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**ANNEX VI      CHEMICAL REPORTS****Respiratory sensitizers**

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<b>Acid Anhydride</b>
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**Weight-of-evidence approach**

Evaluation of the compounds:

Classification	CAS	# Pub	R phrase	LLNA	human data	Publ score	Total score
Acid anhydride		13 (2)			1	1	
<b>Compounds</b>							
Chlorendic anhydride	115-27-5	1	0 (R37/R38)	0	0	1	1
Hexahydrophthalic acid anhydride	85-42-7	2(1)	1(R42/R43)	0	1	1	3
Himic anhydride	826-62-0	(1)	1(R42/R43)	0	0	0	1
Maleic anhydride	108-31-6	2(1)	1(R42/R43)	1(strong)	1	1	4
Methyltetrahydrophthalic acid anhydride	34090-76-1	3	1(R42/R43)	0	1	1	3
Phthalic anhydride	85-44-9	5(2)	1 (R37/R38/R42/R43)	1(strong)	1	1	4
Pyromellitic dianhydride	89-05-4	2(1)	1(R42/R43)	0	1	1	3
Tetrachlorophthalic anhydride	117-08-8	1	1(R42/R43)	0	0	1	2
Trimellitic anhydride	552-30-7	2(1)	1(R37/R42/R43)	1 (moderate)	1	1	4

**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

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Both males and females are reported.

Age

The exposure affects 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.

<b>Various Acrylates</b>
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**Weight-of-evidence approach**

Evaluation of the compounds:

Classification	CAS	# Pub	R phrase	LLNA	human data	Publ score	Total score
Acrylate		4(4)			1	1	
<b>Compound</b>							
ethyl acrylate	140-88-5	1	1(R43/R37/R38)	0	0	1	2
Ethyl methacrylate	97-63-2	1	1(R43/R37/R38)		0	1	2
Ethylene glycol dimethacrylate	97-90-5	1(1)	1(37/R43)	1(weak)	1	1	4
2 hydroxyethyl methacrylate	868-77-9	1(1)	1(43/R38)	0	1	1	3
Glycidyl methacrylate	106-91-2	1	1(R43/R38)	0	0	1	2
hydroxypropyl methacrylate	27813-02-1	1(1)	0(R37/R38)	0	1	1	2
methyl cyanoacrylates	137-05-3	1	0(R37/R38)	0	0	1	1
Methyl methacrylate	80-62-6	3(2)	1(37/R38/R43)	0	1	1	3

**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.

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#### 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 shown in Finland

<b>Amines in general</b>
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**Weight-of-evidence approach**

Evaluation of the compounds:

Classification	CAS	# Pub	R phrase	LLNA	human data	Publ score	Total score
Amine		16(1)			1	1	
<b>Compounds</b>							
Aminoethylethanolamine	111-41-1	2	1(R43)	0	0	1	2
EPO60		1	0	0	0	0	0
Ethylenediamine	107-15-3	1	1(R42/R43)	1 (moderate)	1	1	4
hydroxylamine	7803-49-8	(1)	0	0	0	1	1
Isophorone diamine	2855-13-2	1	0	0	0	1	1
N-methylmorpholine	109-02-4	1	0	0	1	1	2
N-methyl-piperazine	109-01-3	1	0	0	0	1	1
piperazine	110-85-0	5	1(R42/R43)	0	1	1	3
Piperazine dihydrochloride	142-64-3	2	1(R37/R38/R42)	0	1	1	3
Triethanolamine	102-71-6	1	0	0	0	1	1
Triethylene tetramine	112-24-3	1	1(R43)	0	0	1	2
Trimethylhexanediamine		1	0	0	0	1	1

**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

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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:

Classification	CAS	# Pub	R phrase	LLNA	human data	Publ score	Total score
Aliphatic amine		5			1	1	
<b>Compounds</b>							
Aminoethylethanolamine	11141-1	2	1(R43)	0	1	1	3
Ethylenediamine	107-15-3	1	1(R42/R43)	1 (moderate)	1	1	4
Triethanolamine	102-71-6	1	0	0	0	1	1
Triethylene tetramine	112-24-3	1	1(R43)	0	0	1	2

**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:

Classification	CAS	# Pub	R phrase	LLNA	human data	Publ score	Total score
Heterocyclic amine		8			1	1	
<b>Compounds</b>							
N-methyl-morpholine	109-02-4	1	0	0	1	1	2
N-methyl-piperazine	109-01-3	1	0	0	0	1	1
Piperazine	110-85-0	5	1(R42/R43)	0	1	1	3
Piperazine dihydrochloride	142-64-3	2	1(R37/R38/R42)	0	1	1	3

**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.

**Azobisformamide**  
**CAS: 123-77-3**
**Weight-of-evidence approach**

Evaluation of the compounds:

Compound	CAS	# Pub	R phrase	LLN A	human data	Publ score	Total score
Azobisformamide	123-77-3	2	1(R42/R43)	0	1	1	3

