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The Association Between Dimethylacetamide Exposure and Liver Toxicity
A Large Retrospective Analysis in Workers From Four European Factories

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Objective: This study examines the association between 8-h time weighted average (TWA) values of N,N-dimethylacetamide (DMAc) air exposure and potential hepatocellular injury in a retrospective study among fibre-production workers in four European factories. Methods and Results: Twenty-nine (1.5%) of 1844 workers during slight physical workload and 5 ppm is as well the actual German Occupational Exposure Limit (OEL). In the MAK Value Documentation, it is also mentioned that damage to the embryo or fetus is unlikely when the MAK value is observed and DMAc remains assigned to Pregnancy Risk Group C. The European Indicative Occupational Exposure Limit Value (IOELV) as well as nearly all other national OELs are still 10 ppm for 8-h weighted average (TWA) values.

DMAc can be passed through the skin, and therefore dermal as well as inhalation exposure contributes to the body burden. A dermal contribution, even if protective gloves are used (as done in MMF industry) to avoid direct skin contact to liquid DMAc, of about 40% to the total body burden has been estimated for exposure to DMAc vapors. The metabolism of DMAc proceeds via hydroxylation to N-hydroxymethyl-N-methylacetamide as a first step. Under the high temperature conditions during gas chromatographic analysis, formaldehyde is eliminated, leading to N-methylacetamide (NMAc) that can be used for biological monitoring in urine.

Liver toxicity was observed in long-term studies with rats and mice starting at inhalation concentrations of 100 ppm with a NOAEC (No Observed Adverse Effect Concentration) of 25 ppm. Apart from studies in experimental animals, some epidemiological investigations in humans have been published. Spies et al. studied parameters for liver disease [aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma-glutamyl transferase (GGT), alkaline phosphatase (AP) and bilirubin] at least once during a 1-y observation period in 127 full-shift (12 h/d) exposed workers in comparison to 217 controls. Exposure was monitored by urinary concentrations of NMAc. In addition, the amounts of urinary DMAc were calculated by urinary NMAc and acetamide. In 21 of the 127 workers the urinary NMAc concentration exceeded 60 mg/g creatinine (Cr) (two times the German BAT value) or urinary DMAc 136 mg DMAc/g Cr. The mean inhalation exposure was 1.9 ppm DMAc (12 h shift) corresponding to about 3 ppm over 8 h. No indications were obtained for liver toxicity in exposed workers in comparison to controls. The authors concluded that the chronic exposures in the workforce studied, and brief excursions were not hepatotoxic.

In contrast, two recent studies reported adverse liver effects in exposed Asian populations. Newly enrolled workers in 2002 to 2004 (or 2001 to 2004) in an elastane fiber factory (440 workers...
over 31 mo, Lee study) or a Spandex factory (1045 workers over 43 mo, Jung study) were monitored for alteration of liver parameters (ALT, AST, and GGT). However, both studies lack sufficient quantitative data on occupational DMAc exposure, as there were no air or dermal exposure measurements for DMAc provided.

Due to the insufficient data (small sample size) from the European workforce and the limited quantitative data available from the Asian studies, the aim of the present investigation is to provide further data on European workers and current exposure data in Europe as opposed to the specific Asian data.

METHODS

Participating Companies

Six European MMF companies from Germany, Ireland, Portugal and Spain representing polyacrylonitrile (PAN), meta-aramid and elastane fibre producers were invited to participate and asked to provide data about their workforce in March 2020. The data collection was considered complete once all companies had contributed their available data until December 2020.

From the six companies, one company was not allowed to participate due to internal data protection reasons, and a second company was only able to deliver data partly due to the pandemic lockdown and severe influence to their business.

The protocol of this study and its amendments are publicly available via the Open Science Framework (https://osf.io/pt5qu/) and were approved by the Ethics Committee of the federal state of Hessen in Germany.

Study Population

The start of the inclusion to the study was considered the first exposure to DMAc and corresponding liver measurement of the worker. Data from workers having information on both air and liver measurements in the same year were included in the dataset. As the half-life time of DMAc exposure is short, with 9h after dermal and 5.6h after inhalation exposure, while annual repeated measurements of air exposures and matched liver values were available, each worker was considered to be at risk again at the next measurement leading to multiple exposure-outcome observations per worker. In total 2795 exposure-outcome observations were available for analysis. Two companies provided anonymized individual data with repeated measurements and two companies provided the data due to data protection rules, on an aggregation level, that is, in annual exposure-outcome groups consisting of at least 10 workers per group.

