A Cross-Sectional Survey of 32 Workers Exposed to Hexahydrophthalic and Methylhexahydrophthalic Anhydrides

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Abstract: The relation between exposure and sensitization or the appearance of symptoms of the eyes and airways was investigated in a cross-sectional study on 32 workers from a plant using epoxy resin with a mixture of hexahydrophthalic anhydride (HHPA) and methylhexahydrophthalic anhydride (MHHPA) as a hardener. The main component in the hardener was HHPA, and the geometric mean concentrations of HHPA in the workplaces were extremely low (<40 µg/m³) in recent years, compared to the Occupational Exposure Limit-Ceiling for phthalic anhydride (2 mg/m³). However, specific IgE antibody to HHPA was detected in serum from 8 (25%) out of the workers: of those, 5 workers experienced symptoms of the eyes and nose during work (group sensitized symptomatic (SS)) and 3 workers did not (group sensitized nonsymptomatic (SN)). The other 24 workers had no signs of sensitization and did not complain of work-related symptoms. Based on occupational history and anamnestic data, it was concluded that one subject in the SS group and all the subjects in the SN group had been sensitized by higher exposures in the past. The symptoms of 4 subjects in the SS group occurred only when carrying out short-time, particular tasks (15–30 min) a few times a day, such as the resin mixing procedures, manual application of the resin, or opening of ovens. High peak exposures were estimated to have occurred during the particular tasks. Our results suggest that short-time peak exposures may have a great impact on the development of specific IgE or work-related symptoms. Therefore, to minimize the risk of sensitization and work-related symptoms, a reduction of exposure during particular tasks with high peak exposures, along with a decrease in mean 8-h time-weighted average exposure, should be achieved.

Key words: Exposure-response relationship, Hexahydrophthalic anhydride, Methylhexahydrophthalic anhydride, Occupational allergy, Asthma, Rhinitis, Specific IgE

Introduction

Since epoxy resins have good adhesive strength, electrical insulation, and chemical resistance, they are widely used in adhesives, coatings, materials for molds and composites, and encapsulation. In the electronic components industry, methyltetrahydrophthalic anhydride (MTHPA) or a mixture of hexahydrophthalic anhydride (HHPA) and methylhexahydrophthalic anhydride (MHHPA) is used as a hardener in an epoxy resin system for electric insulation and protection, and typically requires a high curing temperature (100–150°C) which facilitates the escape of anhydride vapours. On the other hand, adverse health effects of occupational exposure to acid anhydrides are mucosal and skin irritation and sensitization of the respiratory tract1). MTHPA, HHPA, and MHHPA have been reported to induce IgE-mediated respiratory allergy, including asthma2–8). Therefore, safe use in industry demands control of the level of exposure causing allergic diseases in the workshop. However, exposure-response investigations providing data
upon which occupational exposure limits may be based are few. In the present investigation, the relation between exposure and sensitization or the appearance of symptoms of the eyes and airways in workers exposed to HHPA and MHHPA (Fig. 1) were investigated in a cross-sectional study.

Subjects and Methods

Production and subjects
Thirty-two workers in a plant manufacturing light-emitting diodes (LEDs) for portable telephones were studied by questionnaire and serologic investigations in November, 2000. An epoxy resin system with a mixture of HHPA and MHHPA as a hardener was located in three separate sections of the plant where the LEDs were encapsulated in the epoxy resin mixture for protection. The amounts of the hardener used in a month in workplaces A, B, and C were about 1800 kg, about 60 kg, and about 15 kg, respectively. According to the material safety data sheet, the main component in the hardener is HHPA, but MHHPA has also been used as an added ingredient to HHPA. In workplaces A and C, the encapsulation process was made by use of two big enclosed epoxy coating and hardening systems and one small system of that type, respectively. Air of the workplaces was contaminated by the anhydride vapor from the curing ovens (temperature 100–150°C). In workplace B, the encapsulation process consisting of the coating department and the hardening department, it was made by use of five small enclosed epoxy coating systems, and coated LEDs were transported to curing ovens by workers. It was visually demonstrated by smoke tubes that air currents from the hardening department flowed to the coating department. All exposed workers were involved in monitoring work, the resin mixing procedure, or both.

