Human Health Effects Isocyanates

Isocyanates and Health Conference

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Human Health Effects of Isocyanates

- Clinical spectrum
- Pathogenesis
- Epidemiology
- Diagnosis (Phil Harber)
- Outcomes and Management
- Surveillance / Prevention (Phil Harber)
History Isocyanate-Induced Disease

- 1950: Fuchs TDI 1951
- 1956: Woodbury TDI
- 1951: Gerritsen HDI 1951
- 1960: Munn/MDI 1965
- 1957: Blake 1965
- 1976: Charles 1976
- 1970: Peters, Wegman FEV1 loss 1970, 4, 5 Persistent asthma
- 1976: HDI HP+Asthma
- 1979: Karol 1979 TDI-IgE
- 1979: Butcher 1979 SIC TDI
- 1980: Malo 1983 HDI HP+Asthma
- 1980: Zeiss 1980 HP / MDI
- 1980: MDI use > TDI 1980s
- 1983: Malo 1983 HDI HP+Asthma
- 1985: Brooks 1985 RADS
- 1979: Tarlo, Liss, Lemiere Bernstein
- 1976: Asford 1976 Chemical bronchitis firefighters

1950-1990: Timeline of isocyanate-induced disease events.
Clinical Spectrum Disease

- Rhinitis
- Contact dermatitis
- **Asthma**
- Hypersensitivity pneumonitis
- Chronic airflow obstruction – accelerated loss of lung function
Rhinitis Conjunctivitis

Common in workers with OA HMW > LMW

Allergic / irritant

Malo 1997

70 to 90% isocyanate asthmatics reported nasal / eye symptoms at some time

Ameille 2012 – large series 596 cases OA

52% LMW vs (72% HMW)

Less likely to precede asthma

? due to co-exposures, irritants
Allergic Contact Dermatitis

Aalto-Korte *Contact Dermatitis* 2012
54 patients isocyanate ACD
9 IPDI, 12 MDI, 6 TDI, 1 HDI
Motor vehicle, paint industries, construction work

Recent cases with
Toilet seat
Jewelry – isocyanates in resin
PMDI adhesives

Issues with patch testing
Uncommon or are we missing some cases?
Hypersensitivity Pneumonitis

First reported 1976
TDI, MDI, HDI

Acute – flu-like illness, fever, SOB, fatigue, cough
Chronic – progressive SOB, fibrosis, hypoxia
Non-specific
Ddx – flu, pneumonia
Chest xray – infiltrates
Likely overlaps with isocyanate asthma
Clinical Spectrum Disease

- Rhinitis
- Contact dermatitis
- **Asthma**
- Hypersensitivity pneumonitis
- Chronic airflow obstruction – accelerated loss of lung function
Isocyanate Asthma – Key features

Clinical presentation similar to “atopic” asthma
Onset months to yrs after exposure (usually in first yr)
Acute / delayed / atypical responses – asthma symptoms immediate and / or hrs after exposure common
Once “sensitized” exposure to very low levels triggers asthma
Most cases occur in settings where “no exposure” – air levels very low / non-detectable
Skin exposure likely key route sensitization
Large number end-user settings – frequently mixed variable intermittent exposures – especially difficult measure
No simple diagnostic test
Over time respond to multiple triggers, less specific
<table>
<thead>
<tr>
<th>ID numbers</th>
<th>756</th>
<th>770</th>
<th>771</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age yrs</td>
<td>35</td>
<td>43</td>
<td>50</td>
</tr>
<tr>
<td>Prior asthma</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Job title</td>
<td>Energy auditor</td>
<td>Insulator</td>
<td>Insulator</td>
</tr>
<tr>
<td>Tasks</td>
<td>Inspect homes, Spray foam</td>
<td>Spray foam</td>
<td>Helper, set up, clean up</td>
</tr>
<tr>
<td>Onset symptoms after new / modified job</td>
<td>4 months, 1 month after main sprayer</td>
<td>5 yrs, 2 months after very large job</td>
<td>1 yr, progress over 2 ½ yrs before diagnosis</td>
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<tr>
<td>Symptoms</td>
<td>WR cough, wheeze, SOB</td>
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<td>WR eye cough, SOB, Halo vision</td>
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<td>Initial diagnosis</td>
<td>Asthma in ER</td>
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<td>Former</td>
<td>½ ppd</td>
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Isocyanate Asthma: Diagnosis

1) Confirm diagnosis of asthma
2) Assess exposures associated with asthma
3) Determine association between isocyanate exposure and asthma
   - History / questionnaire
   - Peak flows
   - SIC
   - Isocyanate-specific IgE
Definition Asthma

**Harrison’s** - Asthma is a syndrome characterized by airflow obstruction that varies both spontaneously and with specific treatment.