All companies provided data from the area of fibre production, that is, the workplace with the highest exposures where compliance with OELs is controlled, whereas one company provided data also from several working areas with lower exposure.

A description of the population and the main measurements are displayed in Table 1. In brief, all companies provided data of ALT liver values, while company A provided data of AP values as well. 959 ALT values (based on 150 workers with an average of six measurements per person) were provided by company A, 100 values (based on 62 workers with an average of two measurements per person) by company B, 513 values by company C and 272 values of ALT by company D, respectively. Due to data protection policies, for companies C and D, we are not able to match the number of workers to the number of observations. Subsequently, all the statistical analyses are performed on the number of observations.

Only company A provided 951 AP values. All companies provided calculated 90th percentiles of DMAc exposure measurement based on 8h-TWA measurements in the fibre production area while company A provided measurements in other areas as well (see footnote below Table 1). Companies A and B provided liver values in consecutive years, while companies C and D provided the data in certain years where DMAc exposure measurements were available, and according to the data protection rules based on grouping of at least 10 workers per group.

Outcome Measurements

To assess potential liver toxicity in DMAc exposed workers, first it had to be decided which enzymes to rely on, on the appropriate upper limit of normal (ULN) and what multiples of the ULN should be used. In our study we decided to: (a) concentrate on ALT because for this enzyme (apart from GGT) the most measurements in our workforce are available and an isolated elevation of GGT is insufficient to qualify for liver disease. Furthermore, ALT is the transaminase most frequently used in clinical practice to screen for liver disease, (b) use an ULN for ALT of 40 IU/L because lower ULNs were only obtained by exclusion from the analysis of subsets of the normal population with some abnormalities, such as high BMI or frequent metabolic disorders; such subsets must not and cannot be excluded from an analysis like the present one, (c) use a factor of 2 to define an ”indication for possibly drug-induced liver toxicity (DILI) with different levels of
The following groups, which were used as dummy variables in the statistical analysis, were constructed based on DMAc exposure measured in ppm: (1) 0.00 to 1.00 ppm, (2) 1.01 to 2.00 ppm, (3) 2.01 to 3.00 ppm, (4) 3.01 to 4.00 ppm, (5) 4.01 to 5.00 ppm, (6) 5.01 to 6.00 ppm, (7) 6.01 to 7.00 ppm, (8) 7.01 to 8.00 ppm, (9) 8.01 to 9.00 ppm. There were no data available for exposure ranges between 7.01 and 9.00 ppm. For the analyses with DMAc as continuous variable the midpoint ppm value was calculated for each exposure category.

Statistical Analysis

Descriptive Statistics

The number of observations, means, medians and range for the ALT and AP liver enzymes were calculated per ppm group exposure (Table 2).

Elevated Liver Values

Regression Analyses

The number of elevated ALT values was calculated and presented based on the group exposures (in ppm). Two random effects regression models were performed allowing for the estimation of the variance between subject (at a company level) and the within-subject variance (at a participant level). All individual measurements were assumed to be independent.

For the companies where information was not given at a participant level, the company level effect was only used.

In the first regression model the continuous exposure of DMAc (in ppm) was used as the independent variable and in the second exposure groups of ppm were used as the independent variable (Tables 3 and 4). In both models the number of elevated values was calculated and presented based on the group exposures (in ppm). Two random effects regression models were performed allowing for the estimation of the variance between subject (at a company level) and the within-subject variance (at a participant level). All individual measurements were assumed to be independent.

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liver values (that is ALT higher or equal to 2 x ULN) was used as the dependent variable. To perform the logistic regression model the cases (number of elevated liver values based on the aforementioned criteria in the outcome measurements) were coded with the value 1 and the non-cases with the value 0. Linearity of the logit for the continuous exposure variable was tested.

Patterns of Liver Injury
The number of indicative cases of liver injuries were calculated per ppm group exposure. Due to the limited number of observations indicative for a liver injury, no further logistic regression analyses on the association between DMAc exposure and liver injury could be performed (Table 5).

Continuous ALT Values
Regression Analyses
Two random effects regression models were conducted which calculated fixed and random effects due to the variance between subject (at a company level) and the variance within-subject (at a participant level) respectively.

In the first analysis, the continuous exposure of DMAc (assuming a linear exposure-outcome relationship) was used as the independent variable and in the second analysis, the exposure groups of ppm were used as the independent variable (Tables 6 and 7). In both models, the ALT continuous liver values were used as the dependent variable. The mean values presented in Table 7 are the predicted values based on the regression analysis considering the variance between the workers and across the companies and they may differ from the actual values (Table 2).

