



OPEN ACCESS

Original research

Occupations and exposure events in acute and subacute irritant-induced asthma

Irmeli Lindström ,¹ Jussi Lantto,^{2,3} Kirsi Karvala,^{1,4} Satu Soini,⁵ Katriina Ylinen,⁶ Hille Suojalehto,¹ Katri Suuronen¹

► Additional material is published online only. To view please visit the journal online (<http://dx.doi.org/10.1136/oemed-2020-107323>).

¹Occupational Medicine, Finnish Institute of Occupational Health, Helsinki, Finland

²Pulmonary Medicine, Helsinki University Hospital Heart and Lung Center, Helsinki, Finland

³University of Helsinki Faculty of Medicine, Helsinki, Finland

⁴Varma Mutual Pension Insurance Company, Helsinki, Finland

⁵Occupational Health, Finnish Institute of Occupational Health, Oulu, Finland

⁶Work Environmental Laboratories, Finnish Institute of Occupational Health, Helsinki, Finland

Correspondence to

Dr Irmeli Lindström, Työterveyslaitos, Helsinki, Uusimaa, Finland; irmeli.lindstrom@ttl.fi

Received 18 December 2020

Revised 16 February 2021

Accepted 8 March 2021

Published Online First

31 March 2021

ABSTRACT

Background Exposures leading to irritant-induced asthma (IIA) are poorly documented.

Methods We retrospectively screened the medical records of patients with IIA diagnosed in an occupational medicine clinic during 2000–2018. We classified the cases into acute (onset after single exposure) and subacute (onset after multiple exposures) IIA. We analysed in detail, occupations, causative agents and their air levels in the workplace, exposure events and the root causes of high exposure.

Results Altogether 69 patients were diagnosed with IIA, 30 with acute and 39 with subacute IIA. The most common occupational groups were industrial operators (n=23, 33%), metal and machinery workers (n=16, 11%) and construction workers (n=12, 8%). Among industrial operators significantly more cases had subacute IIA than acute IIA (p=0.002). Forty cases (57%) were attributable to some type of corrosive acidic or alkaline chemical. Acute IIA followed accidents at work in different types of occupation, while subacute IIA was typical among industrial operators performing their normal work tasks under poor work hygiene conditions. The most common root cause was lack of information or false guidance in acute IIA (n=11, 36%) and neglect of workplace hygiene measures in subacute IIA (n=29, 74%).

Conclusions Accidents are the main causes of acute IIA, whereas subacute IIA can develop in normal work in risk trades with poor work hygiene. Airborne strong acids or bases seem to be the most important causative agents of acute and subacute IIA. The different risk profiles of acute and subacute IIA should be considered in the prevention and identification of the cases.

INTRODUCTION

Population-based studies have shown that accidental peak exposure to airborne irritant chemicals (later referred to as irritants) at work may cause a three-fold increase in the risk of asthma.^{1,2} Brooks *et al* first described how a single instance of high-level exposure to irritative agents can cause asthma: reactive airways dysfunction syndrome or acute irritant-induced asthma (IIA).^{3,4} Later, repeated, not so high-level exposure to irritants has also been connected to asthma onset: not-so-sudden IIA or subacute IIA.^{5,6} Usually, IIA is work-related and accounts for 5%–18% of all occupational asthma cases.⁷ Irritants are less known than sensitizers as causative agents of occupational asthma, which hampers the recognition of IIA and the

Key messages

What is already known about this subject?

- Irritant-induced occupational asthma (IIA) is a rare disease, current knowledge on its causative agents is based on case reports and a few case series.

What are the new findings?

- The occupational exposure is evaluated elaborated in this large series of clinically verified cases of acute and subacute IIA.
- Operation and maintenance workers in metal, paper, chemical and food industry, construction workers, farmers and transport workers are at risk of IIA.
- Airborne substances classified as skin corrosive, such as acids and bases are potential causative agents of IIA.
- Acute IIA (onset after single exposure) followed accidents at work in many different types of occupation. The root cause of accidents was usually lack of information or poor guidance.
- Subacute IIA (onset after multiple exposures) was typical among industrial operators performing their normal work tasks under poor work hygiene conditions.

How might this impact on policy or clinical practice in the foreseeable future?

- Novel information about the risk occupations, agents and work tasks of acute and subacute IIA helps occupational safety authorities, workplaces and clinicians to direct preventive actions to relevant workers and to identify occupational asthma. The different risk profiles of acute and subacute IIA need to be considered.

understanding of the hazards of irritative agents at workplaces. The health impact of irritants is potentially high, because in IIA, persistent symptoms and abnormal lung function have still been reported years after diagnosis.⁸ Recently, the role of irritants as causes of adult-onset asthma in general has also been discussed.⁹

IIA is a rare disease and the current knowledge on its causative agents is based on case reports and a few case series. The cases have typically been connected to spills, accidental fires or the release of irritants resulting in high exposure to, for example, chlorine



© Author(s) (or their employer(s)) 2021. Re-use permitted under CC BY-NC. No commercial re-use. See rights and permissions. Published by BMJ.

To cite: Lindström I, Lantto J, Karvala K, *et al*. *Occup Environ Med* 2021;**78**:793–800.

gas, di-isocyanates, acids, alkali, sulfuric gases, oxidising agents or different mixtures.^{3 5 8 10-13} Many reports lack important information on the causative agents and the exposure leading to IIA,¹¹ which hampers the risk assessment and prevention of this serious yet avoidable disease.

Here, we present a large case series of clinically verified occupational IIA. The purpose of our retrospective analysis of patients during the 2000s was to describe in detail risk occupations, work tasks and sectors; causative agents and their estimated air levels; and the root causes of exposure. Through this analysis, we hope to promote the identification and prevention of IIA.

