Original Article

Phenotyping Occupational Asthma Caused by Acrylates in a Multicenter Cohort Study

Hille Suojalehto, MD, PhD[a], Katri Suuronen, PhD[a], Paul Cullinan, MD[b], Irmeli Lindström, MD, PhD[a], Joaquin Sastre, MD[c], Jolanta Walusiak-Skorupa, MD[d], Xavier Munoz, MD[e], Donatella Talini, MD[f], Pavlina Klusackova, MD[g], Vicky Moore, PhD[h], Rolf Merget, MD[i], Cecilie Svanes, MD[j], Paola Mason, MD[k], Marco dell'Omo, MD[l], Gianna Moscato, MD[m], Santiago Quirce, MD[n], Jennifer Hoyle, MD[o], David Sherson, MD[p], Alexandra Preisser, MD[q], Martin Seed, MD[r], Catherine Rifflart, MSc[s], Julien Godet, PharmD, PhD[t], Frédéric de Blay, MD[u,v], and Olivier Vandenplas, MD, PhD[s]; on behalf of the European Network for the Phenotyping of Occupational Asthma (E-PHOCAS) investigators *Helsinki, Finland; London, Birmingham, and Manchester, United Kingdom; Madrid, Spain; Lodz, Poland; Barcelona, Spain; Pisa, Padova, Perugia, and Pavia, Italy; Prague, Czech Republic; Bochum and Hamburg, Germany; Bergen, Norway; Odense, Denmark; Yvoir, Belgium; and Strasbourg, France*

What is already known about this topic? Although several cases of acrylate-induced occupational asthma have been reported, the characteristics of this disease are not known and acrylates are not classified as respiratory sensitizers.

What does this article add to our knowledge? Work-related rhinitis was more frequent in acrylate-induced than in isocyanate-induced occupational asthma, and the increase in postchallenge fractional exhaled nitric oxide was greater than in occupational asthma induced by other low-molecular-weight agents or isocyanates.

How does this study impact current management guidelines? Our study shows that acrylate-induced occupational asthma has phenotypic characteristics suggesting that acrylates may induce occupational asthma through different immunologic mechanisms compared with mechanisms through which other low-molecular-weight (LMW) agents may induce asthma.

[a]Finnish Institute of Occupational Health, Helsinki, Finland
[b]Department of Occupational and Environmental Medicine, Royal Brompton Hospital and Imperial College (NHLI), London, United Kingdom
[c]Department of Allergy, Fundacion Jimenez Dıaz and CIBER de Enfermedades Respiratorias (CIBERES), Madrid, Spain
[d]Department of Occupational Diseases and Environmental Health, Nofer Institute of Occupational Medicine, Lodz, Poland
[e]Hospital Vall d'Hebron, Universitat Autonoma de Barcelona and CIBER de Enfermedades Respiratorias (CIBERES), Barcelona, Spain
[f]Cardio-Thoracic and Vascular Department, University of Pisa, Pisa, Italy
[g]Department of Occupational Medicine, 1st Faculty of Medicine, Charles University, Prague, Czech Republic
[h]Occupational Lung Disease Unit, Birmingham Heartlands Hospital, Birmingham, United Kingdom
[i]Institute for Prevention and Occupational Medicine of the German Social Accident Insurance (IPA), Ruhr University, Bochum, Germany
[j]Department of Occupational Medicine, Haukeland University Hospital, Bergen, Norway
[k]Department of Cardiac-Thoracic-Vascular Sciences and Public Health, University of Padova, Padova, Italy
[l]Department of Medicine, Section of Occupational Medicine, Respiratory Diseases and Occupational and Environmental Toxicology, University of Perugia, Perugia, Italy
[m]Department of Public Health, Experimental and Forensic Medicine, Specialization School in Occupational Medicine, University of Pavia, Pavia, Italy
[n]Department of Allergy, Hospital La Paz Institute for Health Research (IdiPAZ) and CIBER de Enfermedades Respiratorias (CIBERES), Madrid, Spain
[o]Department of Respiratory Medicine, North Manchester General Hospital, Manchester, United Kingdom
[p]Department of Pulmonary Medicine and Occupational Medicine, Odense University Hospital, Odense, Denmark
[q]Institute for Occupational and Maritime Medicine, University Medical Center Hamburg-Eppendorf, Hamburg, Germany
[r]Centre for Occupational and Environmental Health, The University of Manchester, Manchester, United Kingdom
[s]Department of Chest Medicine, Centre Hospitalier Universitaire UCL Namur, Université Catholique de Louvain, Yvoir, Belgium
[t]Groupe Méthode Recherche Clinique, Pôle de Santé Publique, Strasbourg University, Strasbourg, France
[u]Division of Asthma and Allergy, Department of Chest Diseases, University Hospital of Strasbourg, Strasbourg, France
[v]Fédération de Médecine translationnelle, Strasbourg University, Strasbourg, France

