposures. The 5% excess lifetime lung cancer mortality, an estimate with very important qualifying assumptions as stated, is an incentive to further investigate the unexplained excess and underlying assumptions. The 5% mortality estimate, based on an improved approximation, corresponds to lifetime exposure at about 75 ppt TDI. At 18 ppt, the lifetime exposure conferring 1/1000 excess risk of sensitization/asthma, the excess lung cancer would be 1.2 % or 12/1000.

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Institutional and ethics approval/informed consent

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Conflicts of interest

The author declares no conflicts of interest.

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