OPEN

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 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 alanine aminotransferase (ALT) observations had liver values two times above normal; 0.2% three times above normal and 0.05% five times above normal. Two (0.1%) observations were indicative of hepatocellular injury. Logistic regression analyses showed an odds ratio for elevated ALT of 0.88 per 1 ppm (P trend = 0.39). Linear random effects regression analyses showed a decrease of one international unit (IU/L) ALT per 1 ppm increase of DMAc exposure ($P = 0.002$). **Conclusions:** This study found no association between DMAc exposure and hepatoxicity amongst European workers. The prevalence of elevated liver values was lower compared to the general population without occupational exposure.

Keywords: dimethylacetamide, DMA, DMAc, hepatotoxicity, occupational epidemiology

BACKGROUND

N, N-Dimethylacetamide (DMAc; CAS 127-19-5) is a versatile aprotic solvent widely used in the chemical industry, such in the Man-Made Fibres (MMF) industry (eg, for the production of acrylic/polyacrylonitrile, elastane, aramid fibres). It is also used in the coatings industry as an additive in special coating materials, in the adhesive industry and in the production of pharmaceuticals as an excipient or solvent.

A detailed assessment of the toxicological profile of DMAc has been published by the German Maximale Arbeitsplatz-Konzentration (MAK) Commission[1] and was lowered to 5 ppm in 2018 from former 10 ppm taking into account the respiratory volume in workers during slight physical workload and 5 ppm is as well the actual German Occupational Exposure Limit (OEL).[2] 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 8h-time weighted average (TWA) values.[3,4]

DMAc can easily pass 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.[5] 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.[6] For this purpose, the German Biologischer Arbeitsstoff-Toleranz (BAT) value was reevaluated as 25 mg NMAc plus N-hydroxymethyl-N-methylacetamide/L urine in 2020.[7,8]

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.[9]

Apart from studies in experimental animals, some epidemiological investigations in humans have been published. Spies et al[10] 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, DMAc 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[11] (or 2001 to 2004[12] in an elastane fiber factory (440 workers

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Clinical Significance: Occupational exposure to dimethylacetamide has been linked to hepatotoxicity, mainly based on results from animal studies and studies conducted in Asia. However, no association has been found in this large retrospective study in workers from four European factories.

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TABLE 1. Description of Population and Main Measurements

	Company A	Company B	Company C	Company D
N^* of observations included in this study	959 (ALT) + 951 (AP)	100 (ALT)	513 (ALT)	272 (ALT)
Working area	Fibre production and others[†]	Fibre production	Fibre production	Fibre production
DMAc exposure area measurement (8h-TWA)	Calculated 90th percentiles	Calculated 90th percentiles	Calculated 90th percentiles	Calculated 90th percentiles
Liver tests	ALT, AP	ALT	ALT	ALT
Year of DMAc and liver measurement[**]	2012–2019	2016–2020	1977, 1980–1990, 1992, 1994, 1998–2006, 2008, 2011–2014, 2016–2019	1992–2001, 2003–2007, 2010–2011, 2013, 2015, 2017–2019
Type of anonymized liver enzyme data	Individual data	Individual data	DMAc exposure groups[‡]	DMAc exposure groups[‡]

[*]Total N: 2,795 observations (calculated from data on ALT and AP values only).
[†]Others: company A: polymerization, dispersions, solvent recovery, cutter and baler, pack-room, laboratory.
[‡]The exposure groups are presented in Tables 3 and 4.
[**]More information is provided in exposure measurement (page 7).

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 workforces 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 9 h after dermal and 5.6 h after inhalation exposure,[1] 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 fiber 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 elevated ALT'', a factor of 3 to define ''possibly elevated ALT'' and a factor of 5 for ''clearly elevated ALT''. Such factors of 2, 3, and 5 for the ULN were proposed by Bénichou[13] and Aithal et al[14] for drug-induced liver toxicity (DILI) with different levels of

TABLE 2. Descriptive Characteristics of ALT and AP Values Based on ppm Exposure Categories

	ALT, IU/L ($n = 1,844$)				AP, IU/L ($n = 951$)			
DMAc ppm [90th Percentile (8h-TWA) in ppm]	*N* Observations	Mean (SD)	Median (IQR)	Range	*N* Observations	Mean (SD)	Median (IQR)	Range
0.00–1.00	220	28.3 (15.5)	24 (18–33)	5–100	218	68.1 (18.1)	66 (55–78)	27–118
1.01–2.00	214	25.1 (14.1)	22 (16–31)	5–103	94	63.6 (19.1)	60 (51–75)	27–123
2.01–3.00	311	31.0 (20.9)	26 (19–37)	5–201	129	64.4 (17.2)	62 (52–75)	27–117
3.01–4.00	455	30.5 (17.4)	26 (18–37)	6–139	163	66.6 (14.9)	65 (56–75)	29–104
4.01–5.00	377	26.4 (15.5)	22 (17–32)	6–125	192	65.1 (16.1)	64 (54–74)	36–136
5.01–6.00	91	22.2 (12.4)	19 (15–26)	6–100	32	63.8 (14.5)	61 (52–74)	44–103
6.01–7.00	81	26.7 (13.5)	23 (17–34)	11–83	60	67.3 (16.3)	65 (56–78)	38–101
7.1–8.00	No data available	–	–	–	No data available	–	–	–
8.1–9.00	No data available	–	–	–	No data available	–	–	–
≥9.01	95	23.1 (10.6)	21 (15–27)	6–67	63	69.5 (13.9)	69.5 (62–77)	39–123

conservation, d) use Aithal's criteria[14] to identify patterns of liver injury based on ALT and AP values.

