Annex VI

Chemical Reports

Respiratory sensitizers
- Acid Anhydride
- Various Acrylates
- Amines in general
- Amines: Aliphatic amines
- Amines: Heterocyclic amines
- Azobisformamide
- Biocides
- Various chemicals, not specified elsewhere
- Colophony and fluxes
- Diazonium salt and reactive dyes
- Formaldehyde and his resin
- Metals in general
- Metal: Chromium
- Metal: Cobalt
- Metal: Nickel
- Metal: Platinum
- Metal: Zinc
- Persulfate salt
- Polyisocyanates and oligo/polymers
  - Polyisocyanate: Hexamethylene diisocyanate
  - Polyisocyanate: Diphenylmethane diisocyanate
  - Polyisocyanate: Toluene diisocyanate
- Polyvinyl chloride and phthalates (fumes)
- Polyvinyl chloride and phthalates (indoor)
- Styrene
- Wood dust / bark
### Acid Anhydride

#### Weight-of-evidence approach
Evaluation of the compounds:

<table>
<thead>
<tr>
<th>Classification</th>
<th>CAS</th>
<th># Pub</th>
<th>R phrase</th>
<th>LLNA</th>
<th>human data</th>
<th>Publ score</th>
<th>Total score</th>
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<td>Acid anhydride</td>
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#### Compounds

<table>
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<tr>
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<th># Pub</th>
<th>R phrase</th>
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<td>Chlorendic anhydride</td>
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<td>1(moderate)</td>
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#### Analysis

**Sources of exposure**
All the studies are reporting occupational exposure. The most part of exposures occurs in plants manufacturing or handling resins, especially epoxy resins. Also workers, with anhydride-induced OA, employed in chemical and electrical plants are described. Exposure to anhydrides can also occur while power painting and manufacturing aircraft filters.

**Gender**
Both males and females are reported.

**Age**
The exposure effects all ages of the work population: 18-81 years.

**Latency**
The latency period for developing asthmatic symptoms is not often described. It varies from 4 months to several years.

**Temporal pattern**
In many studies, there isn’t focused on the details of the reaction. When reported, it is an immediate asthmatic reaction.

**Associated symptoms**
Associated rhinitis and rhinoconjunctivitis are regularly reported.

**Regional differences**
Valuable cross-sectional studies, investigating a large exposed work population, are published from the UK, Germany and Sweden. Also in Finland reported cases are found.
### Various Acrylates

**Weight-of-evidence approach**
Evaluation of the compounds:

<table>
<thead>
<tr>
<th>Classification</th>
<th>CAS</th>
<th># Pub</th>
<th>R phrase</th>
<th>LLNA</th>
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<th>Publ score</th>
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<tr>
<td><strong>Compound</strong></td>
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<td>ethyl acrylate</td>
<td>140-88-5</td>
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<td>1(R43/R37/R38)</td>
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<td>1(R37/R43)</td>
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<td>1(R43/R38)</td>
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<td>hydroxyethyl methacrylate</td>
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<td>1(R43/R38)</td>
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</table>

**Analysis**

**Sources of exposure**
Acrylates have a wide application in various products, such as the manufacture of dental prostheses and tooth fillings, orthopedic prostheses and splints, soft contact lenses, histological preparations, printing colors, floor waxes floor coatings, textiles and paper products, nail cosmetics, and as glues, sealants and adhesives.

Dental personnel with acrylate-induced asthma are often described. Non-acrylate-material, such as chloramine T and latex, can also be the cause in this working population.

**Gender**
Both male and female patients are reported. Asthma due to the use of artificial nails is only described in women, workers and clients.

**Age**
Adult workers and clients: between 31 and 54 years old.

**Latency**
The latency period is not often reported and range from 2 month to 13.5 years.
Temporal pattern
Late or dual asthmatic reactions are mentioned.

Associated symptoms
ACD due to acrylates is well known and studied. Rhinoconjunctivitis and ACD are commonly associated. Rhinoconjunctivitis develops often prior to the acrylate-induced asthma.

Regional differences
Data were found for the following EU countries: the UK, Spain, and mainly Finland.

Time trends
Since 1992 an increasing frequency of respiratory hypersensitivity among dental personnel is shows in Finland.
### Amines in general

#### Weight-of-evidence approach
Evaluation of the compounds:

<table>
<thead>
<tr>
<th>Classification</th>
<th>CAS</th>
<th># Pub</th>
<th>R phrase</th>
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<td>Aminoethylethanol-amine</td>
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#### Analysis

**Sources of exposure**
The studies describe only cases due to occupational exposures. The amines are handled in the primary (chemical) manufacturing as in the secondary industries; aircraft filter manufacture, soldering, mould production, cleaning, paper recycling, and sales of floor covering material.

**Gender**
Both males and females become allergic to amines. Mostly men are mentioned linked to the job performance.

**Age**
Work population: between 21 and 60 yrs old.

**Latency**
Wide range: 1 week to 10 years

**Temporal pattern**
There is not a specific pattern in the reaction to amines; immediate and also late and dual reactions are described.

**Associated symptoms**
There are many OA cases with rhinitis. Unfortunately in some publications there was no attention for associated symptoms due to amines.

