Occupational respiratory allergy and asthma - sensitizers and disease

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Most airborne allergens are components of, or carried by particles of 1 - 100 µm diameter.
The contact between the respiratory organ and the air containing the allergens is the key factor for the development of respiratory allergy.
Work-related asthma (WRA) phenotypes

Asthma caused by work = Occupational asthma (OA)

Asthma exacerbated by work = work-exacerbated asthma (WEA)

Irritant-induced asthma (IIA)
- Acute-single exposure RADS
- Non-acute multiple exposures

Allergic
- Non-IgE-dependent
- IgE-dependent

According to Moscato et al. 2011, Allergy
Phases of the allergic reaction – IgE-mediated type I-reaction

**Sensitization**
- Antigen
- Dendritic cells
- IL-4
- IL-13

**Immediate type-reaction**
- Antigen
- Mast cell
- IL-4
- IL-13
- IgE
- Histamine
- Leukotriene etc.
- IL-3
- IL-5

Further inflammatory mediators
- Eosinophil
Plant-derived agents
• Henna dye
• Natural rubber latex
• Plant enzymes (papain, bromelain)
• Psyllium
• Vegetable gums (arabic, guar, tragacanth)
• Wheat flour
• Wood dust (Obeche, locust etc.)

Animal and insect-derived agents
• Bird proteins (feathers, serum)
• Crustaceans: snow crab, prawn
• Eggs (chicken)
• Insects
• Mammalian proteins in hair, dander, urine
• Pharmaceutical enzymes, e.g. pancreatic
• Sea squirt (oyster parasite)

Bacterial and fungal-derived agents
• Bacillus subtilis-derived enzymes
• Penicillium casei
• Thermophilic molds
Low molecular weight agents

• **Persulfates** (in hair bleaching solutions)

• **Metals and metal salts**
  - Chromium
  - Cobalt
  - Nickel sulfate
  - Platinum

• **Organic chemicals**
  - Acid anhydrides (prototype: trimellitic anhydride)
  - Acrylates, methacrylate (artificial nail glue)
  - Ethylenediamine
  - Paraphenyldiamine in hair dye
  - Polyisocyanates (prototype: toluene diisocyanate)
  - Pharmaceuticals (antibodies, cimetidine)
# Workplaces with allergen exposure

<table>
<thead>
<tr>
<th>Trade/industry</th>
<th>Allergen sources</th>
</tr>
</thead>
<tbody>
<tr>
<td>Agriculture</td>
<td>Cow hair, pollen, storage mites</td>
</tr>
<tr>
<td>Bakeries, mills</td>
<td>Wheat flour, rye flour, soya flour, α-amylase, xylanase, storage mites, insects</td>
</tr>
<tr>
<td>Fish processing</td>
<td>Fish allergens</td>
</tr>
<tr>
<td>Animal feed</td>
<td>Soya, phytase</td>
</tr>
<tr>
<td>Pharmaceutical industry</td>
<td><em>Gummi arabicum</em>, enzymes</td>
</tr>
<tr>
<td>Laboratory animal care</td>
<td>Mouse allergens, rat allergens</td>
</tr>
<tr>
<td>Health care</td>
<td>Natural rubber latex</td>
</tr>
<tr>
<td>Detergent production</td>
<td>Enzymes: Proteases, cellulases, lipases, amylases</td>
</tr>
<tr>
<td>Wood processing</td>
<td>Wood dust</td>
</tr>
<tr>
<td>Composting plants</td>
<td>Molds, bacteria</td>
</tr>
<tr>
<td>Many others</td>
<td>House dust mites, molds, ubiquitous indoor allergens</td>
</tr>
</tbody>
</table>

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# Occupational allergy

<table>
<thead>
<tr>
<th>BK-No.</th>
<th>Skin- and respiratory diseases</th>
<th>Austria § 177; ASVG-list</th>
</tr>
</thead>
<tbody>
<tr>
<td>1315</td>
<td>Isocyanate initiated diseases (chemical compounds used for the production of synthetics)</td>
<td></td>
</tr>
<tr>
<td>4201</td>
<td>Hypersensitivity pneumonitis (inflammatory changes of the pulmonary alveoli)</td>
<td>43</td>
</tr>
<tr>
<td>4301</td>
<td>obstructive respiratory diseases (incl. rhinopathy) caused by allergenic substances</td>
<td>30</td>
</tr>
<tr>
<td>5101</td>
<td>serious or repeated skin diseases</td>
<td>19</td>
</tr>
<tr>
<td>[5101/4301]</td>
<td>Allergy induced anaphylactic responses after latex sensitization</td>
<td>53</td>
</tr>
</tbody>
</table>
Frequency of causative triggers for occupational asthma/rhinitis in Germany [BK 4301]

