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Evaluation of exposure biomarkers from percutaneous absorption of *N*-methyl-2-pyrrolidone

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Åkesson B, Carnerup MA, Jönsson BAG. Evaluation of exposure biomarkers from percutaneous absorption of *N*-methyl-2-pyrrolidone. *Scand J Work Environ* 2004;30(4):306–312.

Objectives The aim of this study was to evaluate different biomarkers of exposure to *N*-methyl-2-pyrrolidone (NMP), a widely used industrial chemical. For this purpose, differences in toxicokinetics between men and women and between pure and water-mixed NMP were evaluated after dermal absorption.

Methods Six female and six male volunteers (groups 1 and 2) were topically exposed for 6 hours to 300 mg of NMP. An additional group of six male volunteers (group 3) was exposed to 300 mg of NMP in a 50% water solution. Blood and urine were sampled before, during, and up to 9 days after the exposure. Plasma and urine were analyzed using mass spectrometry.

Results For groups 1 and 2, 16% and 18% of the applied dose were recovered in the urine as the sum of NMP and its metabolites. For group 3, 4% was recovered. The maximal concentration of 5-hydroxy-*N*-methyl-2-pyrrolidone (5-HNMP) was 10, 8.1, and 2.1 $\mu\text{mol/l}$ for groups 1, 2 and 3, respectively, in plasma and 420, 360 and 62 $\mu\text{mol/l}$ in urine adjusted for density. For 2-hydroxy-*N*-methylsuccinimide (2-HMSI), the maximal concentration was 5.4, 4.5, and 1.3 $\mu\text{mol/l}$ for groups 1, 2 and 3, in plasma, respectively, and 110, 82 and 19 $\mu\text{mol/l}$ in urine adjusted for density. For 5-HNMP there was a difference in time to reach the maximal concentration depending on whether pure NMP or 50% NMP in water was used. No such difference was seen for 2-HMSI. The differences in kinetics between male and female volunteers were small.

Conclusions Preferably 2-HMSI should be used as the biomarker of exposure to NMP.

Key terms biological monitoring, developmental toxicity, skin uptake, solvent.

N-methyl-2-pyrrolidone (NMP, CAS number 872–50–4) is a small cyclic amide. It is a clear liquid with a boiling point of 202°C. NMP is a strong and selective solvent and is totally miscible in water, and also in most organic solvents. It is widely and increasingly used in all kinds of industrial settings with a broad variety of applications. NMP is used as a solvent in the petrochemical industry, as a catalyst in the polymer industry, as a formulating agent for pesticides and as a cleaning and stripping agent in the microelectronics industry. It is also used as a graffiti remover (1).

NMP has been reported to be a developmentally toxic compound in rat studies (2–4). A human stillbirth after direct skin contact to an unknown level of NMP has been reported in a case report (5). Malley et al have shown that NMP may be oncogenic in mice and rats (6).

Headache and irritation of the eyes and respiratory system have been reported after occupational exposure to NMP at air levels as low as 3 mg/m³; this finding

indicates that NMP may be a moderate to severe irritant (7). Graffiti removers exposed to mixtures of NMP and glycol ethers reported headaches and irritation to the skin, eyes, and upper airways (8). However, in a study by Åkesson & Paulsson (9), volunteers experimentally exposed to 50 mg/m³ in an exposure chamber for 8 hours reported no such effects. The difference may be explained by peak exposures of NMP in the industry or cross-exposure to other substances. Some symptoms can be explained by significant dermal absorption. In rat studies, the importance of dermal NMP uptake has been shown. In these studies nose-only exposure to 1000 mg/m³ gave nasal irritation, whereas whole-body exposure caused severe effects on major organs and a massive increase in mortality (10).

It is known that the human body readily absorbs NMP in the airways (9), in the gastrointestinal tract (11), and through the skin (12). Dermal exposure was suggested to play an important role in a study performed

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on 38 Swedish graffiti removers using cleaning agents containing NMP (13).

