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THE DISTRIBUTION AND EXCRETION OF 1-METHYLNAPHTHALENE IN RATS EXPOSED TO 1-METHYLNAPHTHALENE BY INHALATION

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Abstract

Objectives: 1-Methylnaphthalene (1-MN) is a constituent of polycyclic aromatic hydrocarbons, the chemicals that have become ubiquitous in the environment as result of natural and industrial process. This paper reports a study on the distribution and excretion of 1-MN in rats after single and repeated inhalation exposure to 1-MN vapor. **Material and Methods:** Male Wistar rats were exposed to 1-MN vapor at nominal concentrations of 50 mg/m^3 or 200 mg/m^3 in the dynamic inhalation chambers (TSE Systems Head Nose Only Exposure) for 6 h (single exposure) or 5 days (6 h/day, repeated exposure). Blood, urine and tissue samples were collected during and after the exposure. Blood, urine and tissue concentrations of 1-MN were estimated by gas chromatography using the headspace technique. **Results:** The elimination of 1-MN from blood followed an open 2-compartment model. The concentration in rat tissues was dependent on the magnitude and time of exposure. After repeated exposure, the concentration 1-MN in tissue decreased in comparison to single exposure. The elimination of 1-MN with urine after single and repeated exposure to 1-MN occurred mainly in the samples collected during the first day of collection. **Conclusions:** 1-Methylnaphthalene was rapidly eliminated from the blood and tissues of animals exposed by inhalation to 1-MN. In repeated exposure, there was probably a significant increase of 1-MN metabolism in rats exposed to low and high 1-MN doses. Under conditions of repeated 1-MN exposure, no significant systemic 1-MN accumulation could be observed. Int J Occup Med Environ Health 2018;31(6):763–770

Key words:
Rats, Distribution, Inhalation, Toxicokinetics, Excretion, 1-Methylonaphthalene

INTRODUCTION

1-Methylnaphthalene (1-MN) is a constituent of polycyclic aromatic hydrocarbons (PAHs), the chemicals that have become ubiquitous in the environment as result of natural and industrial process. The extensive human exposure to 1-MN is evidenced by the fact that it is found in rock oil, petrol and Diesel fuel [1,2]. Occupational (inhalation or dermal contact) exposure is the most probable source of high levels of 1-MN derivatives in humans [3–5]. The current Polish 1-MN maximum allowable concentration (MAC) value for time-weighted average (TWA) is 30 mg/m^3 [6].

Examples of sources of low-level 1-MN exposures include ambient air in big cities, polluted drinking water and contaminated water reservoirs [3,7]. 1-Methylnaphthalene was measured concurrently in indoor and outdoor envi-

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ronment of houses at urban and roadside sites [8]. 1-Methylnaphthalene is a component of smokeless tobacco products (STPs) primarily related to health concerns associated with their use [9,10].

No studies were located that examined toxic effects in humans after inhalation exposure to 1-MN. Only fragmentary data on the toxic activity of 1-MN is accessible in the relevant literature. Neurotoxic and sensory respiratory irritation effects of 1-MN in male rats and male Balb/C mice were investigated under conditions of acute inhalation exposure [11]. Cytotoxic effects of 1-MN after intraperitoneal injection were confined to the lung of mice [12]. Pulmonary lesions restricted to the bronchiolar epithelium of rats were observed after intraperitoneal injection of 86.6 mg/kg dose of 1-MN [13]. 1-Methylnaphthalene was accumulated in skin, muscle and liver in flatfish exposed experimentally to oiled sediments [14].

Considering that only few published data from the tests on toxic 1-MN activity in laboratory animals is accessible, it is difficult to assess the hazards associated with 1-MN to human and environmental health. Studies on inhalation exposure to the category of chemicals including 1-MN are exceptionally rare notwithstanding that their systemic penetration under conditions of occupational and environmental exposure occurs primarily by inhalation.

The aim of this study has been to investigate the distribution of 1-MN in the rat after single and repeated inhalation exposure to 1-MN vapor.