METHODS

Study population

The Finnish Institute of Occupational Health (FIOH) is a tertiary outpatient clinic that confirms the diagnosis of most cases of occupational asthma in Finland (population of 5.5 million). We searched FIOH's patient register from 2000 to 2018 and included in our study all the cases with diagnosis number J68 and J45 (ICD-10) with relevant exposure to one or more irritants. We identified 69 patients with IIA diagnosis that fulfilled the criteria.^{5 6} The present study is based on the retrospective analysis of these 69 patients' medical records.

We coded the occupations using the International Standard Classification of Occupations¹⁴ and grouped them into two-digit levels.

Diagnostic criteria

The diagnostic criteria of IIA were (1) exposure to a high concentration of an irritant, (2) occurrence of asthma symptoms in a close temporal relationship to the exposure (usually <24 hours or after few days), (3) reversible obstruction or non-specific airway hyper-responsiveness in methacholine or histamine challenge, (4) persistence of symptoms >3 months, (5) no evidence of active asthma in adulthood before the exposure event and (6) no other pulmonary disorder that would explain the symptoms.^{5 6}

The participants were classified in two groups. The acute IIA group had only one high-level exposure event within 24 hours. The subacute IIA group had repeated exposure events to high levels of irritants during a period of more than 24 hours.^{5 6}

Information on exposure

Our group, consisting of an occupational physician (KK), two pulmonologists (IL and JL) and an occupational toxicologist (KS), reviewed the patient files. We systematically evaluated the sources of information that had been used in the exposure assessment of each patient at the time of IIA diagnosis. In all cases, several types of exposure data were used (table 1).

We evaluated the exposure to irritants case by case, based on the following data: (1) causative agents and their safety data sheets (SDS) as regards physicochemical nature and hazard classifications, (2), information on the exposure event(s) and (3) results of workplace hygiene measurements and other workplace monitoring from the patients' own workplaces. The relevant measurements were selected according to the patients' work tasks, location in the workplace and the date of the measurements.

The main criteria for sufficient exposure were (1) the identification of a corrosive or otherwise irritant agent in the workplace air, (2) the physicochemical form and air concentration of the agent being capable of entering the patient's lungs and (3) exposure evaluated as clearly and/or repeatedly exceeding a relevant

Table 1 Sources of information used for assessment of exposure of patients with irritant-induced occupational asthma

Source of exposure information	Acute N=30 n (%)	Subacute N=39 n (%)	All N=69 n (%)
Safety data sheets*	18 (60)	24 (62)	42 (61)
Workplace hygiene measurements	2 (7)	24 (62)	26 (38)
Patient interview by exposure specialist†	7 (23)	14 (36)	21 (30)
Employer interview by exposure specialist	5 (17)	15 (39)	20 (29)
Accident reports or reports of authorities	9 (30)	2 (5)	11 (16)
Laboratory analyses of workplace materials‡	2 (7)	4 (10)	6 (9)
Personal or stationary online gas detectors at workplace	3 (10)	3 (8)	6 (9)
Biomonitoring	0 (0)	4 (10)	4 (6)

*In cases with exposure to identified chemical products.

†Either specialised occupational hygienist or occupational toxicologist.

‡Including emission measurements or analyses of dust samples.

occupational exposure level (OEL). Modifying earlier classifications of respiratory irritants, we grouped the agents according to their chemistry and physical form into acids, bases and their mixtures; inorganic gases; oxidising agents; irritant dusts; other chemicals; other mixtures and endotoxins.¹⁵

We also determined the single most important *root cause* of the exposure on the basis of professional views and discussions, and classified them into (1) human error, (2) process or machine failure, (3) neglect of use of personal protective equipment (PPE), (4) neglect of work hygiene measures, (5) lack of information or false instructions and (6) other.

Statistical analysis

We used SPSS V.26.0 for the data analysis. We expressed continuous variables as means and SD, and categorical values as percentages. We analysed the differences between the groups of acute IIA and subacute IIA using Student's t-test for age, the χ^2 test and Fisher's exact test for categorical variables. Due to the small number of cases, the number of subjects in each occupational group was compared with the number of subjects in all other occupational groups. Respectively, the number of subjects having each root cause was compared with the number of subjects having all other root causes. A $p < 0.05$ was considered statistically significant.

RESULTS

We identified 30 patients with acute IIA and 39 with subacute IIA, 84% of all patients were men and 59% non-smokers (table 2). The largest occupational group was stationary plant and machine operators, who had significantly more cases of subacute IIA than acute IIA ($p = 0.002$), followed by metal, machinery and related trades workers, and building and related trade workers.

Causative agents and exposure events

Different types of mixtures caused 26% of the cases, followed by acid aerosols or fumes (19%), base aerosols or fumes (13%), dusts (12%) and inorganic gases (9%) (table 3). Forty of the cases (57%) were attributable to some type of corrosive acidic or alkaline chemical, also taking into account dusts, gases and different mixtures. A known respiratory sensitiser (hexamethylene diisocyanate, glutaraldehyde or formaldehyde) was a causative agent in only 6% of the cases. The causatives of acute and subacute IIA

Table 2 Clinical characteristics and occupations of patients with irritant-induced occupational asthma diagnosed at Finnish Institute of Occupational Health between 2000 and 2018

