Chemical Respiratory Allergy: Definitions, Mechanisms, Hazard Identification and Characterisation

Ian Kimber, University of Manchester
Review

Chemical respiratory allergy: Reverse engineering an adverse outcome pathway

Ian Kimber\textsuperscript{a,\,*}, Rebecca J. Dearman\textsuperscript{a}, David A. Basketter\textsuperscript{b,\,*}, Darrell R. Boverhof\textsuperscript{c}

\textsuperscript{a} Faculty of Life Sciences, University of Manchester, Manchester, UK
\textsuperscript{b} DABMEB Consultancy Ltd, Sharnbrook, Bedfordshire, UK
\textsuperscript{c} Toxicology and Environmental Research & Consulting, The Dow Chemical Company, Midland, MI, USA
Some Definitions

• Allergy:
  – Adverse health effects that may result from the stimulation of an immune response

• Chemical allergy:
  – Adverse health effects resulting from allergic sensitisation to a chemical

• Chemical respiratory allergy:
  – Adverse reactions (rhinitis, asthma) resulting from allergic sensitisation of the respiratory tract to a chemical
More Definitions

• **Sensitisation (Induction):**
  – immunological priming resulting in increased responsiveness to a specific (chemical) allergen.

• **Allergic reaction (Elicitation):**
  – Provocation in a previously sensitised subject of an allergic reaction following subsequent exposure to the inducing chemical allergen.
Chemical Respiratory Allergens

- **Acid anhydrides**
  trimellitic anhydride (TMA)

- **Diisocyanates**
  diphenylmethane diisocyanate (MDI)

- **Platinum salts**
  ammonium hexachloroplatinate (AHCP)
The yin/yang of chemical allergy

Sensitisation of the respiratory tract

Chemical respiratory allergy

Allergic contact dermatitis

Skin sensitisation
Skin sensitisation
Adverse Outcome Pathway

1. Access to viable epidermis
2. Creation of hapten-protein complexes
3. Cell trauma and danger signals
4. Activation of DC
5. Recognition, internalisation and processing of antigen
6. Antigen transport to regional lymph nodes
7. Clonal expansion of responsive T lymphocytes
8. Allergic reaction
Allergic contact dermatitis
Asthma

Normal airway

Asthmatic airway

Asthmatic airway during attack

Relaxed smooth muscles

Wall inflamed and thickened

Air trapped in alveoli

Tightened smooth muscles
The Toxicological Challenge

There are currently available no validated or widely accepted methods for the identification and characterisation of chemical respiratory allergens.
Areas of Uncertainty

1. Route of exposure:
   - Inhalation or skin exposure?

2. The role of IgE antibody
## RESPONSES TO MDI IN THE GUINEA PIG

<table>
<thead>
<tr>
<th>Method</th>
<th>Challenge</th>
<th>Inhalation</th>
<th>IgG1</th>
<th>IgE</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>INHALATION</strong></td>
<td></td>
<td>0/16</td>
<td>3/16</td>
<td>0/16</td>
</tr>
<tr>
<td>5 x 3 hr at 21.6 mg/m³</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>= 4 mg total exposure</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>INTRADERMAL</strong></td>
<td></td>
<td>5/8</td>
<td>8/8</td>
<td>3/8</td>
</tr>
<tr>
<td>1 x 100µl at 0.3%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>= 0.3mg total exposure</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>TOPICAL</strong></td>
<td></td>
<td>3/7</td>
<td>7/8</td>
<td>2/8</td>
</tr>
<tr>
<td>1 x 400µl at 100%</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>= 400mg total exposure</td>
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</tbody>
</table>
# THE DEBATE

<table>
<thead>
<tr>
<th>What makes skin suitable?</th>
<th>What makes respiratory tract unsuitable?</th>
</tr>
</thead>
<tbody>
<tr>
<td>immunogenicity</td>
<td>immunogenicity</td>
</tr>
<tr>
<td>professional DC</td>
<td>professional DC &amp; AM</td>
</tr>
<tr>
<td>easy absorption</td>
<td>easy absorption</td>
</tr>
<tr>
<td>many precedents</td>
<td>fewer precedents</td>
</tr>
</tbody>
</table>
The Skin Can Act as a Route of Exposure for Allergic Sensitization of the Respiratory Tract

73% of delegates attending UK Health and Safety Executive Workshop November 1999
Areas of Uncertainty

1. Route of exposure:
   - Inhalation or skin exposure?

2. The role of IgE antibody
IgE antibody and inflammation

IgE ANTIBODY PRODUCTION → MAST CELL SENSITISATION → LEUKOTRIENES, VASOACTIVE AMINES and other inflammatory mediators within minutes of challenge
Is IgE antibody important?