**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:

Classification	CAS	# Pub	R phrase	LLNA	human data	Publ score	Total score
Biocides		8					
<b>Compounds</b>							
Chloramine T	127-65-1	2	1(R42)	1 (strong)	1	1	4
Chlorhexidine	55-56-1	1	1(R37/R38/R43)	0	0	1	2
Glutaraldehyde	111-30-8	2	1(R42/R43)	1 (strong)	1	1	4
Hexachlorophene	70-30-4	1	0	0	0	1	1
Isothiazolinones		1	0	0	0	1	1
Lauryl dimethyl benzyl ammonium chloride		1	0	0	0	0	0

**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.

<b>Various chemicals, not specified elsewhere</b>
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**Weight-of-evidence approach**

Evaluation of the compounds:

Classification	CAS	# Pub	R phrase	LLN A	human data	Publ score	Total score
Chemicals		13(1)					
<b>Compounds</b>							
Ethylene oxide	75-21-8	2	0(R37/R38)	0	1	1	1
Iso-nonanyl oxybenzene sulfonate		1	0	0	0	1	1
Metabisulphite		1	0	0	0	1	1
Methyl blue		2	0	0	0	1	1
Ninhydrin	485-47-2	1	0(R37/R38)	0	0	1	1
Polyethylene	9002-88-4	1	0	0	0	0	0
Polyfunctional aziridine	151-56-4	1	0	0	0	0	0
Tetrazene		1	0	0	0	0	0
Triglycidyl isocyanurate	2451-62-9	1	1 (R37/R38/R42/R43)	0	0	1	2

**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.

<b>Colophony and fluxes</b>
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**Weight-of-evidence approach**

Evaluation of the compounds:

Compound	CAS	# Pub	R phras e	LLNA	human data	Publ score	Total score
Colophony and fluxes		5					
Colophony		3	0	0	1	1	2
fluxes							
Alkylaral polyether alcohol + 5% polypropylene glycol		1	0	0	0	1	1
Zinc chloride and ammonium chloride flux 95%		1	0	0	0	1	1

**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 know 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.





<b>Diazonium salt and reactive dyes</b>
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**Weight-of-evidence approach**

Evaluation of the compounds:

Compound	CAS	# Pub	R phras e	LLNA	human data	Publ score	Total score
Diazonium salt and reactive dyes		14			1	1	
Diazonium salt		2	0	0	1	1	2
Drimaren brilliant yellow K-3GL		2	0	0	0	1	1
Lanasol yellow 4G		2	0	0	0	1	1
Drimaren brilliant blue K-BL		3	0	0	0	1	1
Monascus ruber		1	0	0	0	1	1
Scarlet 32		1	0	0	0	1	1
Cibachrome brilliant scarlet 3R		1	0	0	0	1	1
Levafix brilliant yellow E-36		1	0	0	0	1	1

**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.

<b>Formaldehyde and his resin</b> <b>CAS: 50-00-0</b>
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**Weight-of-evidence approach**

Evaluation of the compounds:

Compound	CAS	# Pub	R phrase	LLNA	human data	Publ score	Total score
Formaldehyde and resin		5(1)			1	1	
Formaldehyde	50-00-00	4(1)	1(R43)	1 (strong)	1	1	4
Urea formaldehyde	9011-05-6	1	1(R43)	0	0	1	2

**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.

<b>Metals in general</b>
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**Weight-of-evidence approach**

Evaluation of the compounds:

Classification	CAS	# Pub	R phrase	LLNA	human data	Publ score	Total score
Metals		19(8)			1	1	
Aluminium	91728-14-2	1	0	0	0	1	2
Chromium	7440-47-3	7	0	0	1	1	2
Cobalt	7440-48-4	2(3)	1(R42/43)	0	1	1	3
Nickel	7440-02-0	5	1(R43)	1 (moderate)	1	1	4
Palladium	7440-05-3	1	0	0	0	1	1
Platinum	7440-06-4	2	0	0	1	1	2
Platinum salt: Disodium hexachloroplatinate	16923-58-3	1	1(R42/R43)	0	1	1	3
Platinum salt: Hexachloroplatinic acid	16941-12-1	1	1(R42/R43)	0	1	1	3
Platinum salt: Potassium tetrachloroplatinate II	10025-99-7	1	1(R38/R42/R43)	0	1	1	3
stainless steel		1	0	0	0	1	1
Tungsten carbide	12070-12-1	1	0	0	0	1	1
Zinc	7440-66-6	2	0	0	0	1	1

**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:

Compound	CAS	# Pub	R phras e	LLNA	human data	Publ score	Total score
Chromium	7440-47-3	7	0	0	1	1	2

### 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.

<b>Metal: Cobalt</b> <b>CAS: 7440-48-4</b>
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**Weight-of-evidence approach**

Evaluation of the compounds:

Compound	CAS	# Pub	R phrase	LLNA	human data	Publ score	Total score
Cobalt	7440-48-4	2(3)	1(R42/43)	0	1	1	3

