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Letter to the Editor

Letter to the Editor Regarding "Risk Assessment for Toluene Diisocyanate and Respiratory Disease Human Studies"

To the Editor,

We would like to provide comments on an article by Park [1] that was recently published in Safety and Health at Work. The article describes an alternative method to address healthy worker effect (HWE) bias as it relates to the interpretation of asthma studies. It would appear that the author's intent was to re-assess existing epidemiology studies on toluene diisocyanate (TDI) exposure and asthma and to correct the published data for the potential existence of a healthy-worker-effect (HWE) prior to performing a risk assessment. A risk assessment approach should be based upon: (A) use of a validated model, (B) transparent selection criteria for studies included, (C) verification of model adequacy, and (D) assumptions supported by literature. As outlined below, we believe that the publication [1] has significant shortcomings with regard to these basic principles.

A. Although the model used in [1] has been used in a prior publication [2] we could not identify a reference demonstrating that it has been theoretically or empirically validated to correctly identify and correct for HWE. Such validation would typically require a comparison between studies in which the HWE was clearly present and quantifiable from the published data, and studies where it was clearly absent. In the absence thereof, any claim that the model is applicable remains unsubstantiated. In addition, since the model was used on a cross-sectional basis (between studies), it seems doubtful that it would be capable of detecting differential misclassification between exposure categories within the individual studies, which would be the basis for a HWE to be present.

B. The author does not provide transparent criteria for study inclusion, therefore elementary information to enable judging the reliability of the work is lacking. In meta-research it is quite common and often mandated to include transparent criteria for the selection or rejection of available studies. Such information is lacking completely. In particular, when using a non-validated model such information is critical and should have been used to verify conclusions. Otherwise, the exercise stays on a purely hypothetical level.

C. There is no verification of the elements that allow for the determination of model adequacy. It is also common to present and discuss elements of model adequacy, such as significance or standard errors of parameter estimates and goodness-of-fit tests. Unfortunately, the information is only in the Supplementary Online Material (SOM) and is not discussed. For instance, for the model of exposure response for TDI-induced adult onset asthma represented in Figure 2 of [1], the parameters are highly intercorrelated, neither of the two is significantly different from zero (errors on the estimates are one order of magnitude larger than the value itself—see SOM2), and the F-test indicates that the model is inadequate with 95% probability. Models of such quality should not be used as a basis for quantitative predictions. The "considerable structure" that is read from the same Figure is merely the consequence of dividing a flat (non-existing) dose response as represented by Figure 1 of [1] (same as Daniels [3]) by the exposure concentration. The resulting "exposure response" (XR) function is obviously hyperbolic and has by definition an infinite value at zero exposure. Modeling XR with an exponentially decreasing function to determine an intercept that does not exist creates artifacts that cannot serve as a sound basis for further assessments.

D. Basic assumptions in the model presented [1] are that the HWE would be dose-dependent and that there is a linear dose-response as a function of exposure. These are not supported by the data used in the analysis. In fact, the results of [4,5] (a study not included in the analysis [1], that investigated a naïve workforce) indicate a high incidence of occupational asthma in the first year of employment. A quick analysis of the results of Adams [6] (a study that was included in the analysis [1], and one of the only studies that provides precise information about number of participants and their reasons for leaving) shows a similar picture, whereby the percentage of first-year leavers does not appear to be correlated with exposure (Fig. 1a and 1b). Regarding the exposure ascertainment itself, Park [1] uses the assumption that process events, continuous emissions and episodic excursions can be represented by a single facility-averaged exposure concentration. Whereas all these effects are included in the average, the average is too unspecific to properly represent them. By way of example, the study performed by Collins et al. [7,8] (not included in Park [1]) has an average exposure of 0.7 ppb, whereas averages of similar exposure groups range between 0 and 3.5 ppb [9; Suppl. 3] with excursions close to 100 ppb [8]. The literature is not unanimous on whether TDI-related occupational asthma is mainly driven by chronic or peak exposure [e.g., 7–10], but a recent review suggests that both C- and Cxt-dependent mechanisms may play a role [11]. In addition, dermal contact by TDI is known to play a role [12], as is the use of personal protective equipment [10]. Whereas a HWE cannot be excluded in the studies considered by Park [1], it would seem highly unlikely that the absence of a dose-response between asthma incidence and facility-average TDI exposure concentrations would be solely attributable to HWE. There are too many other influential parameters that have completely been ignored in the Park article [1].