This work was funded in part by a Task Force of the European Academy of Allergy and Clinical Immunology. O.V. and C.R. were supported by a grant from the Fondation Mont-Godinne. F.de B. was supported by a grant from ADIRAL. J.S. was supported in part by CIBER de Enfermedades Respiratorias [CIBERES], Instituto de Salud Carlos III, Ministry of Economy and Competitiveness, Spain, and Sanofi Genzyme. H.S. and K.S. were supported by a grant from the Finnish Work Environment Fund.
Conflicts of interest: The authors declare that they have no relevant conflicts of interest.
Received for publication September 27, 2019; revised October 11, 2019; accepted for publication October 15, 2019.
Available online October 31, 2019.
Corresponding author: Paul Cullinan, MD, Department of Occupational and Environmental Medicine, Royal Brompton Hospital and Imperial College (NHLI), London, UK. E-mail: p.cullinan@imperial.ac.uk.
2213-2198
© 2019 American Academy of Allergy, Asthma & Immunology
https://doi.org/10.1016/j.jaip.2019.10.017

Abbreviations used
E-PHOCAS- European network for the PHenotyping of OCcupational Asthma
FENO- Fractional exhaled nitric oxide
HI- Hazard index
LMW- Low-molecular-weight
OA- Occupational asthma
ppb- Parts per billion
QSAR- Quantitative structure activity relationship
SIC- Specific inhalation challenge

BACKGROUND: While acrylates are well-known skin sensitizers, they are not classified as respiratory sensitizers although several cases of acrylate-induced occupational asthma (OA) have been reported.
OBJECTIVE: To evaluate the characteristics of acrylate-induced OA in a large series of cases and compare those with OA induced by other low-molecular-weight (LMW) agents.
METHODS: Jobs and exposures, clinical and functional characteristics, and markers of airway inflammation were analyzed in an international, multicenter, retrospective cohort of subjects with OA ascertained by a positive inhalation challenge to acrylates (n = 55) or other LMW agents (n = 418) including isocyanates (n = 125).
RESULTS: Acrylate-containing glues were the most prevalent products, and industrial manufacturing, dental work, and beauty care were typical occupations causing OA. Work-related rhinitis was more common in acrylate-than in isocyanate-induced asthma ($P < .001$). The increase in postchallenge fractional exhaled nitric oxide was significantly greater in acrylate-induced OA (26.0; 8.2 to 38.0 parts per billion [ppb]) than in OA induced by other LMW agents (3.0; −1.0 to 10.0 ppb; $P < .001$) or isocyanates (5.0; 2.0 to 16.0 ppb; $P = .010$). Multivariable models confirmed that OA induced by acrylates was significantly and independently associated with a postchallenge increase in fractional exhaled nitric oxide (≥17.5 ppb).
CONCLUSIONS: Acrylate-induced OA shows specific characteristics, concomitant work-related rhinitis, and exposure-related increases in fractional exhaled nitric oxide, suggesting that acrylates may induce asthma through different immunologic mechanisms compared with mechanisms through which other LMW agents may induce asthma. Our findings reinforce the need for a reevaluation of the hazard classification of acrylates, and further investigation of the pathophysiological mechanisms underlying their respiratory sensitizing potential. **© 2019 American Academy of Allergy, Asthma & Immunology** **(J Allergy Clin Immunol Pract 2020;8:971-9)**

Key words: *Acrylate; Cyanoacrylate; Methacrylate; Fractional exhaled nitric oxide; Low-molecular-weight agent; Occupational asthma*

INTRODUCTION

The terms "acrylic" or "acryl plastic" refer to synthetic polymers produced from acrylate resins. These resins may be composed of a number of different primary cyanoacrylates, methacrylates, and plain acrylates although the generic term "acrylates" is often used for all of them. Table I presents some common acrylate compounds and their uses. The harmful effects of acrylates are coupled to liquid-phase resins containing reactive monomers and/or prepolymers, whereas fully cured acrylic plastics are generally not hazardous to health. Several acrylates are well-known potent skin sensitizers, and their increasing use in nail and lash cosmetics has, in the last decade, resulted in an epidemic of allergic contact dermatitis in beauticians and their customers.[2]

No acrylates are yet classified as a respiratory sensitizer,[3] and there remains some controversy about their respiratory sensitizing potential.[4] Notwithstanding, epidemiological studies have shown increased risks of asthma in populations exposed to cyanoacrylates,[5] methacrylates,[6] and other acrylates.[7] Cases of occupational asthma (OA) confirmed by specific inhalation challenge (SIC) have been reported from various acrylate compounds,[8,9] including cyanoacrylates,[10-12] methacrylates,[13-18] and plain acrylates.[8,19-21] As with many other LMW agents that cause OA, IgE-associated sensitization to acrylates has not been identified.[8,22]

We aimed to evaluate the jobs, exposures, and clinical, functional, and inflammatory characteristics of workers with a diagnosis of acrylate-induced OA ascertained by an SIC. By comparing them with cases of OA caused by other LMW agents and a well-defined subgroup, isocyanate-induced OA, we hoped to identify a distinct phenotypic profile of acrylate-induced OA.