MATERIAL AND METHODS

Chemicals

1-Methylnaphthalene (1-MN, CAS No. 90-12-0) was supplied by Riedel-de Hanën (Seelze, Germany). Its chemical purity was 98%.

Animal groups and collection of biological material

Male Wistar rats IMP:WIST (4 animals in each group), body weight at 234–346 g (2–3 months old), were exposed to 1-MN vapor at the nominal concentration of 50 mg/m^3 or 200 mg/m^3 in the nose-only inhalation system for 6 h (single exposure) or 5 days (6 h/day, repeated exposure). Sixty-four male Wistar rats were used in the experiment. The animals were given standard laboratory food and water *ad libitum*, except for the time when they were exposed to 1-MN vapor.

After 1-week acclimation, animals were divided into 16 treatment groups (4 rats each) and were subjected to 1-MN single or repeated exposure, and biological material was collected. Animals were decapitated immediately after termination of single or repeated inhalation exposure to 1-MN vapor and after 24 h, 48 h or 72 h. Liver, kidneys, spleen, lungs, white fat (abdominal cavity), and brain were collected from those animals. The collected samples were stored in glass vessels at –20°C.

Venous blood samples were collected from the tail vein of the animals into 100 μl heparinized glass capillary tubes before (0 h) and after (0.05 h, 0.25 h, 0.5 h, 1 h, 2 h, 3 h, 4 h, 5 h, 6 h) exposure to 1-MN vapor. The collected samples were stored at +5°C until the determination.

After termination of single or repeated inhalation exposure to 1-MN, urine samples were collected from the animals during 3 days. With repeated exposure to 1-MN, the urine samples were collected between consecutive 6-h exposures. Urine samples were collected in metabolic cages (Tecniplast). During urine collection, the animals were kept in single metabolic cages. The collected urine samples were stored in glass vessels at –20°C.

The Local Ethics Committee for Experiments on Animals approved the study protocol (opinion No. 22/ŁB 544/2011).

Inhalation and exposure monitoring

Inhalation exposure in rats was performed using the TSE Systems Head Nose Only Exposure Units (TSE Systems, Bad Homburg, Germany). Animals were exposed to 1-MN vapor in dynamic airflow of at least 15 air changes/h. During exposure, the rats were placed in glass restrainer tubes. Temperature, humidity and airflow in the head nose

exposure unit were monitored during each exposure period (TSE Daco Software). Vapor was generated by a metering unit equipped with a syringe pump and ultrasonic nebulizer. The desired concentrations of vapor were obtained by diluting them with the air.

Vapor samples (0.5 l) were absorbed on 2 ml liquid sorbent (ethyl alcohol from Polmos, Poland; concentration 95%). Concentrations of solvent vapor in the exposure chamber were measured every 30 min by gas chromatography (Hewlett-Packard 6890) with a flame ionization detector (FID) using capillary column (HP-5; 50 m×0.32 mm×1.05 μm film thickness). The operating conditions were: carrier gas – helium, constant flow mode, column flow 1.4 ml/min; make-up gas (helium) 30 ml/min; air 300 ml/min; oven 110°C; inlet split 230°C, detector 260°C.

The target exposure to 1-MN vapor concentrations was 50 mg/m^3 and 200 mg/m^3. Measured chamber concentrations during the single and repeated inhalation study (mean ± standard deviation (M±SD)) were 50.3±10.6, 53.7±4.1, 225.4±17.8 and 194.5±10.8, respectively. The relative temperature in the chamber was maintained at 20–24°C and humidity – at 39–43%.

Biological material analysis 1-MN

Blood, tissue and urine 1-MN concentrations were estimated by gas chromatography combined with the headspace technique, using naphthalene as an internal standard [15].

The gas chromatography unit (Agilent Technologies 6890N) was equipped with a mass selective detector (MSD 5973 Network). The working temperature of the capillary column (HP-5MS; 30 m×0.25 mm×0.25 μm film thickness) was 170°C. The operating conditions were: carrier gas – helium, constant flow mode, column flow 0.5 ml/min; inlet split 250°C, MS transfer line 250°C, MS source 230°C and MS quadrupole 150°C. Experimental samples were analyzed in a selected ion mode (SIM) monitoring: m/z 142 for 1-MN and m/z 128 for naphthalene.

