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

Supplemental Information - 3

Data verification – Methods and comparison

Workplace atmosphere measurements

TWA exposure values were calculated from the raw workplace analysis data as the sum of 2,4- and 2,6-TDI, as documented, i.e. not converted to an 8-hour value. To maintain comparability with Middendorf et al. (2017), only TWA-samples marked as "Routine" were considered, regardless of the use of respiratory protection, and half the detection limit was used for "non-detects" to calculate cumulative exposure values.

TWA-8 (8-hour adjusted) values were calculated by adjusting for shift duration in accordance with Eq.1:

$$\text{TWA-8} = (\text{measured TWA value}) \cdot (\text{shift duration [min]}) / 480\ \text{[min]} \qquad \text{[Eq.1]}$$

For this reevaluation, TWA-8 values take into account all recorded samples. This includes samples taken under non-routine conditions ("Start-up", "Upset" and "Turnaround"), since these are the circumstances that would typically contribute to peak or unexpected exposures.

The Similar Exposure Groups based upon plant and job function (Plant/SEGs) as defined by Middendorf et al. (2017) were used unaltered in the present review.

Comparison of distribution of TWA-values

To ensure distributions of TWA-values were consistent with those reported by Middendorf et al. (2017), the natural logarithm (LN) of the TWA-values was taken and the respective average (μ_L) and standard deviation (σ_L) of the LN-converted data sets were determined per Plant/SEG. The corresponding geometric means (GM) and geometric standard deviations (GSD) were then calculated using Eqs. 2 and 3:

$$GM = \exp(\mu_L) \qquad \text{[Eq. 2]}$$

$$GSD = \exp(\sigma_L) \qquad \text{[Eq. 3]}$$

Based upon the assumption that the TWA-values would be log-normally distributed (see **Figure S3-1**), the GM and GSD can then be used to reconstitute the average (μ_T) of the corresponding non-transformed TWA-distributions, as given by Eq. 4:

$$\mu_T = \exp(\mu_L + \sigma_L^2/2) \qquad \text{[Eq. 4]}$$

The average of the actual (not LN-converted) TWA-values (μ_A) was calculated per Plant/SEG as well.

Distribution of TWA-values

Table S3-1 summarizes the descriptive statistics of the Plant/SEGs' TWA-distributions as reported in Middendorf et al. (2017) and as recalculated for this reevaluation.

The nomenclature in the "Plant/SEG" column of **Table S3-1** refers to the job function (see caption) and the number refers to the respective TDI production plant.

Table S3-1 confirms data consistency: the GM and GSD determined by Middendorf et al. (2017) and those determined from the anonymized data in this work nearly coincide (Columns [1] and [4], and Columns [2] and [5] respectively). **Table S3-1** also demonstrates the important difference between the GM (Column [1]) and the average value - be it μ_T (Column [3]) or μ_A (Column [6]) - of the TWA distributions. Hence, large differences can be expected in the cumulative exposure calculated in this work in comparison to the cumulative exposure calculated by Middendorf et al. (2017) and used by Collins et al. (2017) for correlation with incidence of cases consistent with TDI-induced asthma.

	Plant/SEG	GM (ppb) [1]	GSD (ppb) [2]	μ_T (ppb) [3]	GM (ppb) [4]	GSD (ppb) [5]	μ_A (ppb) [6]
		Middendorf et al. (2017)			This work		
Support-SEG	Chem - 2	0.027	1.54	0.030	0.027	1.50	0.029
"Support"	C_R_Op - 2	0.025	1.55	0.028	0.025	1.54	0.027
	C_R_Op – 3	0.039	2.27	0.055	0.039	2.27	0.117
	EngSup – 1	0.036	1.88	0.044	0.035	1.81	0.069
	EngSup – 2	0.026	1.40	0.028	0.025	1.46	0.027
	ShiftSup – 1	0.042	2.07	0.055	0.042	2.05	0.068
	ShiftSup – 3	0.043	2.02	0.043	0.043	2.02	0.062
	Tech – 2	0.026	1.66	0.026	0.026	1.65	0.030
Maintenance-SEG	Inst – 1	0.064	3.14	0.123	0.063	3.11	0.173
"Maintenance"	Inst – 2	0.025	1.62	0.028	0.025	1.63	0.028
	Inst – 3	0.052	2.96	0.094	0.049	2.85	0.217
	Lab – 1	0.069	2.97	0.125	0.069	2.93	0.289
	Lab – 2	0.029	2.05	0.038	0.029	1.98	0.039
	Lab – 3	0.038	1.94	0.047	0.038	1.93	0.068
	Maint – 2	0.034	2.31	0.048	0.032	2.27	0.062
	Maint – 3	0.083	3.72	0.197	0.075	3.55	0.203
Field-SEG	FieldOp – 1	0.094	4.41	0.283	0.094	4.41	0.526
"Field Operator"	FieldOp – 2	0.042	3.51	0.092	0.039	3.34	0.291
	FieldOp - 3	0.150	6.97	0.988	0.142	6.83	2.047
Load-SEG	Load – 1	0.290	8.90	3.163	0.294	8.83	3.359
"Loading"	Load – 2	0.089	4.58	0.283	0.084	4.69	0.298
	Load – 3	0.430	4.64	1.396	0.420	4.52	1.145