METHODS

Study design and population

This retrospective, observational study included subjects with acrylate-induced OA who were recruited from 20 tertiary centers participating in the European network for the PHenotyping of OCcupational ASthma (E-PHOCAS).[23,24] The E-PHOCAS cohort recruited all subjects with a diagnosis of OA ascertained by a positive SIC between January 2006 and December 2015. This resulted in 446 patients with OA to LMW agents and complete data on important covariables. Eight of the participating centers reported a total of 28 subjects with OA caused by acrylates (6.3% of all reported cases of OA to LMW agents and 2.9% of all cases) and were asked to enter additional cases identified outside of the 2006 to 2015 period if available, resulting in 31 additional subjects. Of the 59 reported subjects, 1 was excluded because the acrylate was not precisely identified and 3 because of missing information on key clinical outcomes. The 55 subjects with documented acrylate-induced OA who fulfilled the inclusion criteria were compared with subjects with OA due to (1) other LMW agents including isocyanates (n = 418) and (2) isocyanates (n = 125) who fulfilled the same eligibility criteria in the E-PHOCAS database.

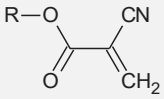
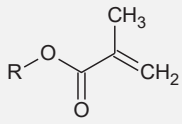
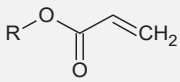
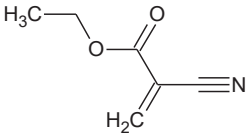
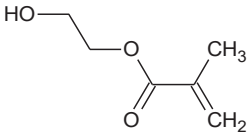
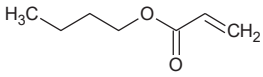
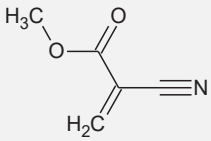
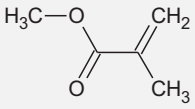
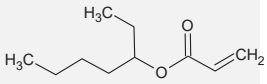
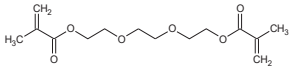
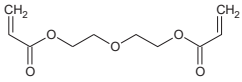
Ethics approval

Each participating center obtained approval from its local institutional review board. The central database at the Strasbourg University was approved by the "Comité Consultatif sur le Traitement de l'Information en Matière de Recherche dans le Domaine de la Santé" and the "Commission Nationale de l'Informatique et des Libertés."

SIC procedure

The SIC aimed to recreate an exposure comparable to the patients' work. Most SICs (49 of 55) were performed by stirring or spreading liquid glues or related materials. Four were done by mixing a 2-pack methacrylate prosthetics kit, and 2 by grinding recently hardened acrylate products (1 case artificial nails and 1 case dental

TABLE I. Common reactive acrylates, their principle structures, and examples of derivatives and relevant products

Acrylate subgroup/ characteristic	Acrylates		
	Cyanoacrylates	Methacrylates	Plain acrylates
Principle structure (R = any hydrocarbon group)			
Typical products	Instant glues, nail and eyelash glues, wound sealants	Floor coatings, artificial nail products, prosthetics, dental sealants and fillings, assembly glues, anerobic sealants and screw lockers, printing colors and plates	Wood lacquers, printing colors and plates, artificial nail products, glues
Common methods of hardening	Atmospheric or tissue humidity	UV light, peroxides	UV light
Examples of derivatives; their CAS numbers, volatility, and asthma HI	 ECA, CAS 7085-85-0, moderate volatility, HI = 1	 HEMA, CAS 868-77-9, high volatility, HI = 1	 BA, CAS 141-32-2, moderate volatility, HI = 0.11
	 MCA, CAS 137-05-3, moderate volatility, HI = 1	 MMA, CAS 80-62-6, high volatility, HI = 1	 EHA, CAS 103-11-7, moderate volatility, HI = 0.11
	 TREGDMA, CAS 109-16-0, low volatility, HI = 1		 DEGDA, CAS 4074-88-8, low volatility, HI = 0.26

BA, Butylacrylate; *DEGDA*, diethyleneglycol-diacrylate; *ECA*, ethyl cyanoacrylate; *EHA*, ethyl hexylacrylate; *HEMA*, hydroxyethyl methacrylate, *MCA*, methyl cyanoacrylate; *MMA*, methyl methacrylate; *TREGDMA*, trietyleneglycol-dimethacrylate; *UV*, ultraviolet.
HI = Hazard index, based on the model by et al.[1]

prothesis). The methodology of SIC conformed with international recommendations in terms of safety precautions, "placebo" challenge, and duration of functional monitoring.[24,25] The cumulative duration of SIC exposure, comprising 1 or more challenges, was 1 to 240 minutes (median, 30 minutes). The placebo control challenges were performed on a separate day using materials without acrylate ingredients, such as glues without acrylates, organic solvents, or saline.

Acrylate categorization and prediction of respiratory sensitization potential from chemical structure

After review of available safety data sheets of involved products, we categorized the causative acrylate compounds into 3 subgroups on the basis of their chemical structure: methacrylates, cyanoacrylates, and plain acrylates.

We obtained the chemical structures of specific acrylate compounds from the online chemical database PubChem[26] and converted structures to molfiles using ChemDraw (Professional v.15.1) software (PerkinElmer, Waltham, Mass). We then entered the molfile for each compound into the most recent iteration of a quantitative structure activity relationship (QSAR) model[1] to generate an "asthma hazard index" (HI). The HI for a given compound is the QSAR model's estimate of the probability that the compound has respiratory sensitization potential based on its chemical structure.