Medical examination
The subjects completed a questionnaire about symptoms (from the eyes, nose, and lower respiratory tract), their relation to work, atopic history, smoking status, duration of exposure, and occupational history. After that, a physical examination was performed by a physician (KY), and venous blood samples were obtained with informed consent for serologic investigations. Rhinitis, conjunctivitis, or asthma in the workplace more than twice a week, with no complaints at the weekends or during holidays, were evaluated as indicating work-related symptoms.

Antibody determinations
Serum samples were stored frozen at –20°C. On the day of measurement, the samples were thawed at room...
temperature before use.

Atopy: The Pharmacia CAP system (Pharmacia, Uppsala, Sweden) was used according to the manufacturer’s instructions to measure specific IgE to Japanese cedar, house dust, and house dust mite. Diagnosis of atopy was based on positive specific IgE to at least one of the three allergens tested.

Specific IgE determinations: Immunocaps with a human serum albumin (HSA) conjugate of MHHPA and of HHPA were not commercially available (Pharmacia). However, immunocaps with the HSA conjugate of HHPA were provided via the special laboratory service by Pharmacia Diagnostics. HHPA-specific IgE levels were measured by the CAP system, and specific IgE values of >0.35 UA/ml were considered positive.

Air sampling and analysis
The measurement of HHPA and MHHPA in workplaces A and C has been made once a year since 1996 and that in workplace B since 1998. N=number of measurements; HHPA=hexahydrophthalic anhydride; MHHPA=methylhexahydrophthalic anhydride. *Significant vs workplaces B (p<0.05) and C (p<0.0002).
**Significant vs workplaces B (p<0.01) and C (p<0.01). ***Significant vs workplace C (p<0.02).

Statistics
Differences were tested by ANOVA with the PLSD test, unpaired Student’s t test, χ² test, or Fisher’s exact test. These analyses were conducted using the SPSS/PC statistical package (SPSS Inc., Chicago, IL, USA). P values of <0.05 were considered significant.

Results
The results of the ambient air monitoring are shown in Table 1. In workplace A, HHPA composed 68% of the anhydride exposure. The figure in workplaces B and C was 84% and 43%, respectively, mainly depending on the anhydride content of the hardener used in each workplace. The geometric mean concentration of HHPA was significantly (p<0.05) higher in workplace A than in the other two workplaces, and significantly (p<0.02) higher in workplace B than in workplace C. Similarly, the geometric mean concentration of MHHPA was significantly (p<0.01) higher in workplace A than in the other two workplaces. These results reflect the difference in the amounts of the hardener used among the three workplaces. The curing ovens leaked up to 15.6 mg HHPA/m³ and 4.3 mg MHHPA/m³ in workplace A, and 7.9 mg HHPA/m³ and 2.5 mg MHHPA/m³ in workplace C. In workplace B, measurements performed at the center of the hardening department showed a HHPA geometric mean concentration of 147 (72–318) µg/m³ (number of measurements=3), when the corresponding MHHPA concentration was 5.5 (5.0–34) µg/m³.

Table 2 shows personal data, rate of participation, duration of exposure, and rate of atopics and sensitization of the workers in workplaces A, B, and C. The differences in smoking habits, age, rate of atopics, and rate of sensitization were not statistically significant. The duration of exposure tended to be shorter in workplace B compared with the other two workplaces, due to recent job rotation of part of the workers. All the specific IgE values for 10 nonexposed subjects were <0.35 UA/ml.

Eight (25%) of the 32 workers tested had positive HHPA-specific IgE. Clinical and immunologic details of the sensitized subjects are shown in Table 3. The sensitized workers had higher frequencies for eyes and nose than did the unsensitized workers (63% vs 0%; p<0.0005). The

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**Table 1. Results of ambient air monitoring (stationary air sampling) in the three workplaces during 1996 to 2000**

<table>
<thead>
<tr>
<th>Anhydrides used at the workplaces</th>
<th>Workplace A</th>
<th>Workplace B</th>
<th>Workplace C</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N/geometric mean/range (µg/m³)</td>
<td>N/geometric mean/range (µg/m³)</td>
<td>N/geometric mean/range (µg/m³)</td>
</tr>
<tr>
<td>HHPA</td>
<td>5/33.0/24.0–62.4*</td>
<td>3/12.0/4.6–25.0***</td>
<td>5/3.8/1.9–7.0</td>
</tr>
<tr>
<td>MHHPA</td>
<td>5/15.8/7.0–52.8**</td>
<td>3/2.3/2.0–3.0</td>
<td>5/5.1/3.4–7.0</td>
</tr>
</tbody>
</table>