Characteristics	Acute N=30	Subacute N=39	All N=69	P value
Age, mean (SD)	45.1 (8)	47.0 (12)	46.2 (10)	0.436
Men	25 (83)	33 (85)	58 (84)	0.570
Smoking:				0.061
Current	5 (17)	9 (23)	14 (20)	
Ex	10 (33)	4 (10)	14 (20)	
Non	15 (50)	26 (67)	41 (59)	
Occupational groups*				
Stationary plant and machine operators	4 (13)	19 (49)	23 (33)	0.002
Metal, machinery and related trade workers	7 (23)	4 (10)	11 (16)	0.190
Building and related trade workers (excluding electricians)	4 (13)	4 (10)	8 (12)	0.720
Drivers and mobile plant operators	2 (7)	3 (8)	5 (7)	1.000
Science and engineering-associated professions	2 (7)	3 (8)	5 (7)	1.000
Market-oriented skilled agricultural workers	1 (3)	3 (8)	4 (6)	0.627
Electrical and electronics trade workers	3 (10)	0 (0)	3 (4)	-†
Production and specialised services managers	0 (0)	2 (5)	2 (3)	-
Cleaners and helpers	2 (7)	0 (0)	2 (3)	-
Others‡	5 (17)	1 (3)	6 (9)	-

The data are presented as numbers (%), if not otherwise stated. P values were calculated using independent variables t-test for age, χ^2 test for the distribution of smoking status, and Fisher's exact test for other classified variables. Each occupational group was compared with all other occupational groups.

*Classified by International Standard Classification of Occupations on two-digit level. P value is calculated for distribution of occupational classes.

†P values missing due to low number of cases.

‡Only one case per occupation group.

were similar apart from endotoxins, which caused only subacute IIA.

Typical work tasks or exposure events were gassing in pulp mills, different types of repair tasks and leaks in heavy industry, cleaning or washing with corrosive chemicals, transporting of chemicals, accidental fires or other overheating of materials, electroplating and other acid bathing of metals (online supplemental e-Table 1). Sludge handling and working in an animal shed caused exposure to irritants in farming. Two occupational hygienists suffered high-level exposure when performing workplace measurements, as did a police officer and an ambulance worker during rescue tasks. In the food industry, ammonium leaks in cooling systems, hydrogen peroxide used to disinfect lines, and endotoxins in potato flour factory and in handling malt caused asthma. Exposure to cement, calcium oxide or other alkaline dusts was substantial when emptying sacks, in silo breakdowns and when transporting ash.

The identification details, OELs and irritancy-related hazard classifications of the causatives according to current European legislation are presented in online supplemental e-Table 2. Most of the present causatives were classified as skin corrosive.

Workplace measurements

We used measurements from the patients' own workplaces in 30 cases (table 4, online supplemental e-Table 3). Most of these were related to subacute IIA and had been taken by a trained occupational hygienist. Some companies' own measurements, usually by online gas detectors, were available. The measurements verified exposure levels exceeding the OEL in 10% of acute and 49% of subacute IIA cases. In many workplaces, for example, in farms, food processing, mines, metal production, pulp mills and chemical plants, the OEL was exceeded several times. Endotoxin levels were as high as 105-fold in a piggery, 280-fold in malt handling in foodstuff production, and 21-fold in a potato flour factory in comparison to, for example, the Dutch OEL.¹⁶

Root causes

Lack of information or false guidance was the root cause in 36% of the acute IIA cases and in 13% of the subacute IIA cases ($p=0.017$) (figure 1A,B). Neglect of workplace hygiene measures was the underlying reason in 7% and 74% ($p<0.001$), and process or machine failure in 27% and 5% of the cases ($p=0.016$), respectively. Neglect of the use of PPE was the root cause in 10% of all cases.

DISCUSSION

This is a retrospective descriptive study of 69 patients with IIA, of which 30 had acute IIA and 39 subacute IIA. The diagnostic criteria of IIA included lung function-based verification of asthma and onset of asthma symptoms in a close temporal relationship with exposure to respiratory irritants whose concentrations were estimated to exceed the OEL. The detailed and critical evaluation of the exposure events, causative agents, and their chemical properties, as well as concentrations in the workplaces using many different information sources, was at the core of this study. These factors also make this study novel.

Risk occupations

The most common occupational groups in our study represented working in production industries that often use large volumes of chemicals. Finnish industry is built on the paper, metal and chemical industry, which naturally affects the high-risk work and causative agents detected in this study. The cases included several mechanics and operators in pulp mills in which many irritants such as hydrogen sulfide, alkaline pulp cooking solutions, oxidising chlorine gases and acidic sulfuric compounds may be present simultaneously. Such work caused both acute and subacute IIA, which may reflect defects in process safety and generally poor air quality. Repeated gassing episodes involving

Table 3 Causative agents of irritant-induced asthma

Main groups of causative agents	Acute N=30	Subacute N=39	Total N=69 (%)
Acid aerosols or fumes	6 Sulfuric acid Hydrofluoric acid Nitric acid Hydrochloric acid Hydrochloric acid and sulfur dioxide	7 Sulfuric acid* and ammonium fluoride Sulfuric acid* and hydrogen sulfide Sulfuric acid*, sulfur dioxide and sulfur trioxide Hydrochloric acid Nitric acid	13 (19)
Base aerosols or fumes	5 Ammonia Sodium hydroxide Black lye	4 Ammonia Sodium hydroxide Alkaline epoxy polyamine hardener and cleaning agent	9 (13)
Mixtures of acid and base aerosols or fumes		3 Ammonia, sulfuric acid, hydrochloric acid, hydrofluoric acid, nitric acid Sodium hydroxide, potassium hydroxide, sulfuric acid, nitric acid	3 (4)
Inorganic gases	3 Chlorine dioxide	3 Chlorine dioxide Chlorine dioxide and hydrogen sulfide Sulfur dioxide	6 (9)
Oxidising agents	1 Ozone	1 Hydrogen peroxide	2 (3)
Other chemicals	5 Formaldehydet Glutaraldehydet Hexamethylene diisocyanat† Naphthalene compounds Pyrethrin	1 Hexamethylene diisocyanat†	6 (9)
Mixtures	6 Bitumen, solvents and their thermal degradation products Sodium hydroxide, sodium hypochlorite Combustion gas Thermal degradation of polyester paint Sulfuric acid, sodium hypochlorite, chlorine dioxide gas Nitric oxides, diesel exhaust, mixture of oil and water	12 Ammonia and hydrogen sulfide Ammonia, hydrogen sulfide and endotoxins Hydrogen sulfide, sulfur compounds, sodium hydroxide, chlorine dioxide Calcium oxide and hydrogen sulfide Rubber chemicals and their thermal degradation products Solvents and mine dust Formic acid, acetic acid, formaldehyde Thermal degradation of polyvinyl chloride-polyurethane fabrics Trifluoroacetic acid and acetonitrile	18 (26)
Dusts	4 Calcium oxide Cement	4 Ash Calcium oxide and alkaline dusts Cement Sulfuric acid-containing titanium oxide powder	8 (12)
Endotoxins	0	4	4 (6)