Demographic and clinical characteristics

We used a standardized Excel database to gather information on the following: (1) causative agent and job; (2) demographic and clinical characteristics; (3) nature and timing of exposure to the causal agent and work-related respiratory symptoms; (4) coexisting

TABLE II. Exposures and jobs of patients with OA caused by acrylates

Profession/branch (n)	Work tasks	Product types	Type of acrylates used (n)
Industrial manufacturing (29)			
Manufacturing workers (11)	Painting, fixing, and gluing to make objects (eg, tires, infusion sets, jewelry, and plastic elements)	Glues	Cyanoacrylates (8)
	Laminating	Paints	Methacrylates (3)
		Molding and laminating resins	
Assemblers or mechanics (8)	Electronic and industrial assembly tasks	Glues	Cyanoacrylates (7)
			Methacrylates (1)
Maintenance workers (4)	Maintenance of industrial machines	Glues	Cyanoacrylates (1)
			Methacrylates (3)
Painters (3)	Spray painting cars	Spray paints	Cyanoacrylates (2)
			Plain acrylates (1)
Other (3)	Pouring ink into machine	Printing inks	Cyanoacrylates (1)
	Printing ink	Glue	Plain acrylates (2)
	Shoe making and repairing		
Dental work (14)			
Dental nurses and dentists (11)	Clinical dental work	Dental primers, adhesives, and fillings	Methacrylates (11)
Dental and medical prosthesis technicians (3)	Mixing raw materials of prostheses (powder and liquid)	Prothesis powders and liquids	Methacrylates (3)
	Molding and grinding prostheses		
Beauty care (12)			
Beauticians (7)	Attaching eyelash extensions	Eyelash glues	Cyanoacrylates (7)
Hairdressers (5)	Molding, structuring, and grinding artificial nails	Nail glues	Methacrylates (2)
		Nail gels, nail powders and liquids	Cyanoacrylates and methacrylates (3)

n = number of workers.

disorders; (5) detailed asthma medications; and (6) technique and materials for SIC.[24] We graded the intensity of asthma treatment, *a posteriori*, according to the steps proposed by the Global Initiative for Asthma.[27] Severe exacerbations were defined as those requiring oral corticosteroids for at least 3 consecutive days or emergency room visit or hospitalization.[28,29]

Lung function assessments

We collected data for the forced vital capacity and FEV_1 measured at the time of the SIC, before challenge exposure to the causal agent. The levels of nonspecific bronchial hyperresponsiveness at baseline and 24 hours after challenge were expressed as the concentration or dose of the pharmacological agent inducing a 15% or 20% fall in FEV_1 according to the bronchoprovocation method used in each center.[24]

Markers of airway inflammation

Data pertaining to markers of airway inflammation were included, whenever available: (1) blood eosinophils (within 1 month of the SIC procedure); (2) fractional exhaled nitric oxide concentration (F_{ENO}) at baseline and 24 hours after the SIC; and (3) sputum eosinophils and neutrophils expressed as a percentage of total cell count at baseline and 24 hours postchallenge. Pre-post challenge increases of greater than or equal to 3% in sputum eosinophil count and of greater than or equal to 17.5 parts per billion (ppb) in F_{ENO} level were considered significant.[30]

Data analysis

We summarized continuous measures by medians and interquartile ranges and categorical variables by their frequencies and proportions. We tested comparisons between subjects with acrylate-induced OA and those with OA due to other LMW agents using Fisher exact or chi-square test for categorical variables and the Wilcoxon rank-sum test for numerical variables. To verify whether post-SIC F_{ENO} increase greater than or equal to 17.5 ppb was independently related to acrylates, we used multivariable logistic regression analyses with a binomial generalized linear model and a stepwise procedure based on the Akaike information criterion to select the most parsimonious models. The potential confounding variables included in this regression were selected on the basis of univariable analyses where $P < .10$ (see Table E1 in this article's Online Repository at www.jaci-inpractice.org).

The potential confounding variables included in this regression were selected on the basis of univariable analyses where $P < .10$. Statistical analysis was performed using R software version 3.4.4 (R core team, Auckland, New Zealand). A P value of less than .05 was considered statistically significant.

RESULTS

HIs of acrylates

The HIs generated by the QSAR model[1] are presented in Table I for specific examples of each of the 3 acrylate subgroups. The HI was 1 for all the examples shown of cyanoacrylates and

TABLE III. Demographic and clinical characteristics of subjects with OA caused by acrylates, other LMW agents including isocyanates, and isocyanates

