Supplemental material

E-Table 1 Causative agents and high-exposure work tasks of patients with irritant-induced occupational asthma.

| Causative agent | Acute<br>N=30<br>number, work tasks/exposure event | Subacute<br>N=39<br>number, work tasks/exposure event | Total |
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| Acids | 6<br>Sulfuric acid:<br>-leak, overwarming and evaporation of battery fluid into truck cabin (truck driver)<br>Sulfuric acid, hydrofluoric acid and nitric acid<br>-equipment failure causing dissolution of aluminum plates in an electrolysis bath, overheating of bath and evaporation of large volumes of acids (metal worker)<br>Hydrochlorid acid<br>-rescue task in chemical accident (ambulance worker)<br>Hydrochlorid acid and sulfur dioxide<br>-process leak in chemical plant (maintenance worker)<br>Hydrofluoric acid and nitric acid<br>-working above an open hydrofluoric and nitric acid container and cleaning acid dust (crane mechanic)<br>Hydrofluoric acid and hydrochloric acid<br>-welding of leaking refrigerator unit pipes containing tetrahydrofluoroethane (refrigerating machine mechanic) | 7<br>Sulfuric acid and ammonium fluoride<br>-washing concrete wall elements using spray detergent (concrete element worker)<br>Sulfuric acid and hydrogen sulfide<br>-working in metal production plant (machine operator)<br>Sulfuric acid, sulfur dioxide and sulfur trioxide<br>-working in chemical plant with many process failures (machine operator)<br>Hydrochlorid acid<br>-washing concrete elements using pressure washer and acid detergent (concrete element worker)<br>-working in hot-zinc coating plant using acid baths for pre-purification, poor ventilation (metal worker)<br>Nitric acid fumes<br>-disturbances in air-conditioning in electroplating process with electrolysis bath containing nitric acid (2 metal workers) | 13 |
| Bases | 5<br>Ammonia<br>-other workers cleaning ammonia tank nearby (electrician)<br>- emission of sludge heap in oil refinery (industrial cleaner)<br>-performing work hygiene measures in a poultry rearing house (occupational hygienist)<br>Sodium hydroxide<br>-other worker poured sodium hydroxide powder into motor washer whose exhaust line led to patient's breathing zone (aircraft engine mechanics)<br>Black lye (in pulp cooking)<br>- sodium hydroxide-containing black lye pipe leak in pulp mill (scaffold mechanic) | 4<br>Ammonia<br>-packing broiler meat, leak in cooling system (food worker)<br>-working in cowshed, cleaning sludge lines and basin (farmer)<br>Sodium hydroxide<br>-repairing output pipe of sodium hydroxide tank in pulp mill, two separate incidents (welder)<br>Mixture of alkaline epoxy polyamine hardener and cleaning agent<br>-tiling large indoor swimming pool area with poor ventilation (construction worker) | 9 |

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| Mixtures of acids and bases | | 3<br>Ammonia, sulfuric acid, hydrochlorid acid, hydrofluoric acid and nitric acid etc.<br>- working in electroplating process with poor ventilation (metal worker)<br>-working in fertilizer plant (industrial cleaner)<br>Sodium hydroxide, potassium hydroxide, sulfuric acid, nitric acid, etc.<br>-mixing industrial detergents in small workshop (engineer) | 3 |
| Inorganic gases | 3<br>Chlorine dioxide<br>- chlorine dioxide bleach leak in pulp mill (3 mechanics) | 3<br>Chlorine dioxide<br>- chlorine dioxide bleach leak in pulp mill (mechanic)<br>Chlorine dioxide and hydrogen sulfide<br>-repeated leaks in pulp mill (operator)<br>Sulfur dioxide<br>-testing processes of different copper and nickel smelters abroad (engineer) | 6 |
| Oxidizing agents | 1<br>Ozone<br>-working in private apartment with ongoing air ozonation (electrician) | 1<br>Hydrogen peroxide<br>-working in pudding factory with poor ventilation and where hydrogen peroxide was excessively used for disinfecting lines (food machine operator) | 2 |
| Other chemicals | 5<br>Formaldehyde<br>-when cleaning, 4 liters of 38% formaldehyde solution spilled from broken fish specimen bowl (school cleaner)<br>Glutaraldehyde<br>- disinfection of piggery with poor ventilation (farmer)<br>Hexamethylene diisocyanate<br>-fire from polyurethane insulation material (construction worker)<br>Naphthalene compounds<br>-washing and mangling sheets which were handled with naphthalene compounds (launderer)<br>Pyrethrin<br>-cleaning after bedbug control treatment without pre-ventilation (cleaner) | 1<br>Hexamethylene diisocyanate<br>-spray painting with malfunctioning respiratory protective device (painter) | 6 |