The limit of detection of 1-MN was 0.01 μg/g of wet tissue and 0.01 μg/ml of blood or urine analysis.

Statistical analysis

An open 2-compartment model plotted with SigmaStat 1.0 for Windows (Jandel Corporation) was used for the kinetic analysis of 1-MN in blood. The differences in 1-MN blood, tissues and urine concentrations between the days of exposure were estimated using the analysis of variance (ANOVA). $P < 0.05$ was considered significant.

RESULTS

All the rats survived inhalation exposure to 1-MN. During and after the exposure, the animals did not exhibit any signs of toxicity.

Blood 1-MN concentration after a single and repeated exposure to 1-MN vapor at nominal concentrations of 50 mg/m^3 or 200 mg/m^3 and the elimination kinetics

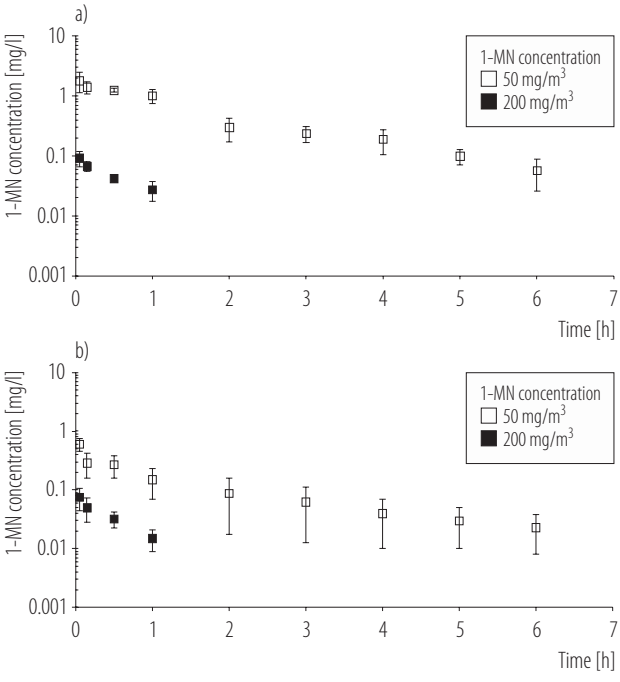


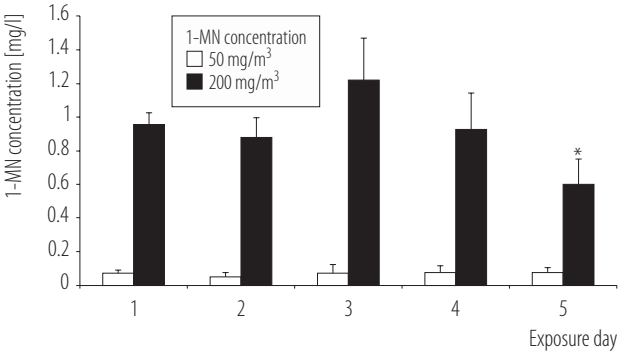
Fig. 1. Concentration of 1-methylnaphthalene (1-MN) (M±SD) in rat (N = 4 per group) blood after a) single (6 h) and b) repeated (5 days, 6 h/day) inhalation exposure to 1-MN vapor at target concentrations of 50 mg/m^3 and 200 mg/m^3

Table 1. Toxicokinetic parameters of 1-methylnaphthalene (1-MN) elimination from rat blood after single or repeated exposure to 1-MN vapor at target concentration of 50 mg/m^3 and 200 mg/m^3

1-MN concentration	Time	Elimination equation	Half-life[a] [min] (M±SD)		AUC[a] [h×mg/l] (M±SD)	
			phase I	phase II	AUC_{0-1}	AUC_{0-6}
50 mg/m^3	6 h	$E = 0.14e^{-39t} + 0.08e^{-1.09t}$	1.08±0.16	39.1±6.9	0.054±0.008	
	5 days	$E = 0.12e^{-32t} + 0.05e^{-1.08t}$	1.35±0.32	41.4±13.8	0.039±0.014	
200 mg/m^3	6 h	$E = 1.9e^{-18t} + 1.1e^{-0.40t}$	2.46±0.78	104.0±11.0		2.65±0.64
	5 days	$E = 0.9e^{-19t} + 0.27e^{-0.48t}$	2.49±0.97	89.0±17.0		0.58±0.32

