

Is the Incidence of Aliphatic Amine-Induced Occupational Rhinitis and Asthma Underestimated?

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Background Amines, some of which are known to cause asthma, are frequently present in the work environment, but are rarely identified as being responsible for occupational rhinitis (OR) or asthma (OA). However, amine-induced OR/OA may be underreported. To discuss this hypothesis, we report a series of patients with positive amine-specific nasal provocation test (NPT).

Methods Review of the medical charts of 37 patients with OR (alone or associated with asthma), submitted to a NPT with an aliphatic or alicyclic amine (except for EDTA) present in a product used at work.

Results Most patients worked in the healthcare sector or for a cleaning company. Amines were mostly present in cleaning products. Seven patients had a positive NPT. NPTs were positive for the following amines: bis(aminopropyl)laurylamine, C12-C18 alkyl dimethylamine oxides, bis(2-hydroxyethyl)tallowamine oxides, 3-dimethylaminopropylamine, 2,2'-dimethyl-4,4'-methylene-bis(cyclohexylamine), lauryl dimethylamine oxide. NPTs were negative for the following amines: monoethanolamine, diethanolamine, triethanolamine, isopropanolamine, triethylamine, triethylenetetramine, aminopropyltriethoxysilane, alkylpropylenediamineguanidine acetate.

Conclusions The frequency of amine-induced OR/OA may be underestimated, particularly when cleaning products are incriminated. Comprehensive investigation of all cases is mandatory to ensure an efficient prevention policy and consequently a good clinical and socio-occupational prognosis of occupational respiratory disease. *Am. J. Ind. Med.* 9999:1–8, 2014. © 2014 Wiley Periodicals, Inc.

KEY WORDS: occupational rhinitis; occupational asthma; amines; nasal provocation test; cleaning products

INTRODUCTION

Over the last two decades, occupational exposure to cleaning products has been shown to be associated with a high risk of asthma. Epidemiological studies have consistently reported an excess of risk of asthma in workers exposed to cleaning products, such as domestic or industrial cleaners, or healthcare professionals [Ng et al., 1994; Kogevinas et al., 1999; Karjalainen et al., 2001; Kogevinas et al., 2007; Folletti et al., 2014]. To elucidate the pathophysiological mechanisms and to implement efficient prevention policies,

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Accepted 30 June 2014

DOI 10.1002/ajim.22373. Published online in Wiley Online Library (wileyonlinelibrary.com).

accurate identification of the agents responsible for the cleaning product-induced respiratory diseases is highly recommended [Zock et al., 2010; Siracusa et al., 2013; Wiszniewska and Walusiak-Skorupa, 2014].

Research on household cleaning carried out on large community-based cohorts has identified spraying as a particularly deleterious exposure modality [Zock et al., 2007; Le Moual et al., 2012], but epidemiological reports have failed to identify which chemical families or types of cleaning purpose are specifically involved [Arif and Delclos, 2012; Dumas et al., 2012]. Exposure assessment in epidemiological studies is based on self-administrated questionnaires, expert judgement or job-exposure matrix that cannot take into account the actual compositions of the products handled. Cleaning products contain a wide variety of ingredients that are potentially sensitizers and/or irritants: solvents, biocides, chelating agents, polishes, perfumes, etc. [Quirce and Barranco, 2010].

The macroscopic approach of epidemiology is too coarse to allow detailed aetiological diagnosis that can only be achieved by individual case investigation. The etiological diagnosis of occupational rhinitis (OR) or asthma (OA) often constitutes a challenge. Patients with OR/OA usually report a history of multiple occupational exposures that each needs to be investigated. Ingredients of cleaning products are mostly low molecular weight molecules for which readily accessible diagnostic methods such as skin tests or laboratory tests are also not available and a specific provocation test is often the only way to confirm the aetiological hypothesis. Comprehensive case investigation is difficult (time-consuming and sometimes laborious) and is not always performed, which explains why documented cases of cleaning product-induced OR/OA are scarce: none of the 41 new low-molecular-weight causal agents of OA identified in Medline during the period 2000–2010 were reported for cleaning purposes (except for ortho-phthalaldehyde and a peracetic acid-hydrogen peroxide mixture employed in the very particular setting of endoscope disinfection) [Pralong et al., 2012].