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| Mixtures | 6<br>Sodium hydroxide, sodium hypochlorite<br>-washing warm garage floor with alkaline cleaning agent with poor ventilation (car mechanic)<br>Sulfuric acid, sodium hypochlorite, chlorine gas<br>-mixing swimming pool chemicals incorrectly leading to generation of toxic fumes (caretaker at sports center)<br>Combustion gas<br>-rescue task in burning building (police officer)<br>Nitric oxides, diesel exhaust, mixture of oil and water<br>-performing work hygiene measurements in tunnel work (occupational hygienist)<br>Bitumen, solvents and their thermal degradation products<br>-doing bitumen insulation indoors with poor ventilation (insulation worker)<br>Thermal degradation of polyester powder paint<br>-due to inoperative washer, metal parts were overheated before powder painting (painter) | 12<br>Ammonia and hydrogen sulfide<br>-emptying sludge in piggery (farmer)<br>Ammonia, hydrogen sulfide and endotoxins<br>- working in piggery (farm worker)<br>-veneer log processing with chemicals to soften them (wheel loader)<br>Hydrogen sulfide, sulfur compounds, sodium hydroxide, chlorine dioxide<br>-process failure in pulp mill (field worker)<br>Calcium oxide and hydrogen sulfide<br>-Working in mine e.g. in calcium oxide storage and in metal sedimentation (machinery mechanic)<br>Trifluoroacetic acid and acetonitrile<br>-keeping cleaning agents in open bowls (research assistant)<br>Formic acid, acetic acid, formaldehyde<br>-working inside furnaces where wood was thermally modified (machinery mechanic)<br>Solvents and mining dust<br>-washing mining vehicles with solvents and pressured air (machinery repairer)<br>Rubber chemicals and their thermal degradation products<br>- weekly occurring fires from rubber material in production of rubber insulation (production worker)<br>Thermal degradation of polyvinyl chloride (PVC)-coated fabrics<br>-heat-seaming plastic-coated canvas with electric charge at 175 °C, poor ventilation (seamstress, foreman and manufacturing worker) | 18 |
| Dusts | 4<br>Calcium oxide<br>-emptying sacks of calcium oxide powder (stevedore)<br>Calcium oxide<br>-cleaning tank of calcium oxide powder with malfunctioning respiratory protective device (lorry driver)<br>Cement<br>-spraying of concrete coating in tunnel, poor ventilation (tunnel worker)<br>-cement silo breakdown during loading (lorry driver) | 4<br>Calcium oxide and alkaline dusts<br>- sulfur removal of exhaust gases by calcium sludge (power plant operator)<br>Cement<br>-emptying sacks of cement (concrete layer)<br>Ash<br>-transporting alkaline ash in a power plant, 5 accidental exposures connected to silo brake-downs (packer)<br>Sulfuric acid-coated titanium oxide powder<br>-working in chemical plant (packer) | 8 |

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| Endotoxins | 0 | 4<br>-washing dough sludge and contaminated insulation in bioethanol plant (driver of industrial sweeper)<br>- transmitting malt in silo (worker in foodstuff company)<br>- washing process of potatoes in potato flour plant (operator)<br>- work in power plant using sod and woodchips (operator) | 4 |