M – mean; SD – standard deviation.
AUC – area under the curve.
[a] Four animals per group.

data are displayed in the Figure 1 and Table 1. The rate of elimination was calculated using an open 2-compartment model. A similar rapid decrease in blood 1-MN levels was noted between single and repeated exposures to similar concentrations of 1-MN vapor. The kinetics analysis showed that the half-lives for phase I were similar. The half-lives for phase II and the area under the curve (AUC) were dependent on the exposure level. On the other hand, the AUC values evidently show decreased blood 1-MN level after repeated exposure as compared with single exposure to 1-MN vapor at concentration 200 mg/m^3.



* Significantly different from day 1, 2, 3 and 4 of exposure at $p < 0.05$.

Fig. 2. Concentration of 1-methylnaphthalene (1-MN) (M±SD) in rat (N = 4 per group) blood during repeated inhalation exposure (5 days, 6 h/day) to 1-MN vapor at target concentration of 50 mg/m^3 and 200 mg/m^3

The Figure 2 presents 1-MN concentrations in the blood collected from tail vein during repeated inhalation exposure to 1-MN vapor. No significant differences in blood 1-MN concentrations could be detected between the consecutive days after daily 6-h exposure to low-level 1-MN. Animals exposed to high 1-MN concentrations had low blood 1-MN levels after the fifth day of exposure compared to the following days.

The distributions of 1-MN concentrations in rat tissue after single and repeated exposure to 1-MN vapor at target concentration of 50 mg/m^3 and 200 mg/m^3 are presented in the Table 2. The increase in 1-MN concentration in rat tissue was dependent on the magnitude of exposure. High levels of 1-MN were observed in fat and kidney tissue after single and repeated exposure to 1-MN vapor at 50 mg/m^3 and 200 mg/m^3. Anyway, after repeated exposure, the concentration of 1-MN in tissue decreased in comparison to single exposure. After 24 h following termination of single exposure to 1-MN at 200 mg/m^3, low concentrations of 1-MN were determined in kidney and fat, and in fat after repeated exposure.

After 72 h following termination of the exposure, 1-MN was not detected in any of the examined rat tissues.

The Table 3 presents 1-MN concentrations in the urine after single and repeated exposure to 1-MN vapor. The urine was collected during 3 days upon the end of exposure to 1-MN.

Table 2. Tissue distribution of 1-methylnaphthalene (1-MN) after single and repeated exposure to 1-MN vapor at target concentration of 50 mg/m^3 and 200 mg/m^3

Exposure time	1-MN concentration	Time	1-MN in tissues[a] [μg/g w.t.] (M±SD)					
			lungs	kidney	spleen	liver	fat	brain
After post-end exposure	50 mg/m^3	6 h	0.41±0.07	1.88±0.52	0.21±0.05	0.16±0.05	1.29±0.71	0.26±0.02
		5 days	0.06***±0.02	0.70*±0.15	0.08**±0.03	0.15±0.03	0.50±0.06	0.11*±0.01
	200 mg/m^3	6 h	1.12±0.67	8.94±2.97	1.09±0.68	2.74±0.96	12.95±8.12	1.46±1.01
		5 days	0.27±0.07	3.28*±0.23	0.37±0.05	0.48*±0.04	5.69±0.56	0.53±0.20
After 24 h post-end exposure	50 mg/m^3	6 h	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
		5 days	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
	200 mg/m^3	6 h	n.d.	0.09±0.03	n.d.	n.d.	1.42±0.78	n.d.
		5 days	n.d.	n.d.	n.d.	n.d.	1.24±0.97	n.d.