*Main causative agent.

†Sensitiser-induced occupational asthma was considered to be unlikely based on the results of specific inhalation test or the anamnesis.

sulfur dioxide and other irritants in pulp mills have previously been connected to asthma onset.^{17 18}

Other work tasks in our study entailed the handling of acids and alkali in mines and metal plants in processes such as smelting and electrolysis, and in the pretreatment of metals. Several of the cases were in the transport sector, in tasks involving loading and unloading irritant materials. This indicates defects in control measures and knowledge on chemical hazards. In construction work, floor surfacing, the cleaning of concrete elements and the handling of cement led to asthma onset. One key risk trade was agriculture, specifically animal husbandry. In sheds and sludge units, ammonia and hydrogen sulfide originate from animal faeces, which may hamper the identification of exposure, although toxic gases have been reported to cause asthma in piggeries.¹⁹

Previously, long-term exposure to ammonia or dust in piggeries has shown to increase bronchial hyper-responsiveness.^{19 20}

Earlier data on the risk occupations of IIA is limited. In a study of 123 workers with IIA in the USA, the most common occupations were (1) precision production, (2) craft and repair and (3) technical, sales and administrative support.²¹ It is difficult to compare this study with ours due to its different classification of occupations and lack of clinical verification of asthma. Epidemiological surveys have identified a high risk of asthma in occupations partly similar to those in our study, for example, metal work and stationary engine and machine work, construction work²² and farming.^{2 23–25} Our series included only two cleaners, but several studies have detected an increased asthma risk in cleaning work.^{1 2 23 26} This may indicate that cleaning work in

Table 4 Workplace measurements when available and relevant for assessment of exposure to irritant factors

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)*	Maximum air concentration in ppm if not given otherwise (% of 8h-OEL)*
Piggery I	Sludge handling, piglet department and open shed	Ammonia (NH ₃)	6.6 (33)	37 (187)
		H ₂ S	NA	4 (80)
		Endotoxins	9500 EU/m ³ (10 500)	NA
Piggery II	Farrowing department, sludge handling and open shed	Ammonia (NH ₃)	1.1–16 mg/m ³ (9–114)	NA
		H ₂ S	>2.5 (50)	14 (280)
Cowshed	Cleaning and emptying sludge pipe and basin	Ammonia (NH ₃)	10–20 (50–100)	214 (>000)
		H ₂ S	5 (100)	20 (400)
Poultry rearing house	Inspection and occupational hygiene measurement	Ammonia (NH ₃)	60–80 (300–400)	NA
Meat packing	Packing chicken meat and cleaning packing line	Ammonia (NH ₃)†	10–150 (50–750)	260 (1300)
Pudding production	Long-lasting and repeated high exposure in normal work	Hydrogen peroxide (H ₂ O ₂)†	1.1 (110)	4.4 (440)
Potato flour factory	Washing potatoes	Endotoxins	1900 EU/m ³ (2100)	NA
Foodstuff production	Handling malt	Endotoxins	25 000 EU/m ³ (28 000)	NA
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
		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	0.78–6.4 mg/m ³ (10–84)‡	NA
		Formaldehyde (CH ₂ O)	0.324 (108)	NA
Metal production plant	Working near wet precipitation processes utilising hydrogen sulfide (H ₂ S)		repeatedly >10 (200)	NA
		H ₂ S†		
Copper and nickel smelters (abroad)	Maintenance campaigns in several old-fashioned copper and nickel smelters abroad	Sulfur dioxide (SO ₂)†	NA	40–120 (800–2400)
Metal mine	Working above precipitation tank where H ₂ S gas was bubbled through metal solutions	H ₂ S†	NA	weekly >20 (>400)
	Loading of calcium oxide powder	Dust (alkaline)	>30 mg/m ³ (>300)	NA
Chemical plant	Process work in different stages of sulfuric acid production	Sulfur dioxide (SO ₂)	0.6–2.98 mg/m ³ (46–230)	1.5–13.4 mg/m ³ (115–1040)
Fertiliser plant	Cleaning of process blockages with high-pressure cleaner and chipping hammer	Hydrofluoric acid	0.45–8.7 mg/m ³ (30–580)	NA
		Phosphoric acid	0.14–0.51 mg/m ³ (14–51)	NA
		H ₂ SO ₄	0.034–0.068 mg/m ³ (68–136)	NA
Chemical plant	Packing titanium dioxide powder coated with sulfuric acid (H ₂ SO ₄)	Dust (acidic)	16.9 mg/m ³ (169)	71.8 mg/m ³ (718)
Bioethanol plant	3 days period cleaning large area of biomass and contaminated insulation	Endotoxins	0.26–340 EU/m ³	NA
Pulp mill I	Handling process disturbances at pulp digester and bleaching unit	Hydrogen sulfide (H ₂ S)†	Daily >5 (>100)	NA
		ClO ₂ †	Daily >0.1 (>100)	0.93 (930)
Pulp mill I, outside	Handling wood chip raw material outside and in a storage tunnel	H ₂ S†	7 (140)	NA
Pulp mill II	Process leak of chlorodioxide (ClO ₂) solution to an open channel on the floor	ClO ₂ †	0.69 (690)	NA
Power plant I	Accidents such as collapse of 150–300-ton silo when loading ash	Dust (alkaline)	3.4 mg/m ³ (34)	NA
Power plant II	Opening wood chip tanks in connection with process disturbances	Endotoxins	1500 EU/m ³ (1700)	NA
Tunnel construction	Concentration of diesel exhaust from tunnel cleaning machine due to ventilation being switched off	Nitrogen oxides†	>100 (400)§	NA
Thermal preservation of wood	Period with technical problems due to which wool piles had to be moved by hand into drying oven	CH ₂ O	0.03–0.19 mg/m ³ (8–51)	0.56 mg/m ³ (150)
		Acetic acid (CH ₃ COOH)	0.91–7.15 mg/m ³ (7–55)	NA
		Formic acid (HCOOH)	0.4–1.2 mg/m ³ (8–24)	NA
		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	H ₂ S†	NA	20–60 (400–1200)