Table S3-1 *– Comparison of GM and GSD published by Middendorf et al. (2017) with those of this review. Comparison of TWA-averages calculated from GM and GSD (μ_T) per Middendorf et al. (2017), which are based upon the assumption that TWA-values would be log-normally distributed, and the averages derived from the actual TWA-measurements (μ_A - this review). All values are in ppb. [Nomenclature: (process) Chem(ist), C(ontrol)_R(oom)_Op(erator), Eng(ineering) Sup(ervisor), Shift Sup(ervisor), Tech(nician), Inst(rumentation technician), Lab(oratory), Maint(enance technician), Field Op(erator), Load(ing operator)].*

Figure S3-1 compares the distribution of the natural logarithms of all TWA-values in this data set with a typical log-normally distributed set of values as reported by Weill et al. (1981) and Diem et al. (1982) for instance. LN(TWA)-values below -2.5 typically represent values below the limit of detection (LoD) of the analysis technique.

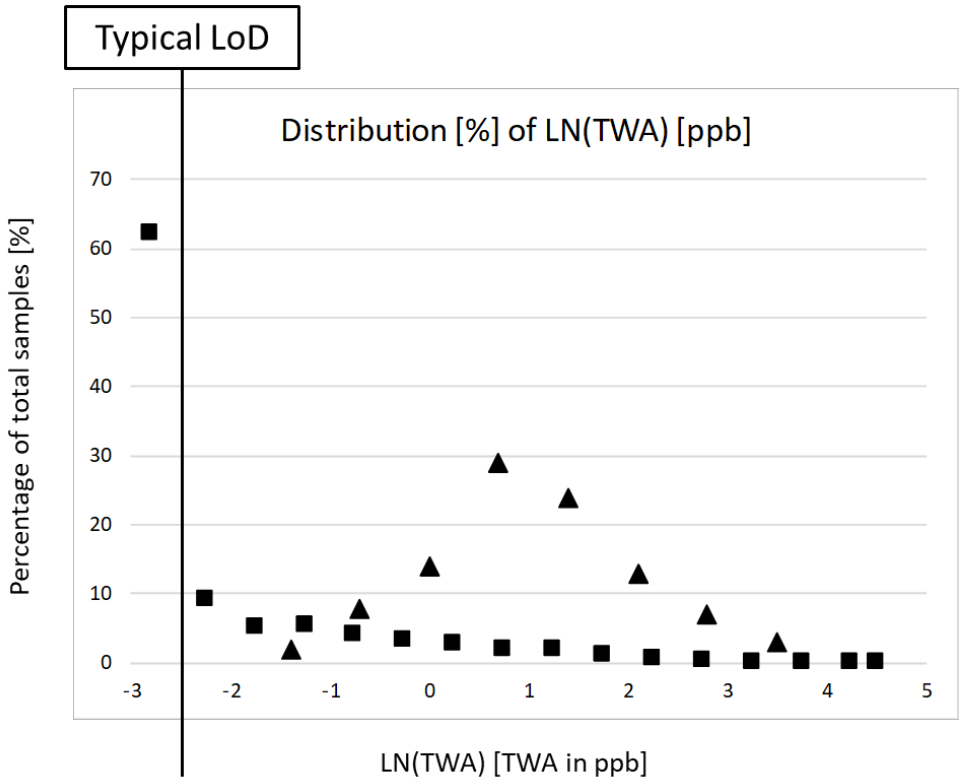

Figure S3-1 *– Comparison of the distribution of natural logarithms of TWA-values. X-axis: LN(TWA), TWA in ppb; y-axis: % of total samples. Squares: all "Routine" TWA-samples in this work; triangles: rendering of a typical log-normal distribution from Weill et al. (1981). X-axis values below -2.5 typically correspond to values below the limit of detection (LoD).*

Whereas a log-normal distribution could be assumed for this data set as well, it is clear from **Figure S3-1** that that distribution would be ill-defined, because the majority of TWA-values is based upon assumed values below the detection limit. Hence, for this reanalysis, the average of the actual (not LN-converted) TWA-values (μ_A) was chosen as a basis to calculate cumulative exposure. A sensitivity was performed using μ_T (see Middendorf et al., 2017) as an alternative assumption.