Many fertile women are exposed to NMP in industry, and it is therefore important to develop methods for assessing NMP exposure. Today, exposure assessments are mainly based on air measurements, but such measurements are insufficient due to the high permeability of NMP through human skin. Thus biological monitoring methods should be used. A human metabolic pathway has been suggested through which NMP is first hydroxylated to 5-hydroxy-*N*-methyl-2-pyrrolidone (5-HNMP), which is oxidized to *N*-methylsuccinimide (MSI) and then further hydroxylated to 2-hydroxy-*N*-methylsuccinimide (2-HMSI). It has been shown that, in humans, about 2% is excreted as NMP, 60–65% as 5-HNMP, 0.1% as MSI, and 35–40% as 2-HMSI (11).

Analytical methods for the analysis of NMP and its metabolites have been developed (9, 14–15), and studies have suggested that 5-HNMP and 2-HMSI are suitable as biomarkers for NMP exposure (16–17). However, Åkrill and his co-workers found differences in the toxicokinetics between inhalation and dermal absorption (12). Thus it is important to establish a sampling strategy that accurately deals with both inhalation and dermal exposure.

In this work we gathered toxicokinetic data for NMP and its metabolites after the dermal absorption of pure and diluted NMP. We also investigated the possibility of a difference in absorption, metabolism, and excretion between male and female volunteers. This information was used to evaluate different biomarkers of exposure to NMP.

Participants and methods

Study design

The skin absorption of NMP in 18 healthy volunteers was studied. Undiluted NMP (300 mg) was administered topically (Finn Chamber, $2 \times 2.5 \text{ cm}^2$) on one forearm of six female (group 1, age 43–47 years) and six male (group 2, age 34–54 years) volunteers. Six other male volunteers (group 3, age 27–56 years) were exposed topically on one forearm to 300 mg of NMP in a 50% aqueous solution ($4 \times 2.5 \text{ cm}^2$). The Finn Chambers were removed after 6 hours, and the application site was washed with water. The Finn Chambers with remaining NMP were added to the swab water, which was analyzed for NMP. During the study the participants were asked about any sign of irritation, and the application site was observed for redness and dryness.

All the volunteers underwent a general health examination with special attention to the liver, kidney, and hematological conditions. The women were also tested for pregnancy before the study. None of the participants

had consumed alcohol within 24 hours of the day of the exposure, and none of them were using any kind of drug at the time of the experiment. There were no diet restrictions during the experiment. The ethics committee of the Medical Faculty of the Lund University approved the study, and all volunteers gave their written, informed consent to participate in the study.

Collection of biological samples

Blood samples were collected from the antecubital vein of the unexposed arm and collected into two 10-ml Ven-oject blood sampling tubes containing sodium heparin (Terumo Europe, Leuven, Belgium). Samples were taken on 9 consecutive days (before the exposure and 1, 2, 4, 6, 8 and 12 hours after the exposure on day 1, 24 and 30 hours after the exposure on day 2, and then every morning on days 3–9). The blood was cooled to room temperature and centrifuged at 1500 g for 15 minutes. The plasma was separated and transferred to polyethylene test tubes and frozen at -16°C until the analysis.

During 9 consecutive days, all the urine excreted was collected (after 0, 2, 4, 6, 8, 10, 12, and 16 hours after the exposure on day 1, 24 and 30 hours after the exposure on day 2, and then every morning on days 3–9). The volumes were determined, and the urine samples were then stored in 10-ml polyethylene test tubes at -16°C until the analysis. To calculate urine concentrations adjusted to urine density, we used the following formula: corrected concentration = observed concentration $\times 16 / (\text{last 2 digits of specific density})$, where 16 originates from an assumed average specific density of 1.016 (18). The mean density was 1.012, 1.016, and 1.016 for groups 1, 2 and 3, respectively. The creatinine concentrations were analyzed according to a modified Jaffe's method (19).

Analytical methods

NMP in the plasma, urine, and swab samples was analyzed according to the method presented by Åkesson & Paulsson (9). MSI in plasma and urine was determined as described by Jönsson & Åkesson (15). The metabolites 5-HNMP and 2-HMSI in plasma and urine were analyzed according to the method described by Carnerup et al (14). In an interlaboratory comparison (Round Robin; Professor Hans Drexler, Institute and Out-Patient Clinic for Occupational, Social and Environmental Medicine, University of Erlangen-Nuremberg), the results for 5-HNMP and 2-HMSI were within the tolerance limits.

