Exposure standards for allergens: history, occurrence, exposure-response relations, risk assessment

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Outline

• Allergens
  – Definition
  – Properties

• Exposure response relations
  – Sensitization
  – Time till sensitization
  – Symptoms, asthma

• Risk assessment for allergens
High molecular weight sensitizers

- Usually proteins, molecular weight >5 kDaltons
- IgE response after sensitization period (T-helper 2 response):
  - Urticaria, conjunctivitis, rhinitis, asthma
- Examples of HMWS with major public health impact:
  - **Latex** (Hevea brasiliensis) Hev b1-b7
  - **Fungal α-amylase** Asp o 1 (51-54 kDa), other proteins (25-27 and 40 kDa)
  - **Rat and Mouse Urinary Proteins**: Rat n 1A (20-21 kD), Rat n 1B (16-17 kD) and Rat albumin (68 kD)
  - **House dust mite**: Der p 1
HDM allergen: >99% of Der p1 in fecal particles
Tovey et al., Nature 1981

*Der p1: MW = 24,000
~0.1 ng/particle (~2.5%(w/w)) \(\rightarrow\) \(3 \times 10^9\) molecules/particle

Mite faeces are a major source of house dust allergens
E. R. Tovey, M. D. Chapman & T. A. E. Platts-Mills
Division of Immunology, Clinical Research Centre, Watford Road, Harrow, Middlesex HA1 3UJ, UK

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Fig. 1  Electron scanning micrograph of two mite faecal balls. Mite faeces range from 10 to 40 \(\mu\)m in diameter with a mean of 22 ± 6 \(\mu\)m s.d. For a similar species it has been reported that the faeces are produced by compacting three to five foodballs covered in a peritrophic membrane. Scale bar. 10 \(\mu\)m.
Low molecular weight sensitizers

- Small molecules, sometimes reactive chemicals
- IgE response after sensitization period (T-helper 2 response) or other (unknown) mechanism (hapten formation and IgE response, cellular responses)
- Urticaria, conjunctivitis, rhinitis, asthma
- Examples of LMWS:
  - Isocyanates
  - Acetic anhydrides
  - Metals: Beryllium, Chromium (Cr III), Nickel, Platinum salts
  - Colophony
  - Disinfectants: Chloramine T
Low molecular weight sensitizers: di-isocyanates in spray painting
Pronk et al., Ann Occup Hyg, 2005

<table>
<thead>
<tr>
<th>HDI factor</th>
<th>TDI factor</th>
<th>MDI factor</th>
</tr>
</thead>
<tbody>
<tr>
<td>42.2%</td>
<td>26.8%</td>
<td>12.8%</td>
</tr>
<tr>
<td>Biuret</td>
<td>2,6-TAI</td>
<td>4,4-MDI</td>
</tr>
<tr>
<td>Diisocyanuraat</td>
<td>4,2-TAI</td>
<td>4,4-MAI</td>
</tr>
<tr>
<td>Uritidone</td>
<td>2,4-TAI</td>
<td>PIC</td>
</tr>
<tr>
<td>Unknown polyHDI</td>
<td>PhI*</td>
<td>PhI*</td>
</tr>
<tr>
<td>Isocyanurate</td>
<td>2,6-TDI</td>
<td></td>
</tr>
<tr>
<td>1,6-HDI</td>
<td>MIC</td>
<td></td>
</tr>
<tr>
<td>1,6-HAI</td>
<td>2,4-TDI</td>
<td></td>
</tr>
<tr>
<td>IPDI*</td>
<td>IPDI*</td>
<td></td>
</tr>
<tr>
<td>IPDI isomer*</td>
<td>IPDI isomer*</td>
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*Present in multiple factors
Platinum salts
Heederik et al., JACI 2015

• Low ng/m³ exposure sufficient for sensitization

• Involves a limited number of particulates

• 5μm particle has a mass of 0.16 ng/m³ and contains $2.5 \times 10^{11}$ molecules

• 10μm particle has a mass of 1.3 ng/m³ and contains $1.9 \times 10^{12}$ molecules

• Under assumptions of MW~400, density=2.5 g/mL
Temporal patterns in exposure
Meijster et al., Ann Occup Hyg 2008

Concentration inhalable dust (mg/m³)

shaking bag

Cleaning with broom

dough
forming and
dusting

dusting

cleaning

pastry dough production and forming

emptying bag
careful dusting

flour from silo
dough cutting
dough


time
Measuring allergens using immunoassays

- Uses antibodies (polyclonal, monoclonal)
- Measurement of single or multiple allergens in dust
- Specific and sensitive

Absence exposure monitoring techniques for high molecular weight allergens until 1980-ies:
- Limited insight in exposure determinants
- No exposure-response (or exposure-effect) relationships described

Immunoblot for fungal $\alpha$-amylase

<table>
<thead>
<tr>
<th>Human IgE</th>
<th>Rabbit IgG</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>5</td>
<td>6</td>
</tr>
<tr>
<td>7</td>
<td></td>
</tr>
</tbody>
</table>
‘... it seems unlikely that exposure measurements, including personal monitoring, .., would ever be sufficiently accurate, .., to permit between individual differences (-due to differences in underlying mechanisms-) in exposure response relationships to be modeled or measured in epidemiological studies ...’