**Wikipedia** - Asthma is the common chronic inflammatory disease of the airways characterized by variable and recurring symptoms, reversible airflow obstruction, and bronchospasm.

**Merck Manual** - Asthma is a disease of diffuse airway inflammation caused by a variety of triggering stimuli resulting in partially or completely reversible bronchoconstriction.
What is Asthma?

*Fishman’s Pulmonary Disorders* - A precise definition of asthma remains elusive.

*Chest Medicine* - Despite a number of formal attempts over a 30-year period, a universally accepted definition of asthma is unavailable. It is likely that asthma is not a specific disease but a syndrome. Important features include asthmatic symptoms, airway inflammation, hyperreactivity …… All of these features need not be present.
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1) Confirm diagnosis of asthma

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<td>Former</td>
<td>½ ppd</td>
<td>Former</td>
</tr>
<tr>
<td>Spirometry</td>
<td>Mild obstruction</td>
<td>Mild obstruction</td>
<td>Mild obstruction</td>
</tr>
<tr>
<td>Bronchodilator resp</td>
<td>Positive</td>
<td>Positive</td>
<td>Positive</td>
</tr>
<tr>
<td>Total IgE IU/ml (nl &lt;100)</td>
<td>19.7</td>
<td>18.3</td>
<td>50.2</td>
</tr>
<tr>
<td>MDI-IgE ratio (nl &lt;2)</td>
<td>2.2</td>
<td>2.1</td>
<td>3.0</td>
</tr>
<tr>
<td>MDI-IgG titer ng/ml</td>
<td>1:5120 9,150</td>
<td>1:2560 3,350</td>
<td>1:5120 10,420</td>
</tr>
<tr>
<td>PPE used</td>
<td>Cartridge respirator Variable No fit testing</td>
<td>Cartridge respirator Variable No fit testing</td>
<td>Cartridge respirator Variable No fit testing</td>
</tr>
<tr>
<td>Skin exposure noted</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Outcome</td>
<td>Left work, unsuccessful attempts to return</td>
<td>Left work, retrained truck driver, Improved</td>
<td>Unemployed for &gt; 1 yr Chronic symptoms</td>
</tr>
</tbody>
</table>
Case: PU spray foam sprayer
MDI-IgG over time

Worse asthma. Leaves PU foam work

Needs job. Returns to PU spray foam work.
Epidemiologic vs Clinical Definition of Asthma

- MD diagnosis
- Symptoms
- Patient diagnosis
- Hospitalizations
- Spirometry + BD
Clinical Disease Research Gaps

Need for better diagnostic tools
Need for marker sensitization
Better understand overlap syndromes
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Inflammatory Cell Influx

Subepithelial Fibrosis

Epithelial Cell Abnormalities

Mucus Hypersecretion

Smooth Muscle Cell Hyperplasia

Inflammatory Cell Influx
Isocyanate Asthma Pathogenesis

Exposure

Skin or airborne

Sensitization

Lung

Skin

APC

T cells

B cells

Iso - GSH – oxidants

Iso-albumin

tachykinins

Mediators/chemokines

IL-4, IL-5

MCP-1

IL-8, IFN-γ, TNF

ICAM-1

Airway Inflammation: Eos, Icyltes, PMNs
Hypothesis

Skin may be an important site for systemic sensitization to environmental / occupational agents – promote development asthma

Factors that facilitate absorption / disrupt skin barrier function may increase skin exposure, promoting sensitization and asthma (e.g. excess hand washing)

Important implications

- Exposure – response relationships (sensitization / elicitation)
- Mechanistic studies – skin vs lung different pathways

Prevention – reduction of airborne exposures may not be effective / sufficient
Isocyanate + Co-exposures

Skin

Lung

- Damaged epithelial barrier
- Initiation of Th2 immune response
- Sensitized host
- Clinical outcomes: atopy and asthma

- Enzymatically active allergen like HDM
- EC
- TSLP
- GM-CSF
- IL-33
- IL-25
- CCL2
- CCL20
- OX40L
- ST2
- Attracting DCs
- Th2
- CD40
- Jagged1
- low IL-12

- NF-κB
- IL-1α
- IL-1β

- Th2-inducing potential
- Maturation

- DC
Isocyanate Asthma: Pathogenesis

• Similar to adult asthma
• Behaves like an immune disease – immune memory
• Problem is
  – Don’t know what the “real” antigen(s) is
  – Don’t have a good marker for sensitization

BUT WHERE KNOWLEDGE IS REALLY LACKING IS .........
Human Health Effects of Isocyanates

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Epidemiology is the study of the patterns, causes, and effects of health and disease in defined populations. It is the cornerstone of public health, and informs policy decisions and evidence-based medicine by identifying risk factors for disease and targets for preventive medicine.
Epidemiology Literature

• How common is isocyanate asthma?