Characteristic	Acrylates (n = 55)	Other LMW agents (n = 418)	Acrylates vs other LMW agents *P* value	Isocyanates (n = 125)	Acrylates vs isocyanates *P* value
Age (y)*	40.0 (31.0-46.5)	44.0 (35.0-53.0)	**0.010**	43.0 (35.0-54.0)	**0.050**
Sex: male	18 (32.7)	233 (55.7)	**0.002**	98 (78.4)	**<0.001**
Body mass index (kg/m^2)*	25.2 (23.1-27.7)	26.9 (24.2-30.2)	**0.020**	27.0 (24.4-29.7)	**0.030**
Smoking			0.580		0.660
Current smoker	10 (18.2)	78 (19.1)		22 (18.0)	
Ex-smoker	14 (25.4)	130 (31.9)		39 (32.0)	
Never-smoker	31 (56.4)	200 (49.0)		61 (50.0)	
Level of education (primary)†	6 (12.2)	103 (29.5)	**0.010**	39 (36.5)	**0.002**
Atopy‡	23 (41.8)	193 (46.2)	0.570	54 (43.2)	1.000
Asthma preexisting to the causal exposure	7 (12.7)	51 (12.2)	0.830	15 (12.0)	1.000
Duration of exposure before asthma onset (mo)*	60.0 (13.0-134.5)	72.0 (24.0-180.0)	0.250	75.0 (24.0-180.0)	0.260
Duration of symptomatic exposure (mo)*	14 (9-36)	26 (12-60)	**0.020**	24 (12-60)	0.070
Interval since last work exposure (mo)*	1.0 (0.2-7.2)	1.0 (0.1-7.0)	0.330	1.0 (0.1-6.0)	0.170
Asthma treatment/severity					
No treatment	14 (24.5)	61 (14.6)	**0.010**	11 (8.8)	**0.002**
Mild (GINA treatment step 1-2)	16 (29.1)	80 (19.1)		21 (16.8)	
Moderate (GINA treatment step 3)	16 (29.1)	133 (31.8)		51 (40.8)	
Severe (GINA treatment step 4-5)	9 (16.4)	144 (34.5)		42 (33.6)	
SABA use ≥1/d	14 (25.4)	136 (32.5)	0.360	39 (31.2)	0.480
≥1 asthma exacerbation (last 12 mo at work)	13 (23.6)	108 (25.8)	0.870	36 (28.8)	0.590
Coexisting conditions					
Work-related rhinitis	36 (65.5)	235 (56.2)	0.250	47 (37.6)	**<0.001**
Oral H_1-antihistamine	14 (25.4)	77 (18.6)	0.270	14 (11.3)	**0.020**
Nasal corticosteroid	11 (20.8)	59 (15.2)	0.320	16 (13.4)	0.260
Work-related conjunctivitis	19 (34.5)	102 (24.9)	0.140	17 (13.7)	**0.002**
Chronic rhinosinusitis	10 (18.2)	50 (12.1)	0.200	10 (8.0)	0.070
Work-related urticaria	9 (17.0)	27 (6.5)	**0.010**	2 (1.6)	**<0.001**
Work-related contact dermatitis	9 (17.0)	62 (14.9)	0.690	9 (7.2)	0.060

GINA, Global Initiative for Asthma[27]; *SABA*, short-acting β_2 agonist.
Data are presented as n (% of available data) unless otherwise specified. Values in bold are statistically significant ($P < .05$).
*Median value with interquartile range within parentheses.
†Number (%) of persons having only primary level education.
‡Atopy defined by the presence of ≥1 positive skin prick test result to at least 1 common allergen.

methacrylates. The HIs for the plain acrylate examples were much lower, but the *di*-(plain)acrylate has a higher HI (0.26) than the *mono*-(plain)acrylates (0.11).

Exposure and work tasks

Table II lists the work tasks and products used by the 55 patients with acrylate-OA. Exposure to acrylates was most common in industrial production in various forms, followed by dental work and beauty care. The commonest products were glues. Most patients had used acrylate products on a daily basis.

Clinical characteristics

In comparison with OA caused by other LMW agents and isocyanates, acrylate-induced OA was associated with younger age, female sex, lower body mass index, higher level of education, more frequent work-related urticaria, and a lower treatment level (Table III). When compared with isocyanate-induced OA, acrylate-induced cases more frequently reported work-related rhinitis, conjunctivitis, urticaria, and use of oral antihistamine medication. Skin prick tests with the causal acrylate compounds were performed in 22 subjects and results were negative in all cases.

Lung function parameters

Baseline spirometry (Table IV) showed higher FEV_1/forced vital capacity ratios in acrylate-induced OA than in OA induced by other LMW agents or isocyanates, but no significant differences in the number of cases with concomitant FEV_1 less than 80% predicted value. There were no significant differences between the groups as regards the pattern of asthmatic reactions, the level of baseline nonspecific bronchial hyperresponsiveness, or change in nonspecific bronchial hyperresponsiveness after SIC.

Markers of airway inflammation

Peripheral blood eosinophilia or baseline FENO did not significantly differ between OA to acrylates and other LMW agents or isocyanates (Table V). In contrast, subjects with acrylate-induced OA had a significantly greater increase in post-SIC FENO (26.0 ppb) compared with both other LMW agent (3.0 ppb) and isocyanate-induced OA (5.0 ppb). Furthermore,

TABLE IV. Functional characteristics of subjects with OA caused by acrylates, other LMW agents including isocyanates, and isocyanates