continued

Table 4 continued

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)*	Maximum air concentration in ppm if not given otherwise (% of 8h-OEL)*
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

Some measurements conducted by trained occupational hygienist and some by respective company's own follow-up.

*Finnish OEL and if not set, other relevant European OEL.

†Measurements company's own follow-up by online gas detectors etc.

‡Only short-term (15 min) OEL set.

§Company-defined exposure limit for total oxides of nitrogen was 25 mg/m³.

EU, endotoxin unit; NA, not available; OEL, occupational exposure limit; PVC, polyvinyl chloride; VOC, volatile organic compounds.

Finland involves long-term exposure to low levels of irritants, which means that it does not meet the criteria of IIA.

Exposure events and causative agents

The exposure events varied, and therefore the thorough description of our cases and exposures in online supplemental e-tables 1 and 3 may help clinicians identify IIA. The most frequently involved agents causing IIA were corrosive inorganic acids and bases (alkali), representing more than half of the cases. Sulfuric acid was the most common unique causative in both acute and subacute IIA. Many of the dust exposures or mixtures in this series were also strongly acidic or alkaline, making classifications of causative agents difficult. Identifying a dust's chemical nature, such as its pH, is essential, when evaluating its potential to cause IIA. An inert dust, for example, titanium dioxide, can be corrosive if covered with sulfuric acid. Alkaline dust (eg, cement or calcium oxide), whose role as an IIA causing agent has increased after the World Trade Center tragedy, was a causative agent in 10% of our patients.²⁷ Isocyanates caused IIA in only two cases in which the high-level exposure to isocyanates had occurred through burning polyurethane insulation material and malfunctioning PPE in spray painting and sensitisation was ruled out. Strong acids, especially sulfuric acid, have been reported to be fairly common causes of IIA,²⁸ but chlorine,^{8 10 11 13 28–30} sulfur dioxide,^{10 13 29} isocyanates,^{5 10 11 13} ammonia, cleaning agents¹⁰ and oxides of nitrogen¹¹ have been the most common. Due to its detailed exposure assessment, we are quite confident that the present study's causatives were identified correctly.

We evaluated that endotoxins caused asthma in four cases. Extremely high concentrations of endotoxins were measured in the piggery, the power plant using wood chips, the foodstuff

production, and the potato flour factory, which is in line with an earlier report on endotoxin exposure in livestock farming.³¹ We are not aware of previous reports on endotoxin-related IIA, but a decline in lung function across the work shift among fibre-glass workers, an increase in bronchial hyper-reactivity among farmers, and greater loss in lung function among cotton workers has shown to be associated with endotoxin exposure.^{32–34}

Identification of irritants and their OELs

According to the classification, labelling and packaging regulation of the European Union, a chemical's irritancy is most often determined via its effect on the skin.³⁵ The most potent airway irritants such as inorganic acids and alkali reported here are classified as corrosive ('Skin Corr 1A' or 'Skin Corr 1B'), defined as irreversible tissue damage on the skin in <3–60 min. In addition to these classifications, the chemical's SDS contains the hazard statement EUH314 'Causes severe skin burns and eye damage' and in some cases also EUH071: 'Corrosive to the respiratory tract'. Another mechanism through which chemicals can cause tissue damage in airways is oxidation; chemicals with such potential are classified in the SDS as oxidative ('Ox Gas' or 'Ox Liq'). Most IIA-causing chemicals' OELs are based on their irritancy. Thus, we advise consulting the relevant OELs when assessing exposure for IIA.

Workplace measurements

Workplace measurements were useful, especially in the subacute IIA cases, as exceeding the OEL was verified in half of these cases. In several workplaces, extremely high concentrations of irritants, even exceeding the OEL by manifold, were measured (table 4). Quantitative measurements in pulp and paper mills are scarce, possibly due to the fact that companies' own follow-up data are seldom published.³⁶ Bråtveit *et al* reported high exposure to acids in electroplating³⁷ and Haddam *et al* to sulfur dioxide in smelters.³⁸ As regards animal facilities, high occupational exposure to ammonia and hydrogen sulfide has been discovered in, for example, swine and poultry sheds.^{39 40} Surprisingly, many of the present patients' employers have not taken preventive measures, despite these worrying findings. The lack of workplace measurements other than online gas detector data is natural in acute cases, as these events are unexpected. Heavy exposure of the two occupational hygienists in present series suggested poor preparation for their core task.