**Regional differences**
Data were found for the following EU countries: the UK, Spain, Sweden, and Finland. In the USA and Canada are also publications describing other secondary industrial settings where amine-induced OA can occur (spray painters, lacquers and beauty culture).
Amines: Aliphatic amines

Weight-of-evidence approach
Evaluation of the compounds:

<table>
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<tr>
<th>Classification</th>
<th>CAS</th>
<th># Pub</th>
<th>R phrase</th>
<th>LLNA</th>
<th>human data</th>
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<tr>
<td>Aminoethylethanolamine</td>
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<td>1(R43)</td>
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<tr>
<td>Ethylenediamine</td>
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<td>1(R42/R43)</td>
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<tr>
<td>Triethylene tetramine</td>
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<td>1</td>
<td>1(R43)</td>
<td>0</td>
<td>0</td>
<td>1</td>
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</tbody>
</table>

Analysis

Sources of exposure
The studies describe only cases due to occupational exposures. Chemical plants and solder manufactures are common, where the metal worker and also the cleaning personnel become asthmatic. Also exposure while producing aircraft filters is mentioned.

Gender
Both males and females become allergic to amines. Mostly men are mentioned linked to the job performance.

Age
Work population: 21 and 61 yrs old.

Latency
Mostly several months of exposure are needed before developing asthma; however cases are described with a latency period of 3 years.

Temporal pattern
If the pattern is mentioned, the symptoms begin directly or hours after contact with the aliphatic amine.

Associated symptoms
Unknown

Regional differences
Data were found for the following EU countries: the UK, Sweden, and Finland. In the USA and Canada are also publications describing other secondary industrial settings where amine-induced OA can occur (spray painters, lacquers and beauty culture).
**Amines: Heterocyclic amines**

**Weight-of-evidence approach**
Evaluation of the compounds:

<table>
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<th>Classification</th>
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<th>R phrase</th>
<th>LLNA</th>
<th>human data</th>
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<td>N-methylmorpholine</td>
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<td>3</td>
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<tr>
<td>Piperazine dihydrochloride</td>
<td>142-64-3</td>
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<td>1(R37/R38/R42)</td>
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</tbody>
</table>

**Analysis**

**Sources of exposure**
The studies mostly describe cases due to occupational exposures in chemical plants.

**Gender**
Both males and females become allergic. Mostly men are mentioned linked to the job performance.

**Age**
Work population: between 21 and 60 yrs old.

**Latency**
There is a wide range between 6 months and 22 years.

**Temporal pattern of manifestation**
If the pattern is mentioned, the symptoms began directly or hours after contact with the heterocyclic amine.

**Associated symptoms**
Associated rhinoconjunctivitis is described.

**Regional differences**
Data were found for the following EU countries: the UK, Sweden.
Annex VI

Chemical reports

<table>
<thead>
<tr>
<th>Compound</th>
<th>CAS</th>
<th># Pub</th>
<th>R phrase</th>
<th>LLNA</th>
<th>human data</th>
<th>Publ</th>
<th>score</th>
<th>Total score</th>
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<td>Azobisformamide</td>
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<td>1(R42/R43)</td>
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<td>1</td>
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</tbody>
</table>

### Analysis

**Sources of exposure**
Azobisformamide (or Azodicarbonamide) is used in the plastic industry for making foams.

**Gender**
Both male and females patients are reported.

**Age**
Work population: 29-63 years

**Latency**
Several months to a year of exposure occur before symptoms develop.

**Temporal pattern**
Mostly late asthmatic reactions are reported and also dual reactions are possible.

**Associated symptoms**
The association with other allergic symptoms is not frequently described.

**Regional differences**
Data were found for the following EU countries: the UK, Germany and Italy. Additional information comes from Canada and USA.
Biocides

Weight-of-evidence approach
Evaluation of the compounds:

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<th>CAS</th>
<th># Pub</th>
<th>R phrase</th>
<th>LLNA 1 (strong)</th>
<th>huma n data</th>
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<td>1(R42)</td>
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<td>0</td>
<td>1 2</td>
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<tr>
<td>Glutaraldehyde</td>
<td>111-30-8</td>
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<td>1(R42/R43)</td>
<td>1</td>
<td>1</td>
<td>1 4</td>
<td></td>
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<tr>
<td>Hexachlorophene</td>
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</tr>
</tbody>
</table>

Analysis

Sources of exposure
The studies describe only cases due to occupational exposures. Primary exposure can occur in the biocide production plants. These biocides are frequently used in the medical sectors. So the most patients are working as hospital staff: the cleaning staff, the sterilization unit, nursing (chlorhexidin) and the endoscopy unit (glutaraldehyde). Chloramine T is a sterilizing agent used in the food and beverage industry (brewery).

Gender
Both males and females become allergic to biocides. Mostly men are mentioned linked to the job performance.

Age
Work population: between 29 and 56 yrs old

Latency
The latency is not often reported. When it is reported, the period ranges from days to 23 years.

Temporal pattern
Many cases are described where the symptoms develop already seconds after the exposure; however also late ad dual reactions are possible.
Associated symptoms
Almost every patient has complaints of rhinitis and conjunctivitis simultaneously with the asthma symptoms.