Characteristic	Acrylates (n = 55)	Other LMW agents (n = 418)	Acrylates vs other LMW agents *P* value	Isocyanates (n = 125)	Acrylates vs isocyanates *P* value
Baseline spirometry					
FVC, % pred*	96 (88-105)	99 (89-108)	.290	98 (88-107)	.600
FEV_1, % pred*	93 (83-100)	91 (82-100)	.570	89 (81-98)	.250
FEV_1/FVC*	81 (76-85)	77 (71-82)	**.001**	76 (70-82)	**<.001**
Airflow obstruction†	3 (5.5)	48 (11.5)	.250	13 (10.4)	.400
Baseline level of NSBH‡	(n = 48)	(n = 390)	.760	(n = 119)	.080
Absent	16 (33.3)	114 (29.2)		21 (17.6)	
Mild	21 (43.8)	169 (43.3)		57 (47.9)	
Moderate-to-severe	11 (22.9)	107 (27.4)		41 (34.5)	
Postchallenge change in NSBH	(n = 24)	(n = 219)		(n = 55)	
Pre/post-SIC NSBH ratio	2.0 (1.0-3.9)	2.0 (1.0-4.3)	.730	2.3 (1.0-4.9)	.430
Pattern of bronchial response to SIC	(n = 54)	(n = 385)		(n = 113)	
Isolated early	12 (21.8)	112 (27.1)	.270	23 (18.7)	.680
Isolated late	24 (43.6)	141 (34.1)	.270	44 (35.5)	.320
Both early and late components	18 (32.7)	132 (31.9)	.270	46 (36.8)	.610

FVC, Forced vital capacity; *NSBH*, nonspecific bronchial hyperresponsiveness.

Data are presented as n (% of available data) unless otherwise specified. Values in bold are statistically significant ($P < .05$).

*Median value with interquartile range within parentheses.

†Airflow obstruction defined by an FEV_1 <80% predicted value and an FEV_1/FVC ratio <70%.

‡See Vandenplas et al[24] for the threshold values used for grading the level of NSBH.

the proportion of subjects with a significant increase in FENO (≥17.5 ppb) was significantly higher in the acrylate-induced asthma group (56%) compared with other LMW agent–induced (20%; $P = .002$) and isocyanate-induced asthma (24%; $P = .03$) groups. Multivariate analysis showed that OA induced by acrylates was significantly and independently associated with a significant post-SIC increase in FENO (odds ratio, 5.59; 95% CI, 1.87-17.58; $P = .002$) (see Table E1).

The number of acrylate-induced OA cases with available sputum samples before and after SIC was small (n = 9). The proportion of subjects who demonstrated a greater than or equal to 3% postchallenge increase in sputum eosinophils was higher among those with acrylate-induced OA (88%) than among those with OA caused by the other LMW agents (48%; $P = .060$). All subjects with acrylate-induced OA showed a postchallenge eosinophilic inflammatory pattern, whereas this pattern was present in only 61% of OA cases induced by other LMW agents ($P = .020$) and 67% of isocyanate-induced cases ($P = .071$). Among 65 subjects with OA caused by other LMW agents and available sputum samples before and after the SIC, 10 of 35 (29%) with a baseline noneosinophilic inflammatory pattern developed a postchallenge eosinophilic pattern, whereas the 3 subjects with acrylate-induced OA who showed a noneosinophilc inflammatory pattern at baseline became eosinophilic at the postchallenge assessment ($P = .034$). Furthermore, both baseline and postchallenge sputum neutrophil percentages were lower in the acrylate-induced asthma group than in those with OA caused by other LMW agents (Table V).

DISCUSSION

To our knowledge, we present the largest series (n = 55) of acrylate-induced OA cases ascertained by an SIC, confirming the respiratory sensitizing hazard of these compounds. In addition, this study identified phenotypic characteristics of acrylate-induced OA compared with other LMW agents that are similar to those in OA due to high-molecular-weight agents.

Acrylate compounds contain a reactive double bond (vinyl group) adjacent to a carbonyl group, making them easily polymerized and therefore useful in various coating, molding, and sealing applications (Table I). The reaction is usually initiated with peroxides or ultraviolet light, after which polymerization proceeds rapidly until the starting materials are consumed. The curing of *cyanoacrylate* products is initiated by water; they polymerize quickly in humid surroundings and are almost exclusively used as instant glues in wound sealing, eyelash extension and nail work, and various mechanical assembly tasks. *Methacrylate* products, often hardened with peroxides or ultraviolet light, are used in dental and prosthetic work, artificial nails, industrial glues, coatings, and lamination resins. *Plain acrylates* (having no cyano- or methyl group attached to the double-bond carbon) are typically ultraviolet-hardened and are encountered in, for example, printing, gluing, and industrial coatings.

The same reactive vinyl group that allows polymerization has also been proposed as the reactive group responsible for respiratory sensitization potential of methacrylates and plain acrylates.[31] The outward-facing electrophilic carbon atom of this vinyl group is considered to have the ability to react with an amine group of an amino acid side chain, such as lysine, present on a protein molecule in the lining of the lung. The resulting hapten-protein conjugate can then potentially trigger an immune response and ultimately cause bronchoconstriction. Cyanoacrylates have also been deemed by mechanistic chemists to have potential for reactivity with similar protein side chains as a result of having a sufficiently high "electrophilic index."[32]

The QSAR model[1] estimates the probability (HI) that an LMW organic compound can cause asthma by sensitization on

TABLE V. Airway inflammation markers in subjects with OA caused by acrylates, other LMW including isocyanates, and isocyanates