All statistical analysis was performed in STATA15 and a P value of =0.05, or a confidence level of 95%, was considered statistically significant.

RESULTS

Descriptive Statistics
Table 2 presents the number of observations, means, medians and range of values for the two liver enzymes based on ppm group exposure. Mean values of ALT and AP values were generally within the normal range (that is, less than the UNL). Slightly higher ALT means were observed for the groups with exposure between 2.01 to 3.00 ppm.

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Elevated Liver Values

Regression Analyses

The results of the logistic regression (Table 3) showed a non-significant inverse association between DMAc exposure and ALT values for continuous ppm exposure [OR = 0.88 (95% CI: 0.65–1.18), P value = 0.39] and for groups of exposure (ORs ranging from 0.83 to 4.18, P values ranging from 0.11 to 0.93) (Table 4). Similar results were observed when a multilevel mixed Poisson regression was performed (because of the outcome count responses).

Patterns of Liver Injury

Twenty-nine (1.5%) of 1844 observations with more or equal than twice the upper limit normal of ALT and four (0.2%) observations with more or equal than three times the upper limit normal of ALT were identified. When the 5×ULN threshold for ALT was used, one observation (0.05%) with clearly elevated ALT value was identified (not shown in table).

Based on the criteria for the identification of liver injury, two (0.1%) observations of hepatocellular liver injuries and five (0.3%) observations of mixed injury were detected (Table 5). No observations of cholestatic injury were identified.

Continuous ALT values

Regression Analysis

The results from the random effects linear regression analysis confirmed a significant decrease of 0.57 IU/L (SE = 0.18, P value = 0.002) in ALT enzyme for every ppm increase of DMAc, that is, an inverse relationship between exposure and liver injury (Table 6).

When we used groups of ppm exposure as the categorical exposure, we also observed a significant (full model P value = 0.004) but very small decrease of the ALT mean values for every category of ppm exposure, again an inverse relationship between exposure and ALT (Table 7). For the separate exposure categories all P values were < 0.001. Similar results were observed when the ALT values were log transformed.

CONCLUSIONS

Very few observations indicative of elevated liver values were detected in our study. 1.5% of the observations were “indicative of possible elevated” ALT values, 0.2% of “possible elevated” ALT levels, and 0.05% of “clearly elevated” ALT values. An indication of liver injury when the R-criteria were met was reported for 0.1% observations of hepatocellular injury and for 0.3% observations of mixed injury. The analysis of the continuous data suggested even a slight decrease of 0.57 IU/L per 1 ppm increase in DMAc exposure and mean ALT values were within the normal range. In essence, we observed no association between DMAc exposure and increased liver values.

The prevalence of elevated liver values estimated in our study is lower when compared to the prevalence observed in the general population without occupational exposure. Increased transaminases are observed in about 2.5% of healthy persons while intraindividual day-to-day variations of transaminases amount to 10% to 30%. In addition, according to Bruguera the prevalence of increased transaminases has been estimated to be between 5% and 10% of the population, a percentage expected to increase with the global rise of obesity. Moreover, increased transaminases with transient and chronic effects, are defined by Medix if they are persistent over ≥6 mo. This was substantiated in the NHANES III study where 36%, 31%, 17% and 12% of elevated AST, ALT, AP and GGT concentrations, respectively, normalized in the course of a repeat measurement (mean of 17.5 d apart), while originally normal

### TABLE 6. Effect of Continuous Exposure on Continuous ALT Values

| ALT | Beta Coefficient | Standard Error | 95% Confidence Intervals | P Value |
|-----|------------------|----------------|--------------------------|--------|
| PPM | –0.57            | 0.18           | –0.92 to –0.21           | 0.002  |

Beta coefficient: the degree of IU/L change in ALT for every ppm increase of DMAc.

Number of observations in the regression model: 1,844.

### TABLE 7. Effect of Groups of Exposure on Continuous ALT Values

| DMAc Group [90th Percentile (8h-TWA) in ppm] | N Observations | Mean (IU/L) | Standard Error (IU/L) | 95% Confidence Intervals (IU/L) | P Value |
|---------------------------------------------|----------------|-------------|-----------------------|---------------------------------|--------|
| 0.00–1.00                                   | 220            | 29.9        | 1.09                  | 27.76–32.02                     | 0.004  |
| 1.00–2.00                                   | 214            | 29.3        | 0.97                  | 27.35–31.16                     |        |
| 2.01–3.00                                   | 311            | 28.6        | 0.90                  | 26.86–30.38                     |        |
| 3.01–4.00                                   | 455            | 27.9        | 0.88                  | 26.28–29.71                     |        |
| 4.01–5.00                                   | 377            | 27.4        | 0.91                  | 25.90–29.14                     |        |
| 5.01–6.00                                   | 91             | 26.7        | 0.99                  | 24.80–28.66                     |        |
| 6.01–7.00                                   | 81             | 25.1        | 1.10                  | 23.93–28.26                     |        |
| ≥9.01                                       | 95             | 25.5        | 1.25                  | 23.01–27.92                     |        |

3.00 ppm (mean of IU/L 31.0, SD: 20.9) and 3.01 to 4.00 ppm (mean IU/L 30.5, SD: 17.4).

