

Cleaning agent occupational asthma in the West Midlands, UK: 2000–16

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Background	Cleaning agents are now a common cause of occupational asthma (OA) worldwide. Irritant airway and sensitization mechanisms are implicated for a variety of old and new agents.
Aims	To describe the exposures responsible for cleaning agent OA diagnosed within a UK specialist occupational lung disease service between 2000 and 2016.
Methods	The Birmingham NHS Occupational Lung Disease Service clinical database was searched for cases of OA caused by cleaning agents, and data were gathered on age, gender, atopic status, smoking history, symptom onset, diagnostic investigations (including Occupational Asthma SYStem analysis of workplace serial peak expiratory flow measurements and specific inhalational challenge), proposed mechanism, industry, occupation and causative agent.
Results	Eighty patients with cleaning agent OA (77% female, 76% arising <i>de novo</i>) were identified. The median annual number of cases was 4 (interquartile range = 2–7). The commonest cleaning agents causing OA were chloramines (31%), glutaraldehyde (26%) and quaternary ammonium compounds (11%) and frequently implicated industries were healthcare (55%), education (18%) and leisure (8%).
Conclusions	Certain cleaning agents in common usage, such as chlorine-releasing agents, quaternary ammonium compounds and aldehydes, are associated with sensitization and asthma. Their use alters over time, and this is particularly evident in UK healthcare where cleaning and decontamination practice and policy have changed. Vigilance for OA in workplaces such as hospitals, nursing homes, leisure centres and swimming pools, where these cleaning agents are regularly used, is therefore essential.
Key words	Cleaning agents; healthcare; leisure; occupational asthma.

Introduction

Work-related asthma includes occupational asthma (OA) caused by inhalation of either a sensitizing agent or an airway irritant used in the workplace and work-exacerbated asthma (WEA) is pre-existing asthma worsened by workplace factors, for example, cigarette smoke or diesel exhaust fumes. In industrialized countries, professional cleaning constitutes a large occupational group and is associated with both OA and WEA [1]; moreover, exposure to cleaning agents occurs through cleaning as part of other job roles and through indirect exposure in indoor working environments [2]. In the UK, cleaning agents are the third most commonly reported cause of OA (behind isocyanates and flour or grain) [3], and

European surveillance schemes have shown increasing incidence of OA caused by some cleaning agents [4]; increased use and potency of agents and better recognition of cases have been proposed as explanations. The majority of causative agents demonstrate an irritant effect, although a few are airway sensitizers, such as chloramines and aldehydes [1]. Despite being an emergent problem, cleaning agent OA has not received much attention from UK policy makers. The Birmingham Regional National Health Service (NHS) Occupational Lung Disease Service has been documenting new cases of OA since 1990 in order to report to UK-based surveillance schemes, retaining information on agent, exposure and likely mechanism. The aim of this study was to describe agents and exposures implicated in diagnoses

of cleaning agent OA made at a tertiary occupational respiratory clinic over a 16-year period.

Methods

A Microsoft Excel clinical database of all patients seen clinically and diagnosed with OA at Birmingham Regional NHS Occupational Lung Disease Service, and subsequently reported to the Health and Safety Executive's (HSE) Surveillance of Work-related Respiratory Disease (SWORD) scheme, has been kept since 1990. For each patient, the data comprise age, gender, date of diagnosis, date of onset of symptoms, industry of employment, occupation and causative agent. A clinical diagnosis of OA is made on the balance of probabilities (i.e. when more likely than not), and all patients exhibit asthma with a history showing work-relatedness. For the majority of patients seen at the unit, diagnosis is also confirmed by objective tests (70% by OASYS [Occupational Asthma SYStem] analysis of serial peak flow measurements and 11% by specific inhalation challenge [SIC] tests); a summary of this has been described elsewhere [5]. For the benefit of reporting to SWORD, a mechanism, either sensitization or irritant, is suggested by the clinician at the time of recording in the database. OA by sensitization is diagnosed when there is (i) a latent interval from first exposure to first symptoms of asthma, with subsequent deterioration with usual levels of exposure and improvement away from work, together with exposure to a known sensitizer, or (ii) a positive SIC test. Irritant-induced asthma (IIA) is diagnosed when persistent asthma follows either within a few hours of a sudden large exposure to a respiratory irritant, or arises *de novo* or reactivated from chronic exposures to airway irritants, in the absence of a known sensitizer, with or without a latent period of exposure.