Amines, common ingredients of cleaning products [Bello et al., 2009], are candidates that must be included among the causal substances of cleaning product-induced respiratory diseases. In our occupational health unit, we use specific nasal provocation tests (NPT) with all potentially sensitising substances present in work exposure products to investigate patients presenting with OR (alone or associated with OA). We have previously published an original series of ethylenediamine tetraacetic acid (EDTA)-induced OR/OA [Laborde-Casterot et al., 2012]. In the present study, we focused on other aliphatic or alicyclic amines challenged with a specific NPT, in a series of OR or OA + OR cases exposed to these agents. After a clinical description of the cases, we will discuss the place of amines among OR/OA causes and particularly in cleaning product-exposed workers.

PATIENTS AND METHODS

For all suspected cases of OR (alone or associated with OA) investigated in our unit, a thorough survey is conducted to identify all commercial products present in the workplace and the complete composition of each preparation implicated is then obtained from the Paris poison control centre (a separate unit of our department). Finally, patients are successively tested with all possible allergens identified in their occupational environment.

For the present study, all patients investigated by NPT with an aliphatic or alicyclic amine for the diagnosis of OR (alone or associated with asthma) in our occupational health unit between January 2002 and July 2011 were retrieved. Cases challenged with EDTA but no other amine were excluded because they have already been reported in a previous study [Laborde-Casterot et al., 2012].

After suspecting the occupational origin of the patient's respiratory symptoms on the basis of their chronology (recurrence of symptoms after exposure to the suspected products in the workplace and resolution of symptoms after cessation of exposure), the complete composition of each product used in the workplace was obtained from the manufacturers. NPT were performed with all potentially sensitising substances present in the formulation of one or more products. Only one concentration per substance was used for each patient, corresponding to the concentration generally proposed for patch testing, as this concentration is considered to be both sufficient to elicit an allergic response and not high enough to induce irritation after a 15-minute contact with the nasal mucosa.

NPT were performed after stopping antihistamine, corticosteroid or vasoconstrictor treatment for at least one week. The response of the nasal mucosa was measured by posterior rhinomanometry. A pretest measurement of the nasal resistance (NR) detected the presence of any baseline nasal obstruction, in which case the NPT was postponed. The NR measurement 15 min after applying the vehicle into each nostril was used as the baseline value. The substance to challenge, diluted in its vehicle, was then applied into each nostril immediately after maximum inspiration to prevent the solution from entering the lower airways. A nose clamp was immediately attached and maintained for 15 min before the subject was allowed to blow his/her nose. NR was measured 15 min after the end of the challenge. The criterion for a positive NPT was doubling of the baseline value. A single operator performed all tests according to the same protocol. NPT were performed as usual procedures and written informed consent from the patients was not required.

The following data were collected from the patients' medical records: occupational activity, amine concentration in the product suspected to be responsible for OR, clinical history and NPT results. Atopy was defined as the presence of a positive prick test to a common respiratory allergen or a

positive Phadiatop test. In pulmonary function tests, distal obstructive syndrome and nonspecific bronchial hyperreactivity (NSBHR) were respectively defined as: 1) forced expiratory volume in one second (FEV_1)/forced vital capacity (FVC) < 70%; 2) midexpiratory flow between 25% and 75% of FVC (MEF_{25-75}) < 70%; 3) a decrease in FEV_1 of at least 20% for a cumulative dose of methacholine of 1600 μ g or less. Ethics Committee approval was not required by the French Law for this review of medical charts.

RESULTS

An NPT was performed with an aliphatic or alicyclic amine in 37 patients whose main characteristics are reported in Table I. Most patients presented rhinitis associated with asthma-like symptoms. Women were overrepresented (F/M sex ratio = 1.5). Nearly 40% of patients were considered to be atopic. Six patients reported a history of asthma ($n=4$), rhinitis ($n=1$) or atopic dermatitis ($n=1$, patient G), before they develop their work-related symptoms. All of them fulfilled our criteria of atopy. More than two thirds worked as cleaners (industrial or domestic) or paramedics. An amine was tested in nearly 4 out of 5 patients, as it was present in the composition of a cleaning product (detergent, disinfectant, wax-remover, stripper, etc.) and, in most cases, it was sprayed. The other kinds of amine-containing products in this series were: lubricant/cutting fluids ($n=3$ patients), resin hardeners ($n=2$), polishing agents ($n=1$), hair colour products ($n=1$), a brazing product ($n=1$).

