Human toxicokinetics of inhaled monochlorobenzene: latest experimental findings regarding re-evaluation of the biological tolerance value

Abstract Objective: The aim of this study was to obtain toxicokinetic data on the absorption and elimination of monochlorobenzene (MCB) in blood and its main metabolite 4-chlorocatechol (4-CICat) as well as on the isomeric chlorophenols (o-CIPh, m-CIPh, and especially p-CIPh as the main CIPh metabolite) in urine for re-evaluation of the biological tolerance (BAT) value of MCB. Methods: Eight subjects performed 8-h inhalation tests daily over five successive days in an exposure chamber, at a maximum allowable concentration at the workplace (MAK) value of 10 ppm MCB. Five and two probands carried out the test series during physical activity levels of 75 and 50 W, respectively, for 10 min/h on a bicycle ergometer, and one subject was exposed continuously while at rest. MCB and its metabolites were analyzed by gas chromatography in combination with mass spectrometry. Results: The mean MCB blood concentration of the five subjects exposed during physical activity of 75 W was 217 ± 42 μg/l. The relationship of the mean blood concentration measured under the conditions of rest or 50 and 75 W activity levels was in a ratio of about 1:1.7:2.8. The half-life values in the first hour after ending the exposures were 53 min and 150 min for the ensuing period, with steady-state being reached after 45 min. The mean 4-CICat concentration in urine at the end of the five days was 150 ± 13 mg/g creatinine in the case of the subjects exposed at 75 W, which decreased to 25 mg/g creatinine at the beginning of the next exposure. The analogous p-CIPh concentrations were 25 ± 2 and 9 ± 2 mg/g creatinine. The elimination half-life values of the CIPh isomers ranged from 12.4 to 16.5 h, and the half-life of 4-CICat was 6.4 h. There was no apparent tendency for MCB and its metabolites to accumulate in blood or urine.

Conclusions: The results are in accordance with relevant field and laboratory studies. Taken into consideration with the 95th percentile, the evaluated BAT values should be set at levels of 300 μg MCB/l blood, 175 mg 4-CICat/g creatinine or alternatively at 30 mg p-CIPh/g creatinine in urine after the end of a shift. At the beginning of the next shift, the BAT values of the metabolites should be 35 and 15 mg/g creatinine, respectively.

Key words Monochlorobenzene (MCB) · Standardized long-term exposures · Toxicokinetics · MCB in blood · MCB metabolites in urine

Introduction

Monochlorobenzene (MCB), an organic solvent and chemical intermediate, is used extensively in industry. There is potential for exposure for personnel engaged in the manufacture and handling of this compound. MCB is a central nervous system (CNS) depressant. Degeneration of the liver and kidneys has been observed following absorption of toxic doses. The histopathological changes may progress as exposure becomes more severe or as the period of exposure is lengthened. Liver injury may progress to necrosis and parenchymatous degeneration [5]. Acute MCB intoxication begins, depending on the dose, with headaches and spells of dizziness, and can lead to gastro-intestinal complaints, shortness of breath, tachycardia, and circulatory insufficiency. Chronic MCB poisoning expresses itself usually with unspecific symptoms such as dizziness, somnolence and/or digestive complaints. In addition, paresthesia, a peripheral polyneuropathy, disturbances of the autonomous nervous system and a bone marrow depression can develop [16]. MCB is rapidly absorbed from the lungs. Data of skin absorption are not available. Intake via the gastrointestinal tract occurs and is probably increased in the presence of fats or oils [5]. In humans, MCB is metabolized to 4-chlorocatechol (4-CICat) and to the o-, m- and p-isomers of chlorophenol (o-CIPh, m-CIPh and...
The glutathione adduct 4-chlorophenyl mercapturic acid has only been detected in comparatively small amounts [21, 22]. The metabolism of MCB is presented in Fig. 1.

Occupational exposure to MCB is generally monitored by measuring the concentration in air and comparing it with the maximum allowable concentrations at the workplace (MAK). In addition to this, measurement of the MCB metabolite 4-ClCat in urine of occupationally exposed workers has been proposed as a biological monitoring method that takes into consideration the biological tolerance (BAT) value established for this compound. In Germany, the BAT value for occupational exposure to MCB was last set in 1992. The MAK value of 50 ppm valid at that time served as the basis. The BAT value amounted to 300 mg total 4-ClCat/g creatinine at the end of exposure or shift and 70 mg 4-ClCat/g creatinine at the beginning of the next shift, and was based on the relationship between external and internal exposure. The correlation was derived in the first place from an experimental study performed by Ogata et al. [23] and should be regarded as provisional due to the limited database [12].

More recently, liver and kidney were the main target organs after repeated exposure of animals to MCB at levels of up to 50 ppm, and human subjects showed subjective discomfort such as headache and somnolence after short-term exposure to 60 ppm MCB [7]. Therefore, in 1995 the MAK value was reduced to 10 ppm [6]. The discrepancy between the current MAK value and the original BAT value thus requires a re-evaluation of the latter threshold.

The objective of the present study was to evaluate additional data for biological monitoring of MCB exposure and to expand existing knowledge of the toxicokinetics in order to establish BAT values for this compound. For that purpose we have carried out laboratory studies with volunteers who were exposed to MCB at the current MAK value. In contrast to the study of Ogata et al. [23] we have taken into consideration the influence of physical workload on the conception of the BAT value [14].

**Material and methods**

**Subjects**

Eight volunteers (six male and two female) with an average age of 29 years (range 22–56) participated in this study. All were considered healthy according to routine medical examinations before the start of the experiment. The subjects were not occupationally exposed to solvents and were instructed to avoid any contact with organic solvents and to refrain from drinking alcoholic beverages or taking any medication before, during, and at least two days after the exposure session. The experiments were approved by the Ethical Committee of the Justus-Liebig-University, Giessen, Germany. The study was performed only with informed consent of the

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**Fig. 1** Main metabolic pathways of monochlorobenzene (MCB) [22]