Regional differences
Most part of the publications is from the UK. Also in the Netherlands and in Hungary, cases are described.
Various chemicals, not specified elsewhere

Weight-of-evidence approach
Evaluation of the compounds:

<table>
<thead>
<tr>
<th>Classification</th>
<th>CAS</th>
<th># Pub</th>
<th>R phrase</th>
<th>LLN</th>
<th>human data</th>
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<th>Total score</th>
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<tr>
<td>Chemicals</td>
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<tr>
<td>Compounds</td>
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<tr>
<td>Ethylene oxide</td>
<td>75-21-8</td>
<td>2</td>
<td>0(R37/R38)</td>
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<tr>
<td>Iso-nonanoyl oxybenzene sulfonate</td>
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<td>0</td>
<td>0</td>
<td>0</td>
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<td>Metabisulphite</td>
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<td>0</td>
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<tr>
<td>Methyl blue</td>
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<tr>
<td>Ninhydrin</td>
<td>485-47-2</td>
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<td>0(R37/R38)</td>
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<td>Polyethylene</td>
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<td>Polyfunctional aziridine</td>
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<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Tetrazene</td>
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<tr>
<td>Triglycidyl isocyanurate</td>
<td>2451-62-9</td>
<td>1</td>
<td>1(R37/R38/R42/R43)</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>2</td>
</tr>
</tbody>
</table>

Analysis

Sources of exposure
All the cases reported are due to occupational exposures. The main occupational settings are laboratory, hospital, detonator manufacturing and painting.

Gender
Both males and females with low molecular weight chemical-induced asthma are reported.

Age
Work population: 19 and 52 years old.

Latency
The latency period seems not so long: the period varies from 2 weeks to 2 years maximum.
Temporal pattern of manifestation
All types of asthmatic reactions are described.

Associated symptoms
Associated nasal, eyes and skin symptoms are described.

Regional differences
The reported case lived in the UK, Finland, Belgium and Germany.
Colophony and fluxes

Weight-of-evidence approach
Evaluation of the compounds:

<table>
<thead>
<tr>
<th>Compound</th>
<th>CAS</th>
<th># Pub</th>
<th>R phras e</th>
<th>LLNA</th>
<th>human data</th>
<th>Publ score</th>
<th>Total score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colophony and fluxes</td>
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<td></td>
<td></td>
<td></td>
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<td>Colophony</td>
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<td>0</td>
<td>1</td>
<td>1</td>
<td>2</td>
<td>2</td>
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<tr>
<td>fluxes</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alkylarul polyether alcohol + 5% polypropylene glycol</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Zinc chloride and ammonium chloride flux 95%</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>1</td>
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</tr>
</tbody>
</table>

Analysis

Sources of exposure
All the studies describe sensitization due to colophony-based solder fumes, in solder manufactures and in electronics industry where it is used as flux to prevent corrosion. Another flux containing zinc chloride and ammonium chloride and one containing polyester alcohol-polypropylene glycol are reported to cause occupational asthma.

Gender
Both males and females become allergic to colophony.

Age
Because the studies are held in an occupational setting, the patients are adults. It is however striking that the described cases are young: between 25-39 years.

Latency
Latency is difficult to known in the investigations we found.

Temporal pattern
Immediate, late and dual asthmatic reactions are mentioned.

Associated symptoms
Contact dermatitis and rhinitis are reported.

Regional differences
The UK has done the most part of the work; especially Burge PS and colleagues have an expertise on the field.
### Diazonium salt and reactive dyes

**Weight-of-evidence approach**  
Evaluation of the compounds:

<table>
<thead>
<tr>
<th>Compound</th>
<th>CAS</th>
<th># Pub</th>
<th>R phrases</th>
<th>LLNA human data</th>
<th>Publ score</th>
<th>Total score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diazonium salt and reactive dyes</td>
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<td>1</td>
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<td>Diazonium salt</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Drimaren brilliant yellow K-3GL</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
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<tr>
<td>Lanasol yellow 4G</td>
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<td>0</td>
<td>0</td>
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<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Drimaren brilliant blue K-BL</td>
<td>3</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Monascus ruber</td>
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<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Scarlet 32</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Cibachrome brilliant scarlet 3R</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Levafix brilliant yellow E-36</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
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</tr>
</tbody>
</table>

**Analysis**

**Sources of exposure**  
Diazonium salts are used in photocopying process. Exposure to several reactive dyes is possible while manufacturing, mixing and weighing the compounds. The main occupational setting with exposure to reactive dyes is the textile industry. Also sensitization in a delicatessen plant is described where reactive dyes are used as food colorant.

**Gender**  
Both males and females become allergic.

**Age**  
Work population: 30-63 years old

**Latency**  
Latency is not often mentioned. The latency period ranges between 8 months and 9 years.

**Temporal pattern**
Immediate, late and dual asthmatic reactions are described.

**Associated symptoms**
Associated rhinitis is often reported. Occasionally skin and eye symptoms are described.

**Regional differences**
Data were found for the following countries: the UK, Belgium, Finland, Italy and Sweden.
Formaldehyde and his resin
CAS: 50-00-0

Weight-of-evidence approach
Evaluation of the compounds:

<table>
<thead>
<tr>
<th>Compound</th>
<th>CAS</th>
<th># Pub</th>
<th>R phrase</th>
<th>LLNA</th>
<th>human data</th>
<th>Publ score</th>
<th>Total score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Formaldehyde and resin</td>
<td>5(1)</td>
<td></td>
<td></td>
<td></td>
<td>1</td>
<td>1</td>
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<tr>
<td>Formaldehyde</td>
<td>50-00-00</td>
<td>4(1)</td>
<td>1(R43)</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>Urea formaldehyde</td>
<td>9011-05-6</td>
<td>1</td>
<td>1(R43)</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>2</td>
</tr>
</tbody>
</table>

Analysis

Sources of exposure
The most studies studying air pollution at home suggest that formaldehyde plays an important role. Formaldehyde has been used as insulation in many buildings.

