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Chemosensory effects during acute exposure to *N*-methyl-2-pyrrolidone (NMP)

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Abstract

Organic solvents are still essential in many industrial applications. To improve safety and health in the working environment lower occupational thresholds limits have been established and less toxic substitutes were introduced. *N*-Methyl-2-pyrrolidone (NMP) is a versatile solvent that is used as a substitute for dichloromethane in paint strippers. Due to conflicting results, there is a debate whether NMP causes irritations of the upper airways/eyes or not. In a human experimental study we examined the chemosensory effects of NMP under controlled conditions. Fifteen healthy males were investigated in a cross-over study. NMP vapor concentrations were 10, 40 and 80 mg/m^3 for 2 × 4 h with an exposure-free lunch break of 30 min. To maximize chemosensory effects a peak exposure scenario (25 mg/m^3 baseline, 160 mg/m^3 peaks 4 × 15 min, time-weighted average: 72 mg/m^3) was tested. The four different conditions were conducted with and without moderate physical workload. Chemosensory effects were measured physiologically by anterior rhinomanometry, eye blink rate and breathing frequency. Subjectively, ratings of acute health symptoms and intensity of olfactory and trigeminal sensations were collected repeatedly throughout the exposures. All physiological variables were unaffected by the different NMP concentrations and even the peak exposures were non-effective on these measures. Olfactory mediated health symptoms increased dose-dependently. For these symptoms a strong adaptation was observable, especially during the first 4 h of the exposures. Other acute symptoms were not significantly affected. Comparable to the symptoms, only olfactory sensations increased dose-dependently. Trigeminal sensations (e.g. eye and nose irritations) were evaluated as being barely detectable during the different exposures, only during 160 mg/m^3 exposure peak weak and transient eye irritation were reported. The results clearly suggest that NMP concentrations of up to 160 mg/m^3 caused no adverse sensory irritation or undue annoyance.

Keywords: Sensory irritation; Eye blink frequency; Breathing frequency; Odor annoyance; Occupational exposure limit

1. Introduction

To advance safety and health in the work environment the regulation of chemicals by occupational exposure limits (OELs) is one appropriate method of disease prevention (DFG, 2006). Additionally, legislative authorities may recommend the substitution

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of particular chemicals by less toxic compounds. To improve safety and health in work environments where organic solvents are needed for technical and industrial applications the German Federal Ministry of Labor and Social Affairs recommended the substitution of dichloromethane (DCM) by other compounds in a Technical Rule for Hazardous Substances (TRGS 612). In Sweden a comparable approach exists (Langworth et al., 2001).

One frequently used substitute for DCM is *N*-methyl-2-pyrrolidone (NMP, CAS-No. 872-50-4) a cyclic amide with a weak amine-like odor. NMP is miscible with water and most organic solvents. In the work environment NMP has been used for surface cleaning such as graffiti and resin removal (Anundi et al., 1993, 2000; Bader et al., 2006; Langworth et al., 2001) or in the microelectronics industry (Beaulieu and Schmerber, 1991). The acute toxicity of NMP seems to be relatively low (Payan et al., 2002) and aside from its developmental toxicity concerns (Lee et al., 1987; Saillenfait et al., 2002, 2003) there are conflicting results concerning the irritant potency of NMP.

Sensory irritation are an important and widely used endpoint for the regulation of chemicals (Dick and Ahlers, 1998; Edling and Lundberg, 2000) and it is important to provide adequate data for the evaluation of acute health effects due to irritant exposures (van Thriel et al., 2006b).

In case of NMP, Beaulieu and Schmerber (1991) investigated an unknown number of workers at two work sites from the microelectronic industry exposed to NMP during cleaning operations. On average air monitoring revealed exposure levels of 0.1–6 mg/m^3 but in the older, poorly ventilated plant airborne concentrations of up to 276 mg/m^3 were measured. The authors reported that "... via observation and by informal interview" NMP levels between 62 and 70 mg/m^3 were evaluated by the workers as leading to "immediate perception, immediately uncomfortable . . . willing to continue exposure only for about 30 s, minor eye irritations for this short exposure time" (p. 878). Based of their observations at these workplaces Beaulieu and Schmerber concluded that sensory irritation, namely chronic eye irritation might be developed by workers exposed to as little as 3 mg/m^3 of NMP. Due to severe methodological problems, e.g. sample size not given, no personal air monitoring from the breathing zone, no psychometric scales and no statistical analysis the interpretation of the study results is difficult. There are too many confounding factors and methodological shortcomings to conclude that the reported irritations can be attributed solely to NMP at this low level.

Another workplace study (Langworth et al., 2001) investigating 38 graffiti removers in the Stockholm subway system exposed to NMP and other solvents (e.g. glycol ethers and aromatic hydrocarbons) also confirmed some irritative effects during 8 h work shifts. Due to the considerable co-exposures the higher prevalence of symptoms related to upper airway irritations among graffiti removers cannot be related to certain NMP concentrations.

In contrast to workplace studies, experimental exposure studies can address specific effects of specific substances and provide useful information for the regulation of chemicals by OELs. In the case of NMP the results of a controlled 8 h exposure study with six healthy male volunteers (Akesson and Paulsson, 1997) revealed no irritative effects at concentrations of 50 mg/m^3. Neither pulmonary function nor nasal cavity volumes were affected by the three investigated concentrations of 10, 25 and 50 mg/m^3. Only two volunteers reported an acetone-like smell during the 50 mg/m^3 condition. These odor perceptions were not described as being uncomfortable. Strong odor annoyance might be unlikely at the investigated exposure levels. Even though no irritative effects were confirmed by their study, Akesson and Paulsson (1997) concluded that NMP is a mild irritant that, at least in a concentration higher than the investigated 50 mg/m^3, might cause sensory irritation.

The existing epidemiological data (Beaulieu and Schmerber, 1991; Langworth et al., 2001) on chemosensory effects of NMP is not or hardly interpretable. In contrast, the experimental study (Akesson and Paulsson, 1997) used validated and sensitive measures of sensory irritations (Doty et al., 2004), but did not investigate concentrations as high as under discussion for OEL setting. Recently (DFG, 2006), the Commission for the Investigation of Health Hazards in the Work Area of the Deutsche Forschungsgemeinschaft (DFG) has re-established a workplace limit value (MAK-value, maximum allowable concentration in the workplace) for NMP in Germany of 20 ppm (82 mg/m^3) and a corresponding short-term exposure limit (STEL) of 40 ppm (164 mg/m^3).

The knowledge about chemosensory effects, either undue odor annoyance or sensory irritation due to occupational exposure to NMP, is far from being conclusive. To improve the database on this critical effect a comprehensive human experimental study was carried out and exposure-scenarios comparable to workplace conditions were investigated. These realistic scenarios included peak-exposures, moderate physical load, and steady-state concentrations as high as the current German MAK-value. A multilevel, multimethod approach was