All diagnoses of OA in the database made between 1 January 2000 and 31 December 2016 were reviewed, and all cases caused by exposure to a cleaning agent identified, irrespective of occupation or industry. These were cross-checked with medical records to eliminate transcription error, excluding cases where a substance often used as a cleaning agent was actually used in a different process (for example, chlorine as a chemical intermediary). For each case identified, further demographic data were gathered on smoking status, atopy (one or more positive skin prick tests to common aeroallergens) and pre-existing childhood or adult asthma, and diagnostic data were gathered on (i) latency of exposure to symptom onset, (ii) OASYS software analysis of two-hourly peak expiratory flow (PEF) measurements using OASYS score [6], 'Area Between the Curves' (ABC) score [7] and time point analysis [8], (iii) positive or normal SIC tests and (iv) non-specific bronchial reactivity undertaken while exposed. Quiescent childhood asthma was defined as asthma diagnosed in childhood but neither symptomatic nor requiring

treatment in adult life; active asthma was defined as symptomatic asthma or asthma requiring treatment. The asthma hazard index (AHI) of agents identified as causes was calculated using a quantitative prediction tool based on the structure–activity relationship of low-molecular-weight (LMW) compounds (<1000 Daltons) [9].

Normally distributed data are presented as mean and SD, non-normally distributed data are given as median and interquartile range (IQR) and categorical data are noted by number and percentage. Ethical approval was sought and granted by National Institute of Health Research North West (Greater Manchester West) Research Ethics Committee on 4 November 2016 (reference: 16/NW/0817).

Results

Of the 975 patients diagnosed with OA, 80 patients with cleaning agent OA were identified (8% patients); for nine of these patients, no full medical records were retrievable in addition to the database record, limiting the data accessible. The median annual number of cases was 4 (IQR = 2–7) and mode was 13 (in 2002). Demographics and diagnostic characteristics for all cases are given in Table 1. Cleaning agent OA was diagnosed predominantly *de novo* (76%) in female workers (77%), with a variable latency (1–348 months, mean = 73). Seventy per cent (50 of 71) of patients had diagnoses based on OASYS analysis with at least one or more positive score; in the other 21 cases, the diagnosis was based on clinical history alone. In 67 cases (84%), the mechanism of disease was suggested to be sensitization, 10 (13%) as airway irritation and a further 3 (4%) as acute IIA (previously reactive airways dysfunction syndrome).

Reported agents are chloramines (25, 31%), glutaraldehyde (21, 26%), chlorine (4, 5%), quaternary ammonium compounds (9, 11%), isothiazolinones (3, 4%), peracetic acid (2, 3%), cleaning agent unspecified (10, 13%), sodium hydroxide (1, 1%), alcohol degreaser (1, 1%), denatonium (1, 1%), ethylene diamine (1, 1%), ethylenediaminetetraacetic acid (EDTA) (1, 1%) and triclosan (1, 1%). Chlorine was responsible for the three cases of acute IIA but also for one case of IIA in a sewage worker with daily exposure to chlorine gas, through sampling a vessel containing sodium hypochlorite. Annual cases due to common agents are shown in Figure 1. Thirteen SIC tests were undertaken (16% of cases) on patients with positive OASYS analyses, from which eight were positive (glutaraldehyde 3/3, quaternary ammonium compounds 1/2, chloramines 1/4, denatonium 1/1, peracetic acid 1/2, triclosan 1/1). Where specific organic LMW molecules were identified, the AHIs were as follows: glutaraldehyde (CAS: 111-30-8) = 0.82, ortho-phthalaldehyde (CAS: 643-79-8) = 0.73, benzalkonium chloride (CAS: 8001-54-5) = 0.91, *N*-decyl-*N,N*-dimethyl-1-decanaminium chloride (CAS:

Table 1. Demographics and diagnostic characteristics for all included patients

Variable	Summary
Age at diagnosis, mean (SD)	47 (11)
Gender, number of males (%)	18 (23)
Atopy ^a , number of atopic individuals (%)	36 (51)
Pre-existing asthma ^a , number (%)	
Never	54 (76)
Quiescent childhood	10 (14)
Quiescent adult	7 (9)
Active adult	0 (0)
Smoking status ^a , number (%)	
Never	34 (48)
Ex-smoker	27 (38)
Active smoker	10 (14)
Latency (exposure to symptom onset), mean months (SD)	
Total	58 (79)
Reported as sensitization	73 (86)
Reported as irritant	25 (31)
Acute IIA	0 (0)
OASYS record ^a , number (%)	
Positive (by one or more scores)	50 (70)
Negative	8 (11)
Inadequate or not done	13 (19)
OASYS score ^b , mean (SD)	3.0 (0.8)
ABC score ^c , mean l/min/h (SD)	28.2 (30.6)
Time point positive ^{a,d} , number (%)	
Yes	30 (42)
No	23 (32)
Inappropriate data for time point test	18 (25)
NSBR while exposed result ^a , number (%)	
Normal	46 (65)
Mild	15 (21)
Moderate	6 (8)
Severe	3 (4)
Unavailable	1 (1)

IIA, irritant-induced asthma; NSBR, non-specific bronchial reactivity.