**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:

Compound	CAS	# Pub	R phrase	LLNA	human data	Publ score	Total score
Nickel	7440-02-0	5	1(R43)	1 (moderate)	1	1	4

### 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).

<b>Metal: Platinum</b> <b>CAS: 7440-06-4</b>
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**Weight-of-evidence approach**

Evaluation of the compounds:

Classification	CAS	# Pub	R phrase	LLNA	human data	Publ score	Total score
Platinum and salts		4					
<b>Compound</b>							
Platinum	7440-06-4	2	0	0	1	1	2
Ammonium tetrachloroplatinate	13820-41-2		1(R38/R42/R43)	0	1	1	3
Disodium hexachloroplatinate	16923-58-3	1	1(R42/R43)	0	1	1	3
Hexachloroplatinic acid	16941-12-1	1	1(R42/R43)	0	1	1	3
Potassium tetrachloroplatinate II	10025-99-7	1	1(R38/R42/R43)	0	1	1	3

**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

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There is general consensus that skin-prick testing is a useful technique for surveillance and early detection of sensitized workers because of 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.

<b>Metal: Zinc</b> <b>CAS: 7440-66-6</b>
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### Weight-of-evidence approach

Evaluation of the compounds:

Compound	CAS	# Pub	R phras e	LLNA	human data	Publ score	Total score
Zinc	7440-66-6	2	0	0	0	1	1

### 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.

<b>Persulfate salt</b>
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**Weight-of-evidence approach**

Evaluation of the compounds:

Compounds	CAS	# Pub	R phras e	LLNA	human data	Publ score	Total score
Persulfate salts		6	0	0	1	1	2

**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.

<b>Polyisocyanates and oligo/polymers</b>
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**Weight-of-evidence approach**

Evaluation of the compounds:

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

**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. Polyisocyanates 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.

<b>Polyisocyanate: Hexamethylene diisocyanate</b> <b>CAS: 822-06-0</b>
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**Weight-of-evidence approach**

Evaluation of the compounds:

Compound	CAS	# Pub	R phrase	LLN A	human data	Publ score	Total score
Hexamethylene diisocyanate	822-06-0	6	1(R37/R38/R42/R43)	0	1	1	3

**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.



**Polyisocyanate: Diphenylmethane diisocyanate**  
**CAS: 101-68-8**

**Weight-of-evidence approach**

Evaluation of the compounds:

Compound	CAS	# Pub	R phrase	LLN A	human data	Publ score	Total score
Diphenylmethane diisocyanate	101-68-8	9	1(R37/R38/R42/R43)	0	1	1	3

**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.

<b>Polyisocyanate: Toluene diisocyanate</b> <b>CAS: 26471-62-5</b>
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**Weight-of-evidence approach**

Evaluation of the compounds:

Compound	CAS	# Pub	R phrase	LLNA	human data	Publ score	Total score
Toluene diisocyanate	26471-62-5	8(2)	1(R37/R38/R42/R43)	1(strong)	1	1	4

**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.

<b>Polyvinyl chloride and phthalates (fumes)</b>
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**Weight-of-evidence approach**

Evaluation of the compounds:

Classification	CAS	# Pub	R phras e	LLNA	huma n data	Publ score	Total score
Heated PVC and phthalates		6					
<b>Compounds</b>							
Polyvinyl chloride	9002-86-2	3	0	0	1	1	2
di(2-ethylhexyl) phthalate	117-81-7	1			0	0	
di- <i>n</i> -octyl phthalate	117-84-0	2	0	0	0	0	0

**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

Rhinoconjunctivitis, 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.

<b>Polyvinyl chloride and phthalates (indoor)</b>
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**Weight-of-evidence approach**

Evaluation of the compounds:

Classification	CAS	# Pub	R phras e	LLNA	huma n data	Publ score	Total score
PVC flooring, walls		10			1	1	
<b>Compounds</b>							
Polyvinyl chloride	9002- 86-2	6	0	0	1	1	2
butyl benzyl phthalate	85-68- 7	3	0	0	1	1	2
di(2- ethylhexyl) phthalate	117- 81-7	3	0	0	1	1	2
Diethyl phthalate	84-66- 2	1	0	0	1	1	2
dimethyl phthalate	131- 11-3	1	0	0	1	1	2
di- <i>n</i> -butyl phthalate	84-74- 2	1	0	0	1	1	2
di- <i>n</i> -octyl phthalate	117- 84-0	2	0	0	1	1	2
<b>Derivate</b>							
2-ethyl-1- hexanol	104- 76-7		0(R38)	0	1	1	2

**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.

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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

Rhinoconjunctivitis, 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:

Compound	CAS	# Pub	R phrase	LLNA	human data	Publ score	Total score
Styrene	100-42-5	7(1)	0 (R38)	0	1	1	2

### 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.

<b>Wood dust / bark</b>
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**Weight-of-evidence approach**

Evaluation of the compounds:

Classification	CAS	# Pub	R phrases	LLNA	human data	Publ score	Total score
Wood dust		30			1	1	

**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.