Root causes

The main root cause of acute IIA was found to be lack of information or false guidance, which stresses the need to identify risk chemicals and guide employees in matters related to them at

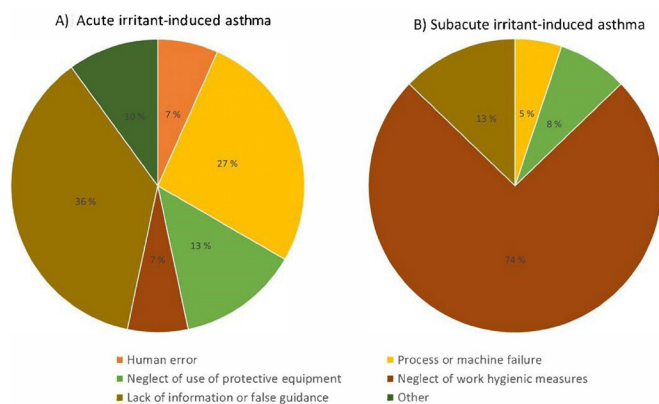


Figure 1 The root causes of acute (A) and subacute (B) irritant-induced asthma.

workplaces. Guidance should include lifesaving first aid procedures. Earlier analyses of chemical accidents have identified equipment failure, human error, lack of effective PPE or other contraventions of safety regulations as leading causes.^{29–41} The neglect of work hygiene measures was found to be the most important background reason for subacute IIA. In these cases, air quality was often clearly deficient, and important, general control measures were not routinely applied. As regards PPE defects, we observed cases with no PPE at all, but also cases in which PPE was unsuitable, broken or used incorrectly. There are often several reasons for high-level exposure and identification of a single most important root cause based on medical records is quite demanding. The risk of misclassification was, however, reduced by the generous amount of data, extended evaluation of exposure events (table 1) and multidisciplinary discussions.

Subacute IIA

Subacute IIA is a controversial diagnosis due to little medical evidence and difficulties in separating this type of IIA from asthma related to low dose exposure to irritants.^{5–6} Brooks described 25 cases of subacute IIA, but only 15 had new-onset asthma. We report 39 cases with subacute IIA. The evidence of exposure to respiratory irritants exceeding the OELs convinced us that the cases really had subacute IIA rather than low-dose exposure IIA. For half of the cases we had measurement data on high-level exposure from the patients' workplace and for the rest of the cases we had other information strongly indicating this (eg, high volumes of irritants in confined spaces or repeated process failures with visible gas or aerosols). Some reports have suggested a maximum length of exposure time for subacute IIA, but we did not apply limits to the length of exposure.^{5–10} The causative agents of subacute IIA were similar to those of acute IIA, but otherwise we found many differences between the groups. The patients with acute IIA represented varied occupational groups, whereas half of the cases with subacute IIA worked as stationary plant and machine operators in metal processing, mines, pulp mills, power plants or in the chemical, plastic or food industry. This reflects neglect of work hygiene measures in many sectors of heavy industry, which was also the main root cause of subacute IIA. It is noteworthy that in many cases of subacute IIA, employees had been exposed to high levels of irritants when performing their normal work tasks, and not during exceptional situations.

CONCLUSIONS

Based on this large case series of clinically verified IIA, physicians should suspect IIA among patients with asthma onset after high-level exposure to airborne agents with corrosive or oxidising properties, for example, strong acids or bases. Acute IIA is typical after chemical accidents or other hazardous events, but subacute IIA can develop in risk trades in employees' normal work tasks if work hygiene measures are poor. Production and maintenance workers in the metal, paper, chemical and food industry, miners, farmers, transport workers and construction workers seem to be especially at risk of IIA. Control measures for clearly hazardous chemicals may be deficient even in a country considered to have good workplace hygiene standards.

Lack of information and false guidance on chemical hazards and neglect in elementary hygiene measures in cases of repeated exposure seem to be important underlying reasons for IIA. This suggests that increasing chemical risk knowledge and control by educating health safety authorities, employees, employers and

occupational health services plays a key role in the prevention of IIA and other irritant-induced respiratory complaints.

Acknowledgements We thank The Finnish Work Environment Fund for supporting the study.

Contributors IL had full access to all the data and takes responsibility for the integrity of the data and the accuracy of the data analysis. IL, JL, KK, SS, KY, HS and KS contributed substantially to the study design, data collection, analysis and interpretation, and the writing of the manuscript.

Funding The Finnish Work Environment Fund supported the study (grant number 190390).

Competing interests None declared.

Patient consent for publication Not required.

Ethics approval The study was approved by the ethics committee of Helsinki University Central Hospital (approval number HUS/611/2020). According to the local legislations and ethical committees, no approval was needed because no patient intervention was involved at the FIOH.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement No data are available. The data are archived in the repository of Finnish Institute of Occupational Health.

Supplemental material This content has been supplied by the author(s). It has not been vetted by BMJ Publishing Group Limited (BMJ) and may not have been peer-reviewed. Any opinions or recommendations discussed are solely those of the author(s) and are not endorsed by BMJ. BMJ disclaims all liability and responsibility arising from any reliance placed on the content. Where the content includes any translated material, BMJ does not warrant the accuracy and reliability of the translations (including but not limited to local regulations, clinical guidelines, terminology, drug names and drug dosages), and is not responsible for any error and/or omissions arising from translation and adaptation or otherwise.

Open access This is an open access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited, appropriate credit is given, any changes made indicated, and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>.

