Dimethylethylamine in mould core manufacturing: exposure, metabolism, and biological monitoring

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Abstract

The exposure and metabolism of dimethylethylamine (DMEA) was studied in 12 mould core makers in four different foundries using the Ashland cold box technique. The mean time weighted average (TWA) full work shift DMEA exposure concentration was 3.7 mg/m^3 . Inhaled DMEA was excreted into urine as the original amine and as its metabolite dimethylethylamine-N-oxide (DMEAO). This metabolite made up a median of 87 (range 18-93) % of the sum of DMEA and DMEAO concentrations excreted into the urine. Occupational exposure did not significantly increase the urinary excretion of dimethylethylamine or methylethylamine. The data indicate half lives after the end of exposure for DMEA in urine of 1.5 hours and DMEAO of three hours. The postshift summed concentration of DMEA and DMEAO in plasma and urine is a good indicator of the TWA concentration in air during the workday, and might thus be used for biological monitoring. An air concentration of 10 mg/m^3 corresponds to a urinary excretion of the summed amount of DMEA and DMEAO of 135 mmol/mol creatinine.

Amines are common in the chemical and pharmaceutical industries. Tertiary aliphatic amines are often used as catalysts in polymer production, in the synthesis of pharmaceuticals, and as pH adjusters.¹ Dimethylethylamine (DMEA), an aliphatic tertiary amine, is frequently used in foundries as a catalyst in the core making process.²

Tertiary amines used as catalysts are corrosive and are known to be local irritants that affect the eyes, the mucous membranes of the nose and throat, and the skin, and they may cause headache, nausea, and faintness.² N-methylmorpholine has been associated with bronchial hyperreactivity.³ The most frequently reported adverse effects, however, are visual disturbances.^{2,4,5} Thus experimental exposure to DMEA (40 mg/m^3)⁶ and to triethylamine (TEA; 20 mg/m^3)⁷ produced foggy vision due to epithelial corneal oedema. In the occupational setting, these effects were caused by eight hour exposure concentrations (time weighted average (TWA)) of DMEA of $1-45 \text{ mg/m}^3$ and TEA of $12-13 \text{ mg/m}^3$.⁸⁻¹¹

Tertiary aliphatic amines are absorbed through the respiratory¹² and gastrointestinal¹³⁻¹⁵ tracts, and through the skin.¹⁶ The most important route of biotransformation is oxygenation of the nucleophilic nitrogen by a flavin-containing monooxygenase (FMO; Ziegler's enzyme)¹⁷ to stable amine-N-oxides.¹⁸ The amines and their amine-N-oxides, which appear in plasma, are quantitatively excreted in urine.^{14,15} and B Ståhlbom, T Lundh, B Åkesson, unpublished data.

For trimethylamine (TMA) and TEA¹⁹ a substantial interindividual variation in the degree of oxygenation exists and an inherent deficiency of TMA metabolism is present in about 2% of a British population²⁰ (fish odour syndrome; trimethylaminuria).²¹

Evaluation of workers' exposure and risk by air sampling is difficult and expensive. Also, any absorption through the skin is disregarded. Thus there is a need for biological monitoring of occupational exposure to DMEA, as has been used for TEA.¹⁹ For DMEA, concentration of the amine and dimethylethylamine-N-oxide (DMEAO) in blood plasma and urine may be useful. This requires information, however, on the relation between occupational exposure and concentrations in biological index media and on metabolism, including interindividual variations and kinetics.

Experimental studies in four subjects showed that inhaled DMEA was readily absorbed and biotransformed into DMEAO (unpublished data). The

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average half life of DMEA in plasma was 1.3 hours and DMEAO 3.6 hours. DMEA was quantitatively excreted into the urine partly as the original amine, and 90% as DMEAO. The urinary excretion indicated a two phase pattern. The average half lives of DMEA in urine were 1.5 hours (first phase) and five hours (second phase). Those of DMEAO were 2.5 hours and seven hours. Further information on industrial exposure is needed.