• What are the major (modifiable) risk factors?
How common is isocyanate asthma today? What % currently exposed workers have isocyanate asthma? (prevalence)

a) < 5 %
b) 5-10%
c) 15 – 25%
d) > 30%
e) None of the above
<table>
<thead>
<tr>
<th>Study</th>
<th>Agent</th>
<th>Process / Occupation</th>
<th>Study Group</th>
<th>Outcomes</th>
<th>Follow-Up (years)</th>
<th>Diagnosis / Testing</th>
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</thead>
<tbody>
<tr>
<td>Woodbury, 1956</td>
<td>TDI</td>
<td>TDI Production</td>
<td>25</td>
<td>5.0%</td>
<td>1</td>
<td>Sxs, MD</td>
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<tr>
<td>Peters, 1968, 1970, 1974</td>
<td>TDI</td>
<td>TDI Production</td>
<td>38</td>
<td>Decline FEV1</td>
<td>3</td>
<td>PFTs</td>
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<tr>
<td>Wegman, 1974, 1977, 1982</td>
<td>TDI</td>
<td>TDI Production</td>
<td>112 to 37 (at 4 yrs)</td>
<td>Decline FEV1</td>
<td>4</td>
<td>PFTs</td>
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<tr>
<td>Adams, 1975</td>
<td>TDI</td>
<td>TDI Production</td>
<td>565</td>
<td>5.6%</td>
<td>11</td>
<td>MD</td>
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<td>Porter, 1975</td>
<td>TDI</td>
<td>TDI Production</td>
<td>300</td>
<td>0.9%</td>
<td>18</td>
<td>PFTs</td>
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<td>Butcher, 1977</td>
<td>TDI</td>
<td>TDI Production</td>
<td>277</td>
<td>3%</td>
<td>5.5</td>
<td>PFTs</td>
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<tr>
<td>Diem, 1982</td>
<td>TDI</td>
<td>TDI Production</td>
<td>277</td>
<td>1.0%</td>
<td>5</td>
<td>PFTs</td>
</tr>
<tr>
<td>Weill, 1979, 1981</td>
<td>TDI</td>
<td>TDI Production</td>
<td>277</td>
<td>0-1%</td>
<td>1.5</td>
<td>Immunologic SIC</td>
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<td>Musk, 1982</td>
<td>TDI</td>
<td>TDI Production</td>
<td>259 to 94 at 5 yr</td>
<td>FEV1 neg</td>
<td>10</td>
<td>PFTs</td>
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<tr>
<td>Grammer, 1988</td>
<td>HDI</td>
<td>Spray painters</td>
<td>150</td>
<td>0%</td>
<td>1.5</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>126 f/up</td>
<td>1%</td>
<td></td>
<td></td>
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<tr>
<td>Jones, 1992</td>
<td>TDI</td>
<td>TDI Production</td>
<td>386</td>
<td>0.7%</td>
<td>4</td>
<td>PFTs</td>
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<td>Clark, 1998, 2003</td>
<td>TDI</td>
<td>TDI foam 12 UK factors</td>
<td>780</td>
<td>10 left resp illness</td>
<td>5</td>
<td>PFTs</td>
</tr>
<tr>
<td></td>
<td></td>
<td>f/up 251</td>
<td></td>
<td>FEV1 neg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ott, 2000</td>
<td>TDI</td>
<td>TDI Production</td>
<td>297</td>
<td>1.1%</td>
<td>29</td>
<td>PFTs</td>
</tr>
<tr>
<td>Bodner, 2001</td>
<td>TDI</td>
<td>TDI Production</td>
<td>305</td>
<td>FEV1 neg</td>
<td>26</td>
<td>PFTs</td>
</tr>
<tr>
<td>Petsonk, 2000</td>
<td>MDI</td>
<td>Wood products</td>
<td>214</td>
<td>10 to 14%</td>
<td>2</td>
<td>Symptoms air levels ND</td>
</tr>
<tr>
<td></td>
<td></td>
<td>f/up 144</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cassidy</td>
<td>HDI</td>
<td>HDI Production</td>
<td>100 + control</td>
<td>FEV1 neg</td>
<td>&gt; 10 yrs</td>
<td>PFTs</td>
</tr>
</tbody>
</table>
# Selected Cross-Sectional Studies Isocyanate Exposed Workers

