A biological monitoring assessment of exposure to methylene dianiline in manufacturers and users

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Abstract
This paper describes a cross sectional study in which biological monitoring was used to assess exposure to methylene dianiline (MDA) in a selection of United Kingdom industries that manufacture or use MDA. Samples of urine were collected from 411 workers, representing 45 factories engaged in various activities. All urine samples were analysed for MDA and its acetyl metabolites and results are reported as total MDA. In this study, 91% of postshift urine samples and 88% of preshift samples had less than 50 nmol MDA/mmol creatinine. Some evidence was obtained which showed that when exposure to MDA was through inhalation (as solid material or contaminated dust), postshift urine samples had higher MDA concentrations than samples taken preshift the next day. When exposure was most likely to be through the dermal route, urine samples taken preshift next day tended to have higher MDA concentrations than urine samples collected immediately postshift on the day of exposure. Therefore a biological monitoring sampling strategy for MDA must take account of the route of entry into the body. If exposure is likely to be via inhalation, postshift samples should be collected and if exposure is likely via the skin, preshift samples next day are more appropriate. The results show that in most factories, regardless of the route of exposure, it is possible to keep urinary MDA concentrations below 50 nmol/mmol creatinine. In the absence of a health based or hygiene based standard, the use of a "yardstick" as a target to aim for, which has been derived from good working practice across the industry, may be a useful way of helping to control exposure.

Methods

STUDY DESIGN
Forty five companies participated in the study, which was carried out during 1989–90. They were selected on a random one in five basis from manufacturers’ sales lists to give a representative cross section of activities in which MDA was manufactured or used in the United Kingdom. The activities fell into nine categories—namely, manufacturing and formulation, paint making, formulation and packing, pattern and tool making, composite materials, potting and encapsulation, casting
Distribution of urinary MDA concentrations in postshift and preshift samples

<table>
<thead>
<tr>
<th>Urine MDA concentration (nmol/mmol creatinine)</th>
<th>Postshift samples (%)</th>
<th>Preshift samples (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>None detected</td>
<td>57</td>
<td>42</td>
</tr>
<tr>
<td>&lt;30</td>
<td>88</td>
<td>82</td>
</tr>
<tr>
<td>30-50</td>
<td>91</td>
<td>88</td>
</tr>
<tr>
<td>&lt;100</td>
<td>96</td>
<td>94</td>
</tr>
</tbody>
</table>

and moulding, miscellaneous, and unknown. Information was collected on the nature of the work and the approximate use of MDA. Four hundred and eleven workers (all men) who were potentially exposed to MDA gave their informed consent and volunteered to give urine samples (25ml), which were collected at the end of the working shift (postshift) and again on the next day (preshift) before work began. Samples arrived in the laboratory within 24 hours where they were stored at −20°C until ready for analysis. Urine samples collected on a Friday were stored at −20°C and dispatched on the next Monday.

**Analytical Method**

The method used to analyse the acetyl and diacetyl metabolites of MDA has been reported elsewhere. Briefly, the metabolites were hydrolysed in 5 M sodium hydroxide to MDA, extracted and then derivatised with pentafluoropropionic anhydride. The MDA derivative was separated on a capillary gas chromatographic column and measured by gas chromatography-mass spectrometry. An internal quality control scheme for MDA was in operation and the day to day coefficient of variation was less than 10%. Creatinine was measured by an automated version of the Jaffe method. The results were expressed as "total" MDA (hydrolysed metabolites plus unchanged parent MDA) in nmol/mmol creatinine.

**Results**

Nine hundred and sixty samples were received; 230 workers provided both postshift and preshift (next day) urine samples and a further 396 gave only a postshift sample. Some workers provided only preshift samples. If it was not clear whether the preshift sample was taken on the day of exposure or on the next day the sample was analysed but excluded from the data set.

Most of the urine samples (about 95%) had MDA values below 100 nmol MDA/mmol creatinine. Very high concentrations (>1300 nmol/mmol) were recorded in three samples. The maximum urinary MDA concentration, 6871 nmol/mmol, was found in a postshift urine sample. Examination of the data showed that 91% of postshift and 88% preshift (next day) urine samples contained less than 50 nmol/mmol (table). The shape of the frequency distribution curve was skewed and was similar for both preshift and postshift samples. Over 42% of the samples had no detectable MDA.

**Industry Picture**

In only three factories (out of 45) was the group average greater than 50 nmol/mmol, although 15 factories had at least one worker whose urinary MDA concentration exceeded 50 nmol/mmol. A similar picture was noted if the preshift (next day) urine data (38 factories) were examined. The workers in factories that had high concentrations in postshift samples tended also to have high concentrations in preshift samples.

Figure 1 shows the group average of urinary MDA plotted against the type of use. The 11 workers in the five factories that used MDA for casting and making moulds had no MDA in their urine samples. All other groups showed a range of urinary MDA values. The
range was particularly wide among the manufacturers and formulators, for whom one factory had a group average of 450 and a maximum of 6871 nmol/mmol creatinine and another factory had a group average of 9 and a maximum of 30 nmol/mmol creatinine.

There was no correlation between the average amount of MDA processed per factory and average urinary output of MDA.

**Discussion**

The principles behind the development of a biological monitoring strategy have been well rehearsed. Clearly, it is imperative that the analytical method employed must be sufficiently sensitive and specific to monitor the uptake of the toxic substance or its metabolites, which in turn must be stable enough to be measured. Also, the procedure must include an adequate quality assurance programme, particularly when longitudinal studies or regular monitoring are being conducted. Some indications of the route of absorption and toxicokinetics of the compound are also essential so that the most appropriate sampling time can be established.

After the strategy has been developed, and the methodology well validated, we are left with the problem of how to interpret the results. The American Conference of Governmental Industrial Hygienists (ACGIH) and Deutsche Forschungsgemeinschaft (DFG) publish annual lists of biological exposure standards for certain substances and these reflect different philosophies in the setting of standards. The ACGIH Biological Exposure Indices (BEI) is based either on the relation between exposure and uptake (a hygiene based standard) or in some cases on known health effects. The DFG Biological Tolerance Value (BAT) is a health based limit. In the case of MDA, no limits have been set. The absence of health based data however, does not preclude the use of biological monitoring for helping to control exposure, particularly where absorption of the material can occur by non-inhalation routes. In some cases, it may be appropriate to set an interim biological monitoring standard that is related to what is achievable in most industries and reflects good practice.

Biological monitoring has been used in this study to assess the uptake in exposed workers. The data give a cross sectional picture of the extent of exposure to MDA in the United Kingdom. The results indicate that where inhalation is the main route of entry into the body there is a relatively rapid absorption and elimination and peak excretion is reached at...
the end of the shift. When the material landed on the skin, the uptake was slower and the maximum excretion occurred the next morning. This study has identified the need to take into account the most likely route of exposure when devising a biological monitoring strategy. Suitable judgements need to be made as to whether postshift or preshift urine samples collected the next day would give the better indication of uptake.

In this study about 90% of workers had urinary MDA values less than 50 nmol/mmol creatinine. The results collected from various groups of users and manufacturers show that it is possible to control MDA exposure to keep urine concentrations below 50 nmol/mmol. This value has been proposed as a "yardstick" by the United Kingdom Health and Safety Executive.  

References:
8 Health and Safety Executive. Biological monitoring for chemical exposures in the workplace. United Kingdom: HSE, 1992 (Guidance Note EH 56).

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