Clinical Diagnosis of Occupational Asthma – practice and challenges/opportunities
ECETOC 2016

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A case ...

- 41 year old material technician who works for X
- Professor X (elsewhere) ‘occupational asthma’; agent unspecified
- ‘he should give up his work as soon as possible’
A case ...

- 41 year old material technician who works for X
- He has worked there since October 2011 - first as a laboratory technician, but since August 2014 in his current role
- He had no respiratory problems until May 2015 when he developed a cold which did not resolve and he thought his symptoms might be due to new onset hay fever.
- He saw his GP and was noted to be wheezy and breathless, particularly when using a fence paint
- He went on holiday in August for ten days when he was entirely well
- He returned on 15th August and within 48 hours of being back at work his symptoms returned
- In early September the suggestion of asthma was raised and he was prescribed a blue inhaler and amoxicillin.
- Spirometry on 23rd September was normal but due to persistent symptoms he was started on an inhaled steroid ...
- ... and referred to Professor X ...
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Is this occupational asthma – and if so, what has caused it?

available tools:

• immunology
• functional assessment at and away from work
• individual, experimental assessment
• analogy
Immunology

- works very well with protein (high molecular mass) agents ...
- ... if you have a good lab.
  - very high sensitivity (few false negatives)
  - *may* have very high specificity (flour ± latex)

- works poorly with most chemical (low molecular mass) agents
  - reflects our poor understanding of the immunology of much ‘chemical’ OA
Functional assessment at and away from work

- serial measurements
- usually of peak expiratory flow
- tedious and lengthy
- doesn’t distinguish agent ...
- ... or OA from WEA
- requires expert assessment or computer-aided analysis
Serial PEF measurements; baker with OA
Individual, experimental assessment

- specific inhalational challenge
- ≡ bronchial provocation test
- controlled
- indications vary
- ‘new’ agents

<p>| | |</p>
<table>
<thead>
<tr>
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</thead>
<tbody>
<tr>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>individual response</td>
<td>time-consuming</td>
</tr>
<tr>
<td>specific agent</td>
<td></td>
</tr>
<tr>
<td>reference standard</td>
<td>highly specialised</td>
</tr>
<tr>
<td>consistent</td>
<td>(in)consistent</td>
</tr>
</tbody>
</table>
SPECIFIC INHALATION CHALLENGES WITH OCCUPATIONAL AGENTS: ERS PRACTICAL RECOMMENDATIONS and CLINICAL GUIDANCE
Olivier Vandenplas, Hille Suojalehto and Paul Cullinan, on behalf of the ERS Task Force on Specific Inhalation Challenges with Occupational Agents

HANDBOOK OF PROCEDURES FOR SPECIFIC INHALATION CHALLENGE TESTING IN THE DIAGNOSIS OF OCCUPATIONAL ASTHMA
European Taskforce on SIC
June 2013 (to be updated 2018)
‘Pepys’ method
Day 1

FEV₁ (NSBHR)* ± FeNO

Exposure → control

Day 2

FEV₁ (NSBHR)* ± FeNO

active

± Day 3*

FEV₁ (NSBHR)* ± FeNO

active

24 hours post-exposure

FEV₁ NSBHR ± sputum cell count ± FeNO

FEV₁ (6-8 hours) NSBHR ± sputum cell count
### Which agent(s) to test?