Characteristic	Acrylates (n = 55)	Other LMW agents (n = 418)	Acrylates vs other LMW agents *P* value	Isocyanates (n = 125)	Acrylates vs isocyanates *P* value
Blood eosinophils	(n = 28)	(n = 213)		(n = 58)	
Cells/μL*	200 (97 to 321)	212 (110 to 338)	0.310	242 (145 to 396)	0.180
>300/μL	9 (32.1)	72 (33.8)	1.000	22 (37.9)	0.640
Baseline FENO	(n = 25)	(n = 222)		(n = 51)	
ppb*	15.0 (10.0 to 29.0)	19.0 (10.0 to 32.8)	0.300	20.0 (12.0 to 35.0)	0.140
Post-SIC change in FENO	(n = 18)	(n = 155)		(n = 34)	
ppb*,†	26.0 (8.2 to 38.0)	3.0 (−1.0 to 10.0)	**<0.001**	5.0 (2.0 to 16.0)	**0.010**
Pre/post-SIC change in FENO ≥17.5 pp†	10 (55.6)	31 (20.0)	**0.002**	8 (24.2)	**0.030**
Baseline sputum eosinophils	(n = 9)	(n = 79)		(n = 19)	
%*	5 (2 to 10)	2 (1 to 6)	0.290	2.0 (1.0 to 8.5)	0.620
Postchallenge sputum eosinophils	(n = 8)	(n = 65)		(n = 17)	
%*	10.0 (5.0 to 14.4)	7.0 (2.0 to 15.5)	0.300	8.5 (2.2 to 13.2)	0.520
Post-SIC change (%)*	6.1 (3.0 to 11.5)	2.0 (0.8 to 8.0)	0.110	4.0 (0.0 to 8.0)	0.220
Post-SIC increase in sputum eosinophils ≥3%	7 (87.5)	31 (47.7)	0.060	10 (58.8)	0.210
Baseline sputum neutrophils	(n = 9)	(n = 84)		(n = 21)	
%*	45.0 (37.0 to 50.0)	58.5 (44.4 to 72.2)	**0.040**	55.0 (42.0 to 78.5)	0.170
Postchallenge sputum neutrophils	(n = 8)	(n = 70)		(n = 19)	
%*	45.0 (41.0 to 47.0)	61.0 (45.0 to 73.0)	**0.020**	49.0 (28.0 to 64.0)	0.490
Post-SIC change (%)	−1.5 (−11.8 to 5.0)	1.0 (−12.4 to 14.2)	0.620	−2.0 (−20.5 to 11.5)	0.710
Baseline sputum inflammatory pattern‡	(n = 9)	(n = 79)		(n = 19)	
Eosinophilic	6 (66.7)	33 (41.8)	0.180	9 (47.9)	0.435
Neutrophilic	0	13 (16.5)		4 (21.1)	
Paucigranulocytic	3 (33.3)	31 (39.2)	0.193	6 (31.6)	1.000
Mixed granulocytic	0	2 (2.5)		0	
Postchallenge sputum inflammatory pattern‡	(n = 9)	(n = 66)		(n = 18)	
Eosinophilic	9 (100.0)	40 (60.6)	**0.020**	12 (66.7)	0.071
Neutrophilic	0	5 (7.6)		1 (5.6)	
Paucigranulocytic	0	5 (7.6)		4 (22.2)	
Mixed granulocytic	0	16 (24.2)		1 (5.6)	

Data are presented as n (% of available data) unless otherwise specified. Values in bold are statistically significant ($P < .05$).
*Median value with interquartile range within parentheses.
†Compared with baseline value.
‡The sputum inflammatory pattern was characterized as "eosinophilic" (ie, ≥3% eosinophils and <76% neutrophils); "neutrophilic" (ie, ≥76% and <3% eosinophils); "paucigranulocytic" (ie, <3% eosinophils and <76% neutrophils); and "mixed granulocytic" (ie, ≥76% neutrophils and ≥3% eosinophils).

the basis of analysis of its substructures. The HI value of 1 obtained for the cyanoacrylates and methacrylates implies that the QSAR model interprets their chemical structures as having the features required to cause asthma by sensitization, without making any a priori assumptions about the chemical or pathophysiological mechanism. This high HI value needs to be interpreted in the context of the model's external validation statistics,[1] which suggested that applying a cutoff point HI of 0.39 enables respiratory sensitizers to be discriminated from controls with sensitivity 90% and specificity 96%. The potency of a chemical to cause respiratory sensitization also depends on its physicochemical properties, even if theoretically it has the required chemically reactive structural components. The HI values for the mono- and di-(plain)acrylate are much lower than for cyanoacrylates and methacrylates. One possible explanation is that the QSAR model assigns these compounds falsely low HIs; another might be that they have lower potential to react with native lung proteins than do cyanoacrylates or methacrylates.