584 cases in total

- Flour, flour products, pasta, baking products etc. 63.7%
- Dust from food or animal feed 2.4%
- Hair, bristles, feathers, horn from animals 6.0%
- Fruits, vegetables, plants 2.4%
- Hair care products 5.0%
- Natural rubber latex 0.5%
- Desinfectants 1.9%
- Enzymes 1.9%
- Moulds 1.2%
- Others 15.1%
Relevance of baker's asthma

• One of the oldest recognized occupational diseases (First described by Bernardino Ramazzini (1633-1714) in “De Morbis artificum diatriba”)

• One of the most common forms of occupational asthma Examples:

  in France: Incidence of baker's asthma among young bakers ranges from 0.3 to 2.4 cases per 1000 person-years [Remen et al. 2010]

  in Norway: Incidence of occupational asthma among male bakers 2.4 and female 1 case per 1000 person-years [Leira et al. 2005]

  in Germany: Incidence of occupational asthma among bakers ~2 cases per 1000 person-years [BGN, personal communication]

  ~ 10 % of all bakers develop asthma during their working life period
Potential allergens in bakeries

- **Wheat flour**
- **Rye flour**
- Further cereal flours (e.g. barley)
- Enzymes (α-amylase, cellulase etc.)
- Soy, Lupine flour
- Storage mites
- Flour pests (including flour worm, flour moth)
- Moulds
- Egg yolk and white, sesame seed, nuts, poppy etc.
Specific IgE in 244 bakers with work-related complaints

- RAST-Class 1: 57%
- RAST-Class 2: 60%
- RAST-Class 3: 16%
- RAST-Class 4: 12%
- RAST-Class 5: 14%
Enzymes used in bakeries

α-Amylase
starch degradation ⇒ yeast fermentation, CO₂ ↑ ⇒ volume ↑, dough processing, browning, cripness ↑

- Glucoamylase
- Xylanase
- Cellulase

Often produced in Aspergillus oryzae and A. niger
Exposure Prevention: Granulation of enzymes
(α-amylase since 90ies, Baking granulate Novo)

- Reduces exposure by inhalation of enzyme dust
- Aim: no sensitization to enzymes
- Aim: no allergies to enzymes

Partikels instead of 5 - 50 µm
200 - 400 µm
Enzymes causing allergies - in food industry

- Alpha-amylase
- Glucoamylase
  - Aspergillus oryzae
  - Aspergillus niger

- Cellulases
- Hemicellulases: Xylanases
  - Aspergillus niger
  - Trichoderma reesei
  - Bacillus subtilis

- Papain, Bromelain
  - Papaya *Carica papaya*
  - Pineapple *Ananas comosus*

- Phytase
  - Aspergillus niger
  - Trichoderma reesei

- Pepsin, Chymosin, microbial Rennet, Pancreatin
  - Cow *Bos domesticus*
  - Pig *Sus scrofa*
  - Cryphonectria, Rhizomucor

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Enzymes causing allergies - in detergent industry

- **Proteases:**
  - Maxatase
  - Alcalase
  - Savinase
  - *Bacillus subtilis*

- **Termamyl (α-amylase):**
  - *Bacillus subtilis*

- **Carezyme (Cellulase):**
  - *Bacillus subtilis*
Exposure to animals

Private area

Occupational setting
Allergy to laboratory animals

• Predominantly a typical occupational respiratory allergy

• First cases were described in the 50s
  – Chafee FH: *Bronchial asthma due to rat and mouse hair; report of two cases*. J Allergy 1952;

• Epidemiological cross-sectional studies were performed during the 1970s and 1980s (Bush RK and Stave GM: *Laboratory animal allergy: An update*. ILAR J 2003)
  – pharmaceutic industry
  – Universities and research institutes
  – commercial laboratory animal breeding
  – medical and veterinary universities
Laboratory animals