<table>
<thead>
<tr>
<th>Substance Name</th>
<th>Frequency of use in Materials Lab</th>
</tr>
</thead>
<tbody>
<tr>
<td>ESCIDE</td>
<td>Once</td>
</tr>
<tr>
<td>ESC CC 80</td>
<td>Once</td>
</tr>
<tr>
<td>ESC 26P3 MB</td>
<td>Once</td>
</tr>
<tr>
<td>Co International Standard</td>
<td>As required for calibration.</td>
</tr>
<tr>
<td>75 cSt Base Oil Blank</td>
<td>As required for calibration.</td>
</tr>
<tr>
<td>V23 Wear Metals - 10 micrograms/g</td>
<td>As required for calibration.</td>
</tr>
<tr>
<td>V23 Wear Metals - 50 micrograms/g</td>
<td>As required for calibration.</td>
</tr>
<tr>
<td>V23 Wear Metals - 100 micrograms/g</td>
<td>As required for calibration.</td>
</tr>
<tr>
<td>V23 Wear Metals - 500 micrograms/g</td>
<td>As required for calibration.</td>
</tr>
<tr>
<td>Oxalic Acid Dihydrate</td>
<td>Infrequently</td>
</tr>
<tr>
<td>3M Surface Pre-Treatment 2-Part Mix</td>
<td>Weekly</td>
</tr>
<tr>
<td>Sulphuric Acid</td>
<td>Infrequently</td>
</tr>
<tr>
<td>Copper sulphate</td>
<td>Infrequently</td>
</tr>
<tr>
<td>Aluminium sulphate</td>
<td>Infrequently</td>
</tr>
<tr>
<td>Sodium dichromate</td>
<td>Infrequently</td>
</tr>
<tr>
<td>Swarfega Jizer (Red)</td>
<td>Once</td>
</tr>
<tr>
<td>Swarfega Jizer Bio (Green)</td>
<td>Once</td>
</tr>
<tr>
<td>Swarfega Jizer Aerosol (Yellow)</td>
<td>Once</td>
</tr>
<tr>
<td>Metasol</td>
<td>Once</td>
</tr>
<tr>
<td>Alustar 200</td>
<td>Once</td>
</tr>
<tr>
<td>Amity Leksol</td>
<td>Weekly</td>
</tr>
<tr>
<td>Amity AG101</td>
<td>Not used.</td>
</tr>
<tr>
<td>HPCC #1 Grease</td>
<td>Once</td>
</tr>
<tr>
<td>TDS5201116-Petronas GT0-M4</td>
<td>Weekly</td>
</tr>
<tr>
<td>Methyl Ethyl Ketone (MEK)</td>
<td>Twice</td>
</tr>
<tr>
<td>Onto EP1021</td>
<td>Once</td>
</tr>
<tr>
<td>EA 9394 Part A</td>
<td>Infrequently</td>
</tr>
<tr>
<td>EA 9394 Part B</td>
<td>Infrequently</td>
</tr>
<tr>
<td>EA 9394-C2 Part A</td>
<td>Weekly</td>
</tr>
<tr>
<td>EA 9394-C2 Part B</td>
<td>Weekly</td>
</tr>
<tr>
<td>Petroleum ether PC13</td>
<td>Once</td>
</tr>
<tr>
<td>DF273</td>
<td>Once (burning trials)</td>
</tr>
<tr>
<td>Hydrogen Peroxide</td>
<td>Infrequently</td>
</tr>
<tr>
<td>Isopropyl Alcohol</td>
<td>Weekly</td>
</tr>
<tr>
<td>Methyl Ethyl Ketone (MEK)</td>
<td>Once</td>
</tr>
<tr>
<td>Sodium hydroxide</td>
<td>Infrequently</td>
</tr>
<tr>
<td>Anticor</td>
<td>Infrequently</td>
</tr>
<tr>
<td>Loctite 270</td>
<td>Monthly</td>
</tr>
<tr>
<td>Loctite 401</td>
<td>Infrequently</td>
</tr>
<tr>
<td>Loctite 435</td>
<td>Infrequently</td>
</tr>
<tr>
<td>Loctite 648</td>
<td>Monthly</td>
</tr>
<tr>
<td>Loctite 2701</td>
<td>Monthly</td>
</tr>
<tr>
<td>Loctite ESP108</td>
<td>Monthly</td>
</tr>
<tr>
<td>Teroson MS 939 FR</td>
<td>Once</td>
</tr>
<tr>
<td>Dow Corning 736</td>
<td>Once</td>
</tr>
<tr>
<td>Bismaleimide (BMI)</td>
<td>Twice</td>
</tr>
<tr>
<td>MTM-49-3 Pre-Preg Material</td>
<td>Monthly</td>
</tr>
<tr>
<td>CYCOM 2040 Structural Pre-Preg</td>
<td>Monthly</td>
</tr>
<tr>
<td>Cannon S60 Oil</td>
<td>Only used once.</td>
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</table>
1. Identification of the substance/preparation and of the company/undertaking

Trade name:
EA 9394 PART A 50ML SEMPAK

Intended use:
Part A of 2-K-Epoxy Adhesive

2. Hazards identification

The product is classified as hazardous within the meaning of the valid (EU) preparation directive.