As well as N-oxygenation, tertiary aliphatic amines may also undergo C-oxidative dealkylation to secondary amines,¹⁵ a toxicologically important aspect, in regard to the possibility of formation of carcinogenic nitrosamines in the case of DMEA—for example, N-nitroso-dimethylamine. It is not known whether this occurs with DMEA.

We report data here on the exposure to and metabolism of DMEA in occupationally exposed workers.

Methods

SUBJECTS

The metabolism of DMEA was studied in 12 mould core workers (mean age 38, range 23–62 years; 10 men and two women) in four different foundries. Six workers were smokers. One of the workers used metformin and glibenclamide for diabetes and metoprolol for hypertension.

PROCESS

Cores were made from a mixture of silica sand, liquid phenolic resin, and methylenediphenyl diisocyanate (MDI) in a core box machine (the Ashland cold box technique; Isocure process). The cores were cured by a few seconds of exposure to gaseous DMEA. Dry air was then blown through the core to purge any remaining DMEA. In all four foundries, the cold box machine had a standard local exhaust ventilation. Also general workroom ventilation systems were in operation. In one of the foundries, the machines were new and situated in a large production hall; the three others had older equipment in small rooms. As well as DMEA, the workers were exposed to 1,1,1-trichloroethane (TCE), waxes, and MDI.

AIR SAMPLES

The TWA exposure to DMEA was measured in each worker, in his or her personal breathing zone by absorption in impinger flasks during the full work shift (eight hours) divided into about one hour sampling periods.²²

BLOOD SAMPLING

Blood samples (20 ml) were collected by venepuncture before the start of exposure, and immediately after the end of exposure. The samples were collected (in a room free from exposure) in heparinised tubes.

After 30 minutes the samples were centrifuged (1500 g for 15 minutes), 2 ml plasma was acidified with 0.5 ml 1 M hydrochloric acid (HCl; 37%; Merck pa, Darmstadt, Germany) and stored at 4°C until analysis.

URINE SAMPLING

In all workers, urine samples were collected for 24 hours during two periods before the start of exposure (night and am before the start of work), four two hour periods during exposure, and six periods after the end of exposure (four two hour periods, overnight, and am before the start of work). The urine samples were acidified with concentrated HCl (2 ml per 100 ml urine), and refrigerated (4°C) until analysis (within three months).

ANALYSES

The analyses of DMEA and DMEAO in air samples, plasma, and urine were performed by gas liquid chromatography.²² There was no interference from the other compounds present in workroom air, blood, or urine.

The acidity of urine was determined by strip test (Acilit pH 0–6, 5–10, Merck, Germany), and the creatinine concentrations in urine were determined according to a modified kinetic Jaffé method.²³ The precision, as determined from duplicate analyses, was 5%.

Results

EXPOSURE

The mean TWA full work shift DMEA exposure concentration in the foundries studied was 3.7 (range 0.5–14) mg/m³. The concentrations of 96 one hour sampling periods ranged from 0.1 to 22 mg/m³ with no systematic trend over shifts. Lower concentrations were recorded in the foundry with new machines in a large workroom (eight hour TWA 1.3, range 0.5–2.4 mg/m³) and higher concentrations in the three with old equipment in small rooms (eight hour TWA 5.4, range 2.5–14 mg/m³). No DMEAO was detected in air samples (<0.002 mg/m³).

CONCENTRATIONS OF DMEA AND DMEAO IN PLASMA

Before exposure, the average concentrations of DMEA and DMEAO in plasma were below the detection limits (0.04 µmol/l for DMEA and 0.07 (range <0.04–0.20) µmol/l for DMEAO). Postshift the concentrations were 0.21 (range <0.04–1.0 µmol/l for DMEA) and 1.8 (range 0.3–7.2) µmol/l for DMEAO. These differences are statistically significant ($p < 0.001$; Wilcoxon's matched pairs ranked sign test). The mean DMEAO fraction of the summed amounts of DMEA and DMEAO in post-shift plasma was 91% (range 74–100%).