Six patients presented one positive NPT with an amine and another patient presented three positive NPTs performed with three different surfactant solutions (A, B1, B2: detergent A contained surfactant A and detergent B contained surfactants B1 and B2) present in the patient's cleaning

products (patient G in Table II). These surfactant solutions contained various alkylamine oxides: surfactant B1 contained a mixture of bis(2-hydroxyethyl)tallowamine oxides and surfactants A and B2 were both mixtures of C12-C18 alkyldimethylamine oxides (these mixtures were supplied for challenge by their respective industrial furnishers). Table III reports the list of all amines tested. Chemical structures of amines responsible for a positive NPT are provided in Figure 1.

Of the seven patients who had a positive NPT with an amine, at least one additional NPT with other compounds was performed in six patients and two patients had at least one positive additional NPT. Two of the four patients challenged with didecyldimethylammonium chloride had a positive response. Most patients (25 out of 30 patients) with a negative amine-NPT were subsequently tested with other agents. These additional NPTs were positive in eight patients with the following substances: EDTA (5 out of 17 positive tests), formaldehyde (2 out of 4), polyquaternium 30 (1 of 1), didecyldimethylammonium chloride (1 out of 15).

DISCUSSION

Seven cases of amine-related OR (or OR + OA) were finally documented in this series. With the exception of 3-N, N-dimethylaminopropylamine (3DMA) [Sargent et al., 1976], the amines responsible for a positive NPT in this series have not been previously reported to be responsible for OR/OA. These amines were tested because all amines must be suspected to be possible asthmagens: many amines are known to be OA inducers (Table IV) and quantitative structure-activity relationships have shown an association between amines and OA hazard [Jarvis et al., 2005]. For 3DMA (Fig. 1e), Sargent et al. [1976] reported significant decreases in lung function in workers of a snow-ski manufacturing plant with the highest exposure to this amine, used as an epoxy resin hardener.

In the present series, the amines responsible for a positive NPT (7 out of 9 positive tests in 5 of the 7 patients with a positive NPT) were mostly long-chain alkylamines, namely bis(hydroxyethyl)tallowamine oxides (Fig. 1d), C12-C18 alkyldimethylamine oxides (e.g. Fig. 1b and c), lauryldimethylamine oxide (Fig. 1b), bis(aminopropyl)laurylamine (Fig. 1a). In patient G (Table II), the positive responses obtained with three different preparations can be explained by the very similar chemical compositions of surfactants A and B2 and the structural similarity of long-chain alkylamine oxides in all three preparations. Long-chain alkylamines and alkylamine oxides, especially bis(aminopropyl)laurylamine and lauryldimethylamine oxide, are widely used in detergents because of their good surfactant properties. They also have a biocidal activity exploited in disinfectant cleaners. Bis-(aminopropyl)laurylamine has been demonstrated to be a

TABLE I. Patient Characteristics

	Patients with a NPT to an amine	
	Positive NPT	Negative NPT
Number	7	30
Gender, female	5	17
Median age [range]	39 [22,53]	43 [25,62]
Atopic	2	13
Occupation		
Paramedics	4	9
Cleaners	2	10
Others	1	11
Symptoms		
Rhinitis alone	1	6
Rhinitis and asthma-like symptoms	6	24

NPT: nasal provocation test.