C - Corrosive
N - Dangerous for the environment
R21/22 Harmful in contact with skin and if swallowed.
R34 Causes burns.
R43 May cause sensitisation by skin contact.
R51/53 Toxic to aquatic organisms, may cause long-term adverse effects in the aquatic environment.
Specific inhalation challenge to E9394 (epoxy adhesive)
June 2016

- % change in baseline FEV₁
- Time after challenge
- (hours)

histamine PC₂₀ mg/ml
- control
- epoxy
- 24 hrs post-challenge

baseline FEV₁
- control
- epoxy
- 24 hrs post-challenge
New measurements in SIC

- FeNO
- sputum eosinophils
- nasal tryptase …
Analogy: qSAR

- *in silico*
- no presumptions about mechanism
- very high specificity (few false positives)
- screening
- quick/cheap

![Plot](Image)  

(a) Area under curve = 0.86  
(b) Area under curve = 0.95
When is a chemical a ‘respiratory sensitiser’?

- ‘positive’ SIC
  - >1 patient
  - >1 centre
- ‘weaker’ evidence
  - case series
  - sPEF
  - immunology
- high HI on qSAR
- epidemiologic evidence
Difficulties

- cases are sporadic
- acceptability of incorporating new methods into clinical SIC
- inconsistencies (some) in interpretation of SIC
- no ready repository for reports of new agents
Is azodicarbonamide (ADCA) a respiratory sensitising agent in humans?

<table>
<thead>
<tr>
<th>reference</th>
<th># cases</th>
<th>response: (maximum fall)</th>
<th>FEV&lt;sub&gt;1&lt;/sub&gt;</th>
<th>response: NSBHR</th>
<th>specific immunology</th>
<th>notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>1</td>
<td>• none during SIC&lt;br&gt;• isolated, late (50%) after workplace challenge</td>
<td>pre ‘normal’&lt;br&gt; (acetylcholine)</td>
<td>not reported</td>
<td>Reaction to ADCA after workplace challenge abolished by cromoglycate</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>2</td>
<td>• isolated, late (24%)&lt;br&gt;• dual; early and late (21%)</td>
<td>pre 2mg/ml; post 0.28mg/ml&lt;br&gt;pre 0.5mg/ml; post 1.2 mg/ml</td>
<td>not attempted</td>
<td>No response to lactose control exposure</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>2</td>
<td>• isolated, late (22%)&lt;br&gt;• late ‘asthma attack’ (unrecorded)</td>
<td>not reported</td>
<td>not reported</td>
<td>No control exposure</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>1</td>
<td>• prolonged, late</td>
<td>pre 4.7mg/ml; post 0.47 mg/ml</td>
<td>SPT negative&lt;br&gt;(patch test +)</td>
<td>No response to lactose control exposure</td>
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The accompanying epidemiological evidence comprises cross-sectional surveys of three exposed workforces. In a US facility that milled various compounds including ADCA each of the 11 exposed workers, but none of six office workers, reported nocturnal cough; interviews with seven symptomatic workers indicated improvement at weekends in three or four of them. Cross-shift measurements of lung function, again in only a sample of men, demonstrated reductions in FEV<sub>1</sub> after work. Slovak surveyed 151 employees of a plant that manufactured ADCA in the UK. Twenty eight (19%) reported symptoms consistent with new-onset, work-related asthma; all developed the condition within a year of first exposure to ADCA. Pre- and post-shift measurements of lung function in this group revealed no significant differences; and skin prick tests to several concentrations of ADCA (dissolved in dimethyl-sulphoxide) were uniformly negative. Finally, a survey of 227 employees of a US plastics factory (94% of those eligible) reported on current symptoms and cross-shift measurements of lung function.

... ADCA has an asthma hazard index of 0.92 in the Manchester qSAR model, strongly suggestive of an asthmagenic potential.
Is azodicarbonamide (ADCA) a respiratory sensitising agent in humans?

The above, taken as a whole, is strong evidence that inhaled ADCA is asthmagenic in humans, with an immune mechanism that is probably hypersensitive in nature despite the apparent absence of a positive skin prick response to ADCA alone. The most compelling evidence comes from the six case reports, identified in four different centres. Each case developed new-onset, work-related symptoms of asthma after a period of asymptomatic exposure to ADCA without, apparently, ‘toxic’ exposures such as those that have been associated with ‘irritant-induced’ asthma ....
“It was a pleasure to see Mr X, his wife and his little baby girl X in the clinic today.

I understand that he has had meetings with both yourself and the Health and Safety officer and that better **local extraction ventilation** has been fitted in the laboratory where he works. **He has been wearing an FP3 mask on exposure to all epoxy resins and is now asymptomatic.**

His spirometry today was excellent with an $\text{FEV}_1$ of 4.5, $\text{FVC}$ of 5.6. He continues to take Clenil 100 two puffs bd but **has not used salbutamol** since his discharge. I have suggested that he can stop the Clenil in the near future.”

**PS: September 2016**