The cases of occupational asthma were reported as formaldehyde is used in a wide variety of occupational settings: chemical plant, furniture manufacturing and plants with resin exposures.

Gender
Both males and females become allergic to formaldehyde exposure.

Age
The indoor exposure to formaldehyde affects children and adults.

The occupational exposure affects the work population.

Latency
Latency is difficult to know in the investigations we found.

Temporal pattern
The details of the asthmatic reaction are not often investigated. If reported, it is a late reaction.

Associated symptoms
Associated symptoms are not often reported; some cases with rhinitis are seen.

Regional differences
Data were found for the following countries: Belgium, France, Poland, Turkey and the UK. Additionally, we included 3 studies from abroad the EU because of the power of the study (New Zealand) and the similarity of the circumstances with the EU (Canada).

Time trends
All the reports of indoor pollution of formaldehyde date from after 1990. The possible explanation is that the knowledge and the scientific interest have increased. It is not clear that the indoor exposure of formaldehyde was not present before the 90s.
Exposure-effect relation
Several studies have suggested that the prevalence of asthma symptoms is higher in exposed workers than in the general population. Moreover is there a higher prevalence of asthmatic symptoms found in workers with higher exposure compared with the prevalence due to lower exposure.
### Metals in general

#### Weight-of-evidence approach

Evaluation of the compounds:

<table>
<thead>
<tr>
<th>Classification</th>
<th>CAS</th>
<th># Pub</th>
<th>R phrase</th>
<th>LLNA</th>
<th>human data</th>
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<td>Aluminium</td>
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<td>2</td>
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<tr>
<td>Chromium</td>
<td>7440-47-3</td>
<td>7</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Cobalt</td>
<td>7440-48-4</td>
<td>2(3)</td>
<td>1(R42/43)</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Nickel</td>
<td>7440-02-0</td>
<td>5</td>
<td>1(R43)</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>Palladium</td>
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<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>1</td>
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<tr>
<td>Platinum</td>
<td>7440-06-4</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Platinum salt:</td>
<td>16923-58-3</td>
<td>1</td>
<td>1(R42/R43)</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Disodium hexachloro-</td>
<td>16941-12-1</td>
<td>1</td>
<td>1(R42/R43)</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Platinum salt:</td>
<td>10025-99-7</td>
<td>1</td>
<td>1(R38/R42/R43)</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Hexachloroplatinic</td>
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<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>acid</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stainless steel</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tungsten carbide</td>
<td>12070-12-1</td>
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<td>0</td>
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<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>1</td>
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</tbody>
</table>

#### Analysis

**Sources of exposure**

All studies report asthma due to occupational exposure. In very diverse industries where heated metals are handled are cases of asthma described. However in several metal-fabricating industries asthma is due to non-metallic compounds.
Gender
Both males and females are described with asthmatic symptoms due to metal exposure. However more males are reported, there is not evidence of more susceptibility. Presumably there are a higher amount of males in these specific jobs.

Age
Work population: between 20 and 59 years old.

Latency
Latency is diverse and range from some hours to 28 years.

Temporal pattern of manifestation
The most publications did not give information on the time between exposure and reaction. If mentioned there is mostly a late reaction.

Associated symptoms
Nasal and skin associated symptoms are often reported. Development of contact dermatitis prior to asthma can be important issue for prevention.

Regional differences
Data were found for the following countries: Belgium, France, Poland, Spain, Finland, Italy, Germany and the UK. Additionally, we included studies from not-EU countries because of the power of the study (USA) and the similarity of the circumstances with the EU (Canada, USA) and also the expertise of the reporting centre and the novelty of the investigation (Japan).

Exposure-effect relation
Studies have concluded that the prevalence of respiratory symptoms is higher among welders compared with workers with negligible exposure. There are also suggestions that fumes of stainless steel are more responsible for the development of asthma than "mild steel" welding fumes. Stainless steel contains more chromium and nickel.
### Metal: Chromium
**CAS: 7440-47-3**

#### Weight-of-evidence approach
Evaluation of the compounds:

<table>
<thead>
<tr>
<th>Compound</th>
<th>CAS</th>
<th># Pub</th>
<th>R phrase</th>
<th>LLNA</th>
<th>human data</th>
<th>Publ score</th>
<th>Total score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chromium</td>
<td>7440-47-3</td>
<td>7</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>2</td>
</tr>
</tbody>
</table>

#### Analysis

**Sources of exposure**
All studies report asthma due to occupational exposure. Chromium is widely used in metal alloys (welders, metal workers), electroplating processes and construction material, especially cement (roofer and floorer). Although chromium metal is thought to be nonallergic, chromate salts are unequivocally allergenic.

**Gender**
Both males and females can develop asthma due to chromate salt. Mostly men are reported, linked to the job performance.

**Age**
Work population: between 20 and 59 years old.

**Latency**
Latency is not often mentioned and is not specific: months to 28 years.

**Temporal pattern of manifestation**
Mostly late reactions are reported.

**Associated symptoms**
A prior history of contact dermatitis is noted several times. Also rhinitis is often associated with chromate-induced asthma.