TABLE II. Patients With a Positive Amine NPT

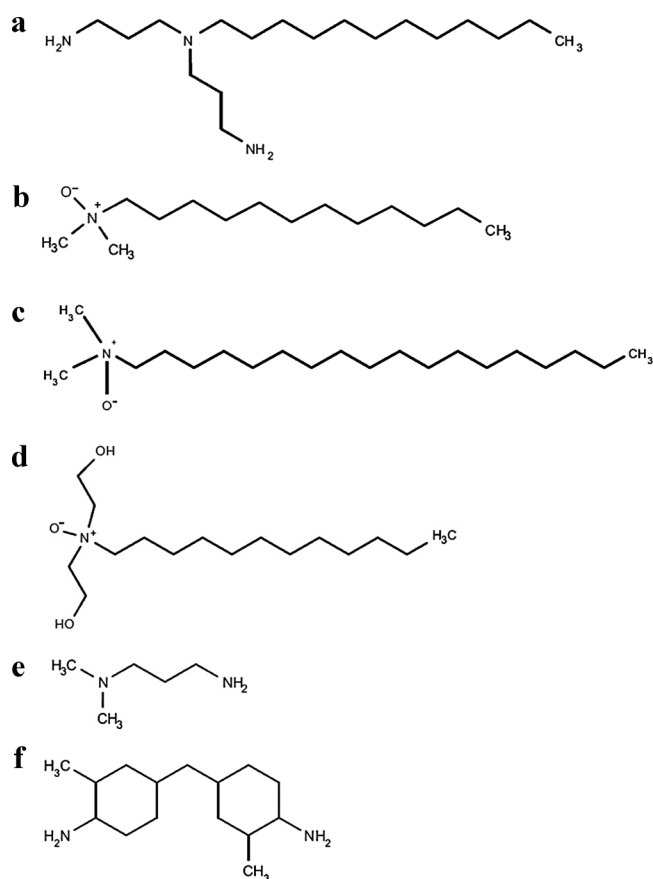
N ^o	Gender, age	Lung function				Amine-containing products		NPT	
		Atopy	Occupation	Symptoms	Obstructive syndrome	MSBHR (PD20)	Purpose family Contained amines & concentration in products		
A	M, 47	Yes	Cleaner	Rhinitis alone	No	Yes (600 µg)	<i>Detergent A</i> Bis(aminopropyl)laurylamine 2.25% <i>Detergent B</i> Bis(Aminopropyl)laurylamine 2.25% <i>Detergent C</i> Lauryldimethylamine oxide 2.97% <i>Detergent D</i> Lauryldimethylamine oxide 4.8% <i>Detergent</i> 3-N,N-dimethylaminopropylamine 0.2%	Lauryldimethylamine oxide 0.5%	Didecyl dimethylammonium chloride (+) Ethylenediaminetetraacetic acid (+) Glutaraldehyde (-) N-decyl-N- isononyl-N,N-dimethylammonium chloride (-) Didecyl dimethylammonium chloride (+)
B	F, 22	Yes	Nurse-aide	Rhinitis and asthma-like symptoms	Yes, global			3-N,N-dimethylaminopropylamine 1%	Ethylenediaminetetraacetic acid (-) Diluted detergent (-) N,N-didecyl-N- methylpoly(oxyethyl) ammonium propionate (-) Diluted resin hardener (-)
C	M, 39	Yes	Plastic molder	Rhinitis and asthma-like symptoms	Yes, distal	Yes (392 µg)	<i>Resin hardener</i> 2,2'-dimethyl-4,4'-methylene- bis (cyclohexylamine) 45–50%	2,2'-dimethyl-4,4'-methylene- bis (cyclohexylamine) 0.5%	Didecyl dimethylammonium chloride (-)
D	F, 25	No	Nurse	Rhinitis and asthma-like symptoms	No	No	<i>Detergent</i> Bis(aminopropyl)laurylamine 5.5%	Bis(aminopropyl)laurylamine 0.5%	Didecyl dimethylammonium chloride (-)
E	F, 52	No	Nursery nurse-aide	Rhinitis and asthma-like symptoms	No	Yes (800 µg)	<i>Detergent</i> Bis(aminopropyl)laurylamine 5.5%	Bis(aminopropyl)laurylamine 1%	Ethylenediaminetetraacetic acid (-) Didecyl dimethylammonium chloride (-)
F	F, 38	No	Dental assistant	Rhinitis and asthma-like symptoms	Yes, distal	Yes (271 µg)	<i>Detergent</i> Bis(aminopropyl)laurylamine 0.01%	Bis(aminopropyl)laurylamine 1‰	None
G	F, 53	No	Maid	Rhinitis and asthma-like symptoms	No	Yes (300 µg)	<i>Wipes</i> Bis(aminopropyl)laurylamine 0.15 g/l <i>Detergent A</i> C12-C18 alkyl dimethylamine oxides 0.3–3% <i>Detergent B</i> Bis(2-hydroxyethyl) tallowamine oxides 0.3–1.5% C12-C18 alkyl dimethylamine oxides 0–0.3%	<i>Surfactant A</i> C12-C18 alkyl dimethylamine oxides ≈1% <i>Surfactant B1</i> Bis(2-hydroxyethyl) tallowamine oxides ≈3‰ <i>Surfactant B2</i> C12-C18 alkyl dimethylamine oxides ≈1%	Diluted detergents (-)

NPT: nasal provocation test; M: male; F: female; NSBHR: nonspecific bronchial hyperreactivity defined as a decrease in FEV1 of at least 20% for a cumulative dose of methacholine of 1600   g or less (PD20).

