Asthmatics as a susceptible population in health risk assessment of airborne chemicals

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• 10 million inhabitants
• IKEA, Volvo, Spotify, Skype, H&M
• The fundament of the US Marine Corps War Memorial (Washington) is made from Swedish stone.
• Almost free daycare + 18 months parental leave (of which 12 months with 80% salary)
• PCB:s was discovered as an environmental pollutant in Stockholm
• Karolinska Institutet is Sweden’s single largest centre of medical academic research.
• Since 1901 the Nobel Assembly at Karolinska Institutet has selected the Nobel laureates in Physiology or Medicine.
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Outline

• A conceptual framework for researchers roles and responsibilities in risk assessment and science-to-policy
• Do risk assessors include asthmatics?
• Are asthmatics more susceptible?
• Are current values protective for asthmatics?
• Can we use mice models to study susceptibility among asthmatics?
• Concluding remarks
References


Researchers’ roles and responsibilities in risk assessment

• Develop toxicological and medical information relevant to decisions involving chemical regulations to protect health and environment
• Provide risk managers (in state and local government agencies + private sector) with information
• Involve and equip students and other researchers in this process
• Use systematic improvement strategies for societal interaction
• Consider Science-to-policy as a research area of itself
Research within Science-to-policy

- Identify areas of improvement
- Communicate results
- Evaluate outcome
- Analyse legislation
- Follow up! (Policy)

Analyse legislation
Evaluate outcome
Identify areas of improvement
Communicate results
Follow up!
Research within Science-to-policy

- Can we use experimental models to evaluate the sensitivity among asthmatics?
- Are asthmatics more susceptible than healthy individuals?
- How large should an assessment factor be?
- How large is the difference?
- Are asthmatics included in health risk assessment?
- How does different guidelines recommend to use data from asthmatics?

Policy flow:

1. Identify areas of improvement
2. Communicate results
3. Analyse legislation
4. Follow up
5. Evaluate outcome
6. Policy

Questions:
- How does different guidelines recommend to use data from asthmatics?
- Are asthmatics more susceptible than healthy individuals?
- How large should an assessment factor be?
- How large is the difference?
- Are asthmatics included in health risk assessment?
Three steps

**Regulation**
Inclusion of asthmatics in health risk assessment

**Assessment factors**
Systematic evaluation of human experimental data

**Experimental asthma model on mice**
Airway response after Cl₂ exposure
Inclusion of asthmatics in the Acute Exposure Guideline Levels (AEGLs)

- AEGL-values for preparedness, emergency and response
- Threshold levels: AEGL-1, -2, -3
- Duration 10min - 8hours

- “...general public, including susceptible subpopulations, such as infants, children, the elderly, persons with asthma, and those with other illnesses...” (NRC 2001, p. 3)

Experimental data on asthmatics in ten acute to short-term guideline values

General population

Working population

Number of support documents

AEGL
ERPG
MRL
REL
VSTAF
DECOS
MAK
SCOEL
Sweden
TLV

Conclusions

Are asthmatics included in acute to short-term guideline values?

Not always...

• asthmatics are frequently disregarded in the setting acute to short-term guideline values for both the general and the working population.

• we suggest that available data on asthmatics should be considered carefully in the derivation of guideline values, and if such data are lacking, this should be indicated explicitly in the case of respiratory irritants.
Evaluation of the experimental basis for assessment factors to protect individuals with asthma from health effects during short-term exposure to airborne chemicals.

- Are asthmatics more susceptible than healthy to exposure of airborne chemicals?
- If so, how large is the difference?

Human Exposure Chambers

- Acute exposure to airbourne chemicals
- Irritation symptoms
- Airway responses
- Biomarkers of inflammation
- With or without work load
- Low doses – typically up to OEL
- Kinetics
Difference in airway response between asthmatic and healthy subjects

- Asthmatics and healthy subjects tested under similar conditions \( n=103 \)

- Lowest Observed Adverse Effect Concentration (LOAEC)
  - Adverse effect: Lung function, symptoms, inflammation markers

- Estimated Differential Response Factor (EDRF) \( = \frac{\text{LOAEC}_{\text{healthy}}}{\text{LOAEC}_{\text{asthma}}} \)

- EDRF = 2
  - “Asthmatics are two times more sensitive as compared with healthy subjects”
Asthmatics are more susceptible to 11 out of 30 tested chemicals/mixtures

<table>
<thead>
<tr>
<th>Chemical (n)</th>
<th>Young et al., (2009)</th>
<th>Johansson et al., 2016</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acetaldehyde (3)</td>
<td></td>
<td>3</td>
</tr>
<tr>
<td>Ammonium bisulfate (4)</td>
<td></td>
<td>&gt;1</td>
</tr>
<tr>
<td>Chlorine (1)</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Formaldehyde (3)</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Nitrogen dioxide (14)</td>
<td>3-5</td>
<td>&gt;1</td>
</tr>
<tr>
<td>Ozone (25)</td>
<td>2</td>
<td>&gt;1</td>
</tr>
<tr>
<td>Sulfuric dioxide (8)</td>
<td>3-4</td>
<td>&gt;2</td>
</tr>
<tr>
<td>Sulfuric acid (14)</td>
<td>1.3-5</td>
<td>&gt;1</td>
</tr>
<tr>
<td>Toluenediisocyanate (1)</td>
<td></td>
<td>&gt;1</td>
</tr>
<tr>
<td>Zink ammonium sulfate (1)</td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Diesel particles (1)</td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Second hand smoke (2)</td>
<td></td>
<td>&gt;1</td>
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<tr>
<td>Ozone in ambient air (1)</td>
<td></td>
<td>&gt;1</td>
</tr>
<tr>
<td>Ozone + SO₂ (1)</td>
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<td>&gt;1</td>
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<tr>
<td>Ozone + H₂SO₄ (1)</td>
<td></td>
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</tr>
</tbody>
</table>