## Prevalence of Isocyanate Asthma / Symptoms

<table>
<thead>
<tr>
<th>Study</th>
<th>Agent</th>
<th>Process / Occupation</th>
<th>Study Group N</th>
<th>Prevalence IA %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bruckner, 1968</td>
<td>TDI</td>
<td>R&amp;D</td>
<td>26</td>
<td>19%</td>
</tr>
<tr>
<td>Tanser, A.R.</td>
<td>MDI</td>
<td>PU rigid foam</td>
<td>57</td>
<td>7%</td>
</tr>
<tr>
<td>White, 1980</td>
<td>TDI</td>
<td>PU seat covers</td>
<td>57</td>
<td>30%</td>
</tr>
<tr>
<td>Baux, 1981</td>
<td>TDI</td>
<td>Plastics, varnish</td>
<td>195</td>
<td>28%</td>
</tr>
<tr>
<td>Tse, 1985</td>
<td>MDI</td>
<td>Foundry</td>
<td>76</td>
<td>13%</td>
</tr>
<tr>
<td>Liss, 1988</td>
<td>MDI</td>
<td>Foundry</td>
<td>27</td>
<td>31%</td>
</tr>
<tr>
<td>Wang, 1988</td>
<td>TDI</td>
<td>Adhesive</td>
<td>38</td>
<td>0 to 85% symptoms</td>
</tr>
<tr>
<td>Huang, 1991</td>
<td>TDI</td>
<td>Varnish 3 factories</td>
<td>48</td>
<td>0 to 27%</td>
</tr>
<tr>
<td>Vandenplas, 1993</td>
<td>HDI</td>
<td>Spraying</td>
<td>9</td>
<td>45%</td>
</tr>
<tr>
<td>Bernstein, 1993</td>
<td>MDI</td>
<td>Injection mold plant</td>
<td>243</td>
<td>4%; Occ rhinitis 36%</td>
</tr>
<tr>
<td>Kim, 1997</td>
<td>TDI</td>
<td>Spraying</td>
<td>81</td>
<td>10%</td>
</tr>
<tr>
<td>Woellner, 1997</td>
<td>MDI</td>
<td>wood products</td>
<td>~ 130</td>
<td>14%</td>
</tr>
<tr>
<td>Redlich 2001</td>
<td>HDI</td>
<td>auto body</td>
<td>75</td>
<td>0% (34% HDI-IgG)</td>
</tr>
<tr>
<td>Pronk, 2007</td>
<td>HDI</td>
<td>241 spray painters</td>
<td>241</td>
<td>8.3% occ asthma symptoms 20% Occ rhinitis</td>
</tr>
</tbody>
</table>
Other sources information

- Surveillance reporting systems
- Workers compensation data
- Population studies
- Medical surveillance
• How common is isocyanate asthma?

• What are the major (modifiable) risk factors?
  a) Home pets
  b) Smoking
  c) Atopy
  d) Work exposures
  e) All of the above
Risk Factors Isocyanate Asthma

• EXPOSURE is by far the most important risk factor
• Atopy, smoking, exposure to other allergens are not risk factors
• Genetic factors – Dr. Bernstein

• What types of exposures pose the greatest risks?
• Skin, air, peak exposures, specific isocyanate formulations, particulates, thermal degradation products ????
Research Gaps

• Need for longitudinal epidemiology studies of highest risk populations (new workers)

• Better understand risks – incidence / prevalence

• Best understand risk factors – especially exposure
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<tr>
<th>Study</th>
<th>Number Subjects</th>
<th>Duration of Follow-Up (yrs)</th>
<th>Persistence of Symptoms</th>
<th>Persistence NSBRI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paggiaro, 1984</td>
<td>12</td>
<td>1-3</td>
<td>66%</td>
<td>58%</td>
</tr>
<tr>
<td>Lozewicz, 1987</td>
<td>50</td>
<td>&gt;4</td>
<td>82%</td>
<td>63%</td>
</tr>
<tr>
<td>Rosenberg, 1987</td>
<td>20</td>
<td>0.5 to 4</td>
<td>50%</td>
<td>75%</td>
</tr>
<tr>
<td>Tarlo, 1997</td>
<td>114</td>
<td>1.9</td>
<td>80%</td>
<td>69%</td>
</tr>
<tr>
<td>Piirila, 2000</td>
<td>235</td>
<td>10</td>
<td>82%</td>
<td>51%</td>
</tr>
<tr>
<td>Padoan, 2003</td>
<td>87</td>
<td>&gt; 10 yrs</td>
<td>71%</td>
<td>25%</td>
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Workers who left exposure had better asthma outcomes than those who had on-going exposures

**Recommendation:** Removal from further exposure (ERS, ACCP, Industry)
Isocyanate Asthma: Outcomes

Persistent asthma away from causative agent(s) common
Earlier removal from exposure better outcome
Socioeconomic outcomes poor
Unemployed – 25-40%
Loss income – 40-80%
High costs – medical, workers comp etc

Vandenplas ERJ 2003

MANAGEMENT
Remove from exposure
Standard asthma medications
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Thank you

Questions ????