E-Table 2 Agents causing irritant asthma: identification details, occupational exposure limits and relevant (irritancy-related) hazard classifications according to current EU legislation.

| Chemical name | Chemical formula | CAS number | OEL for 8 hours, (ppm if not marked otherwise) | OEL for 15 min (ppm if not marked otherwise) | Classification according to CLP |
|---|---|---|---|---|---|
| Acids | | | | | |
| Sulfuric acid | $H_2SO_4$ | 7664-93-9 | 0.05 mg/m$^3$ | 0.1 mg/m$^3$ | Skin Corr 1A |
| Sulfurous acid | $H_2SO_3$ | 7782-99-2 | NA | NA | Skin Corr 1B |
| Hydrochloric acid | HCl | 7647-01-0 | NA | 5 (7.6 mg/m$^3$) | Skin Corr 1A |
| Nitric acid | $HNO_3$ | 7697-37-2 | 0.5 (1.3 mg/m$^3$) | 1 (2.6 mg/m$^3$) | Skin Corr 1A<br>Ox. Liq. 2 |
| Hydrofluoric acid | HF | 7664-39-3 | 1.8 (1.5 mg/m$^3$) | 3 (2.5 mg/m$^3$) | Skin Corr 1A |
| Formic acid | HCOOH | 64-18-6 | 3 (5 mg/m$^3$) | 10 (19 mg/m$^3$) | Skin Corr 1A |
| Acetic acid | $CH_3COOH$ | 64-19-7 | 5 (13 mg/m$^3$) | 10 (25 mg/m$^3$) | Skin Corr 1A |
| Trifluoroacetic acid | $CF_3COOH$ | 76-05-1 | NA | NA | Skin Corr 1A |
| Bases | | | | | |
| Ammonia | $NH_3$ | 1336-21-6 | 20 (14 mg/m$^3$) | 50 (36 mg/m$^3$) | Skin Corr 1B |
| Sodium hydroxide | NaOH | 1310-73-2 | NA | 2 mg/m$^3$ | Skin Corr 1A |
| Potassium hydroxide | KOH | 1310-58-3 | NA | 2 mg/m$^3$ | Skin Corr 1A |
| Irritant gases | | | | | |
| Sulfur dioxide | $SO_2$ | 7446-09-5 | 0.5 (1.3 mg/m$^3$) | 1 (2.7 mg/m$^3$) | Skin Corr 1B |
| Chlorine | $Cl_2$ | 7782-50-5 | NA | 0.5 (1.5 mg) | Ox. Gas 1<br>Skin Irrit 2 |
| Chlorine dioxide | $ClO_2$ | 10049-04-4 | 0.1 (0.28 mg/m$^3$) | 0.3 (0.84 mg/m$^3$) | Ox. Gas 1<br>Skin Corr 1B |
| Hydrogen sulfide | $H_2S$ | 7783-06-4 | 5 (7 mg/m$^3$) | 10 (14 mg/m$^3$) | Acute Tox 2[a] |
| Nitrogen oxides | $NO_x$ (e.g. NO, $NO_2$) | NO: 10102-43-9<br>$NO_2$:10102-44-0 | 10 (12.5 mg/m$^3$)<br>1 (1.9 mg/m$^3$) | NO: NA<br>$NO_2$: 2 (mg/m$^3$) | NO: Skin Corr 1B[b]<br>$NO_2$: Ox. Gas 1,<br>Skin Corr 1B |
| Other | | | | | |
| Hydrogen peroxide | $H_2O_2$ | 7722-84-1 | 1 (1.4 mg/m$^3$) | 3 (4.2 mg/m$^3$) | Ox. Liq 1<br>Skin Corr 1A |
| Ozone | $O_3$ | 10028-15-6 | 0.05 (0.1 mg/m$^3$) | 0.2 (0.4 mg/m$^3$) | Ox. Gas 1[b]<br>Skin Corr 1B[b] |
| Isocyanates | -NCO [c] | various | NA | 0.035 mg/m$^3$ [c] | Skin Corr 1C[b] |
| Formaldehyde | HCHO | 50-00-0 | 0.3 (0.37 mg/m$^3$) | 1 (1.2 mg/m$^3$) | Skin Corr 1B |
| Glutaraldehyde | $C_3H_6(CHO)_2$ | 111-30-8 | | 0.1 (0.42 mg/m$^3$) | Skin Corr 1B<br>(Resp Sens 1) |
| Sodium hypochlorite | NaClO | 7681-52-9 | NA | NA | Skin Corr 1B |