ORCID iD

Irmeli Lindström <http://orcid.org/0000-0002-6399-8846>

REFERENCES

- Lillienberg L, Andersson E, Janson C, *et al*. Occupational exposure and new-onset asthma in a population-based study in northern Europe (Rhine). *Ann Occup Hyg* 2013;57:482–92.
- Kogevinas M, Zock J-P, Jarvis D, *et al*. Exposure to substances in the workplace and new-onset asthma: an international prospective population-based study (ECRHS-II). *Lancet* 2007;370:336–41.
- Brooks SM, Weiss MA, Bernstein IL. Reactive airways dysfunction syndrome (rads). persistent asthma syndrome after high level irritant exposures. *Chest* 1985;88:376–84.
- Tarlo SM, Broder I. Irritant-induced occupational asthma. *Chest* 1989;96:297–300.
- Brooks SM, Hammad Y, Richards I, *et al*. The spectrum of irritant-induced asthma: sudden and not-so-sudden onset and the role of allergy. *Chest* 1998;113:42–9.
- Vandenplas O, Wiszniewska M, Raulf M, *et al*. EAACI position paper: irritant-induced asthma. *Allergy* 2014;69:1141–53.
- Gautrin D, Boulet LP, Boutet M, *et al*. Is reactive airways dysfunction syndrome a variant of occupational asthma? *J Allergy Clin Immunol* 1994;93:12–22.
- Malo J-L, L'archevêque J, Castellanos L, *et al*. Long-Term outcomes of acute irritant-induced asthma. *Am J Respir Crit Care Med* 2009;179:923–8.
- Dumas O, Laurent E, Bousquet J, *et al*. Occupational irritants and asthma: an Estonian cross-sectional study of 34,000 adults. *Eur Respir J* 2014;44:647–56.
- Baur X, Bakehe P, Vellguth H. Bronchial asthma and COPD due to irritants in the workplace - an evidence-based approach. *J Occup Med Toxicol* 2012;7:19.
- Shakeri MS, Dick FD, Ayres JG. Which agents cause reactive airways dysfunction syndrome (rads)? A systematic review. *Occup Med* 2008;58:205–11.
- Takeda N, Maghni K, Daigle S, *et al*. Long-term pathologic consequences of acute irritant-induced asthma. *J Allergy Clin Immunol* 2009;124:975–81.
- Ross DJ, McDonald JC. Asthma following inhalation accidents reported to the sword project. surveillance of work-related and occupational respiratory disease. *Ann Occup Hyg* 1996;40:645–50.
- (ILO) ILO. *International standard classification of occupations 2008*, 2008.

- 15 Vandeplas OSH. Work-Related Asthma: Occupational Asthma and Work-Exacerbated Disease. In: Newman Taylor AJ, Cullinan P, Blanc P, *et al*, eds. *Occupational lung disorders*. Taylor&Francis Group, 2017: 343.
- 16 Netherlands THHCot. *Endotoxins. Health-based recommended occupational exposure limit*, 2010.
- 17 Chang-Yeung M, Lam S, Kennedy SM, *et al*. Persistent asthma after repeated exposure to high concentrations of gases in pulpmills. *Am J Respir Crit Care Med* 1994;149:1676–80.
- 18 Andersson E, Knutsson A, Hagberg S, *et al*. Incidence of asthma among workers exposed to sulphur dioxide and other irritant gases. *Eur Respir J* 2006;27:720–5.
- 19 Cormier Y, Coll B, Laviolette M, *et al*. Reactive airways dysfunction syndrome (RADS) following exposure to toxic gases of a swine confinement building. *Eur Respir J* 1996;9:1090–1.
- 20 Vogelzang PF, van der Gulden JW, Folgering H, *et al*. Longitudinal changes in bronchial responsiveness associated with swine confinement dust exposure. *Chest* 2000;117:1488–95.
- 21 Henneberger PK, Derk SJ, Davis L, *et al*. Work-related reactive airways dysfunction syndrome cases from surveillance in selected US states. *J Occup Environ Med* 2003;45:360–8.
- 22 Karjalainen A, Kurppa K, Martikainen R, *et al*. Work is related to a substantial portion of adult-onset asthma incidence in the Finnish population. *Am J Respir Crit Care Med* 2001;164:565–8.
- 23 Eng A, T Mannetje A, Douwes J, *et al*. The New Zealand workforce survey II: occupational risk factors for asthma. *Ann Occup Hyg* 2010;54:154–64.
- 24 Karjalainen A, Kurppa K, Virtanen S, *et al*. Incidence of occupational asthma by occupation and industry in Finland. *Am J Ind Med* 2000;37:451–8.
- 25 Omland Øyvind, Hjort C, Pedersen OF, *et al*. New-onset asthma and the effect of environment and occupation among farming and nonfarming rural subjects. *J Allergy Clin Immunol* 2011;128:761–5.
- 26 Svanes Øistein, Bertelsen RJ, Lygre SHL, *et al*. Cleaning at home and at work in relation to lung function decline and airway obstruction. *Am J Respir Crit Care Med* 2018;197:1157–63.
- 27 Wisnivesky JP, Teitelbaum SL, Todd AC, *et al*. Persistence of multiple illnesses in World Trade Center rescue and recovery workers: a cohort study. *Lancet* 2011;378:888–97.
- 28 Tarlo SM, Liss G, Corey P, *et al*. A workers' compensation claim population for occupational asthma. Comparison of subgroups. *Chest* 1995;107:634–41.
- 29 Sallie B, McDonald C. Inhalation accidents reported to the SWORD surveillance project 1990–1993. *Ann Occup Hyg* 1996;40:211–21.
- 30 Lemièrè C, Malo JL, Boutet M. Reactive airways dysfunction syndrome due to chlorine: sequential bronchial biopsies and functional assessment. *Eur Respir J* 1997;10:241–4.
- 31 Basinas I, Sigsgaard T, Kromhout H, *et al*. A comprehensive review of levels and determinants of personal exposure to dust and endotoxin in livestock farming. *J Expo Sci Environ Epidemiol* 2015;25:123–37.
- 32 Milton DK, Wypij D, Kriebel D, *et al*. Endotoxin exposure-response in a fiberglass manufacturing facility. *Am J Ind Med* 1996;29:3–13.
- 33 Smit LAM, Heederik D, Doekes G, *et al*. Occupational endotoxin exposure reduces the risk of atopic sensitization but increases the risk of bronchial hyperresponsiveness. *Int Arch Allergy Immunol* 2010;152:151–8.
- 34 Wang X-R, Zhang H-X, Sun B-X, *et al*. A 20-year follow-up study on chronic respiratory effects of exposure to cotton dust. *Eur Respir J* 2005;26:881–6.
- 35 ECHA. *Guidance to regulation (EC) No 272/2008 on classification, labelling and packaging (CLP) of substances and mixtures. Version 5.0*, 2017: 275–6. https://echa.europa.eu/documents/10162/23036412/clp_en.pdf/58b5dc6d-ac2a-4910-9702-e9e1f5051cc5
- 36 Teschke K, Ahrens W, Andersen A, *et al*. Occupational exposure to chemical and biological agents in the nonproduction departments of pulp, paper, and paper product Mills: an international study. *Am Ind Hyg Assoc J* 1999;60:73–83.
- 37 Bråtveit M, Haaland IM, Moen BE, *et al*. Exposure to sulfuric acid in zinc production. *Ann Occup Hyg* 2004;48:159–70.
- 38 Haddam N, Samira S, Dumont X, *et al*. Lung epithelium injury biomarkers in workers exposed to sulphur dioxide in a non-ferrous smelter. *Biomarkers* 2009;14:292–8.
- 39 Park J, Kang T, Heo Y, *et al*. Evaluation of short-term exposure levels on ammonia and hydrogen sulfide during Manure-Handling processes at livestock farms. *Saf Health Work* 2020;11:109–17.
- 40 Whyte RT. Occupational exposure of poultry stockmen in current barn systems for egg production in the United Kingdom. *Br Poult Sci* 2002;43:364–73.
- 41 Welles WL, Wilburn RE, Ehrlich JK, *et al*. New York hazardous substances emergency events surveillance: learning from hazardous substances releases to improve safety. *J Hazard Mater* 2004;115:39–49.