TABLE III. Amines Tested and NPT Results

Substances tested	Concentration used in NPT	Number of positive NPT/total
<i>Aminoalcohols</i>		
Monoethanolamine	1%	0/10
	2%	0/6
	all	0/16
Diethanolamine	1%	0/3
Triethanolamine	1%	0/6
	2%	0/1
	all	0/7
Isopropanolamine	0.5%	0/1
<i>Alkylamine oxides</i>		
Bis(2-hydroxyethyl)tallowamine oxides	≈ 3‰	1/1
C12-C18 alkyl dimethylamine oxides	≈ 1%	2/2
Lauryl dimethylamine oxide	0.5%	1/1
	1%	0/1
	all	1/2
<i>Other alkylamines</i>		
3-N,N-dimethylaminopropylamine	1%	1/1
2,2'-dimethyl-4,4'-methylene-bis(cyclohexylamine)	0.5%	1/1
Alkylpropylenediamineguanidine acetate	2‰	0/1
Aminopropyltriethoxysilane 1%	1%	0/1
Bis(aminopropyl)laurylamine	0.1%	1/1
	0.5%	1/6
	1%	1/1
	all	3/8
	1%	0/1
Triethylamine	1%	0/1
Triethylenetetramine	0.5%	0/1

NPT: nasal provocation test.

**FIGURE 1.** Chemical structures of amines responsible for a positive NPT (a. bis(-aminopropyl)laurylamine; b. lauryl dimethylamine oxide *ie* C12 alkyl dimethylamine oxide; c. octadecyl dimethylamine oxide *ie* C18 alkyl dimethylamine oxide; d. an example of bis(2-hydroxyethyl)alkylamine oxides; e. 3-dimethylaminopropylamine; f. 2,2'-dimethyl-4,4'-methylene-bis(cyclohexylamine))

happen in detergent-disinfectant-induced allergic contact dermatitis [Dejobert et al., 1997; Dibo and Brasch, 2001; Schliemann et al., 2010]. Villar-Gomez et al. [2009] recently highlighted the possible health effects of these amino compounds in surfactants, reporting a case of OA related to exposure to a surfactant agent composed of an aqueous solution of “alkylamine ethoxylate and a mixture of alkyleneoxy and ethylenediamine”.

Although previously reported cases of OR/OA related to aliphatic amines were mostly due to short-chain alkylamines or alkanolamines (Table IV), only one such case was observed in this series (the case due to 3DMA; see above and Table II), and all 27 NPT performed with short-chain alkanolamines (which are also common components of detergents solutions) were negative (Table III).

All NPT were performed with nonirritant concentrations of the test substances. Indeed, these concentrations do not usually cause a skin irritation after an application for two days

under occlusion in patch testing. Besides, for practical reasons (because NPTs are time consuming: for each patient several substances had to be tested, and only one NPT can be performed each day), only one nonirritant concentration was tested for each substance. When positive, the NPT constitutes a strong argument in favor of the accountability of the substance in the respiratory disease and a nonirritant mechanism of the disease. However, in two of our cases, the exclusive responsibility of the amine was not clearly determined due to a positive reaction on another specific NPT. As an irritant mechanism can be excluded, a positive reaction during a NPT can be explained by an immunoallergic or pharmacological mechanism.

To date, very limited data are available concerning the mechanism of amine-induced rhinitis or asthma. Most authors have suggested an immunoallergic reaction, but this mechanism has rarely been demonstrated. An IgE-mediated reaction was established on the basis of Prausnitz-Küstner tests for

TABLE IV. Reported Cases of Amine-Induced Occupational Asthma

Chemical	Activity sectors	References
<i>Aliphatic amines</i>		
<i>Alkylamines</i>		
Ethylenediamine	Epoxy resins Rubber industry Beauty culture, lacquer and shellac industries Plastics industry Photography laboratory Chemical industry	Dernehl [1951] Dernehl [1963] Gelfand [1963] Gelfand [1963] Gelfand [1963], Popa et al. [1969] Lam and Chan-Yeung [1980] Hagmar et al. [1982] Aldrich et al. [1987] Nakazawa and Matsui [1990] Ng et al. [1991] Casas et al. [2002]
Ethylenediamine tetraacetic acid	Cleaning, paramedics	Laborde-Casterot et al. [2012]
Diethylenetriamine	Epoxy resins	Dernehl [1963]
Triethylenetetramine	Epoxy resins	Dernehl [1963] Fawcett et al. [1977]
Hexamethylenetetramine	Plastics industry Lacquer and shellac industry	Gelfand [1963] Gelfand [1963]
Tetraethylenepentamine	Epoxy resins	Lambourn et al. [1992]
3-N,N-dimethylaminopropylamine	Snow-ski manufacturing plant (epoxy resin)	Sargent et al. [1976]
Mixture of aliphatic amines	Chemical industry Pork industry	Lewinsohn and Ott [1991] Ng et al. [1995] Villar-Gomez et al. [2009]
<i>Aminoalcohols</i>		
Monoethanolamine	Beauty culture industry Detergents	Gelfand [1963] Savonius et al. [1994] Makela et al. [2011]
Diethanolamine	Metal workers (cutting fluid)	Piipari et al. [1998]
Triethanolamine	Metal workers (cutting fluid) Detergent	Savonius et al. [1994] Makela et al. [2011]
Aminoethylethanolamine	Aluminium soldering	Sterling [1967] Pepys and Pickering [1972]
Diethylethanolamine	Anticorrosive steam system additive	Gadon et al. [1994]
Dimethylethanolamine	Painting	Vallieres et al. [1977]
<i>Other</i>		
Hydroxylamine	Paper recycling industry	Tran et al. [2009]

