Practical learnings from an epidemiology study on TDI-related occupational asthma. Part I - Cumulative exposure is not a good indicator of risk.

Supplemental Information - 2

Summary of ACC-NIOSH study elements relevant for the relationship between asthma incidence and cumulative exposure

As a quick reference, **Table S2-1** provides a summary of elements of the ACC-NIOSH study that are of relevance for assessing the relationship between asthma symptoms or incidence and cumulative exposure. For a more thorough and complete understanding, the reader is referred to the original publications (Cassidy et al., 2017; Collins et al., 2017; Middendorf et al., 2017; Wang et al., 2017).

The overview in **Table S2-1** has been structured according to the Matrix elements as published by Burns et al. (2019) and LaKind et al. (2020). It also highlights where the reanalysis performed in this work has added assessment elements. Items printed in *italics* in the right column of **Table S2-1** are comments to the corresponding items on the left.

References in addition to those mentioned in the main paper

Burns CJ, LaKind JS, Mattison DR, et al. (2019) A matrix for bridging the epidemiology and risk assessment gap. *Global Epidemiology* 1: 100005.

LaKind JS, Burns CJ, Erickson H, et al. (2020) Bridging the epidemiology risk assessment gap: an NO_2 case study of the Matrix. *Global Epidemiology* 2: 100017.

Pauluhn J (2011) Interrelating the acute and chronic mode of action of inhaled methylene diphenyl diisocyanate (MDI) in rats assisted by computational toxicology. *Respiratory Toxicology and Pharmacology* 61: 351-364.

	ELEMENTS OF THE ACC-NIOSH STUDY RELEVANT TO THE LINK BETWEEN ASTHMA INCIDENCE AND CUMULATIVE EXPOSURE	***COMMENTS**** **AND ADDITIONAL CONTRIBUTIONS FROM REANALYSIS**
Hazard Identification		
1.	***Confirm Outcome***	
	Information used for identification of asthma cases (Cassidy et al., 2017: Figure 1): • Intake and periodic questionnaires about self-reported respiratory symptoms • Intake and annual spirometry • Exposure data as well as self-reporting after acute incidents • Secondary questionnaire upon trigger questions or FEV1 decline indicators Identification and classification of asthma cases (Cassidy et al., 2017): • By consulting pulmonologist based upon above mentioned information toward the end of the study duration • No physical examination or confirmatory clinical diagnosis was done Cases identified and classification (Collins et al., 2017: page S23 and Table 1, page S24): • 7 cases "consistent with TDI-induced asthma" • 2 cases "indeterminate regarding work-relatedness" Uncertainties identified by authors (Collins et al., 2017: pages S25-S26): • Potential influence of workers leaving prior to study initiation • Potential influence of "latency period" (*post hoc* cases) • Absence of clinical diagnosis	Reanalysis included a consistency check of the anonymized data set and the published information. The anonymized data set mentions: • 2 cases consistent with being induced by TDI • 4 cases indeterminate regarding work-relatedness • 1 case consistent with asthma The reanalysis was performed based on the 7 cases reported in the anonymized data set.
2.	***Confirm Exposure***	
	Exposure data collection (Middendorf et al., 2017): • Full-shift (TWA) personal samples were taken in the breathing zone of the workers; 2300 samples in total, 1594 TWA samples • The method used was similar to the OSHA-42 method (1,2-PP derivatizing agent), spiked controls were included for quality control • LoQ was 0.1 ppb or lower on the sum of both TDI isomers • Exposure distributions could be well characterized based on the number of samples and the analysis method used (Middendorf et al., 2017: page S7)	Consistency of the anonymized data with the published exposure distributions was verified (Part I: Supplemental Information - 3).

	Sample collection (Middendorf et al., 2017: page S2) included: • Differentiation between "Routine", "Upset", "Start-up" and "Turnaround" conditions • Documentation of presence of engineering controls and use of respiratory protection (almost exclusively SCBA when used) Similar Exposure Groups (Plant/SEGs) were defined per plant and function. Later, aggregate ("Super")SEGs were developed by statistical methods (Middendorf et al., 2017: pages S3-S4).	
3.	***Report Methods Fully and Transparently***	
	Duration used for cumulative exposure calculation (Middendorf et al., 2017: pages S4-S5): • Study participation starting with hiring date for participants hired after study initiation • Study participation plus pre-study exposure for those participants that self-reported their first work with TDI (1/4 of the participants) • Study participation starting with study registration for all other participants Exposure concentration used for cumulative exposure calculation (Middendorf et al., 2017: page S4): • Would seem to be based upon the reconstituted average value calculated from the log-transformed data (μ_T)	*Please refer to comments under Matrix element 6.* Pre-study exposure was not included in the reanalysis. *On this basis, however, we could not reconstruct Figure 3 of Middendorf et al. (2017). It would appear that the (much lower) geometric mean was used instead. This would result in reported exposures to be lower than actual.* Sensitivity analysis was performed to evaluate whether using a different average (μ_T versus μ_A) had an impact on conclusions (Part I: Supplemental Information – 5).