**Regional differences**
Data were found for the following countries: Belgium, UK, France, Spain, and Finland.
### Metal: Cobalt
**CAS:** 7440-48-4

#### Weight-of-evidence approach
Evaluation of the compounds:

<table>
<thead>
<tr>
<th>Compound</th>
<th>CAS</th>
<th># Pub</th>
<th>R phrase</th>
<th>LLNA</th>
<th>human data</th>
<th>Publ score</th>
<th>Total score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cobalt</td>
<td>7440-48-4</td>
<td>2(3)</td>
<td>1(R42/43)</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>3</td>
</tr>
</tbody>
</table>

#### Analysis

**Sources of exposure**
Cobalt incorporated into high-speed polishing discs represents a significant source of exposure for diamond polishers. The largest work population exposed to cobalt dust is in the hard-metal industry.

**Gender**
More men are described due to the job performance.

**Age**
Work population: between 30-55 years old.

**Latency**
Latency is diverse and ranges from some months to 20 years.

**Temporal pattern**
Unknown

**Associated symptoms**
Rhinitis is reported; however this association is not thoroughly investigated.

**Regional differences**
Data were found for the following countries: Belgium, Poland, and Italy.
Metal: Nickel  
CAS: 7440-02-0

**Weight-of-evidence approach**  
Evaluation of the compounds:

<table>
<thead>
<tr>
<th>Compound</th>
<th>CAS</th>
<th># Pub</th>
<th>R phrase</th>
<th>LLNA</th>
<th>human data</th>
<th>Publ score</th>
<th>Total score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nickel</td>
<td>7440-02-0</td>
<td>5</td>
<td>1(R43)</td>
<td>1 (moderate)</td>
<td>1</td>
<td>1</td>
<td>4</td>
</tr>
</tbody>
</table>

**Analysis**

Sources of exposure  
In settings involved in electroplating and welding with an exposure to nickel salts, cases of nickel-induced asthma are described.

Gender  
Both males and females are described with asthmatic symptoms due to nickel exposure. Mostly men are reported, linked to the job performance.

Age  
Work population: 20 and 59 years old.

Latency  
The latency period differs from 1.5 year to 16 years.

Temporal pattern of manifestation  
Unknown

Associated symptoms  
Not often are associated symptoms reported.

Regional differences  
Data were found for the following countries: UK, Spain, Finland and Italy. In U.S.A there are many workers potentially exposed to nickel, the occurrence of asthma induced to these salts is proportionally uncommon (Bernstein IL and Merget R, 2006).
Annex VI

Metal: Platinum  
CAS: 7440-06-4

Weight-of-evidence approach  
Evaluation of the compounds:

<table>
<thead>
<tr>
<th>Classification</th>
<th>CAS</th>
<th># Pub</th>
<th>R phrase</th>
<th>LLNA</th>
<th>human data</th>
<th>Publ score</th>
<th>Total score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Compound</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Platinum and salts</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Platinum</td>
<td>7440-06-4</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Ammonium tetrachloroplatinate</td>
<td>13820-41-2</td>
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<td>1(R38/R42/R43)</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Disodium hexachloroplatinate</td>
<td>16923-58-3</td>
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<td>1(R42/R43)</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Hexachloroplatinic acid</td>
<td>16941-12-1</td>
<td>1</td>
<td>1(R42/R43)</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Potassium tetrachloroplatinate II</td>
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<td>1(R38/R42/R43)</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>3</td>
</tr>
</tbody>
</table>

Analysis

Sources of exposure
The main exposure is during refining of platinum. Platinum salt allergy is also reported in catalyst production workers; the work processes in catalyst production are however automated to a high degree in industrialized countries. The exposure happens during maintenance, cleaning and recycling.

Gender
Both male and females patients are reported.

Age
All the cases are of the work population what resemble in the ages: 21-60 years.

Latency
Not defined

Temporal pattern
Not often defined, immediate or dual responses are described.

Associated symptoms
Cases of rhinitis, rhinoconjunctivitis and contact dermatitis are reported. Rhinitis is often associated.

Cause-effect relation
There is general consensus that skin-prick testing is a useful technique for surveillance and early detection of sensitized workers because the excellent specificity (Bernstein LI and Merget R, 2006).

Regional differences
Data were found for the following EU countries: the UK, Italy and mainly in Germany. Additional information comes from Canada and USA.
Metal: Zinc  
CAS: 7440-66-6

Weight-of-evidence approach  
Evaluation of the compounds:

<table>
<thead>
<tr>
<th>Compound</th>
<th>CAS</th>
<th># Pub</th>
<th>R phrase</th>
<th>LLNA</th>
<th>human data</th>
<th>Publ score</th>
<th>Total score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zinc</td>
<td>7440-66-6</td>
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<td>1</td>
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</tr>
</tbody>
</table>

Analysis

Sources of exposure  
All studies report asthma due to occupational exposure. The significant exposure to zinc occurs when welding or galvanizing metals which results in fumes of various metals. There is an extensive usage of zinc containing metal with only several reported cases of OA.

Gender  
The industrial sector where exposure of zinc occurs has a male working population.

Age  
Work population: 18 - 56 years old.

Latency  
Unknown

Temporal pattern of manifestation / Associated symptoms  
The exposure to fumes containing zinc is often associated with metal fume fever. The flu-like illness begins 4-12 hours after exposure and persists 24-48 hours.

Regional differences  
Data were found for the following countries: UK, Germany. Additional information comes from Canada and the USA.
**Persulfate salt**

**Weight-of-evidence approach**
Evaluation of the compounds:

<table>
<thead>
<tr>
<th>Compounds</th>
<th>CAS</th>
<th># Pub</th>
<th>R phrase</th>
<th>LLNA</th>
<th>human data</th>
<th>Publ score</th>
<th>Total score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Persulfate salts</td>
<td>6</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td></td>
<td>2</td>
</tr>
</tbody>
</table>

**Analysis**

**Sources of exposure**
Hairdressing

**Gender**
Both males and females become allergic to persulfate salt. Due to the higher percentage of female employees in the hairdressing, almost all the cases are females.

