Combined Exposures to Dangerous Substances in the Workplace; An epidemiological perspective

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Institute for Risk Assessment Sciences

An interfacultary research institute within the faculties Veterinary Medicine, Medicine, Pharmaceutical Sciences and Biology of Utrecht University

The mission of IRAS is to provide education and research on the human health risks of exposure to potentially harmful agents in the environment, at the workplace and through the food chain.
Dr. Roel Vermeulen

• Background:
  – Environmental Health
  – Toxicology
  – Epidemiology

• Focus area IRAS
  – Cancer Epidemiology
    • Hemato- Lymphopoietic disorders
    • Lung
  – Molecular epidemiology
Focus Area Environmental Cancer

- **Hemato- Lymphopoietic disorders**
  - Benzene
  - Dioxin
  - Electromagnetic fields
  - Formaldehyde
  - Trichloroethylene
  - Selected pesticides

- **Lung**
  - Asbestos
  - Diesel exhaust
  - Indoor air pollution
  - Metals
  - Polycyclic Hydrocarbons
Exposures in the Workplace are by Definition Complex

- Combined exposures to multiple chemicals
  - Multiple exposures / complex mixtures

- Combined exposures to chemicals and psychosocial risk factors
  - Occupational exposures and stress

- Combined exposures and lifestyle factors
  - Occupational exposures and nutritional status
Synergistic or Antagonistic?

- Antagonistic
  - Saturation of metabolic systems

- Synergistic
  - Inflammation + genotoxicity
Epidemiological Evidence?

Lung cancer risk associated with working in A) cotton textile industry and B) agricultural industry.

A

Henderson (1973)
Merchant (1981)
Levin (1987)
Koskela (1980)
Hodgson (1990)
Wu-Williams (1993)
Szeszenia-Dabrowska (1999)
Fritschl (2004)
Kuzmickiene (2007)
Astrakianakis (2007)
Mastrangelo (2008)

B

Burmeister (1981)
Levin (1988)
Wilkund (1988)
Stark (1990)
Gunnardottir (1991)
Alberghini (1991)
Ronco (1992)
Faustini (1993)
Wilkund (1994)
Mastrangelo (1996)
Pukkala (1997)
Sperati (1999)
Jahn (1999)
Alavanja (2005)
Mastrangelo (2005)
Lee (2006)
Laakkonen (2008)
Overall (I-squared = 97.8%, p = 0.000)

Lenters et al., submitted
Combined Exposures to Multiple Chemicals

• Rubber industry
  – Cross-sectional survey on genotoxic exposures in the rubber industry

• RAPTES
  – to characterize the physical, chemical and oxidant properties of inhaled particulate matter and establish which of these characteristics are critical determinates of adverse systemic and respiratory effects

• Synergy
  – Synergistic effects of multiple exposures to lung carcinogens
The Rubber Industry

• The rubber industry has been associated with increased cancer risks: lung, bladder, larynx and leukemia

• Exposure to a complex mixture of compounds
  ▪ Aromatic amines
  ▪ PAHs
  ▪ Carbon black
  ▪ Nitrosamines
  ▪ Solvents

• Both inhalation and dermal exposure

  → Current genotoxic risks largely unknown

1. IARC Monographs “The rubber industry” (1982)
Rubber Industry; Complex Mixture of Compounds
Particulate exposure; Mass and Mutagenicity

Geometric mean particulate exposure (mg/m³) for each production function in each plant
Potency Measures of Combined Exposures

• Relevance of potency measures?
  – Mutagenicity
  – Oxidant properties
  – Metabonomics

• Legislation?

Figure 1 | Hierarchical cluster analysis using group average linkage based on median \(^1\)H NMR urine spectra, by population sample and gender

Holmes et al., 2008
Pooled Analysis of European Case-control Studies on the Interaction of Occupational Carcinogens in the Development of Lung Cancer

Included case-control studies:

- HDA Germany
- AUT Germany
- LUCAS Sweden
- TURIN-ROME Italy
- EAGLE Italy
- INCO-Copernicus Czech Republic, Hungary, Poland, Romania, Russia, Slovakia, UK
- LUCA France
- PARIS France
- ICARE France
- EPIC The Netherlands
- Montreal Canada

Overall almost 30,000 cases and controls
## Targeted Exposures – Lung Carcinogens

<table>
<thead>
<tr>
<th>Substance</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Asbestos</strong></td>
<td>chrysotile (white asbestos); amphibole; other type</td>
</tr>
<tr>
<td><strong>Chromium</strong></td>
<td>chromium VI; total chromium</td>
</tr>
<tr>
<td><strong>Nickel</strong></td>
<td>soluble nickel compounds; insoluble nickel compounds; total nickel</td>
</tr>
<tr>
<td><strong>PAHs</strong></td>
<td>benzo(a)pyrene; naphthalene</td>
</tr>
<tr>
<td><strong>Respirable Crystalline Silica</strong></td>
<td>respirable quartz; respirable cristobalite; respirable tridymite; respirable crystalline silica</td>
</tr>
</tbody>
</table>
Challenges in Detecting Interactions

The power to detect interactions in epidemiological studies is low:

- Increase in study size
- Improved exposure assessment methods

Table 2  Minimum number of cases (case:control ratio = 1) required to detect a 2-fold multiplicative gene-environment interaction ($OR_{10} = 2.0$, $OR_{01} = 2.0$, $OR_{11} = 8.0$) for different levels of accuracy of the environmental and genetic factors$^a$