*The measurement of HHPA and MHHPA in workplaces A and C has been made once a year since 1996 and that in workplace B since 1998. N=number of measurements; HHPA=hexahydrophthalic anhydride; MHHPA=methylhexahydrophthalic anhydride. *Significant vs workplaces B (p<0.05) and C (p<0.0002). **Significant vs workplaces B (p<0.01) and C (p<0.01). ***Significant vs workplace C (p<0.02).
IgE Antibody Against HHPA and Symptoms

Median latency time was 5 (range 1–10) months. None of the subjects had yet had symptoms of work-related asthma. Five (63%) of the sensitized workers were atopics compared with nine (38%) of the unsensitized workers, and the corresponding figures for smoking were 75% and 42%, respectively. The differences were not statistically significant.

Discussion

In spite of the fact that HHPA and MHHPA have been used for decades in the industry, no occupational exposure limits (OELs) have been established for the two acid anhydrides in air. The geometric mean concentrations of the two acid anhydrides in the three workplaces were fairly low during the period between 1996 and 2000 (Table 1), compared to the OEL-C for phthalic anhydride (2 mg/m³). The concentrations were below the OEL value for trimellitic anhydride (40 µg/m³). However, a prevalence of 25% of workers with HHPA-specific IgE was found in a group of 32 workers from a plant manufacturing light-emitting diodes. Data are given in this report only on specific IgE antibodies to HHPA, although the workers have been exposed to MHHPA as well. However, data from previous studies show a very close correlation between HHPA and MHHPA in RAST and skin-prick tests, probably due to cross-reactivity.

In this study, the workers were investigated in 2000, and no measurements of the exposure levels were performed before 1996. The number of sensitized workers may be attributable to higher exposures in the past. In addition, no exposure-response relationships were found in the formation of specific IgE antibodies to HHPA in exposed workers (Table 2); a healthy worker selection may have occurred. Hence, the interpretation of the results from cross-sectional studies must be handled carefully.

In workplace A, the epoxy system has been used since 1982. The main exposure originates from leaks from the curing ovens. Work-related symptoms of the eyes and nose were frequently reported until 1991, and some workers with severe rhinitis were moved to work with no exposure. Therefore, local exhaust ventilation on the air vents of the

### Table 2. Personal data, duration of exposure and prevalence of atopy and sensitization among workers investigated in the three workplaces

<table>
<thead>
<tr>
<th>Workplace</th>
<th>A</th>
<th>B</th>
<th>C</th>
</tr>
</thead>
<tbody>
<tr>
<td>Persons exposed (n)</td>
<td>17</td>
<td>13</td>
<td>5</td>
</tr>
<tr>
<td>Persons examined (n)</td>
<td>16 (94)</td>
<td>11 (85)</td>
<td>5 (100)</td>
</tr>
<tr>
<td>Female (n)</td>
<td>6</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Current smokers (n)</td>
<td>6 (38)</td>
<td>8 (73)</td>
<td>2 (40)</td>
</tr>
<tr>
<td>Age (years, mean (range))</td>
<td>46 (37–56)</td>
<td>40 (24–58)</td>
<td>44 (37–51)</td>
</tr>
<tr>
<td>Duration of exposure (years, mean (range))</td>
<td>12.6 (0.7–21)*</td>
<td>4.1 (0.2–19.5)</td>
<td>8.8 (4–18.8)</td>
</tr>
<tr>
<td>Atopics (n)</td>
<td>7 (44)</td>
<td>5 (45)</td>
<td>2 (40)</td>
</tr>
<tr>
<td>Positive HHPA-specific IgE (n (%))</td>
<td>3 (19)</td>
<td>4 (36)</td>
<td>1 (20)</td>
</tr>
</tbody>
</table>

* Values of >0.35 UA/ml were considered positive. * Significant vs workplace B (p<0.005).