**Age**
The female patients are rather young when developing asthma: 21 years to 38 years.

**Latency**
Wide range between 3 months and 10 years

**Temporal pattern**
Immediate and late reactions are reported.

**Associated symptoms**
All the reported cases with OA due to persulfate salt have associated symptoms. Nasal, skin and eye reactions are common; mostly even a combination of rhinoconjunctivitis, contact dermatitis and asthma. An evolution from prior nasal and skin symptoms to asthmatic symptoms is described and important for prevention.

**Regional differences**
Several EU countries have reported and studied the consequences of persulfate salt: the UK, Spain, Germany, and Italy.
Annex VI

Polyisocyanates and oligo/polymers

Weight-of-evidence approach
Evaluation of the compounds:

<table>
<thead>
<tr>
<th>Classification</th>
<th>CAS</th>
<th># Pub</th>
<th>R phrase</th>
<th>LLNA</th>
<th>human data</th>
<th>Publ score</th>
<th>Total score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diisocyanates and Prepolymers</td>
<td>22(2)</td>
<td></td>
<td></td>
<td>1</td>
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<tr>
<td>Compounds</td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Diphenylmethane diisocyanate</td>
<td>101-68-8</td>
<td>9</td>
<td>1(R37/R38/R42/R43)</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Hexamethylene diisocyanate</td>
<td>822-06-0</td>
<td>6</td>
<td>1(R37/R38/R42/R43)</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Naphthylene diisocyanate</td>
<td>3173-72-6</td>
<td>2</td>
<td>1(R37/R38/R42)</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Toluene diisocyanate</td>
<td>26471-62-5</td>
<td>8(1)</td>
<td>1(R37/R38/R42/R43)</td>
<td>1(strong)</td>
<td>1</td>
<td>1</td>
<td>4</td>
</tr>
</tbody>
</table>

Analysis

Sources of exposure
Polyisocyanates are able to catalyze the production of polyurethane, a commercial important product. So exposure in various industries is possible. Polyisocyanates are used in the production of external coatings, paints, foams (automobile seats, footwear, bedding, adhesives and sealants. There are also required for mould and core processes in modern foundries. The application possibilities are still growing.

Much variation in the exposure levels is measured between tasks, plants. The average personal exposure levels are the highest while continuous foaming, and the lowest with low or no heating processes (Sennbro CJ, 2003).

Diisocyanate oligomers and polymers, mainly based on HDI and MDI are now increasingly being used because they have inherently lower vapor pressures and volatility in comparison with the isocyanates.

Environmental exposures can occur when using polyurethane products: glues, insulation products and foam mattresses. These are certainly low exposures in comparison with the occupational settings.

Gender
Both males and females are described with asthmatic symptoms.
**Age**
Work population: 18-62 years old

**Latency**
If mentioned, the latency period is 2 to 9 years.

**Temporal pattern**
The type of reaction is not always investigated. Immediate and late reaction are described.

**Associated symptoms**
Associated rhinitis and dermatitis is described.

**Cause-effect relation**
Medical problems in workers were described very soon after the production. Polysocyanates are the most commonly identified cause of OA.

The dose-response relation remains unclear; In general, there is evidence that greater exposure leads to a higher prevalence of respiratory diseases.

Polymers have lower vapor pressures and volatility. Due to the increased use of these polymers the air exposures are much lower. The expected reduction of asthma associated with the lower exposure levels is not seen. Skin exposure can be important.

The possible respiratory problems due to low exposure at home are still controversial (by e.g. foam mattresses containing free isocyanates groups) (Krone CA 2005).

**Regional differences**
Data were found for the following countries: UK, Italy, Finland and Germany and Albania. Additional information comes mainly from Canada.
Polyisocyanate: Hexamethylene diisocyanate
CAS: 822-06-0

Weight-of-evidence approach
Evaluation of the compounds:

<table>
<thead>
<tr>
<th>Compound</th>
<th>CAS</th>
<th># Pub</th>
<th>R phrase</th>
<th>LLN</th>
<th>huma n data</th>
<th>Publ score</th>
<th>Total score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hexamethylene diisocyanate</td>
<td>822-06-0</td>
<td>6</td>
<td>1(R37/R38/R42/R43)</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>3</td>
</tr>
</tbody>
</table>

Analysis

Sources of exposure
HDI polymers are primarily used in external coatings and paints. Asthma due to HDI is mainly reported in the polyurethane foam production and in occupational setting where spray painting (especially car painting) occurs. HDI is highly volatile at room temperature.

Gender
Both males and females are described with asthmatic symptoms due to Hexamethylene diisocyanate.

Age
Work population: 18-62 years old

Latency
If investigated, the latency period is 2 to 3 years.

Temporal pattern
Undefined.

Associated symptoms
Associated rhinitis and contact dermatitis are described.