Adjusting for potential HWE bias is a fundamental component of any occupational worker study. However, based on the above, we are of the opinion that the unvalidated approaches presented in

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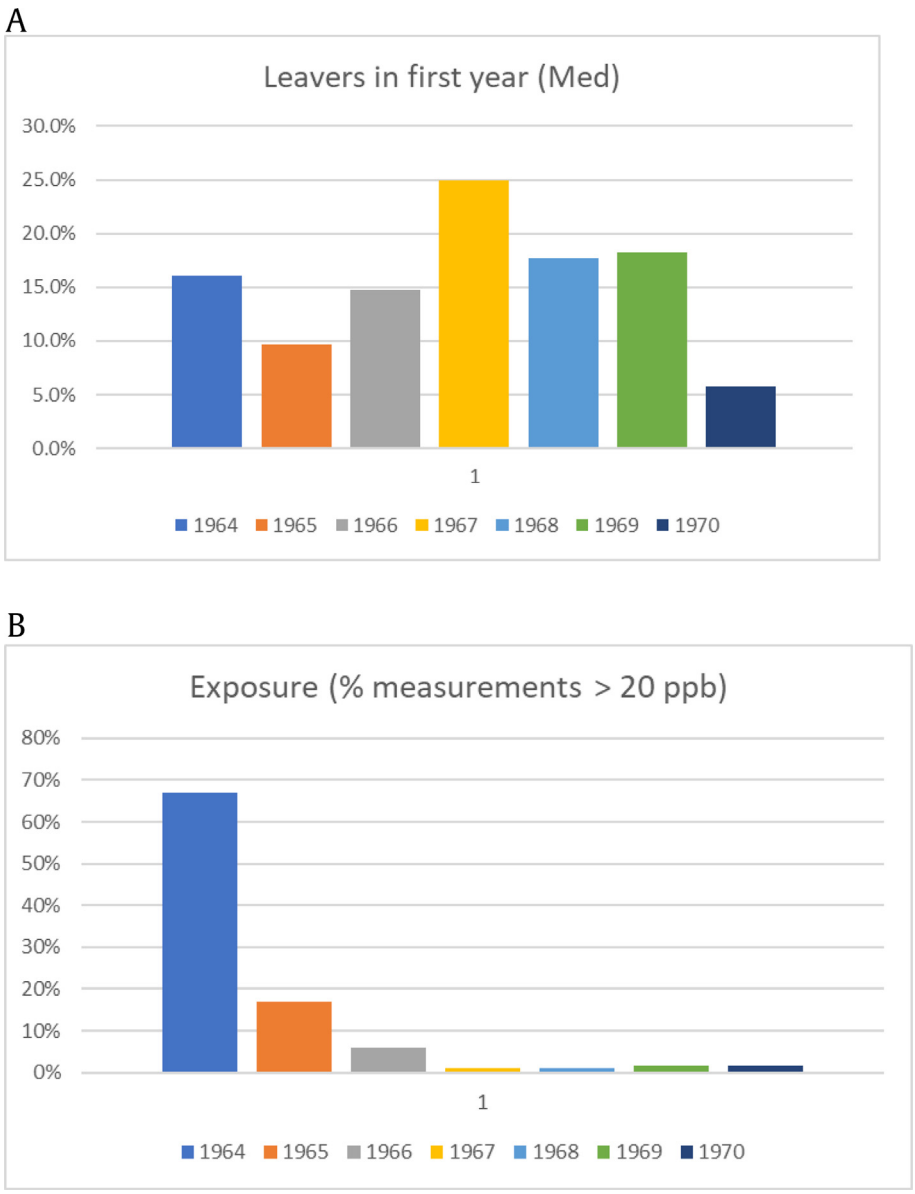

Fig. 1. A) Percentage of workers leaving for medical reasons during their first employment year as a function of hiring year (data derived from Table 1 of Adams et al. (1975)). B) Percentage of atmosphere samples exceeding 20 ppb as a function of calendar year (data derived from Table 2 of Adams et al. (1975).

Park [1] are significantly flawed and are therefore inappropriate to include in diisocyanate risk assessments.

Appendix A. Supplementary data

Supplementary data to the Park [1] article can be found online at https://doi.org/10.1016/j.shaw.2020.12.002.

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