### Table 3. Details of eight workers with positive specific IgE and/or occupational symptoms

<table>
<thead>
<tr>
<th>Workplace</th>
<th>Worker No</th>
<th>Atopy</th>
<th>Smoked</th>
<th>HHPA (UA/ml)</th>
<th>Occupational symptoms</th>
<th>Exposure time to onset (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>2</td>
<td>+</td>
<td>Yes</td>
<td>0.44</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td>13</td>
<td>–</td>
<td>Yes</td>
<td>0.51</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td>16</td>
<td>+</td>
<td>No</td>
<td>0.91</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>B</td>
<td>20*</td>
<td>–</td>
<td>Yes</td>
<td>21.2</td>
<td>+</td>
<td>10</td>
</tr>
<tr>
<td></td>
<td>23</td>
<td>+</td>
<td>Yes</td>
<td>1.10</td>
<td>+</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>26*</td>
<td>+</td>
<td>Yes</td>
<td>26.0</td>
<td>+</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>27*</td>
<td>–</td>
<td>Yes</td>
<td>27.0</td>
<td>+</td>
<td>10</td>
</tr>
<tr>
<td>C</td>
<td>32*</td>
<td>+</td>
<td>No</td>
<td>1.93</td>
<td>+</td>
<td>4</td>
</tr>
</tbody>
</table>

curing ovens was installed in 1992, with the result that the hygiene conditions at the workplace were improved (Table 1). Of the evaluated workers, 3 (19%) were sensitized against HHPA, but displayed no work-related symptoms (Table 3). They had been exposed, on average, for 18.8 years. None of the six workers assigned to the workplace after 1992 showed evidence of sensitization. Hence, higher exposures were estimated to have occurred among workers from 1982 to 1991. A geometric mean exposure to <40 µg/m³ may protect workers from the significant risk of sensitization or ocular and respiratory effects.

By contrast, in workplaces B and C, exposure levels were estimated to have remained unchanged since the beginning of production (Table 1), because no major changes in the production process or ventilation systems occurred. The geometric mean concentrations were comparable with the exposure limit for HHPA recommended by Welinder et al. for protection against sensitization (permissible average exposure level 20 µg/m³), but the sensitization was found. In workplace C, worker 32 was the only one who had positive HHPA-specific IgE. This worker had worked in workplace A in 1982–1986 and since 1995 in his present job. In 1982 he experienced the first symptoms of rhinitis after 4 months’ exposure and improved when moved to no exposure jobs. It seems evident that at that time he had been sensitized. After transfer to workplace C, he displayed rhinitis symptoms only when mixing liquid epoxy resin on the hotplate (temperature 65°C) and washing dishes for holding the resin. On the other hand, in workplace B, specific IgE to HHPA was detected in 4 (36%) of the workers, who developed their symptoms within a year (Table 3). Their mean period of exposure was 1.1 (range 0.6–2) years. All of them except worker 23 displayed work-related symptoms only when they carried out short-time, particular tasks (15–30 min) a few times a day, such as the resin mixing and dishwashing procedures, manual application of the resin, or opening of ovens. Although airborne exposure during the particular tasks has not yet been measured, the present results show the possibility that sensitization and work-related symptoms were caused by high peak exposures.

There are conflicting reports on the effects of atopy and smoking on the formation of specific IgE antibodies in workers exposed to acid anhydrides. In this study, no effects of either atopy or smoking habits were found on the findings of sensitized subjects. Further extensive studies are required to assess conclusively the effects of these factors.

In summary, sensitization showed a strong association with work-related symptoms (p<0.0005), almost certainly due to the short-time, particular tasks. Welinder et al. stated that 5 of 7 workers positive for HHPA-specific IgE in the group with lowest exposures reported frequent short-time (minutes per day) exposures exceeding 50 µg/m³. In our previous study of a condenser plant using MTHPA, no significant differences were found in the frequency of positive specific IgE or work-related symptoms between workers continuously and intermittently exposed. These findings indicate that short-time peak exposures may have a great impact on the development of specific IgE or work-related symptoms. Hence, to minimize the risk of sensitization and work-related symptoms, a reduction of exposure during particular tasks with high peak exposures, along with a decrease in mean 8-h time-weighted average exposure, should be achieved.

References

in air using gas chromatography with electron-capture detection. Ind Health 37, 364–8.