Regional differences
Data were found for the following countries: UK, Netherlands, Finland and Germany. Additional information comes from Canada and USA.
Annex VI

Polyisocyanate: Diphenylmethane diisocyanate  
CAS: 101-68-8

**Weight-of-evidence approach**
Evaluation of the compounds:

<table>
<thead>
<tr>
<th>Compound</th>
<th>CAS</th>
<th># Pub</th>
<th>R phrase</th>
<th>LLN A</th>
<th>human data</th>
<th>Publ score</th>
<th>Total score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diphenylmethane diisocyanate</td>
<td>101-68-8</td>
<td>9</td>
<td>1(R37/R38/R42/R43)</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>3</td>
</tr>
</tbody>
</table>

**Analysis**

**Sources of exposure**
MDI is used in the production of foams, adhesives and sealants. So exposure to MDI is often in the automobile industry for several parts and finished coatings. In modern steel foundries MDI is used in the mold and core processes. The applications are still in evolution; manufacturing synthetic leather, foam mattresses. While handling laminated wood products, exposure of MDI can occur. MDI is solid at room temperature and release vapors after being heated.

**Gender**
Both males and females are described with asthmatic symptoms due to Diphenylmethane diisocyanate.

**Age**
Work population: 18-62 years old

**Latency**
The latency period range from 7 months to 3 years.

**Temporal pattern of manifestation**
If mentioned, it is mainly an immediate asthmatic reaction.

**Associated symptoms**
Associated rhinitis and dermatitis is described.

**Regional differences**
Data were found for the following countries: UK, Switzerland, Finland and Italy, Albania and Germany. Additional information comes from Canada.
Annex VI  Chemical reports

Polyisocyanate: Toluene diisocyanate
CAS: 26471-62-5

Weight-of-evidence approach
Evaluation of the compounds:

<table>
<thead>
<tr>
<th>Compound</th>
<th>CAS</th>
<th># Pub</th>
<th>R phrase</th>
<th>LLNA</th>
<th>human data</th>
<th>Publ score</th>
<th>Total score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Toluene diisocyanate</td>
<td>26471-62-5</td>
<td>8(2)</td>
<td>1(R37/R38/R42/R43)</td>
<td>1(strong)</td>
<td>1</td>
<td>1</td>
<td>4</td>
</tr>
</tbody>
</table>

Analysis

Sources of exposure
TDI exposure is described in various industries. TDI –together with MDI- is used in the production of polyurethane foams, adhesives and sealants. So exposure to TDI is often in the automobile industry for several parts and finished coatings. TDI exposure is frequent while spray painting.

Gender
Both males and females are described with asthmatic symptoms.

Age
Work population: 18-62 years old

Latency
If mentioned, the latency period is 2 to 9 years.

Temporal pattern
The type of reaction is not often investigated. Immediate and late reaction are described.

Associated symptoms
Associated rhinitis and dermatitis is described.

Regional differences
Data were found for the following countries: UK, Italy, Finland and Germany and Albania. Additional information comes mainly from Canada.
Polyvinyl chloride and phthalates (fumes)

Weight-of-evidence approach
Evaluation of the compounds:

<table>
<thead>
<tr>
<th>Classification</th>
<th>CAS</th>
<th># Pub</th>
<th>R phrase</th>
<th>LLNA</th>
<th>human data</th>
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<th>Total score</th>
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</thead>
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<td>1</td>
<td>2</td>
</tr>
<tr>
<td>di(2-ethylhexyl) phthalate</td>
<td>117-81-7</td>
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<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>di-n-octyl phthalate</td>
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<td>2</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Analysis

Sources of exposure
Global phthalate ester production and consumption has increased from very low to approximately 3.5 million metric tons/yr. This production consists for 50% of DEHP, whereof 95% is used for PVC (Bornehag CG, 2004).

Occupational exposure to heated PVC fumes is mainly described in PVC processing plants. Cases are also reported in a bottle cap production, artificial leather manufacture, vacuum packaging of fish products; In the USA many reports describe exposure while meat wrapping.

Gender
Both males and females become allergic.

Age
Work population: 26-51 years old

Latency
The latency period is not often mentioned; 1 week to 6 months.

Temporal pattern
The pattern is not often investigated. If mentioned, it is a late asthmatic reaction.

Associated symptoms
Rhinocconjunctivitis, rhinitis and, to a lesser extent, eczema has reported.

Regional differences
Data were found for the following EU countries: Italy, Spain, France and Denmark. Additional information comes from USA.
## Polyvinyl chloride and phthalates (indoor)

### Weight-of-evidence approach
Evaluation of the compounds:

<table>
<thead>
<tr>
<th>Classification</th>
<th>CAS</th>
<th># Pub</th>
<th>R phrase</th>
<th>LLNA</th>
<th>human data</th>
<th>Publ score</th>
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</thead>
<tbody>
<tr>
<td>PVC flooring, walls</td>
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<td><strong>Compounds</strong></td>
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<td></td>
</tr>
<tr>
<td>Polyvinyl chloride</td>
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</tr>
<tr>
<td>butyl benzyl phthalate</td>
<td>85-68-7</td>
<td>3</td>
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<td>1</td>
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<td>2</td>
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<tr>
<td>di(2-ethylhexyl) phthalate</td>
<td>117-81-7</td>
<td>3</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Diethyl phthalate</td>
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<td>1</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>dimethyl phthalate</td>
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<td>0</td>
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<td>1</td>
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</tr>
<tr>
<td>di-n-butyl phthalate</td>
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<td>0</td>
<td>1</td>
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<td>2</td>
</tr>
<tr>
<td>di-n-octyl phthalate</td>
<td>117-84-0</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>2</td>
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</tr>
<tr>
<td>2-ethyl-1-hexanol</td>
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<td>0</td>
<td>1</td>
<td>1</td>
<td>2</td>
<td></td>
</tr>
</tbody>
</table>

### Analysis

**Sources of exposure**
Global phthalate ester production and consumption has increased from very low to approximately 3.5 million metric tons/yr. This production consists for 50% of DEHP, whereof 95% is used for PVC (Bornehag CG, 2004).