2 997 153 animals for scientific purposes in 2013

Data from Federal Ministry of Food and Agriculture BMEL
Allergy to laboratory animals

• Prevalence rate between 11 and 44% (depending on the study)
• Affected people: keeper, technical assistant, scientists, veterinarians
• Species: mouse, rat, guinea pig, rabbit, hamster, dog, cat, primates
• Symptoms:
  — allergic rhinitis and conjunctivitis (up to 80%)
  — skin reactions (ca. 40%)
  — asthma (up to 22%)
  — anaphylaxis (very rare, e.g. by bites)
• Latency between begin of exposure and start of the difficulties is 3 years on average
• Risk depends strongly on the exposure intensity
Airborne features

• Animal allergens exhibit a tendency, to bind on small particles in the range of <1 µm to 20 µm

• Good „hovering properties“ the allergens stay in the air for a longer time and can easier be inhaled

• Binding on clothes and hair of exposed persons easy transfer to initially not charged areas („unexpected contamination“)
The determination of allergen exposure is necessary to

a) Detect the association between exposure and work-related allergic diseases,

b) Establish and also to monitor suitable measures for reduction or avoidance of allergen exposure.
Dust exposure is not the same as allergen exposure

- Filling of the purified cages with bedding: High dust exposure, No allergen exposure
- Emptying of contaminated animal cages: High dust exposure, High allergen exposure

It is a need to quantify the allergens

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Aeroallergen monitoring is a stepwise process

- Definition of objectives and setting
- Exposure assessment strategy
- Sampling methods
- Extraction Procedure
- Allergen quantification
- Evaluation

Air sampling (some common sampler)

Gravikon VC 25  Rotorod/Impactor; >10 µm  GSP/filter sampling
Reservoir dust sampling

Settled dust sampling

Vacuum cleaning of a surface

Electrostatic dust collector (EDC)
Allergen analysis: Sandwich enzyme immunoassay (EIA)
EDC-sampler, Rat allergens

![Graph showing Rat n 1 (ng/tissue) levels across different areas]

- Animal rooms/ open cages
- Animal rooms/ IV/Cs
- Rooms without animals
- Homes/Controls
- Median

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Aim:
Prevention strategies

EAACI Position Paper: Prevention of work-related respiratory allergies among pre-apprentices or apprentices and young workers

G. Moscato¹, G. Pala¹, M. A. Boillat², I. Folletti³, R. Gerth van Wijk⁴, D. Olgiati-Des Gouttes⁵, L. Perfetti⁴, S. Quirce⁶,⁷, A. Siracusa³, J. Walusiak-Skorupa⁸ & S. M. Tarlo⁹,¹⁰

Guidelines for the management of work-related asthma.


AWMF-Register Nr. 002/025 Klasse: $1

Leitlinie der Dt. Ges. f. Arbeitsmedizin und Umweltmedizin (DGAUM)

Prävention arbeitsbedingter obstruktiver Atemwegserkrankungen
Recommendation for prevention and management

- Screening in high risk areas.
- For job starter the incidence of work-related symptoms is highest in the first 2-3 years after begin of exposure (baseline-measurements recommended).
- Especially for HMW-allergens atopy is a risk factor.
- Persistent exposure at symptomatic is also a risk factor.
- Reduction of exposure cannot be routinely recommended as an alternative to cessation of exposure in the management of occupational asthma. (meta-analysis, Vandenplas et al., Eur Respir J 2011).
- Sector specific special programs, recommendations and guidelines should be used or realized.
Key messages

- Occupational allergy (OA) is the result of an interaction between multiple genetic, environmental and behavioral influences.
- More than 400 agents are identified as sensitizers of occupational asthma, but only very few are characterized.
- Baker’s asthma is one of the most frequently occurring forms of occupational asthma caused by workplace-related inhalation of cereal flour mainly wheat.
- Diagnosing OA is a complex undertaking; its primary goal is to demonstrate a causal relation between exposure to a specific agent encountered at work, allergic responses and symptoms.
- Environmental control of exposure is crucial for prevention, an every effort should be made to keep the workplace without an exposure hazard.
- Immunological methods are helpful to quantify allergens
Thank you for your attention!!

Bochum, Germany