**NO**

Plasma IgE antibody not detected in many subjects with diisocyanate asthma

**Yes**

- IgE antibody has ‘previous’ in respiratory allergy
- IgE antibody has been associated with all known chemical respiratory allergens
- IgE antibody is very difficult to detect
- IgE antibody levels drop following last exposure
The Debate

The role of IgE antibody

**EITHER:** There are immunological mechanisms other than/in addition to IgE antibody that cause sensitisation of the respiratory tract to chemicals and occupational asthma

**OR:** IgE antibody plays a mandatory universal role in sensitisation of the respiratory tract to chemicals and occupational allergy
T lymphocyte heterogeneity

- Th CD4
- Tc CD8
- Th 1
- Th 2
- Th 17
Th1 cell/Th2 cell balance and chemical allergy

CONTACT ALLERGY

CHEMICAL RESPIRATORY ALLERGY
Th2 cells drive IgE antibody production
Proposal:

For the purposes of hazard identification, adopt as a common element in sensitisation of the respiratory tract to chemicals the development of Th2 cell responses.
Pathway (1)

Exposure → Immune activation → Th2 cells

Sensitisation of respiratory tract

-IgE + IgE
Pathway (2)

Exposure → Immune activation

- IgE → +IgE

Th2 cells

Th1 cells

Skin sensitisation

Sensitisation of respiratory tract
Peptide binding

The Direct Peptide Reactivity Assay: Selectivity of Chemical Respiratory Allergens

Jon F. Lalko,*† Ian Kimber,* G. Frank Gerberick,† Leslie M. Foertsch,† Anne Marie Api,‡ and Rebecca J. Dearman*

*Faculty of Life Sciences, The University of Manchester, Manchester M13 9PT, UK; †The Procter & Gamble Company, Cincinnati, Ohio 45253; and ‡Research Institute for Fragrance Materials, Inc., Woodcliff Lake, New Jersey 07677

†To whom correspondence should be addressed at Research Institute for Fragrance Materials, Inc., 50 Tice Blvd., Woodcliff Lake, NJ 07677. E-mail: jialko@rifm.org.

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Chemical-Protein Reactivity, Metabolism and Skin Sensitization

Nucleophilic-electrophilic interaction:

- The correlation of skin protein reactivity and skin sensitization is well established.
- Leads to stable association with proteins to form immunogenic complex.
- Requires that the chemical is inherently protein reactive, or can be transformed in a protein reactive species within the skin.

(Landsteiner and Jacobs, 1936; Dupuis and Benezra, 1982; Lepoittevin et al, 1998)
Calculation of peptide depletion

**HPLC/PDA**

Percent Peptide Depletion = \[
1 - \left( \frac{\text{Peptide Peak Area in Replicate Injection}}{\text{Mean Peptide Peak Area in Reference Controls}} \right) \times 100
\]

**Prediction Model**

- Mean of Cys & Lys % depletion
  - Avg Score < 22.62%
  - Avg Score > 22.62%
- Mean of Cys & Lys % depletion
  - Avg Score < 6.38%
  - Avg Score > 6.38%
- Mean of Cys & Lys % depletion
  - Avg Score < 42.47%
  - Avg Score > 42.47%

**Stages**
- Minimal Reactivity
- Low Reactivity
- Moderate Reactivity
- High Reactivity
Differential amino acid selectivity of contact and chemical respiratory allergens
Pathway 3

Exposure → Amino acid Selectivity → Black Box → Immune activation

Sensitisation of respiratory tract

Th2 cells

-IgE

+IgE