NO$_2$ – Concentration/Response relationships (oronasal breathing during exercise)

SO$_2$ – Concentration/Response relationships (oronasal breathing during exercise)

SO$_2$ - Benchmark concentration (BMC) analysis

Critical Effect Size = 20% SRaw
Asthmatics (3.7 mg/m$^3$)
Healthy individuals (33.7 mg/m$^3$)

EDRF $= \frac{33.7}{3.7} \approx 9$

Conclusions

Are asthmatics more susceptible than healthy to exposure of airborne chemicals?
• Yes, this was confirmed by 11 out of 15 chemicals/mixtures

How large is the difference?
• 3, 2, >2, >1

Benchmark dose analysis for sulfur dioxide
• 9

• It was not possible to estimate the difference in response for 15 out of 30 chemicals tested in exposure chambers

• Overall, the experimental findings on inter-individual variation provide support for the use of an inter-individual assessment factor of 10
Does industry take the susceptible subpopulation of asthmatic individuals into consideration when setting Derived No-Effect Levels (DNELs)?

Derived No-Effect Levels (DNELs)

EU legislation Registration Evaluation, Authorisation and Restriction of Chemicals (REACH).

- Industry should derive DNELs for all substances >10 tons/year

Acute inhalation DNELs (a) for workers and (b) the general population

The European Chemicals Agency (ECHA) registration database

- Not available: Full dossiers (risk assessment documents)
- Available: DNEL values, Assessment factors and key studies
DNEL = NOAEL/Accessment factors

- Interspecies differences (x10)
  - Alomeric scaling (Rat = x4, Mouse = x7)
  - Remaining differences (x2.5)
- Human variability (x10)
  - Sometimes an extra factor for children (x10)
  - Workers (x5)
- Duration extrapolation (x1-6)
  - E.g. subchronic-to-chronic (x2)
- Only LOAEL (x3)
- Quality of database (x1-100)
Are asthmatics protected by acute to short-term guideline values?

- 22 chemicals data
- 14 registered REACH
- 9 cited
- 4 used

For three substances, the worker DNELs were higher than our estimated overall LOAECs.
For two of these also the DNELs for the general population were higher than the overall LOAEC.
Conclusions

Are asthmatics protected by acute to short-term guideline values?

No...

• REACH registrants do not routinely take asthmatics into consideration when setting acute/short-term DNELs.

• Several DNELs for acute inhalation were higher than NOAEC/LOAEC from human studies with asthmatics, indicating low or no safety margin.

• Especially evident for workers.

• The DNELs do not differ distinctly from the other ten sets of acute/short-term guideline values (see previous study).

• Updated ECHA guidance concerning susceptible subgroups in connection with the setting of DNELs may improve the derivation of these values.
A mice model for asthma?

• Can we learn more about the susceptibility of asthmatics by the use of an experimental model?
Experimental design (BALB/c mice)

- Systemic sensitization: OVA
- Airway inflammation: OVA
- Exposure to chlorine
  - Respiratory frequency
  - Respiratory mechanics
  - Metacholine challenge
  - Bronchoalveolar lavage
  - Blood
  - Lung lobes
  - Weights

- Respiratory mechanics
Respiratory frequency

50% reduction in respiratory frequency ($RD_{50}$) = 5 ppm

If Threshold Limit Values are on average 0.03 times the $RD_{50}$ (Alarie, 1981)...

- 0.15 ppm limit value based on this study
- 0.4 ppm symptoms observed in asthmatics (D’Allessandro et al., 1996)
- 0.5 ppm AEGL-1 value
Respiratory resistance during metacholine challenge

Air

80 ppm chlorine

![Graph showing respiratory resistance during metacholine challenge for air and 80 ppm chlorine.](image)
Neutrophilic and eosinophilic cells in bronchoalveolar lavage fluid

Neutrophils

Eosinophils

Naive

OVA-sensitized mice

Number of cells/ml

Chlorine concentration (ppm)
Histopathological samples

Naive (severity score 0)  OVA-sensitized (severity score 4)
Conclusions

Can we learn more about the susceptibility of asthmatics by the use of an experimental model?

Maybe, but difficult with this model...

• Similar chlorine-dependent reductions in respiratory frequency.
• At 80-ppm chlorine in naïve, but not in OVA-sensitized mice
  • Increase in airway hyperresponsiveness
  • Increased number of neutrophils in BALF
• Very strong airway inflammation in the sensitized mice
Overall conclusions

- Asthmatics are not protected by all acute to short-term guideline values.
- Exclusion of asthmatics in the derivation of acute to short-term guideline values may interfere with trustful and efficient health-protective actions.
- Asthmatics are more susceptible than healthy to exposure of several airborne chemicals.
- Our experimental model did not support increased susceptibility of asthmatics.
- The use of an inter-individual assessment factor of 10 may be adequate to protect asthmatics from the deleterious respiratory effects of airborne chemicals.
Future perspectives

We see that data on asthmatics are often not included in the assessment for the working environment. This view stems from a time when a worker was thought to be a young and healthy man. If you were a woman, sick or elderly, you should stay away from the labor market.

Exacerbation of asthma is clearly an adverse health effect and we argue that individuals who constitute one-tenth of the general population, as well as a large part of the working population, should be taken into consideration.

Another example from EU:
DNEL for BPA = 4 ug/kg/d
Worker-DNEL for BPA = 8 ug/kg/d
Thank you for listening!