Occupational asthma and exposure response studies (Becklake M, in Bernstein et al. Asthma in the Workplace, 1999)
Exposure response relationships: wheat allergen exposure in bakers
Exposure sensitization relationships for three different allergens
Heederik et al., Occup Environ Med 1999 with Brisman et al., 2004 added

Log (Allergen concentration) (ng/m^3)

Prevalence Ratio

- Rat Urine Allergen (Heederik et al., 1999)
- Wheat (Houba et al., 1998)
- Fungal α–Amylase (Houba et al., 1996)
- Fungal α–Amylase (Nieuwenhuijsen et al., 1999)
- Fungal α–Amylase (Brisman et al., 2004)
WR-symptom prevalence by sensitization and wheat exposure

<table>
<thead>
<tr>
<th>Sensitised WF (36)</th>
<th>Work Related Symptoms</th>
<th>Prevalence</th>
</tr>
</thead>
<tbody>
<tr>
<td>LOW</td>
<td>1/7</td>
<td>14.3%</td>
</tr>
<tr>
<td>INTERMEDIATE</td>
<td>4/10</td>
<td>40.0%</td>
</tr>
<tr>
<td>HIGH</td>
<td>10/19</td>
<td>52.6%</td>
</tr>
</tbody>
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<table>
<thead>
<tr>
<th>Non-sensitised WF (310)</th>
<th>Work Related Symptoms</th>
<th>Prevalence</th>
</tr>
</thead>
<tbody>
<tr>
<td>LOW</td>
<td>17/110</td>
<td>15.5%</td>
</tr>
<tr>
<td>INTERMEDIATE</td>
<td>21/97</td>
<td>21.6%</td>
</tr>
<tr>
<td>HIGH</td>
<td>25/103</td>
<td>24.3%</td>
</tr>
</tbody>
</table>
Time till development of symptoms in a retrospective cohort study among 99 LA Workers
Kruize et al., Occup Environ Med 1997

<table>
<thead>
<tr>
<th></th>
<th>LAA cases</th>
<th>Median time till LAA (months)</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non atopics</td>
<td>9</td>
<td>98</td>
<td>7-270</td>
</tr>
<tr>
<td>Atopics</td>
<td>10</td>
<td>27</td>
<td>&lt;1-117</td>
</tr>
<tr>
<td>Exp &lt;2 hrs/wk</td>
<td>2</td>
<td>83</td>
<td>30-36</td>
</tr>
<tr>
<td>2≤Exp&lt;15</td>
<td>6</td>
<td>113</td>
<td>83-270</td>
</tr>
<tr>
<td>15≤Exp&lt;38</td>
<td>7</td>
<td>56</td>
<td>1-192</td>
</tr>
<tr>
<td>Exp≥38</td>
<td>4</td>
<td>14</td>
<td>&lt;1-36</td>
</tr>
</tbody>
</table>
Platinum salt surveillance study
Heederik et al., JACI 2015

exposure just before sensitization was strongest related to sensitization

Spline model with 3d.f. not-lagged/lagged 0.5 and 1.0 year comparable models fits (AIC 1195-1197)
Lagging > 1.5 year AICs >1208
Exposure standards for allergens

- ACGIH standard for subtilisin adopted in 1975 60 ng/m³

- Nordic expert group 1996 (wheat flour) 1994 (industrial enzymes). ACGIH standard does not protect against development of sensitization and allergy

- Netherlands Health Council advice for an exposure standard for wheat dust 10th August 2004
“... existing data on exposure-response relationships do not allow the identification of a NOAEL for flour dust. Due to the nature of allergy it is unlikely that the setting of a NOAEL for flour dust will be practicable even in the near future.”

“... since sensitization is not a disease”, and the relationship between sensitization and symptoms is weak and the predictive value of sensitization with respect to development of disease is unclear, it “appears unrealistic and not sufficiently founded to suggest and OEL to prevent sensitization” ().
“... an OEL should prevent against allergic sensitization, as sensitization plays a crucial biological role and is a prerequisite for the development of allergy.

... the exposure level below which no allergic sensitization develops for most allergens is so low, that OELs are difficult to set with the current knowledge and technical feasibilities.

... An alternative approach is to accept exposure, which carries a small predefined risk in developing allergic sensitization.”

RISK based approach
Health based exposure standard for wheat dust (HBROEL)

- Netherlands Health Council risk based approach
  - No exposure threshold
  - Estimation of exposure level associated with 1% excess sensitization risk
  - Wheat sensitization background (Gautrin et al., 1997)
  - Exposure response (Houba et al., 1998)
  - Assessment factor for variability allergen content of 2
  - 0.5 mg/m³ proposed at 1% additional risk point

- Parallel with DMEL in REACH
Deriving exposure standards for allergens

• Feasible
• Transparent
• Evidence based

• Several examples:
  – DECOS wheat, soy, amylase, isocyanates
  – OSHA beryllium