Calculation of toxicokinetic parameters

On the assumption that 100% of the absorbed dose was eliminated as NMP or as one of the proposed metabolites,

Table 1. Maximal concentrations, half-times, and time spans for the calculation of the half-times of *N*-methyl-2-pyrrolidone and its metabolites in plasma and urine.

Analyte	Plasma					Urine				
	Concentration (μmol/l)		Half-time (h)		Time span (h)	Concentration ^a (μmol/l)		Half-time (h)		Time span (h)
	Median	Range	Median	Range		Median	Range	Median	Range	
<i>N</i> -methyl-2-pyrrolidone										
Group 1	7.1	5.5–44	..	..	..	10	7.8–15	2.9	2.2–4.4	5–27
Group 2	8.0	5.1–13	..	..	..	8.9	6.8–11	3.7	3.1–5.1	5–27
Group 3	5.1	0.76–33	..	..	..	1.3	0.55–1.8	3.5	2.1–5.5	11–27
5-hydroxy- <i>N</i> -methyl-2-pyrrolidone										
Group 1	10	8.4–13	6.9	4.9–10	8–48	420	290–650	4.0	1.9–5.2	9–39
Group 2	8.1	7.4–12	6.2	4.9–11	8–48	360	250–520	4.1	3.6–4.7	9–39
Group 3	2.1	0.85–2.8	5.1	4.4–9.3	12–48	62	32–100	3.4	2.4–4.7	20–39
<i>N</i> -methylsuccinimide										
Group 1	3.5	2.8–3.6	6.8	5.7–7.4	12–48	5.2	3.9–5.7	5.0	4.0–7.8	14–39
Group 2	2.4	2.0–3.1	6.4	6.0–8.0	12–48	3.7	3.2–4.5	4.4	4.0–6.0	14–39
Group 3	0.65	0.25–0.87	7.0	5.1–7.4	24–48	0.93	0.49–1.5	4.9	3.9–8.0	20–39
2-hydroxy- <i>N</i> -methylsuccinimide										
Group 1	5.4	3.8–6.8	17	16–36	24–144	110	98–170	18	11–19	27–156
Group 2	4.5	3.2–5.1	16	13–23	24–144	82	63–85	17	15–20	27–156
Group 3	1.3	0.86–1.7	21	16–36	30–120	19	11–26	18	12–22	27–156

^a Concentrations of 5-hydroxy-*N*-methyl-2-pyrrolidone and 2-hydroxy-*N*-methylsuccinimide in urine adjusted for urine density.

Table 2. Recoveries of *N*-methyl-2-pyrrolidone (NMP) and its metabolites in urine and swab water according to group.

	Urine (%)		Swab water (%)		Unrecovered (%)	
	Mean	Range	Mean	Range	Mean	Range
Group 1	16	14–17	63	60–65	21	19–24
Group 2	18	12–21	63	57–70	19	15–22
Group 3	4	2–6	83	74–93	13	3–22

the systemic dose of NMP was calculated as the total molar amount of NMP, 5-HNMP, MSI, and 2-HMSI excreted in urine. The systemic dose of 5-HNMP was calculated as the total molar amount of 5-HNMP, MSI, and 2-HMSI excreted in urine. The systemic dose of MSI was calculated as the total molar amount of MSI and 2-HMSI excreted in urine, and the systemic dose of 2-HMSI was calculated as the total molar amount of 2-HMSI excreted in urine. All the toxicokinetic parameters were calculated according to Rowland & Tozer (20). The area under the time curve for plasma concentration (AUC) was calculated using the trapezoidal rule. The renal clearance was calculated as the total amount of the analyte excreted unchanged divided by the AUC, and the total clearance was calculated as the systemic dose divided by the AUC. The linear regression slopes of the semi-logarithmic plasma concentration–time curves gave the elimination rate constants. The time spans for the determination of the linear regression slopes were fixed for the groups and are shown in table 1. The elimination half-times were then obtained from the corresponding elimination rate constants, and the volume of

distribution was calculated as the total clearance divided by the elimination rate constant.