Supplemental material

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

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

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

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

Endotoxins	0	4 -washing dough sludge and contaminated insulation in bioethanol plant (driver of industrial sweeper) - transmitting malt in silo (worker in foodstuff company) - washing process of potatoes in potato flour plant (operator) - 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 ₂ SO ₄	7664-93-9	0.05 mg/m ³	0.1 mg/m ³	Skin Corr 1A
Sulfurous acid	H ₂ SO 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 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 ₃ COOH	64-19-7	5 (13 mg/m ³)	10 (25 mg/m ³)	Skin Corr 1A
Trifluoroacetic acid	CF ₃ COOH	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 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 Skin Corr 1B
Hydrogen sulfide	H ₂ S	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 NO ₂ :10102-44-0	10 (12.5 mg/m ³) 1 (1.9 mg/m ³)	NO: NA NO ₂ : 2 (mg/m ³)	NO: Skin Corr 1B ^b NO ₂ : Ox. Gas 1, Skin Corr 1B
Other					
Hydrogen peroxide	H ₂ O ₂	7722-84-1	1 (1.4 mg/m ³)	3 (4.2 mg/m ³)	Ox. Liq 1 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 Skin Corr 1B ^b
Isocyanates	-NCO ^c	various	NA	0.035 mg/m ^{3c}	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 ₃ H ₆ (CHO) ₂	111-30-8		0.1 (0.42 mg/m ³)	Skin Corr 1B (Resp Sens 1)
Sodium hypochlorite	NaClO	7681-52-9	NA	NA	Skin Corr 1B

Ammonium Fluoride	NH ₄ F	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 ₂ S)	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 ₂ S)	>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 ₂ S)	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 ₂ O ₂) ^b	1.1 (110)	4.4 (440)	Online gas detector at workplace;

	exposure in normal work				several workers had experienced respiratory irritation; bleaching of hair and eyebrows was observed
Potato flour factory	Washing potatoes	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 ₂ O)	0.324 (108)	NA	
Metal production plant	Working nearby wet precipitation processes utilizing hydrogen sulfide	Hydrogen sulfide (H ₂ S) ^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

Metal mine	Working above precipitation tank where H ₂ S gas was bubbled through metal solutions	Hydrogen sulfide (H ₂ S) ^b	NA	weekly >20 (>400)	Online gas detector alarms were set to 20 ppm H ₂ S which is 4 x OEL; irritant and toxic H ₂ S 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)	0.6–2.98 mg/m ³ (46–230)	1.5–13.4 mg/m ³ (115–1040)	Direct-reading device; Gas leaks increasingly detected due to corroded process lines; 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); occasional very high exposure peaks exceeding capacity of online gas detectors at workplace. Exposed despite relevant respiratory protective equipment.
		Phosphoric acid (H ₃ PO ₄)	0.14–0.51 mg/m ³ (14–51)	NA	
		Sulfuric acid (H ₂ SO ₄)	0.034–0.068 mg/m ³ (68–136)	NA	
Chemical plant	Packing titanium dioxide (TiO ₂) powder coated with sulfuric acid (H ₂ SO 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 ₂ SO 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 ₂ S) ^b	daily >5 (>100)	NA	Online gas detectors at workplace

	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 ₂ S) ^b	7 (140)	NA	Two high exposure occasions: first outside plant when cloud of H ₂ S 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 ₂ S, 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 ₂ O)	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 ₃ COOH)	0.91–7.15 mg/m ³ (7–55)	NA	
		Formic acid (HCOOH)	0.4–1.2 mg/m ³ (8–24)	NA	

		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 ₂ S) ^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/m³