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| Ammonium Fluoride | $NH_4F$ | 12125-01-8 | NA | NA | Skin Corr 1C[b] |
| Inorganic dust | can be any, and be a mixture | can be any, and be a mixture | 10 mg/$m^3$ | NA | hazard evaluation must be based on the composition of the dust |
| Endotoxins | - | - | 90 EU/$m^3$ [d] | NA | - |

OEL= Finnish occupational exposure limit, NA=not available, CLP= The Classification, Labelling and Packaging Regulation (EC No 1272/2008)

[a] E.g. systemic and neurological effects, locally pulmonary edema

[b] Unharmonized classification

[c] Isocyanate (-NCO) groups of any isocyanate compounds

[d] Dutch OEL

E-Table 3. Workplace measurements in cases where available and relevant for assessment of exposure to irritant factors, and remarks on exposure. Some measurements were conducted by a trained occupational hygienist and some by respective company's own follow-up.

| Workplace or process | Specific work process with high level of exposure | Substance measured | Mean air concentration in ppm, if not given otherwise (% of 8h-OEL)[a] | Maximum air concentration in ppm, if not given otherwise (% of 8h-OEL)[a] | Remarks |
|---|---|---|---|---|---|
| Piggery I | Sludge handling, piglet department and open shed | Ammonia ($NH_3$) | 6.6 (33) | 37 (187) | Direct-reading device; generally poor workplace hygiene and ventilation; measurements taken after cleaning and additional ventilation, which possibly underestimates real situation |
| | | Hydrogen sulfide ($H_2S$) | NA | 4 (80) | |
| | | Endotoxins | 9500 EU/$m^3$ (10500) | NA | |
| Piggery II | Farrowing department, sludge handling and open shed | Ammonia ($NH_3$) | 1.1–16 mg/$m^3$ (9–114) | NA | Poor ventilation in several departments |
| | | Hydrogen sulfide ($H_2S$) | >2.5 (50) | 14 (280) | |
| Cowshed | Cleaning and emptying sludge pipe and basin | Ammonia ($NH_3$) | 10–20 (50–100) | 214 (>1000) | Direct-reading device; high levels of ammonia also in everyday animal care |
| | | Hydrogen sulfide ($H_2S$) | 5 (100) | 20 (400) | |
| Poultry rearing house | Inspection and occupational hygiene measurement | Ammonia ($NH_3$) | 60–80 (300–400) | NA | Direct-reading device measurement over one-hour inspection visit |
| Meat packing | Packing chicken meat and cleaning packing line | Ammonia ($NH_3$) | 10–150 (50–750) | 260 (1300) | Online gas detector at workplace; high concentrations detected during 2 months with problems in cleaning system, including two larger ammonia leaks with especially high exposure |
| Pudding production | Long-lasting and repeated high | Hydrogen peroxide ($H_2O_2$)[b] | 1.1 (110) | 4.4 (440) | Online gas detector at workplace; |