Results

None of participants reported any kind of irritation. All of them displayed a slight redness at the site of application, which faded within 4 (range 2–6) hours. Shortly after the redness disappeared, a slight dryness occurred which disappeared within 4 (range 2–12) days.

The mean total recoveries of NMP and its metabolites in urine and of NMP in the swab water are shown in table 2. The mean amounts of unchanged NMP excreted in urine corresponded to 1–2% of the total amount excreted as NMP or the metabolites. The mean amounts were 53–58% for 5-HNMP, 1–2% for MSI, and 39–45% for 2-HMSI.

The time curves of the mean NMP plasma concentration showed an irregular pattern for the members of groups 1 and 2, but not for group 3, in which a maximal concentration was obtained after 8 hours. For 5-HNMP in plasma a peak was found 4, 6, and 12 hours after the start of exposure for groups 1, 2, and 3, respectively (figure 1). For plasma MSI the peak was reached 8 hours after the exposure for both groups 1 and 2, and after 12 hours for group 3. For 2-HMSI, the maximal concentration in plasma was obtained after 24 hours from the start of the exposure for groups 1 and 2 and after 24–30 hours for group 3 (figure 2). The semi-logarithmic plots of the time curves of the plasma concentration indicated

Figure 1. Mean 5-HNMP plasma concentrations before, during, and after the NMP exposure of six female (○) and six male (●) volunteers exposed to 300 mg of undiluted NMP and six male volunteers exposed to 300 mg of NMP in a 50% water mixture (■). The upper ranges of the standard deviations are shown.

Figure 2. Mean 2-HMSI plasma concentrations before, during, and after the NMP exposure of six female (○) and six male (●) volunteers exposed to 300 mg of undiluted NMP and six male subjects exposed to 300 mg of NMP in a 50% water mixture (■). The upper ranges of the standard deviations are shown.

Figure 3. Mean concentrations of 5-HNMP in urine (corrected for density) before, during, and after the NMP exposure of six female (○) and six male (●) volunteers exposed to 300 mg of undiluted NMP and six male volunteers exposed to 300 mg of NMP in a 50% water mixture (■). The upper ranges of the standard deviations are shown.

linear elimination patterns for all the analytes except NMP, for which it was impossible to calculate an elimination rate constant due to the irregular pattern. The median maximal concentrations and half-times in plasma are listed in table 1.

In urine a maximal peak was seen for NMP for groups 1 and 2, 2–4 hours after the start of the exposure. For group 3, a broad peak was found 8–10 hours after the start of exposure. The concentration time curve showed an irregular pattern for 5-HNMP that was not changed by adjustment for density (figure 3) or creatinine (data not shown). For MSI in urine the peak concentrations were found after 8–10 hours for groups 1 and 2, and after 12–16 hours for group 3. The levels of

2-HMSI in urine also showed an irregular pattern that was eliminated after adjustment to density (figure 4) but not to creatinine (figure 5). The semi-logarithmic plots of the time curves of the urine concentration indicated linear elimination patterns for all the analytes. The median maximal concentrations and half-times in urine are listed in table 1.

The creatinine excretion in urine was approximately 34% less for the female volunteers than for the male volunteers. Comparisons of the concentrations in female and male volunteers after creatinine and density adjustment are shown in table 3.

The median toxicokinetic parameters for NMP and the metabolites are shown in table 4.

Figure 4. Mean concentrations of 2-HMSI in urine (corrected for density) before, during, and after the NMP exposure of six female (○) and six male (●) volunteers exposed to 300 mg of undiluted NMP and six male volunteers exposed to 300 mg of NMP in a 50% water mixture (■). The upper ranges of the standard deviations are shown.

Figure 5. Mean concentrations of 2-HMSI in urine (corrected for creatinine concentration) before, during, and after the NMP exposure of six female (○) and six male (●) volunteers exposed to 300 mg of undiluted NMP and six male volunteers exposed to 300 mg of NMP in a 50% water mixture (■). The upper ranges of the standard deviations are shown.

Table 3. Comparison between the maximal concentrations of 5-hydroxy-*N*-methyl-2-pyrrolidone (5-HNMP) and 2-hydroxy-*N*-methylsuccinimide (2-HMSI) in the plasma and urine of female and male volunteers after dermal NMP exposure.

