Do amines induce occupational asthma in workers manufacturing polyurethane foams?

A number of amines have been described as causing occupational asthma.1–5 Recently, Belin and his coworkers suggested that amines, particularly of N-methylmorpholine, might be causative agents in the development of bronchial hyperreactivity in workers manufacturing polyurethanes from isocyanates.6 They studied this problem in 1974,7 focusing particularly on toluendiamine (TDA) which is formed when toluendisocyanate (TDI) comes into contact with water; it is also formed during the chemical processes by which polyurethane foams are produced (fig).

We considered that this TDA might play a part in inducing occupational asthma, and in order to evaluate this possibility 12 subjects occupationally exposed to polyurethane foams and complaining of symptoms of wheezing and breathlessness at work were submitted to a bronchial provocation test with methacholine, TDI, and TDA.

The methacholine test was carried out by administering doses in the range 20–2000 μg by a dosimeter (MEFAR), thus establishing a dose-response curve.8 Sensitivity to methacholine was expressed as the dose of methacholine provoking a 15% fall in the forced expiratory volume in one second (PD15, FEV1) measured by means of a bell spirometer (Volumograph). The TDI challenge was performed by exposing the subject for 15 minutes to an atmosphere containing 0.01 ppm of TDI in an inhalation chamber.9 The test was considered positive when a 15% fall in FEV1 was found after exposure.

Exposure to TDA was carried out in the same chamber on two different days. The amine concentrations to which the subjects were exposed were: on the first day, 1.31 mg/m³ and on the second day 3.21 mg/m³, being the theoretical concentrations of amine corresponding (through chemical reduction) to atmospheric TDI concentrations of, respectively, 0.07 mg/m³ (0.01 ppm) and 0.14 mg/m³ (0.02 ppm).

The table shows the results of our study. A high sensitivity to methacholine was shown in 10 subjects (PD15, FEV < 1000 mcg); subjects 8 and 9 responded to higher doses of methacholine (1320 and 1840 μg) but lower than the minimum dose (2000 μg) at which the normal subjects respond.

All the subjects had positive reactions to TDI but none responded to TDA.

These data do not support the view that TDA produces asthma in workers exposed to polyurethane foams; the agent which provokes their respiratory symptoms appears to be TDI.

The reactivity of TDI with organic compounds is probably so high and so rapid that the onset of

```
\begin{align*}
\text{CH}_3 & \quad N=C=O \\
\text{CH}_3 & \quad \text{H}_2 \text{O} \rightarrow \text{2CO}_2 \quad \text{CH}_3 & \quad \text{NH}_2 \\
\text{2,4-toluendiisocyanate} & \quad \text{2,4-toluendiamine} \\
\text{(from Candura, 1974)} & \\
\end{align*}
```

Production of TDA from TDI during the formation of polyurethane foams.

---

**Results of bronchial provocation tests**

<table>
<thead>
<tr>
<th>Subject</th>
<th>Methacholine PD15, FEV1 (μg)</th>
<th>Toluendiisocyanate 0-01 ppm</th>
<th>Type of response</th>
<th>Toluendiamine 1-31 mg/m³</th>
<th>3.21 mg/m³</th>
<th>Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>132</td>
<td>Late</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>2</td>
<td>86</td>
<td>Immediate</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>3</td>
<td>220</td>
<td>Immediate</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>4</td>
<td>86</td>
<td>Immediate</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>5</td>
<td>610</td>
<td>Late</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>6</td>
<td>68</td>
<td>Immediate</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>7</td>
<td>86</td>
<td>Late</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>8</td>
<td>1320</td>
<td>Dual</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>9</td>
<td>1840</td>
<td>Late</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>10</td>
<td>420</td>
<td>Immediate</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>11</td>
<td>520</td>
<td>Late</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>12</td>
<td>68</td>
<td>Immediate</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
</tr>
</tbody>
</table>

---

552
adverse reaction precedes the biotransformation of isocyanate into amines. It would be interesting, therefore, to perform in vitro studies on the kinetics of the reaction between TDI and organic compounds in the bronchial mucus.

F Candura
Gianna Moscato
Scuola di specializzazione in Allergologia e Medicina del lavoro dell’Università degli Studi di Pavia (Direttore: Prof F Candura) Fondazione Clinica del Lavoro di Pavia.

References

8 Candura F. Elementi di tecnologia ad uso dei cultori di medicina del lavoro. Pavia; Aurora, 1974.