<table>
<thead>
<tr>
<th>Environmental factor sensitivity</th>
<th>Genetic factor sensitivity</th>
<th>Prevalences</th>
<th>$\Psi$</th>
<th>Odds ratios</th>
<th>No. of cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.0</td>
<td>1.0</td>
<td>0.50</td>
<td>0.50</td>
<td>2.00</td>
<td>720</td>
</tr>
<tr>
<td>0.8</td>
<td>1.0</td>
<td>0.40</td>
<td>0.50</td>
<td>1.56</td>
<td>1600</td>
</tr>
<tr>
<td>1.0</td>
<td>0.95</td>
<td>0.50</td>
<td>0.48</td>
<td>1.83</td>
<td>900</td>
</tr>
<tr>
<td>0.8</td>
<td>0.95</td>
<td>0.40</td>
<td>0.48</td>
<td>1.46</td>
<td>2044</td>
</tr>
</tbody>
</table>

$^a$ Specificity for both genetic and environmental factor assessment = 1.0.  
$^b\Psi^*$, observed interaction parameter.
# Joint Exposure Prevalences

<table>
<thead>
<tr>
<th></th>
<th>pah</th>
<th>cr</th>
<th>ni</th>
<th>as</th>
<th>mmmf</th>
<th>rcs</th>
<th>dme</th>
</tr>
</thead>
<tbody>
<tr>
<td>asb</td>
<td>4722</td>
<td>3008</td>
<td>1467</td>
<td>396</td>
<td>1714</td>
<td>933</td>
<td>1748</td>
</tr>
<tr>
<td></td>
<td>(33%)</td>
<td>(21%)</td>
<td>(10%)</td>
<td>(3%)</td>
<td>(12%)</td>
<td>(7%)</td>
<td>(12%)</td>
</tr>
<tr>
<td>pah</td>
<td>3502</td>
<td>2196</td>
<td>2873</td>
<td>1641</td>
<td>3744</td>
<td>4656</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(24%)</td>
<td>(15%)</td>
<td>(20%)</td>
<td>(12%)</td>
<td>(26%)</td>
<td>(32%)</td>
<td></td>
</tr>
<tr>
<td>cr</td>
<td>2217</td>
<td>296</td>
<td>1607</td>
<td>80</td>
<td>62</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>(16%)</td>
<td>(2%)</td>
<td>(11%)</td>
<td>(1%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ni</td>
<td>281</td>
<td>248</td>
<td>81</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>(2%)</td>
<td>(2%)</td>
<td>(1%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>as</td>
<td>81</td>
<td></td>
<td></td>
<td>2389</td>
<td>2346</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>(1%)</td>
<td></td>
<td></td>
<td>(17%)</td>
<td>(16%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>mmmf</td>
<td>723</td>
<td></td>
<td></td>
<td></td>
<td>17</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>(5%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>rcs</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>2902</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(20%)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
## Joint Exposure Prevalences - High

<table>
<thead>
<tr>
<th></th>
<th>pah</th>
<th>cr</th>
<th>ni</th>
<th>as</th>
<th>mmmf</th>
<th>rcs</th>
<th>dme</th>
</tr>
</thead>
<tbody>
<tr>
<td>asb</td>
<td>567 (4%)</td>
<td>7</td>
<td>6</td>
<td>0</td>
<td>0</td>
<td>10</td>
<td>0</td>
</tr>
<tr>
<td>pah</td>
<td>7</td>
<td>7</td>
<td>0</td>
<td>18</td>
<td></td>
<td>686 (5%)</td>
<td>525 (4%)</td>
</tr>
<tr>
<td>Cr</td>
<td>7</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Ni</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>As</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>mmmf</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>rcs</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>438 (3%)</td>
<td></td>
</tr>
</tbody>
</table>
Highest Joint Exposure Prevalences

- Highest joint prevalences found for:
  - Asbestos and PAH (33%; 4% high)
  - PAH and diesel (32%; 4% high)
  - PAH and silica (26%; 5% high)
  - Silica and diesel (20%; 3% high)

Relatively low joint prevalences
Challenges in Detecting Interactions

The power to detect interactions in epidemiological studies is low:

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Table 2  Minimum number of cases (case:control ratio = 1) required to detect a 2-fold multiplicative gene-environment interaction ($OR_{10} = 2.0$, $OR_{01} = 2.0$, $OR_{11} = 8.0$) for different levels of accuracy of the environmental and genetic factors

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<tr>
<td></td>
<td></td>
<td>Environmental factor</td>
<td>Genetic factor</td>
<td>$\Psi^{*b}$</td>
</tr>
<tr>
<td>1.0</td>
<td>1.0</td>
<td>0.50</td>
<td>0.50</td>
<td>2.00</td>
</tr>
<tr>
<td>0.8</td>
<td>1.0</td>
<td>0.40</td>
<td>0.50</td>
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$^b$ $\Psi^{*}$, observed interaction parameter.
Improved Exposure Assessment

Required data:

Personal measurement data is preferred above stationary

Individual data points needed to build multivariate models

Auxiliary data, such as:
• Purpose/strategy of measurement
• Sampling devices
• Analytical procedures
Data collection – So far

- **Canada**
- **Czech Rep.**
- Denmark
- Finland
- **France**
- **Germany**
- **Hungary**
- Iceland
- **Italy**
- **NL**
- Norway
- **Poland**
- **Sweden**
- **UK**
- **Slovakia**
- **Romania**
- **Russia**

Data being entered at moment vs. Data already in ExpoSYN (n ~28,000)
Research Actions

• Integration of functional test systems into epidemiological research

• Improved exposure assessment tools
  – Better utilization of existing data?

• Large epidemiological studies on occupational risk factors
Contact Information

www.iras.uu.nl

www.juliuscenter.nl