URINARY EXCRETION OF DMEA AND DMEAO

DMEA was readily absorbed and eliminated into urine as DMEA and DMEAO. After start of exposure, the DMEA and DMEAO excretion in urine increased until the end of exposure, and then decreased again (fig 1). The mean DMEAO fraction in the urine was 81% (range 18–93%). In the two women (sisters) studied, DMEAO fractions were considerably lower (18% and 63%), compared with the men (84–93%).

In the 12 workers studied, there was no difference in dimethylamine (DMA) concentrations in samples before (mean 16, range 8–19 mmol/mol creatine) or after (mean 13, range 8–19 mmol/mol creatine; two hours postshift) exposure. No methylethylamine (MEA) could be found in the urine sampled.

Half lives of DMEA in urine after the end of exposure had a mean of 1.5 hours (range 1.1–2.2). The average half life of DMEAO in urine was 2.9 hours (range 2.6–3.9).

PLASMA V URINARY CONCENTRATIONS OF DMEA AND DMEAO

A close correlation was found between summed concentrations of DMEA and DMEAO in plasma (postshift) and in urine (samples obtained during two hours postshift) (Spearman's rank correlation; $r_s = 0.96$, $p = 0.002$; fig 2).

EXPOSURE V PLASMA AND URINARY CONCENTRATIONS OF DMEA AND DMEAO

A close association was found between the air concentrations of DMEA on the one hand, and the postshift concentrations of the summed DMEA and DMEAO in plasma ($r_s = 0.92$, $p = 0.002$; fig 3) and the urinary excretion of the summed DMEA and

Figure 2 Relation between plasma (postshift) and urinary excretion (samples obtained during two hours postshift) of the summed DMEA and DMEAO concentrations in 12 core making workers exposed to DMEA. The regression line is shown ($Y = 25X - 6$; $r_s = 0.96$).

DMEAO during two hours postshift ($r_s = 0.91$, $p = 0.003$; fig 4), on the other.

Discussion

Exposure to DMEA at a concentration of 1–14 mg/m³ in the present workers was far below official occupational standards (Denmark and Germany, 75 mg/m³).^{24,25} Exposure to only 6–10 mg/m³ has, however, caused visual disturbances in the workers.⁹ Also, discrete ocular changes have been recorded at an exposure of about 10 mg/m³.⁶

In most subjects, the urinary DMEAO fraction was about 90%. This is in accordance with findings from experimental studies (unpublished data). The fraction is considerably larger than that of TEA¹² and somewhat lower than that of TMA.¹⁴

Two workers (sisters) had a considerably lower DMEAO fraction (18 and 63%). This was probably due to less oxygenation of DMEA to DMEAO, and not to a difference between men (84–93%) and women, as the TMAO fraction (TMAO as a percentage of summed TMA and TMAO) in urine, which occurred as a result of dietary intake of TMA precursors¹⁴ in these two women, was also lower (24 and 92%), than the expected 95% or greater.¹⁴ Thus the low fractions found in the sisters may be an inherited deficiency in oxygenation of tertiary aliphatic amines to amine-N-oxides, similar to that found in trimethylaminuria.²¹

The excretion patterns for DMEA and DMEAO found and the half lives for the concentrations in urine agree with those recorded in experimentally exposed male volunteers (unpublished data). The half life for DMEAO in the urine should be somewhat longer than the half life of the compound in the

Figure 1 Mean urinary concentrations of DMEA and DMEAO in 12 core making workers before, during, and after exposure to DMEA. The range between individual subjects is shown, DMEA to the left, DMEAO to the right.