^aNine missing full medical records.

^bAn OASYS score of >2.5 has a sensitivity of 75% and specificity of 94% for the diagnosis of OA, when using acceptable quality serial PEF records [6].

^cAn ABC score of >15 l/min/h has sensitivity of 72% and specificity of 100% for the diagnosis of OA [7].

^dThe presence of at least one time point difference has a sensitivity of 77% and specificity of 93% for diagnosis [8].

7173-51-5) = 0.98, chlorhexidine di-gluconate (CAS: 18472-51-0) = 1.0, benzisothiazolinone (CAS: 2634-33-5) = 0.14, 2-methyl 1,2- isothiazolinone (MIT; CAS: 2682-20-4) = 0.2, isothiazol-3(2n)-on (CAS: 1003-07-2) = 0.05, peracetic acid (CAS: 79-21-0) = 0.03, denatonium benzoate (CAS: 3734-33-6) = 1.0, triclosan (CAS: 3380-34-5) = 0.0, EDTA (CAS: 60-00-4) = 1.0 and ethylene diamine (CAS: 107-15-3) = 0.27.

Industries implicated were healthcare (44, 55%), education (14, 18%), leisure (6, 8%), local authority (4, 5%), food and catering (4, 5%), manufacturing (3, 4%), water and sewage (2, 3%), industrial cleaning (1, 1%), legal (1, 1%) and veterinary healthcare (1, 1%). All glutaraldehyde-induced cases were seen in healthcare

(20) or local authority (1); chloramine-induced cases were seen in healthcare (13), education (5), leisure (5) and food and catering (2); and quaternary ammonium compounds seen in healthcare (3), education (3), leisure (1), catering (1) and local authority (1). Isothiazolinone-induced asthma was seen in local authority (1) and manufacturing (2), and peracetic acid in healthcare (2). The unspecified cleaning agents were seen in healthcare (5), education (4) and other (1). The occupations responsible for the three commonest causes of cleaning agent OA are shown in Table 2.

Discussion

Chloramines were the commonest cause of OA (31%) frequently seen in swimming pool employees and healthcare workers. Glutaraldehyde was a common sensitizer seen at the start of the study, but there were very few cases after 2003, in keeping with substitution of disinfectants within the healthcare sector. Acute IIA was seen exclusively in workers exposed to chlorine.

The strength of this study is that it is a large series of OA cases, utilizing 16 years of diagnostic clinical data from a well-established UK NHS regional service for occupational lung disease. Each patient has a detailed occupational history where effort is made to establish whether the mechanism is likely to be immunological or not. The main weakness of this study is that where suspected, respiratory sensitization has not been confirmed by SIC testing in the majority of cases. Objective demonstration of a work-related pattern for asthma by serial PEF analysis and a history of exposure to a sensitizing agent is usually sufficient for award of compensation under the UK government's Industrial Injuries Disablement Benefit scheme. Other limitations should be acknowledged: no attempt has been made to estimate risk from specific occupations and exposures, or evaluate the effectiveness of existing control measures and health surveillance, and cases of OA due to cleaning agents where the causative agent was reported as 'unknown' may have been missed. Anecdotally, we encounter workers with confirmed OA on PEF analysis, where the cause is unclear but they are employed in large buildings, e.g. offices and schools where exposures to cleaning agents are noted to occur. All cases identified in this study are diagnosed at a single regional NHS Occupational Lung Disease Service in Birmingham, UK and there is likely to be a geographical variation in expert opinion of diagnosis and mechanism between the few similar UK-based units, particularly in cases where no objective tests are available. However, the occupations and causative agents identified in this study can be considered generalizable to the UK as none are peculiar to work in the West Midlands. For 10 patients, we were able to demonstrate OA but were unable to specify the exact cleaning agent or product used; this was either because patients did not

Table 2. Occupations implicated in cleaning agent occupational asthma caused by chloramines, glutaraldehyde and quaternary ammonium compounds

Cause	Chloramines (<i>n</i> = 25)	Glutaraldehyde (<i>n</i> = 21)	Quaternary ammonium compounds (<i>n</i> = 9)
Occupation	Lifeguards and swimming pool employees (8) Nurses (5) Healthcare cleaner (2) Healthcare assistants (2) Ward hostess Psychiatric ward housekeeper Midwife Physiotherapy assistant Food preparer Vending machine servicing technician Teacher Teaching assistant	Nurses (14) Health care assistants (2) Operating department practitioner (2) Radiologist Radiography technician Fireman	Cleaner (3) Nurse (1) Ward housekeeper (1) Nursery nurse (1) Teacher (1) School administrator (1) Laboratory clerk (1)

Nurses and healthcare assistants were employed in a variety of roles, for example: general ward, endoscopy, theatre and interventional radiology.

