Occupational exposure to hexahydrophthalic anhydride: air analysis, percutaneous absorption, and biological monitoring

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Summary. Urinary hexahydrophthalic acid (HHP acid) levels were determined in 20 workers occupationally exposed to hexahydrophthalic anhydride (HHPA) air levels of 11–220 µg/m³. The levels of HHP acid in urine increased rapidly during exposure and the decreases were also rapid after the end of exposure. The elimination half-time of HHP acid was 5 h, which was significantly longer than in experimentally exposed volunteers, possibly indicating distribution to more than one compartment. There was a close correlation between time-weighted average levels of HHPA in air and creatinine-adjusted levels of HHP acid in urine collected during the last 4 h of exposure \((r = 0.90)\), indicating that determination of urinary HHP acid levels is suitable as a method for biological monitoring of HHPA exposure. An air level of 100 µg/m³ corresponded to a postshift urinary HHP acid level of ca. 900 nmol/mmol creatinine in subjects performing light work for 8 h. Percutaneous absorption of HHPA was studied by application of HHPA in petrolatum to the back skin of three volunteers. The excreted amounts of HHP acid in urine, as a fraction of the totally applied amount of HHPA, were within intervals of 1.4%–4.5%, 0.2%–1.3%, and 0%–0.4% respectively, indicating that the contribution from percutaneous absorption is of minor importance in a method for biological monitoring.

Key words: Hexahydrophthalic anhydride – Hexahydrophthalic acid – Urine – Skin absorption – Biological monitoring

Introduction

Hexahydrophthalic anhydride (HHPA) is used as a hardener in epoxy resins. HHPA-epoxy resins have good properties regarding chemical resistance, electrical insulation, and adhesive strength. HHPA has also been used in the manufacture of alkyd and polyester resins, insecticides, and rust preventives.

HHPA is a sensitizing compound even at very low exposure levels (Welinder 1991). HHPA has been reported to cause occupational asthma and allergic rhinitis (Moller et al. 1985; Nielsen et al., unpublished). In addition, it is an irritant to the eyes and the mucous membranes of the respiratory tract (Venables 1989).

Gaseous HHPA is rapidly and completely absorbed from the respiratory tract, is distributed in the body, probably as hexahydrophthalic acid (HHP acid), in a relatively small volume (Jönsson and Skerfving 1993), and is almost completely excreted as unconjugated HHP acid in the urine (Pfäffli et al. 1989; Jönsson and Skarping 1991; Jönsson and Skerfving 1993). The half-time of HHP acid has been estimated to be 14 h (Pfäffli et al. 1989) and 2–3 h (Jönsson et al. 1991a; Jönsson and Skerfving 1993). Variations in urinary pH do not significantly affect the excretion of HHP acid (Jönsson and Skerfving 1993).

The adverse effects of HHPA require methods for exposure control in the work environment. Methods for determination of HHPA in air have been described (Jönsson et al. 1991b; Jönsson et al., unpublished). However, methods for biological monitoring offer several advantages as a complement to air monitoring. Thus, biological monitoring considers variations in the individual pulmonary ventilation. Moreover, it may also supply important information on the efficiency of respiratory protection devices. There are results indicating that inhalation exposure to HHPA may be determined by monitoring HHP acid in urine (Jönsson et al. 1991a; Jönsson and Skarping 1991; Jönsson and Skerfving 1993) and in plasma (Jönsson and Skerfving 1993).

In addition to absorption by inhalation, percutaneous absorption must be considered in risk assessment of occupational exposure. Thus, if a chemical absorbed through the skin generates the same adverse effects as when inhaled, a method for biological monitoring of the exposure is certainly preferable to surveillance by air levels.
However, if the chemical is less toxic when absorbed percutaneously, a method for biological monitoring will overestimate the risk of the exposure.

Here we report urinary levels of HHP acid in workers occupationally exposed to varying levels of HHPA in air. In addition, urinary levels of HHP acid after percutaneous absorption of HHPA are described.

Materials and methods

Subjects. Twenty workers (19 males and 1 female) participated in the study. Their average age was 40 (range 19-62) years and their weight ranged from 55 to 96 kg. Nine were smokers. None had a history of kidney disease.

