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

Supplemental Information - 6

Inclusion of Collins et al. (2017) data into Daniels (2018) analysis

Figure S6-1 is a redrawing of Figure 1 from Daniels (2018) wherein he presented the results of seven previously published studies. Without having included the Collins et al. (2017) study in his analysis (black markers only), Daniels (2018) reported that the intercept on the y-axis is significant, but that the slope is not, regardless of the type of regression used. We found P=0.18 for the slope parameter of the proposed quadratic function, confirming the author's conclusion. In other words, the fit by a flat line would not be significantly worse. Therefore, the curve fitted by Daniels (2018) is not shown in **Figure S6-1**.
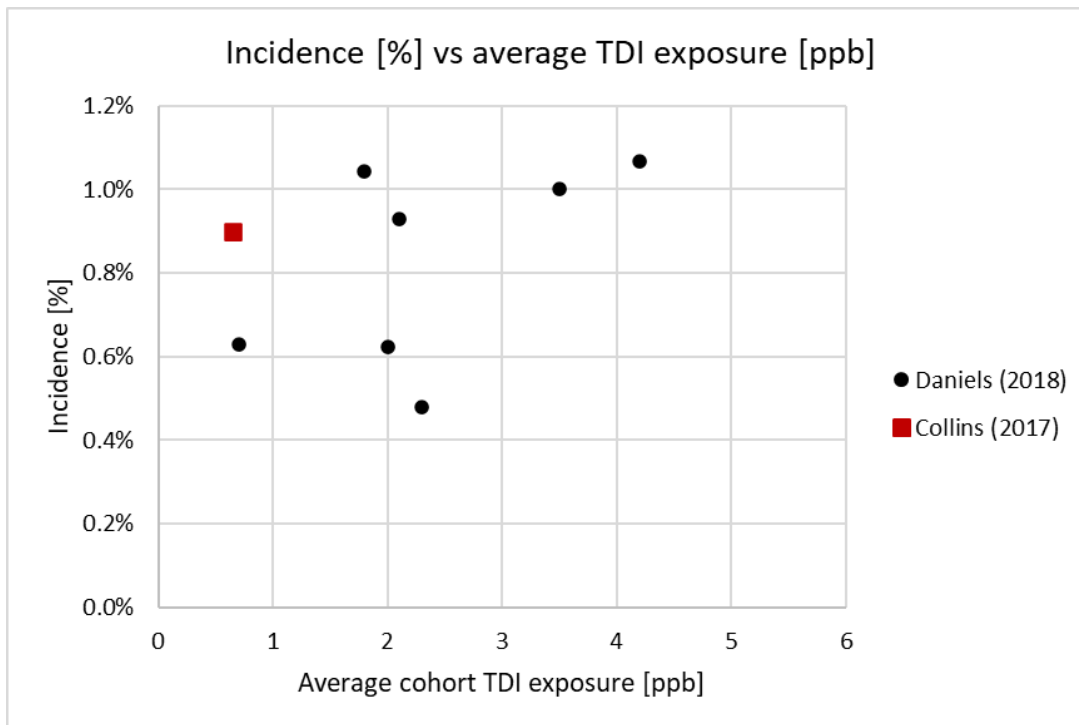

Figure S6-1 *– Data points used by Daniels (2018), showing overall asthma incidence from various studies as a function of average ("gross") TDI exposure of the cohort. The square red marker adds the overall result from Collins et al. (2017), which was not included in the Daniels (2018) study.*

The added red square in **Figure S6-1** adds the overall result from the Collins et al. (2017) study. Inclusion of this data point further lowers the significance of the slope parameter (P=0.23).

A few comments are warranted regarding the two data points on the right side of **Figure S6-1**:

- Weill et al. (1981) [marker at 3.5 ppb average exposure, incidence of 1 per hundred person-years in **Figure S6-1**] studied a group of employees for five years during start-up of a new facility in the mid-70's. Conditions were quite different then compared to the generally low background readings in the ACC-NIOSH study. Average area samples ranged between 10-20 ppb, with several excursions and large spills occurring. Nine of the twelve asthma cases were identified within the first seven months of operation, the other three within 2-3 years.