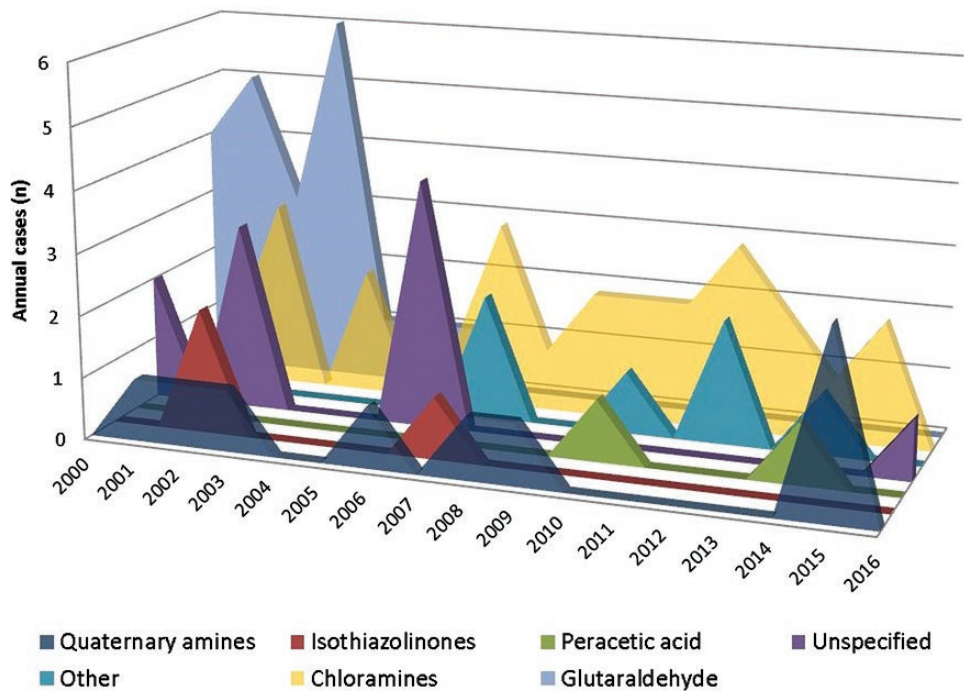


Figure 1. Annual cases of OA attributed to cleaning agents between 2000 and 2016 at Birmingham Regional NHS Occupational Lung Disease Service, UK.

have access to the product (historical employments or exposures) or because assessment could not discriminate when a number of agents were used.

The majority of cases (from a small number of agents) encountered in this series have been previously reported as respiratory sensitizers in medical literature, and clinicians felt in 84% of cases that there was more likely than not to be an immunological mechanism. However, these finding should be interpreted with caution, as although all patients have undergone detailed occupational enquiry, we were only able to provide SIC

data as evidence for respiratory sensitization in a small proportion of cases. Moreover, distinguishing *de novo* asthma caused by chronic low- or moderate-level exposures to irritants from WEA is difficult. Aside from the three cases of chlorine-related acute IIA identified, the root causes (e.g. level and duration of exposure) have not been examined in detail here. Acute IIA has been well documented and there is an obvious temporal relationship between onset and persistence of symptoms, and high-level or accidental exposure. However, Vandenplas *et al.* [10] assert that when a diagnosis of

IIA relies on (i) the presence of *de novo* or reactivated asthma, (ii) chronic exposure to irritants and (iii) the absence of a sensitizer, the evidence for causation at an individual level is weak. From an epidemiological perspective, there is consistent evidence from population-based [2,11,12] and workforce [13] studies that the use of cleaning agents is associated with increased risk of asthma. Furthermore, domestic and other indoor professional cleaning work carries a 50–100% increased risk of developing asthma [2,14,15]. We have seen few cases associated with industrial cleaning processes (for example, using acids, alkalis, solvents) or professional cleaning (domestic or workplaces) with most cases caused through bystander exposure at work. In part at least, this is due to the fact that a number of the agents we have included are used for processes other than manual or surface cleaning, for example, disinfection of endoscopes (glutaraldehyde, peracetic acid) or swimming pools (chlorine/chloramines).