Production and exposure. The workers were from two different plants. In plant A, electrical capacitors were manufactured. In addition to HHPA, the workers were exposed to methyltetrahydrophthalic anhydride, benzylidinemethyamine, epoxy resins (epichlorohydrin based), and acetone. In plant B, ignition systems for cars, motor saws, and lawn mowers were manufactured. In addition to HHPA, the workers were exposed to methylhexahydrophthalic anhydride (MHHPA), acetic anhydride, benzylidinemethyamine, epoxy resin (epichlorohydrin based), and acetone. In both plants the devices were mechanically fixed and electrically isolated by an epoxy resin using HHPA as a hardener. Most work was performed in closed systems or ventilated hoods, but some operations involved handling mixtures with uncured HHPA at elevated temperatures (ca. 40°-70°C). The lengths of the work-shifts were 8 h in both plants and the work load was rather light. All workers had been exposed to HHPA on the day before the monitoring.

Air sampling. Air levels of HHPA were determined by sampling on Amberlite XAD-2 tubes (Cat no 226-30, SKC, Eighty Four, Pa., USA; Jönsson et al. 1991b). The tubes were placed in the workers' breathing zone. Sampling was usually performed at 2-h intervals during the whole work-shift, but when low exposure levels were expected 4-h sampling intervals were used. The sampling rate was 200 ml/min. The XAD-2 tubes were stored in a freezer at −20°C until analysis, which was undertaken not more than a week after sampling.

Urine sampling. Urine was collected from 15 workers immediately before the start of the work-shift and then after 4, 8, 12, 15, 23, and 24 h. All urine during this time was collected. In four of the workers, urine was collected on two different occasions. In addition, urine was collected during the last 4 h of the work-shift from ten workers. Five of these were among the 15 previously mentioned workers. The concentration of creatinine in urine was determined by a modified Jaffe's method (Lustgarten and Wenk 1972). The urine was collected in polyethylene bottles and stored in a freezer at −20°C until analysis.

Analyses. The analyses of HHPA (cis-form; Merck, Darmstadt, Germany) in air were performed by gas chromatography with flame-ionization detection, as previously described (Jönsson et al. 1991a). The limit of detection was 3 μg HHPA/m³ (sampling volume 60 l). Analyses of HHP acid in urine were performed by gas chromatography with mass-selective detection, as reported earlier (Jönsson and Skerfving 1993). The limit of detection was 0.1 nmol/ml urine.

Study of percutaneous absorption. Three healthy male volunteers, aged 22, 32 and 51 years, participated in the study. Their weights were 70, 90, and 90 kg, respectively. They were negative in a RAST assay of specific IgE antibodies to a conjugate between HHPA and human serum albumin (HSA; Welinder and Nielsen 1991) before and 3 weeks after the provocation. The study was performed as epicutaneous skin tests using the Finn Chamber technique. Altogether, 1.4 mg HHPA in a 2% petrolatum mixture was applied in four chambers with a total area of 2.0 cm². The chambers were attached with adhesive to the back skin and removed after 48 h. All urine was collected for 72 h at 4-h intervals. The urine was stored in a freezer at −20°C and analyzed as previously described (Jönsson and Skarpering 1991).

Toxicokinetic calculations. The elimination half-time of HHP acid was calculated by linear regression from diagrams of the natural logarithm of the excretion of HHP acid in urine versus 17 h postexposure time. The midpoints of the time intervals were used.

Statistical evaluation. For the determination of the correlation between pairs of variables, the correlation coefficient (r) was used. This gave a view of the associations, although all observations were not independent. For comparison between the means of two groups, the unpaired t-test was used. The P values were two-tailed and statistical significance was set at P < 0.01.

Results

The time-weighted average (TWA) levels of HHPA in air were 109 (range 28–220) μg/m³ in plant A and 31 (range 11–83) μg/m³ in plant B.

The levels of HHP acid in urine increased rapidly during exposure and the decays were also rapid during the postexposure period (Fig. 1). Only one worker, exposed to 11 μg HHPA/m³, had urinary HHP acid levels below the detection limit on the morning after the monitored exposure. The elimination half-time for HHP acid in the chronically exposed workers was 5 h (CV = 49%, n = 19), which differed statistically significantly from the half-time of 3 h calculated in the same way in briefly HHPA exposed volunteers. These volunteers were exposed in an exposure chamber to levels between 10 and 80 μg HHPA/m³ (Jönsson and Skerfving 1993). There was no statistically significant difference in the volume of urine between the two groups.

There was a close correlation (r = 0.91, n = 29) between TWA levels of HHPA in air and creatinine-adjusted levels of HHP acid in urine, collected during the