Dose Response		
4.	***Include Information on Shape of the Curve***	
	Histogram of cumulative exposure values presented in Figure 3 of Middendorf et al. (2017). No direct report of incidence *versus* cumulative exposure available (Collins et al., 2017). Slope factor [0.73] (and odds ratio) for a logarithmic logistic model in Table 2 of Collins et al. (2017). Table 3 of Collins et al. (2017) shows related risk information.	Histograms of cumulative exposure values presented in Part I, Figures 1 and 2, as well as Supplemental Information – 5. Incidence *versus* cumulative exposure presented in Part I, Tables 2 and 3, as well as Supplemental Information – 5; *versus* UP-3 in Table 1 of Part II. Curve is shown in Figure 2 of Part II.
5a.	***Evaluate Concordance with Previous Results***	
	No verification against previous studies of the identified relationship between incidence and cumulative exposure was performed [discussion against literature was only done for FEV1 and peak exposure] (Collins et al., 2017: page S26). Additional notes by authors (Collins et al., 2017: page S26): • "Reported symptoms of asthma did not show a relationship with exposure" • All seven cases self-reported either detecting TDI odor (6/7) or being present close to a release (5/7)	Comparison with prior literature (Part I: Table 1) shows that conclusions of Collins et al. (2017) are rather the exception than the rule. Results of Collins et al. (2017) were put into perspective against those discussed by Daniels (2018) (Part I: Supplemental Information – 6). Extrapolation of alternative model (Part II: Figure 2) to data from other publications was used for final model selection.
5b.	***Harmonize Exposure Categories***	
	Cumulative exposure was handled as a continuous variable (Middendorf et al., 2017).	A comparison of trends from prior literature is given in Table 1 of Part I. *Some previous studies have used "low/high" groups, exposure quartiles, or other forms of regression basis. Computational methods have gradually enabled more sophistication. The reanalysis is a* post hoc *evaluation: the study design had been fixed at its inception.*

6.	***Describe Direction/Magnitude of Error***	
	Focus of Collins et al. (2017) was on the relationship between incidence and the more common peak and cumulative exposure indicators. "Other combinations of exposure intensity, frequency, duration may be more relevant" (Collins et al., 2017: page S26); these were not investigated, however. Some variability of data collection (number of samples mainly) between plants was noticed (Middendorf et al., 2017). Pre-study exposure was included for part of the participants (please refer to Matrix element 3). Pre-study exposure was only included for the 1/4 of the participants that self-reported the date of their first work with TDI (Middendorf et al., 2017: pages S4-S5).	Potential sources of sensitivities were identified and studied (Part I, Part II). An alternative model was developed and also tested against older data. Sensitivity analyses were performed to assess the impact of assumptions made (Part II: Supplemental Information – 1). *This would cause risk to trend high for higher exposures, since incidence was calculated on duration of study participation only.* *This likely distorts the histogram and therewith the incidence calculation and slope parameter in the logistic model since many non-cases with longer pre-study exposure duration would thus not be accounted for in the higher cumulative exposure range. Please refer to element 9a (left side).*

Exposure Assessment		
7.	***Describe/Evaluate Source-to-Intake Pathways***	
	The focus was on the inhalation exposure pathway (Middendorf et al., 2017). Dermal exposure was not investigated (Middendorf et al., 2017: S2-S3): • It was deemed too "sporadic" so that therefore there would be "limited ability to investigate" • Standard methods to assess dermal exposure were not available	*See Part I: Supplemental Information – 4. In the given chemical production environment, regular dermal exposure is not expected and would be reflected in the inhalation exposure measurements because of the volatility of TDI.*
8.	***Describe Complete Exposure Data***	
	Please refer to Matrix elements 2 and 3.	*Please refer to comments under Matrix elements 3 and 6.*
9a.	***Describe Direction/Magnitude of Error***	
	Note by Collins et al. (2017: page S26): • Prior exposure was not considered for 3/4 of the study population, who "likely had higher exposure to TDI" than accounted for. Note by Middendorf et al. (2017: page S9): • "Cumulative exposure is most appropriate to use when a unit of dose increases the risk of tissue or cell injury by a constant amount, and the risk is independent of the pattern of intensity and the duration of exposure, and the total dose is the most important exposure-related determinant of disease risk."	*Please refer to comments under Matrix elements 3 and 6.* *Animal toxicity data support the existence of a "daily safe dose" for diisocyanates (Pauluhn, 2011), indicating that this condition for using cumulative exposure is not fulfilled. Hence, it is not surprising that neither this reanalysis nor other literature support a relationship between asthma incidence and cumulative exposure.* Sensitivity analyses were carried out for some identified potential sources of error (distribution averages, overtime, net *versus* gross exposure). See Part I: Supplemental Information - 5.

9b.	***Report on Quality Assurance/Quality Control***	
	<u>Outcome</u> Please refer to Matrix element 1.	*The larger uncertainty would appear to lie in the absence of confirmatory clinical diagnosis of the identified asthma cases.*
	<u>Exposure</u> Please refer to Matrix element 2.	*Large number of samples combined with robust sampling and analysis techniques enabled good definition of exposure.*
	<u>Methods</u> Please refer to Matrix elements 3 and 6 (average used in calculating cumulative exposure, partial inclusion of pre-study exposure).	*The methods selected may have introduced sensitivities into the analysis.*
	<u>Conclusions</u> Please refer to Matrix elements 5a and 9a (comparison with results of prior studies, check of assumption against animal toxicity data).	Reanalysis included sensitivity analyses on identified potential influence factors.
	No verification against previous studies of the identified relationship between incidence and cumulative exposure was performed by Collins et al. (2017: page S26).	Table 1 of Part I and Figure 2 of Part II compare results with those of prior studies.

Table S2-1 *– Summary of ACC-NIOSH study elements relevant for the relationship between asthma incidence and cumulative exposure, structured according to the Matrix elements as published by Burns et al. (2019) and LaKind et al. (2020). *Items printed in italics in the right column are comments to the corresponding items on the left.*