The indoor dampness of PVC material, mostly flooring and plastic walls, possibly cause asthma. Many studies measure the house dust, especially in the children’s bedroom and the consequences. Also asthma induced by building dampness in occupational settings is investigated.

**Gender**
Both males and females become allergic.

**Age**
The most studies investigating exposure at home are focused on children: 0-7 years old.
The studies in an occupational setting describe the work population: 21-63 years old.

**Latency**
The latency period is not often investigated. Months to years is described.

**Temporal pattern**
Not defined.

**Associated symptoms**
Rhinocconjunctivitis, rhinitis and, to a lesser extent, eczema has reported.

**Cause effect relation**
The most important studies are big scale epidemiological studies in children: (repeated) cross-sectional and case-control studies; cohort- or population based. The results show associations between indicators of phthalate exposure in the home and risk of asthma and allergy. Unfortunately the accuracy and specificity of the diagnosis is not always present.
The knowledge of mechanisms of emission, exposure and toxicity of the chemical species released from PVC material has to be improved before the hypothesis can be confirmed (Jaakkola JJK, 2008).

**Regional differences**
Data were found for the following EU countries: Bulgaria and especially the Scandinavian countries Sweden, Denmark, Norway and Finland. Jaakkola and colleagues have expertise in epidemiological studies of indoor exposure at home.

**Time trends**
The listed studies are from recent date (1999 until now). The reasons are possibly plural: the increased production and use of plastic material and secondary the increased awareness of the possible medical problems.
**Styrene**  
**CAS: 100-42-5**

**Weight-of-evidence approach**  
Evaluation of the compounds:

<table>
<thead>
<tr>
<th>Compound</th>
<th>CAS</th>
<th># Pub</th>
<th>R phrase</th>
<th>LLNA</th>
<th>human data</th>
<th>Publ score</th>
<th>Total score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Styrene</td>
<td>100-42-5</td>
<td>7(1)</td>
<td>0 (R38)</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>2</td>
</tr>
</tbody>
</table>

**Analysis**

**Sources of exposure**  
Styrene is used for the manufacturing of plastics, rubber and resins. The studies report cases in plastics factories, auto body shops and furniture industry.

**Gender**  
Both male and females patients are reported, male asthmatics however more.

**Age**  
The reported cases are all adult workers between 31 and 54 years old.

**Latency**  
The latency period is not often reported and range from 1 month to 4 years.

**Temporal pattern**  
Not defined.

**Associated symptoms**  
The association with other allergic symptoms is not frequently described.

**Regional differences**  
Data were found for the following EU countries: the UK, Spain, Italy and additionally Turkey.
Wood dust / bark

Weight-of-evidence approach
Evaluation of the compounds:

<table>
<thead>
<tr>
<th>Classification</th>
<th>CAS</th>
<th># Pub</th>
<th>R phrase</th>
<th>LLNA</th>
<th>human data</th>
<th>Publ score</th>
<th>Total score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wood dust</td>
<td>30</td>
<td>1</td>
<td>1</td>
<td></td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
</tbody>
</table>

Analysis

Sources of exposure
The studies report asthma due to occupational exposure in very diverse industries where wood is handled. In Europe it is mostly concentrated in furniture making, carpentry, and parquet floor layers. This means mainly handling dry wood. The highest exposures are measured while sanding and kitchen production.

Woodworkers are exposed to a complex mixture of possible sensitizing compounds. Formaldehyde and Diphenyl-methane diisocyanate resins (LMW agents) are often used to bond wood fragments for industrial use. Some living organisms such as mold can grow on wood and develop asthma (Towey JW, 1932).

Gender
Both males and females are described with asthmatic symptoms due to wood dust exposure. However more males are reported, there is no evidence of more male susceptibility. Presumably there are a higher amount of males in these specific jobs.

Age
Work population: 18 and 59 years old.

Latency
Latency is not often mentioned and is not specific: months to 20 years.

Reaction type
Most studies did not investigate the types of asthmatic reaction. If mentioned, immediate, late and dual reactions are possible.

Associated symptoms
Many patients have concurrently rhinoconjunctivitis; some of them have contact dermatitis.

Exposure-effect relation
The studies indicate the exposure-related airway affects without a clear dose response but there is a significant risk in different woodworking sectors. Differences in measuring and reporting exposure intensity limit the ability to draw conclusions for the level of exposure to prevent allergy. There is evidence that already at low concentrations of wood dust respiratory symptoms develop. So also the low level indirect continuous background exposure is important.
Regional differences
Data were found for the following countries: UK, France, Spain, and Italy. Finland and Denmark have published large epidemiological studies (without specifying the wood type).
The USA and especially Canada have gathered much knowledge about the consequences for woodworkers mostly sawmill workers. The studies handling asthma induced by Western Red Cedar are almost exclusively located in Canada. This is due to the forestation in these regions and the centers of expertise over there.

Time trends
In the seventies, asthma due to wood dust was already recognized. The importation of different new exotic woods still brings new allergies. In Europe more epidemiologic studies, measuring wood dust exposures and the prevalence of allergies, are recently published.
Time trends are with the current knowledge not possible.