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| | exposure in normal work | | | | several workers had experienced respiratory irritation; bleaching of hair and eyebrows was observed |
| Potato flour factory | Washing potatos | Endotoxins | 1900 EU/$m^3$ (2100) | NA | Occasional exposure also to alkaline washing agents |
| Foodstuff production | Handling malt | Endotoxins | 25 000 EU/$m^3$ (28 000) | NA | Extremely dusty work handling malt of several different grains |
| Electroplating | High exposure to acid fumes and nickel especially during night shifts when air conditioning switched off | Nickel in air (Ni) | 0.095 mg/$m^3$ (950) | NA | Two cases working in same shift; biomonitoring of nickel in one revealed high exposure 1–2 days previously, which was used as marker of exposure to all air impurities; the main cause of asthma in both cases was considered to be acid fumes that were visible especially in the night shift; airborne nickel was measured months later during a day shift with ventilation on. |
| | | Nickel in urine (biomonitoring) | U-Ni 2.2 mmol/l (170) | NA | |
| Hot-zinc coating plant | Work near acid baths and hot zinc-coating fumes | Hydrochloric acid (HCl) | 0.78–6.4 mg/$m^3$ (10–84)[c] | NA | Mean HCl levels that represent exposure over a working day were near the short-term OEL, thus exposure was excessive |
| | | Formaldehyde ($CH_2O$) | 0.324 (108) | NA | |
| Metal production plant | Working nearby wet precipitation processes utilizing hydrogen sulfide | Hydrogen sulfide ($H_2S$)[b] | repeatedly >10 (200) | NA | Hydrogen sulfide was monitored by online gas detectors at the workplace; the main causes of asthma were considered to be hydrogen sulfide and sulfuric acid evaporating from process lines; acids were not measured |
| Copper and nickel smelters (abroad) | Maintenance campaigns in several old-fashioned copper and nickel smelters abroad | Sulfur dioxide ($SO_2$)[b] | NA | 40–120 (800–2400) | Online gas detector at workplace; generally poor workplace hygiene in many places; sulfur dioxide the main emission in copper smelters |

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| Metal mine | Working above precipitation tank where $H_2S$ gas was bubbled through metal solutions | Hydrogen sulfide ($H_2S$)[b] | NA | weekly >20 (>400) | Online gas detector alarms were set to 20 ppm $H_2S$ which is 4 x OEL; irritant and toxic $H_2S$ gas and alkaline CaO powder (dust) were thought to be the main causes of asthma |
| | Loading calcium oxide (CaO) powder | Dust (alkaline) | >30 mg/m$^3$ (>300) | NA | |
| Chemical plant | Process work at different stages of sulfuric acid production | Sulfur dioxide ($SO_2$) | 0.6–2.98mg/m$^3$ (46–230) | 1.5–13.4 mg/m$^3$ (115–1040) | Direct-reading device;<br>Gas leaks increasingly detected due to corroded process lines;<br>sulfuric acid and hydrogen sulfide followed by online gas detectors but measurement data not available |
| Fertilizer plant | Cleaning process blockages with high-pressure-cleaner and chipping hammer | Hydrofluoric acid (HF) | 0.45–8.7 mg/m$^3$ (30-580) | NA | Several corrosive agents (acids, bases, hydrogen sulfide and oxides);<br>occasional very high exposure peaks exceeding capacity of online gas detectors at workplace.<br>Exposed despite relevant respiratory protective equipment. |
| | | Phosphoric acid ($H_3PO_4$) | 0.14–0.51 mg/m$^3$ (14–51) | NA | |
| | | Sulfuric acid ($H_2SO_4$) | 0.034–0.068 mg/m$^3$ (68–136) | NA | |
| Chemical plant | Packing titanium dioxide ($TiO_2$) powder coated with sulfuric acid ($H_2SO_4$) | Dust (acidic) | 16.9 mg/m$^3$(169) | 71.8 mg/m$^3$ (718) | Heavy exposure to dust; one of the main products was coated with $H_2SO_4$, which was the main reason for asthma; also nasal and eye irritation, chronic rhinosinusitis and nasolacrimal duct stenosis due to acidic dust |
| Bioethanol plant | 3-day-period cleaning large area of biomass and contaminated insulation | Endotoxins | 0.26–340 EU/m$^3$ | NA | Measurements taken in normal situation and thought to underestimate the exposure during discharging and cleaning period |
| Pulp mill I | Handling process disturbances in pulp | Hydrogen sulfide ($H_2S$) [b] | daily >5 (>100) | NA | Online gas detectors at workplace |