- Ott et al. (2000) [marker at 4.2 ppb average exposure, incidence of 1.06 per hundred person-years in **Figure S6-1**] reviewed data from a similar facility over a thirty year period between 1967 and 1997. The average 8-hour TWA-value was 5.9 ppb before the mid-80's, consistent with area readings reported by Weill et al. (1981). The corresponding incidence rate during that period was 1.8 per hundred person-years. The average 8-hour TWA-value after the mid-80's was 2.8 ppb, with a corresponding incidence rate of 0.7 per hundred person-years. Splitting out the two periods (open circles) leads to the picture shown in **Figure S6-2**.

With high probability, the slope between 0-3.5 ppb of average exposure is not different from zero (P=0.77 from an analysis excluding the right-most data point).

The significant (non-zero) intercept indicates that there would be a non-zero incidence of TDI-related asthma with zero airborne exposure to TDI. The quasi-zero slope below 3.5 ppb indicates that the incidence of asthma classified as TDI-related is nearly independent of the average TDI exposure level of the cohort. Taken together, these suggest that other factors are determinant for the induction of asthma classified as TDI-related in the studies represented in **Figures S6-1** and **S6-2**.
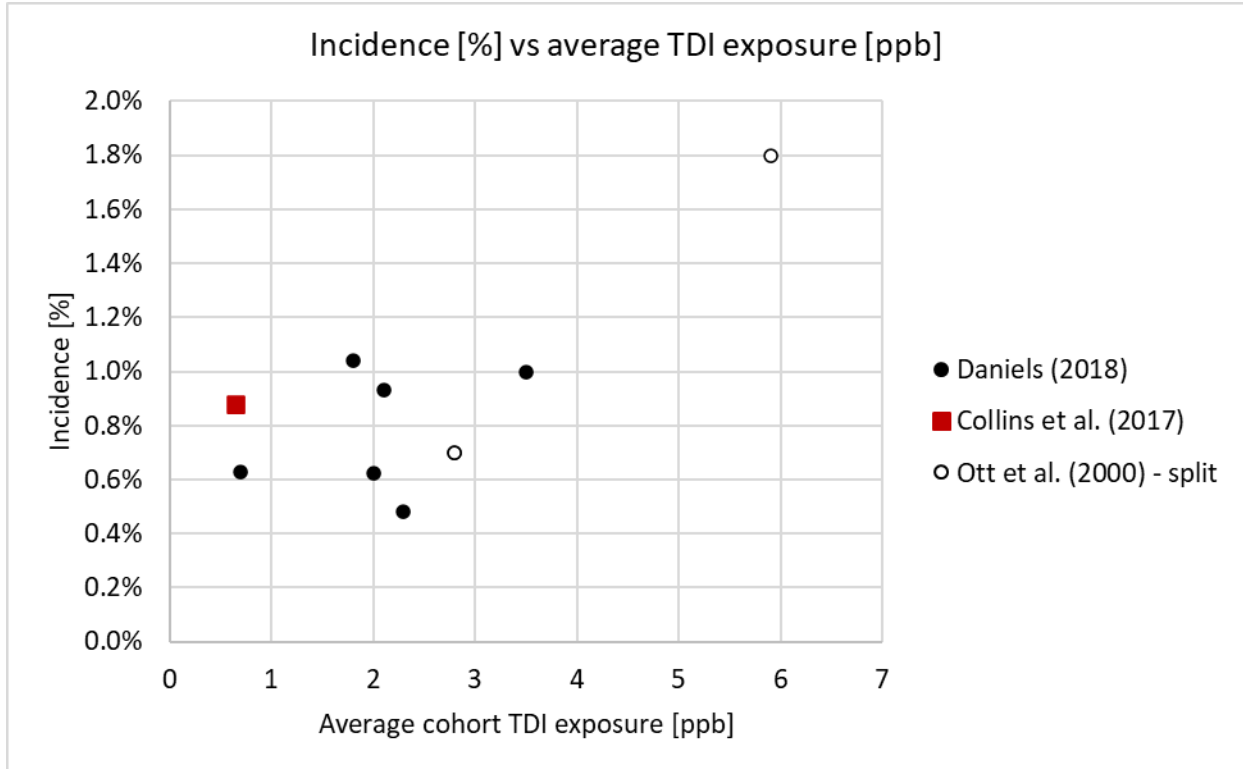
Figure S6-2 – *Data points used by Daniels (2018), showing the split of the Ott et al. (2000) data (open circles) over the two observation periods. The square red marker adds the overall result from Collins et al. (2017), which was not included in the Daniels (2018) study.*