ethylenediamine [Gelfand, 1963] and by RAST for piperazine (which is not strictly speaking an amine) [Hagmar and Welinder, 1986]. However, a pharmacologic mechanism cannot be excluded. Indeed, in an animal study, monoethanolamine showed agonistic effects on histamine- H_1 and muscarinic receptors [Kamijo et al., 2008]. A pharmacological mechanism linked to the calcium-chelating activity of sodium EDTA is also suggested by both experimental and clinical data [Laborde-Casterot et al., 2012].

In most of our cases, occupational exposure to amines resulted from the use of sprayed cleaning preparations. Except when the formulation of the product is fairly simple (such as bleach, acids, aldehydes, chloramine-T, etc.), a clear-causal link between a specific ingredient of a cleaning product and occupational rhinitis or asthma has rarely been demonstrated. To the best of our knowledge, clinical cases

documented by a specific provocation test have only been published for monoethanolamine (MEA) [Savonius et al., 1994], triethanolamine [Makela et al., 2011], EDTA [Laborde-Casterot et al., 2012], and benzalkonium chloride [Burge and Richardson, 1994; Purohit et al., 2000]. Tributyl tin oxide (TBTO) was suspected to be responsible for respiratory symptoms induced by a carpet deodorizer, but this hypothesis was not documented by a specific challenge with TBTO alone [Shelton et al., 1992].

As exposure to cleaning agents is a growing cause of OA and OR in developed countries [Zock et al., 2010], it is therefore essential to rapidly identify which agents are responsible for this increasing incidence. Technically, this could only be achieved by a thorough survey of all commercial products used in the workplace, followed by determination of their complete qualitative compositions, and

finally specific challenge tests with all suspected ingredients. This type of procedure was systematically applied in our unit and revealed that long-chain alkylamines, as well as sodium EDTA [Laborde-Casterot et al., 2012] or quaternary ammonium compounds, were the main causative agents of OR and/or OA in cleaners. Recent publications have explained the dramatic increase of these respiratory diseases in workers exposed to cleaning agents and/or disinfectants by both the widespread use of these agents in the form of sprays and the presence of quaternary ammonium compounds in their formulations [Zock et al., 2010]. Quaternary ammonium compounds have recently been reported to be one of the leading causes of OA in France [Paris et al., 2012; Ameille et al., 2013], although they were only one of the components of the cleaning preparations responsible for the reported cases of OA. These preparations also contained other potential causal agents (often amines) and, in most cases, no specific provocative test was performed with any of the components. The systematic implication of quaternary ammonium compounds by the authors of recent publications is the result of a notoriety bias: quaternary ammonium compounds are a well-known cause of OR/OA, and these agents were present in the incriminated preparations. This bias further emphasizes the absolute necessity of a specific provocative test for the causal diagnosis of OR or OA, not only for scientific purposes, but also to allow definitive eviction of the real causal agent in each individual case.

CONCLUSION

This case series suggest that alkylamines, and especially long-chain alkylamines and alkylamine oxides, are frequent, and likely under-reported, causal agents of OR or OA cases associated with the use of cleaning agents and/or disinfectants. Furthermore, due to chemical similarities between different alkylamines, cross-reactions should be considered. These substances have not been previously reported as a cause of OR/OA, as most OR/OA cases are not documented by specific provocative tests with the suspected causal ingredients of the incriminated commercial products. Systematic application of this type of diagnostic investigation would not only be of scientific interest: it is mandatory for efficient eviction of the causal agent and consequently for a good clinical and socio-occupational prognosis of patients with occupational respiratory disease.

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Conflict of Interest Statement: The authors declare that they have no conflict of interest.