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| | digester and bleaching unit | Chlorodioxide ($ClO_2$) [b] | daily >0.1 (>100) | 0.93 (930) | |
| Pulp mill I, outside | Handling wood chip raw material outside and in storage tunnel | Hydrogen sulfide ($H_2S$) [b] | 7 (140) | NA | Two high exposure occasions: first outside plant when cloud of $H_2S$ and $ClO_2$ from the process reached the patients' working area, another was a week later when working in a storage tunnel with high levels of $H_2S$, as detected by personal online gas detector |
| Pulp mill II | Process leak of $ClO_2$ solution into open channel on floor | Chlorodioxide ($ClO_2$) [b] | 0.69 (690) | NA | Personal online gas detector; one occasion of high exposure |
| Power plant I | Accidents such as collapse of 150–300-ton silo when loading ash | Dust (alkaline) | 3.4 mg/m$^3$ (34) | NA | Alkaline ash dust considered to be main reason for asthma; dust measurements taken in normal work but accidents represent very high exposure levels; 5–6 accidents/five years' employment |
| Power plant II | Opening wood chip tanks in connection with process disturbances | Endotoxins | 1500 EU/m$^3$ (1700) | NA | Repeated high-level exposure to endotoxins over several years |
| Tunnel construction | Concentration of diesel exhaust from tunnel cleaning machine due to ventilation being switched off | Nitrogen oxides ($NO_x$) [b] | >100 (400)[d] | NA | Online gas detector for all nitrogen oxides at workplace |
| Thermal preservation of wood | A period with technical problems due to which wool piles had to be moved by hand into drying oven | Formaldehyde ($CH_2O$) | 0.03–0.19 mg/m$^3$ (8–51) | 0.56 mg/m$^3$ (150) | Moderate levels of formaldehyde, organic acids and VOC measured in general air outside ovens; concentration was thought to be multiple inside ovens where the patient worked without respiratory protection for 2–6 hours/day over a 9-month period |
| | | Acetic acid ($CH_3COOH$) | 0.91–7.15 mg/m$^3$ (7–55) | NA | |
| | | Formic acid (HCOOH) | 0.4–1.2 mg/m$^3$ (8–24) | NA | |

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| | | Terpenes (wood VOC) | 4.2–21 mg/m$^3$ (3–15) | 218 mg/m$^3$ (156) | |
| Veneer log processing with chemicals | Working in log incubator plant | Hydrogen sulfide ($H_2S$) [b] | NA | 20–60 (400–1200) | Online gas detectors at workplace; removal of sludge from incubator wastewater located nearby, this was thought to be the main source of hydrogen sulfide |
| Processing PVC- fabrics | Heat seaming of large PVC-impregnated fabrics; air conditioning problems | Total VOC | 3–5 mg/m$^3$ | 6.5 mg/m$^3$ | Three asthma cases in seaming of PVC at 175 °C; measurements were taken several months after the breakout with normal air conditioning on; also several non- or mildly irritant agents were discovered in low concentrations. |

OEL=occupational exposure limit, ppm=parts per million, NA=not available, EU=endotoxin unit, VOC= volatile organic compounds, PVC=polyvinyl chloride

[a] Finnish OEL and if not set, other relevant European OEL

[b] Measurements from company's own follow-up with on-line gas detectors

[c] Only short-term (15 min) OEL set

[d] Company-defined exposure limit for total oxides of nitrogen was 25 mg/m$^3$