Figure 3 Relation between DMEA exposure (eight hour time weighted air concentrations) and concentrations of summed DMEA and DMEAO in plasma (postshift) in 12 core making workers. The regression line is shown ($Y = 0.59X - 0.17$; $r_s = 0.92$).

body, as there was a continuous formation of DMEAO during the study. The excretion was rather slow and was not fully complete even by the next morning. Thus there should be a slight tendency of accumulation during the work week. Over the weekend, the body should be completely cleared of the agents. There seemed to be a two phase elimination pattern of DMEA and DMEAO in urine, although the observation time, between the end of the exposure one day and the onset of the exposure the next day, was too short for an accurate evaluation. The finding is in accordance, however, with those from an experimental study (unpublished data).

Out of the many other pollutants present in the air of the foundries, the possibility of metabolic interaction between TCE and DMEA should be considered.

Figure 4 Relation between DMEA exposure (eight hour time weighted air concentrations) and urinary excretion (samples obtained during two hours postshift) of summed DMEA and DMEAO in 12 core making workers. The regression line is shown ($Y = 15X - 10$; $r_s = 0.91$).

The TCE, however, is biotransformed by a cytochrome P-450 system, and only to a minor extent,²⁶ whereas probably the major part of DMEA is biotransformed differently by a flavin-containing monooxygenase.¹⁷ Thus an interaction of importance seems unlikely.

There was no indication of any significant demethylation of DMEA, as MEA was not detected in the urine. As to a possible de-ethylation into DMA, considerable DMA concentrations were found both before and after exposure. The main part of this DMA had probably been formed endogenously from dietary sources.²⁰ These amounts of DMA are so large, that a minor degree of de-ethylation of DMEA would be unidentified. It does not seem likely, however, that occupational exposure to DMEA would significantly increase the amount of DMA available for formation of nitrosamines. The present data accord with experimental exposure to DMEA (unpublished data), and with observations on other tertiary aliphatic amines.^{12,14} In accordance with DMA, ethylamine, probably from foods, occurred in urine samples irrespective of exposure. Thus a minor formation from the DMEA could not be excluded. Methylamine was not studied, as the sample handling and analysis were unsuitable for its determination. The presence of N-nitroso-amines in air, derived from impurities of the catalysts or formed from decomposition of DMEA in the process,²⁷ was not studied.

Theoretically, the DMEA concentration in plasma and the corresponding urinary excretion would be useful biological indices for monitoring of uptake, but the inter-individual variation of DMEA oxygenated into DMEAO was large (7–82%). Probably mainly as a result of this, neither DMEA nor DMEAO individually displayed a good correlation with DMEA concentrations in air. Thus the summed DMEA and DMEAO must be used for biological monitoring. This sum in plasma and urine displayed a close association with the air concentration. This indicates that skin absorption is not a main route of uptake, at least not in the occupational setting studied.

Both plasma and urine may be used for biological monitoring; as urine contains more than 100-fold higher concentrations, urine analyses would be simpler and more informative.

Twenty four hour urine samples are better than postshift samples, but 24 hour sampling presents practical difficulties. Instead, postshift concentrations should be used for monitoring; the excreted amounts of the summed DMEA and DMEAO in the two hour postshift samples showed a good correlation with the DMEA concentrations in air. The urinary concentrations should be corrected for the concentration of creatinine.

These data indicate that a TWA exposure of

10 mg/m³ corresponds to a concentration of the summed DMEA and DMEAO in urine of 135 mmol/mol creatinine and in plasma of 5.7 µmol/l, which are plausible as biological exposure limits. Although we have no data on heavy occupational exposure, by linear extrapolation of our results in combination with earlier observations of up to 50 mg/m³, an exposure of 40 mg/m³ would correspond to a urinary concentration of about 570 mmol/mol creatinine and a plasma concentration of about 23 µmol/l and 100 mg/m³ to about 1.4 mol/mol creatinine and 58 µmol/l. This applies to light to moderate physical work; heavy work might result in concentrations several times higher.

Mrs Else-Britt Gustavsson and Mrs Karin Paulsson supplied excellent technical help. The study was supported by a grant (88-0161) from the Swedish Work Environment Fund.

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Accepted 3 September 1990