Thus, the outcome was defined using three methods:

1. By calculating **elevated liver values** based on three factors:
   a. Indication for possible elevated ALT values - ALT higher or equal to 2× ULN.
   b. Possible elevated ALT values - ALT higher or equal to 3× ULN.
   c. Clearly elevated ALT values - ALT higher or equal to 5× ULN.

2. By classifying **patterns of liver injury:**
   The most common clinical presentations of liver injury are hepatocellular, mixed and cholestatic which should be defined based on biochemical criteria[1]:

   Mixed pattern of liver injury will be defined when (ALT ≥ 2× ULN or AP ≥ 2× ULN) & R > 2 & <5.
   Cholestatic pattern of liver injury will be defined when (ALT ≥ 2× ULN or AP ≥ 2× ULN) & R ≤ 2.
3. By calculating ALT values on a continuous scale.

The physicians of the companies provided the liver enzyme values for each year where available. Liver enzyme measurements were carried out in analytical laboratories for clinical medicine according to standard methods in clinical practice. Measurements of ALT were available from all companies, where AP was available from only one company. All enzymes were measured in international units per liter (IU/L).

Exposure Measurement

Area sampling for the DMAc exposure measurements was performed either with permanently installed, continuous measuring systems or with discontinuous sampling procedures during a work shift. The analytical determinations were carried out either in accredited laboratories or with measurement methods controlled and accepted by a competent supervisory authority. All companies expressed the measured DMAc air exposures in ppm. The 90th percentile of the exposure distribution based on 8h-TWA measurements as the higher representation of exposure for each year was used. These exposures were subsequently grouped based on ppm range (with a minimum of 10 observations per category).

[1] R = (ALT/ULN) / (AP/ULN). Upper limit normal (ULN) = 40 IU/L for ALT; 120 IU/L for AP.

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) ≥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

TABLE 3. Effect of Continuous Exposure on Elevated ALT Values*

	ALT			
	Odds Ratio	Standard Error	95% Confidence Intervals	*P* Value
PPM	0.88	0.13	0.65–1.18	0.39

Odds ratio: an OR of 1 suggests no association between exposure and liver values.
*Number of observations included in the regression model: 1,844.
P value: if *P* value is >0.05 then the association is not statistically significant.

TABLE 4. Effect of Groups of Exposure on Elevated ALT Values*

	ALT				
DMAc Groups [90th Percentile (8h-TWA) in ppm]	*N* Observations	Odds Ratio	Standard Error	95% Confidence Intervals	*P* Value
0.00–1.00	220	Reference	–	–	–
1.00–2.00	214	0.83	0.96	0.09–7.94	0.87
2.01–3.00	311	4.18	3.74	0.72–24.12	0.11
3.01–4.00	455	1.41	1.40	0.20–9.99	0.73
4.01–5.00	377	1.32	1.37	0.17–10.19	0.79
5.01–6.00	91	0.95	1.44	0.05–18.63	0.93
6.01–7.00	81	1.30	1.88	0.08–22.15	0.86
≥9.01	95	–	–	–	–

Odds ratio: an OR of 1 suggests no association between exposure and liver values.
*Number of observations included in the regression model: 1,749 (because no elevations were observed for the group with higher than 9.00 ppm exposure, 95 observations were not included in the logistic model.
P value: if *P* value is >0.05 then the association is not statistically significant.

liver values (that is ALT higher or equal to 2× 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 STATA[15] 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

TABLE 5. Number of Indicative Cases

	Elevated ALT Levels*			Indication for Liver Injury (≥2× ULN & R Criteria Met)*		
DMAc Group [90th Percentile (8h-TWA) in ppm]	*N* Observations	*N* Observations ALT ≥ 2× ULN†	*N* Observations ALT ≥ 3× ULN	*N* Observations Hepatocellular‡	*N* Observations Mixed	*N* Observations Cholestatic
0.00–1.00	220	2	0	0	1	0
1.01–2.00	214	2	0	0	1	0
2.01–3.00	311	11	1	0	2	0
3.01–4.00	455	7	1	1	0	0
4.01–5.00	377	5	2	1	0	0
5.01–6.00	91	1	0	0	0	0
6.01–7.00	81	1	0	0	1	0
7.01–8.00	No data available	–	–	–	–	–
8.01–9.00	No data available	–	–	–	–	–
≥9.01	95	0	0	0	0	0
Total	1,844	29	4	2	5	0

*Detailed information about the observations with elevated ALT and indications of liver injury is available upon request.
†ULN = 40 IU/L.
‡Due to limited number of cases, only logistic regression analyses for 2× ULN cases could be performed.

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

		ALT			
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	25.59–29.14	
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).

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 in ALT 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%.[16]

In addition, according to Bruguera[17] 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[16] 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

values were not affected in the second analysis.[18] Raising the cut-off level of ALT elevation to 5× ULN is more likely to exclude clinically non-important liver problems in an evaluation.[14] In our study, when the cut-off level of ALT was raised to 5× ULN, we identified only one (0.05%) 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 on 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[10] found no significant DMAc exposure-related trends in hepatic injury results. Whatsoever, 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.[19] Likewise, although Lee et al[11] 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.[12] 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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