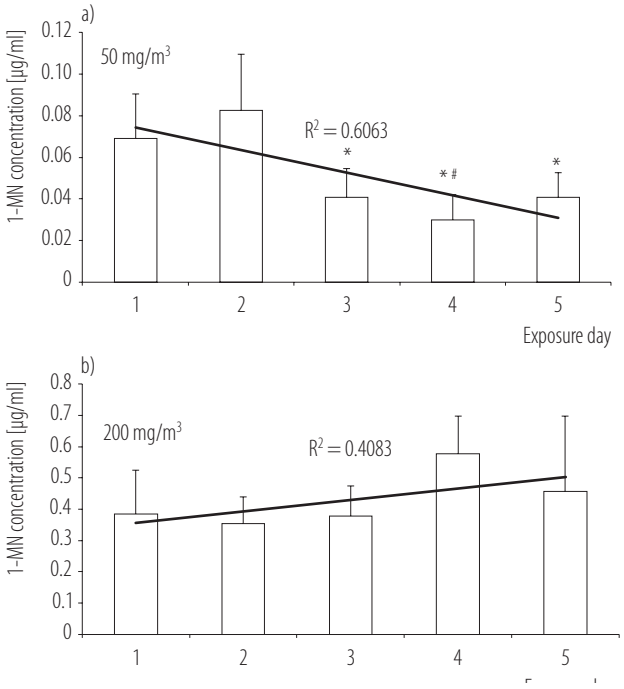
*** $p < 0.001$ vs. 6 h, ** $p < 0.01$ vs. 6 h, * $p < 0.05$ vs. 6 h.
n.d. – no data.
Abbreviations as in Table 1 and 2.

Table 3. Excretion of 1-methylnaphthalene (1-MN) with urine of rats after single and repeated inhalation exposure to 1-MN vapor at target concentration of 50 mg/m^3 and 200 mg/m^3

1-MN concentration	Time	1-MN in urine collected upon the end of exposure[a] [μg/ml] (M±SD)		
		0–24 h	24–48 h	48–72 h
50 mg/m^3	6 h	0.069[a]±0.022	0.012±0.003	0.006±0.002
	5 days	0.041±0.012	0.008±0.002	n.d.
200 mg/m^3	6 h	0.385±0.140	0.043±0.020	0.030±0.013
	5 days	0.377±0.289	0.024±0.009	0.032±0.004

Abbreviations and explanations as in Table 1 and 2.

The elimination of 1-MN with urine took place mainly during the first day of collection (about 85%). On the next days, 1-MN concentrations in urine were reduced and remained at low levels after inhalation exposure to 1-MN vapor at 50 mg/m^3 and 200 mg/m^3. Concentrations of 1-MN in the urine of rats were dependent on the magnitude and not dependent on the duration of exposure to 1-MN vapor. The Figure 3 presents 1-MN concentration in rat urine during repeated inhalation exposure to 1-MN vapor. Animals exposed to low 1-MN concentrations had higher urinary 1-MN levels after first and second days of exposure as compared to the consecutive days. The trend analysis showed a tendency to reduced 1-MN concentration in urine on successive days of exposure to 1-MN. No significant differences in urinary 1-MN concentrations were noted between the consecutive days of exposure to higher-level 1-MN. However, the trend analysis of urinary 1-MN concentration showed increasing 1-MN levels on successive days of exposure to 1-MN.



* Significantly different from day 2 of exposure at $p < 0.05$.
\# Significantly different from day 1 of exposure at $p < 0.05$.

Fig. 3. Concentration of 1-methylnaphthalene (1-MN) (M±SD) in rat (N = 4/group) urine during repeated inhalation exposure (5 days, 6 h/day) to 1-MN vapor at target concentration of a) 50 mg/m^3 and b) 200 mg/m^3

DISCUSSION

A rapid elimination of 1-MN concentration in blood was observed after single or repeated exposure to high- and low-dose of 1-MN; the trends of its elimination from blood were fairly similar. The differences in 1-MN concentration in blood were observed in the calculated AUC values. After repeated exposure to 1-MN, the AUC values were low in comparison to single exposure (Table 1). Similarly, after intraperitoneal administration of ^{14}C-labeled 2-methylnaphthalene (2-MN) to mice, the half-life of radioactivity in the blood was approximately 3 h [16].