Dumas *et al.* [16] have reported that 81% of female hospital workers experience weekly exposure to cleaning or disinfecting tasks, some of which (de-calcifiers, ammonia and moderate-high-intensity sprays) were associated with asthma symptoms. Therefore, it is clear that healthcare work, in a variety of professional and technical roles in hospitals and in care institutions, is associated with frequent exposure to cleaning agents. The nature of this work, sometimes in poorly ventilated enclosed spaces (for example, ward side rooms and x-ray and pathology departments), can lead to exposures sufficient to cause asthma by immunological and non-immunological mechanisms. Some healthcare-related cleaning exposures have dwindled recently; for example, there has been a decline in OA due to glutaraldehyde, caused by its withdrawal from use as a sterilizing agent within the NHS in the UK, and the adoption of enclosed and automated reprocessing of endoscopes [17]. Whereas the emergent concern about healthcare-associated infection has led to more aggressive use of bleaches, chlorine-based products and quaternary ammonium compounds in healthcare institutions. We have seen more cases caused by quaternary ammonium compounds recently, although the annual numbers are low, and it is not clear whether better awareness of exposure or increased use and potency are responsible.

We have observed a number of reports from the leisure industry, almost ubiquitously in swimming pool employees (lifeguards, pool attendants, swimming teachers). Here, chlorinated water reacts with proteins from sweat and urine, releasing chloramines. The most volatile of these is the inorganic nitrogen trichloride, which is associated with asthma symptoms [18] and for which there is evidence of respiratory sensitization [19]. We have also seen OA in healthcare workers exposed

to chlorine-releasing cleaning agents (e.g. Chlorclean, Actichlor). In our experience, SIC tests to chlorine-releasing agents have not demonstrated specific sensitization, though recently we reported a case with a positive SIC test to chloramines where the mechanism was presumed to be sensitization following contact with bodily fluid [20]. None of our workers have been exposed to chloramine-T specifically, a biocide for which respiratory sensitization has been described [21].

We have seen a number of patients with OA where the SIC test to the offending agent was normal. This may be because the work exposure was not reproduced sufficiently, although every effort is made at the time to do so, or because the mechanism is either not immunological or more complex than appreciated. However, there are reported cases of respiratory sensitization to specific cleaning agents, including perchlorethylene [22], chloramine-T [21], benzalkonium chloride [23], detergent enzymes [24], ethanolamine [25] and EDTA [26]. Additionally, we have demonstrated OA with positive SIC tests to triclosan in a nursery nurse [27], as well as peracetic acid in a mycologist exposed regularly during endoscope reprocessing, denatonium benzoate bittering agent (Bitrex) in alcohol gel in an emergency department nurse, and three cases caused by isothiazolinone biocides (not based on SIC tests) in two cleaners and a milling machine operator; these causes have been singly described elsewhere [28–30]. In the case of peracetic acid, which has a low AHI, one ought to be wary of attributing the mechanism solely to sensitization based on two cases with positive SIC test; the majority of notifications from SWORD surveillance suggest an irritant mechanism. Additionally, the low AHIs for isothiazolinones are perhaps anomalous, as their structures are not represented well in the programme model (M. Seed, University of Manchester, personal communication).

A number of cleaning agents in common usage, such as chlorine-releasing agents, quaternary ammonium compounds and aldehydes, cause OA in the West Midlands, UK. Clinical presentation in the majority of these individuals has exhibited a latent period of exposure to agents known to cause asthma by sensitization. Workplace exposure to these agents can be avoided or reduced by substitution of volatile potent sensitizers for less potent compounds, as has occurred with glutaraldehyde in the UK NHS, and through worker education about mopping rather than spraying, appropriate dilution when cleaning and properly fit-tested respiratory protective equipment when unusual exposures are unavoidable. Exposure to these agents is not confined to professional cleaners, and consideration needs to be given to cleaning agents as a cause in workers presenting with new or exacerbated asthma symptoms, particularly in institutions such as hospitals, nursing homes, offices and leisure centres.

Key points

- Cleaning agents have emerged as a leading cause of work-related asthma in industrialized countries, mediated by both irritant and hypersensitivity mechanisms.
- Common causes in the West Midlands, UK during 2000–16 have been chloramines, glutaraldehyde and quaternary amine compounds, seen commonly in the healthcare, education and leisure industries, among others.
- The causes of asthma from cleaning agents have changed as workplace practice and policy have evolved. Policy makers should investigate and address risk of asthma in industries where exposure is common place.

Competing interests

None declared.

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