	Median maximal concentration		Difference (%)
	Women	Men	
Plasma ^a			
5-HNMP	10	8.1	24
2-HMSI	5.4	4.5	20
Urine, unadjusted ^a			
5-HNMP	240	336	−29
2-HMSI	94	90	5
Urine, creatinine adjusted ^b			
5-HNMP	41	33	25
2-HMSI	12	7.9	53
Urine, density adjusted ^a			
5-HNMP	417	355	17
2-HMSI	105	82	29

^a Unit: µmol/l.

^b Unit: mmol/mol creatinine.

Discussion

The main results of our study are the differences found in the toxicokinetics of the dermal application of pure and water-containing NMP. Moreover, we found a similarity in kinetics between male and female volunteers.

The absorbed NMP dose of the volunteers exposed to pure NMP was approximately 4–5 times higher than that of the group exposed to a 50% water mixture although the applied dose was the same and the surface area of the patch used for the 50% mixture was twice as big. Moreover, the maximal concentration of 5-HNMP was delayed about 6–8 hours in the group receiving water-mixed NMP when compared with the values of the participants who received pure NMP. This delay agrees with the results of Akrill and his co-workers (12). In their study, one hand, up to the wrist, of two volunteers was exposed to aqueous NMP solutions (5–25% NMP) for 5 to 15 minutes. A possible explanation for the decreased dermal absorption and the delay of the peak may be that NMP has a higher affinity for the water phase than for the more lipid compartments in human skin. As much as 74–93% was recovered in the swab water after exposure to water-mixed NMP. For 2-HMSI, we found no delay between the groups exposed to pure NMP and the group exposed to the 50% water mixture. Akrill et al did not analyze 2-HMSI (12).

The excretion of creatinine is affected by many factors, for example, gender, age, muscularity, pregnancy, and the like. The variation in excretion may also differ within a day and between days (18). We found a difference in the urinary levels of male and female volunteers when creatinine adjustment was used. However, this difference was diminished after adjustment for

Table 4. Toxicokinetic parameters for *N*-methyl-2-pyrrolidone, 5-hydroxy-*N*-methyl-2-pyrrolidone, *N*-methylsuccinimide, and 2-hydroxy-*N*-methylsuccinimide. (AUC = area under the time curve of the plasma concentration, CL_R = renal clearance, CL = clearance, V = volume of distribution)

Analyte	Amount excreted (μmol)		AUC (μmol · h/l)		CL _R (l/h)		CL (l/h)		V (l)	
	Median	Range	Median	Range	Median	Range	Median	Range	Median	Range
<i>N</i> -methyl-2-pyrrolidone										
Group 1	490	440–520	50	29–220	0.21	0.01–0.39	11	2.0–15	..	..
Group 2	520	370–650	53	36–120	0.11	0.05–0.54	10	3.1–18	..	..
Group 3	140	63–170	21	7.5–120	0.06	0.01–0.26	5.7	0.93–20	..	..
5-hydroxy- <i>N</i> -methyl-2-pyrrolidone										
Group 1	480	430–510	140	120–150	1.9	1.6–2.6	3.6	2.9–3.9	32	28–57
Group 2	510	370–650	130	97–170	2.4	1.7–3.2	4.0	3.0–5.2	34	27–85
Group 3	140	63–170	33	20–44	2.1	1.7–2.5	3.9	3.1–5.2	35	26–44
<i>N</i> -methylsuccinimide										
Group 1	200	170–240	58	49–63	0.15	0.11–0.24	3.6	2.9–4.1	33	26–43
Group 2	230	150–240	49	34–60	0.12	0.07–0.23	4.5	3.6–5.6	41	36–54
Group 3	63	28–87	15	6–23	0.10	0.07–0.13	4.5	3.3–5.8	44	26–60
2-hydroxy- <i>N</i> -methylsuccinimide										
Group 1	190	160–230	230	170–290	0.78	0.60–1.3	0.80	0.61–1.3	23	16–62
Group 2	220	150–240	180	130–260	1.1	0.86–1.5	1.1	0.88–1.5	28	16–35
Group 3	61	27–85	45	36–56	1.1	0.75–2.0	1.2	0.75–2.0	33	22–73

urine density. The differences between the male and female volunteers were small also for the other parameters studied. Thus, for both genders, density adjustment of biomarkers in urine seems to be more applicable than urine biomarkers adjusted for creatinine.