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values were not affected in the second analysis. Raising the cut-off level of ALT elevation to 5× ULN is more likely to exclude clinically non-important liver problems in an evaluation. In our study, when the cut-off level of ALT was raised to 5× ULN, we identified only one (0.03%) observation above this threshold.

In general, transaminases could be influenced by a variety of parameters difficult to control in study populations, like alcohol abuse (eg, >3 drinks/d) and other risk factors unrelated to drug/chemical exposure such as diabetes, metabolic syndrome (increased triglycerides, cholesterol, fasting glucose), elevated body mass index, virus hepatitis and non-alcoholic liver steatosis. However, information on such factors was not always available in this study. In some cases, though of abnormal liver enzymes, specific explanations are available from the plant physicians.

The interpretation of these results should be done in light of some limitations. Firstly, not all companies provided individual data, which could have enabled a more in-depth analysis considering the variation within each worker. Due to certain data protection policies, two companies needed to provide data in groups of observations and not per individual. This limitation is also reflected in the reporting of the number of observations with elevated ALT or indicative liver injuries instead of the number of individuals. However, in our analysis, we did consider the variation within the workers in observations where repeated measurements of liver enzyme values were available. The data were very stable with a standard deviation of 0.97 ppm for repeated measurements in an 8 h period.

Secondly, air and not personal sampling was only available for the analysis. Nevertheless, a static (area) sampling was performed by the participating companies where the position of the sampler was fixed next to the workstation in the breathing area where the worker works most of the time.

Thirdly, three companies did not measure and therefore could not provide data on AP liver values, which could have led to an underestimation of the real number of indicative liver injuries observed in this population. Lastly, this retrospective analysis had no data on important confounders, such as alcohol or drug use amongst workers. Given that these confounders are likely to have caused a bias towards the null, and we already observed a null effect, we expect that confounding could not have played a major role in this analysis.

Despite the aforementioned limitations, which are considered quite common in observational studies, this study is the only one conducted with European workforces and the only one which included a large database for higher DMAc exposures.

Moreover, the availability of a large number of ALT enzyme values available from all companies is a strength of this study, as ALT is the transaminase most frequently used in clinical practice to screen for liver disease and the most frequently measured enzyme in our study. Therefore, the large number of observations adds to the power of this study to allow the detection of minimal effects if those are present. In our study, we used the highest DMAc exposure measured at the 90th percentile, based on 8-h TWA measurements, focusing on areas with the highest exposure and we nevertheless found no effect.

Overall, the results of this study do not support a relationship between DMAc exposure and elevation in liver enzymes or liver injuries in the range of existing European OELs.

Similarly, Spies et al. found no significant DMAc exposure-related trends in hepatic injury results. However, an inverse relationship was observed, that is, every increase in ppm resulted in a decrease of IU/L in ALT. In a study of liver disease in workers exposed to dimethylformamide (DMF), which is similar in toxicity and chemical structure to DMAc, Redlich et al discussed an inverse relationship between duration of exposure and ALT levels. Likewise, although Lee et al. showed a significant relationship between exposure and liver toxicity, they observed higher incidences within the first two months of enrolment and no new cases occurring after seven months. Along these lines, Jung et al. found that after cessation of exposure the elevated liver enzymes returned to baseline relatively quickly for elevated ALT by 50% within 14 d in both studies and by 90% within 31 d. All 38 cases were of the hepatocellular type and none of the cholestatic or mixed type. They further suggested that DMAc exposure induces the liver enzymes that metabolize it, so that chronically exposed workers develop a tolerance to its toxic effect. However, the data from these studies are primarily based on the analysis of urinary NMA as an indicator of exposure to DMAc, which may not be accurate, if not considered together with the analysis of dermal and air absorption of DMAc.

In the future, more long-term studies are needed to shed light into the mechanisms of liver injury in relationship to DMAc environmental exposure and expand on the knowledge we have acquired from the human studies.

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