After exposure to the second isomer of methylnaphthalene, rapidly falling 2-MN concentrations in blood were observed in rats exposed once and repeatedly by inhalation to 2-MN vapor at 200 mg/m^3 or 400 mg/m^3. Anyway, the half-lives in phase I and II of 2-MN elimination from blood were similar and did not depend on the magnitude of exposure. The AUC values evidently increased blood 2-MN level after repeated exposure as compared with single exposure to 2-MN vapor at 200 mg/m^3 [17].

The results of rotarod performance and hot-plate behavior tests of rats exposed for 4 h to vapor of 1- and 2-MN at 152–522 mg/m^3 indicated their similar neurotoxic effects. The concentration reducing the respiratory rate in mice to 50% (RD_{50}) was 129 mg/m^3 and 67 mg/m^3 for 1-MN and 2-MN, respectively [11]. The strong irritating effects of 2-MN in comparison to 1-MN were probably due to different distribution and elimination of those solvents in mice.

The half-live values after single exposure to 1-MN at the target concentration of 200 mg/m^3 were lower as compared with those observed in rats after similar exposure to 2-MN [17]. Since the concentrations of 1- and 2-MN in blood were similar, their elimination from rat blood was dependent on their pattern of release from tissues.

This report presents data on 1-MN distribution in tissues and its excretion with urine; the 1-MN was absorbed rather quickly during exposure and quickly eliminated after termination of the exposure. The elimination of 1-MN essentially ceased on the first day of tissue and urine collection. Similarly, relatively rapid turnover rate in the rat organism was recorded after a single intraperitoneal dose of naphthalene and dimethylnaphthalene isomers [18–21].

The concentrations of 1-MN in kidneys of rats after repeated exposure to 1-MN vapor at target concentration of 50 mg/m^{3}and 200 mg/m^3 decreased at a similar rate (ca. 63%) in comparison to single exposure. This may point to a reduced 1-MN retention in the lungs of the animals and activation of 1-MN metabolism during repeated inhalation exposure. Therefore, after repeated exposure to 1-MN at 50 g/m^{3}and 200 mg/m^3 1-MN concentrations were lower than 1-MN concentrations detected in the

tissues of the animals exposed to the same single 1-MN doses.

The conjecture of boosted 1-MN metabolism is also supported by reduced 1-MN removal with urine during consecutive days of the multiple exposure at 50 mg/m^3 in combination with no differences in blood 1-MN levels. Two days of exposure to 1-MN sufficed to make that its concentration in the blood of rats was lower, probably due to higher metabolism starting from the third and through subsequent days of observation, than urinary 1-MN concentration during the first and second day of the experiment. No differences were recorded in the concentration of 1-MN removed with urine during 5-day cycle of exposure to 1-MN at 200 mg/m^3. This observation suggests that the metabolic capacity of the rat became exhausted with concurrent relocation of a considerable quantity of 1-MN to the adipose tissue, thus increasing the time of 1-MN removal with urine and of 1-MN escape from the adipose tissue.

Distribution of radioactivity after oral administration of 2-[1-3H]methylnaphthalene to guinea pigs in the glad bladder and 8 organs showed the greatest quantities of 3H over a 24 h period for the kidney and the liver [22]. However, intraperitoneal administration of 1-MN to mice for 3 days did not increase microsomal N- and O-demethylase activity [23]. Selective toxicity of 2-MN in mouse lung was evidenced by elevated levels of Cyp2f2 in lung parenchyma and trachea. The Cyp2f2 may play a role in the susceptibility of the mouse to metabolically activated pulmonary toxicants [24].

CONCLUSIONS

In summary, 1-MN was rapidly eliminated from the blood and tissues of animals subjected to inhalation exposure. In repeated exposure, there was probably a significant increase of 1-MN metabolism in rats exposed to low and high 1-MN doses. Anyway, during repeated high 1-MN exposure, 1-MN metabolic capacity of the rats probably became exhausted.

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