We used the total excreted amount of NMP plus the amount of metabolites as a measure of the systemic dose (on molar basis) when we calculated the total clearance and also the apparent volume of distribution. We made no attempts to analyze NMP or any of its metabolites in feces. It is also possible that there are more metabolites than have previously been described. Therefore, it is possible that the systemic doses used in this study were somewhat smaller than in reality. The estimation of both the total clearance and the apparent volume of distribution would therefore be somewhat low. In a study using the oral administration of NMP to three volunteers, 65% of the applied dose was recovered in urine as either NMP or its metabolites (11). In this study 13–21% of the administered amount was not recovered in the urine or swab water.

The toxicokinetics of NMP and its metabolites were similar to those previously found in a study by Jönsson & Åkesson (17). However, the larger volume of distribution for MSI that was suggested in that study was not confirmed. In addition, the half-time of about 11 hours for 5-HNMP after dermal absorption, found by Akrill et al (12), was not confirmed in our study, possibly because the NMP in the study by Akrill et al was more diluted than in our study. Therefore, there could have been a longer distribution phase in the study by Akrill et al (12) that affected the elimination rate constant.

According to previous work, there is a close correlation between the plasma levels of NMP and its

metabolites and air levels of NMP. Åkesson & Paulsson (9) suggested that NMP itself in plasma and urine be used as a biomarker, but there are disadvantages with this approach, such as an increased risk of contamination of the biological samples, a short half-time, and the small fraction excreted as NMP (9). Åkesson & Jönsson (16) have shown that there is a high correlation between the plasma and urinary levels of 5-HNMP and NMP air levels (16). The advantages with this approach are that the levels of 5-HNMP in urine are high and that there is no risk of contamination. MSI can also be used as a biomarker for NMP exposure, but, as with NMP, there are low urinary levels of MSI (21). Jönsson & Åkesson (17) have also shown a high correlation between NMP air levels and biological levels of 2-HMSI. The advantages with 2-HMSI are that the urinary levels are high and that there is no risk of contamination. Moreover, the long half-time makes it suitable for monitoring the exposure for a period of 3 days, and such a time span also compensates for irregular exposure patterns during a workday. Both 5-HNMP and 2-HMSI seem, therefore, to be highly suitable as biomarkers for the biological monitoring of NMP exposure. Moreover, Carnerup et al have developed a simple and quick method for the simultaneous analysis of the two metabolites in plasma and urine, using liquid chromatography coupled to a tandem mass spectrometer (14). However, it is also possible to analyze NMP and its metabolites by gas chromatography–mass spectrometry, a technique that is more common in analytical laboratories (9, 15, 22–23).

The concentrations presented for 5-HNMP and 2-HMSI in plasma in this paper correspond to an 8-hour NMP air exposure of approximately 10 mg/m³ for groups 1 and 2, while the values for group 3 would

correspond to an 8-hour air exposure of approximately 2–3 mg/m³ (16–17). However, the amount applied in this study was small, only 300 mg of NMP. Furthermore, the surface area exposed to NMP was tiny when compared with the whole body area, which is about two thousand times larger. Thus the impact of the dermal uptake of NMP can be very high and probably corresponds to the impact of exposure to air levels of several hundreds of milligrams per cubic meter.

In many applications in industry, workers are at risk of being exposed to mixtures of NMP with water. Because of the delay in absorption of such NMP mixtures, a proper sampling strategy must be worked out. In an inhalation study, Åkesson & Jönsson (16) suggested postshift sampling and analysis for 5-HNMP. However, in light of our results in the present study, this is not a proper method for biological monitoring. Akrill et al (12) suggested preshift sampling the day after exposure and analysis for 5-HNMP. This approach seems to be a better alternative, but it too will suffer from the differences in absorption between inhalation and dermal uptake.

We would suggest the use of 2-HMSI as the choice of biomarker for exposure to NMP. The urine or plasma sampling should take place after at least 3 days of work.

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