Although nothing substantial is known about the mechanisms behind the respiratory sensitizing hazard of acrylates, our findings offer some interesting clues. Acrylate-induced OA cases were younger, better educated, and the proportion of them who were women was higher than among those with OA to other LMW agents, reflecting, presumably, differences in jobs that incur exposure to these agents. Acrylate cases had shorter durations of symptomatic exposure, fewer asthma treatments, and higher FEV_1/forced vital capacity ratios. Taken together these factors suggest that OA from acrylates is identified at a relatively early stage. In addition, the patients reported more work-related rhinitis, conjunctivitis, and urticaria than did isocyanate-induced cases. Increases in FENO after SIC exposure have been associated with high-molecular-weight agents,[33] although increases are also reported after challenge with some LMW agents

including isocyanates.[34] In our series, FENO increase after SIC was more frequently recorded in acrylate-induced OA than in OA induced by isocyanates or other chemical agents. FENO has been previously measured during SIC in only a few case reports of acrylate-induced OA, all included in our series. In 3 cases an increase was reported.[11,17,21] In another case, FENO did not increase during SIC but was higher during a work period when compared with off work.[10] We also found a trend toward more eosinophilic inflammation in induced sputum after SIC in acrylate-induced asthma, although the small number of cases (n = 9) limited these analyses. Several cases of an increase in sputum eosinophils during SIC in acrylate-induced asthma have been reported, some of them included in the present series.[10,12,15,19-21] Comparisons of the eosinophil and FENO responses to challenge with acrylates with those in OA to other LMW agents may suggest greater involvement of T_H2-type mechanisms in the former, but this is speculative without yet having demonstrated this directly in T_H2 cytokines. Skin prick test results with the inciting acrylate compounds were negative in all tested patients. This finding is in line with former studies[8,22] and indicates that this test is insensitive to detect sensitization to acrylates, as it is for most LMW agents.

In the absence of at-risk denominators, our findings cannot shed light on the relative potency of different acrylates. Moreover, the relevant exposures to acrylates will depend also on the physical characteristics of the different acrylates and the environmental circumstances in which they are encountered. Only small volumes of glue are typically used in industrial assembly and artificial eyelash work, meaning that respiratory exposure to acrylates in these tasks is probably low. In painting and molding, in nail care, and in the preparation of prosthetics, the amount of acrylic product is higher, resulting in increased exposures, especially in confined workplaces. Grinding of newly hardened acrylate plastics (eg, prosthesis or nails) may produce high volumes of fine dust that contain residues of reactive starting materials.[15,35,36] Furthermore, respiratory exposure to reactive acrylates is dependent on their volatility and mode of usage and consequently their concentration in the user's breathing zone. Hydroxyethyl methacrylate and methyl methacrylate are examples of volatile acrylates that may produce relatively high airborne concentrations by evaporation, especially in tasks such as coating of large areas or molding of prostheses or artificial nails. Air measurements of acrylates are relatively scarce: small amounts of methacrylates have been detected in Finnish nail salons.[35] Higher levels of methyl methacrylate were detected in dental laboratories[37] and recently in 15 of 17 nail salons[38] in the United States.

The major strength of our study was its international multicenter design, which ensured a sufficient number of acrylate-induced cases of OA and minimized potential selection biases due to local clinical practices and recruitment patterns, enhancing the generalizability of our findings. Limitations were that markers of airway inflammation, FENO and sputum eosinophils, were unavailable in a large proportion of subjects, which restricted comparisons between groups, especially comparisons between different acrylate types.

A barrier to the prevention of OA from acrylates is that the safety data sheets of acrylate products often fail to identify that these compounds are potential respiratory sensitizers. Our series supports the recent Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) substance evaluation process[39] that concluded that methyl methacrylate should be classified as a respiratory sensitizer, warranting the appropriate hazard statement. Hydroxyethyl methacrylate and ethyl methacrylate are currently being evaluated,[40] but there are no such plans for cyanoacrylates, which were a common causative agent in our series.

CONCLUSIONS

Acrylate-induced OA shows some characteristics (concomitant work-related rhinitis and a greater postexposure increase in FENO) that have been previously linked to OA caused by high-molecular-weight agents, suggesting that acrylates may induce OA through immunologic mechanisms that are different from those for other LMW agents. Moreover, the phenotypic differences between acrylates and other LMW agents challenge the practice of pooling a wide variety of LMW agents into a single category, presuming implicitly that they share similar pathophysiologic mechanisms.[24] Physicians, workers, and employers should be informed about the respiratory hazards of acrylate products and how to prevent them.[41] The present and other reports of OA due to acrylates should be taken into account when updating their hazard classifications.

REFERENCES

1. Jarvis J, Seed MJ, Stocks SJ, Agius RM. A refined QSAR model for prediction of chemical asthma hazard. Occup Med (Lond) 2015;65:659-66.
2. Goncalo M, Pinho A, Agner T, Andersen KE, Bruze M, Diepgen T, et al. Allergic contact dermatitis caused by nail acrylates in Europe: an EECDRG study. Contact Dermatitis 2018;78:254-60.
3. European CHemical Agency. Harmonised classification and labelling of hazardous substances. Annex VI to CLP. Helsinki, Finland: European Chemicals Agency; 2018. Updated September 2018. Available from: https://echa.europa.eu/fi/information-on-chemicals/annex-vi-to-clp. Accessed September 2, 2019.
4. Borak J, Fields C, Andrews LS, Pemberton MA. Methyl methacrylate and respiratory sensitization: a critical review. Crit Rev Toxicol 2011;41:230-68.
5. Toren K, Jarvholm B, Brisman J, Hagberg S, Hermansson BA, Lillienberg L. Adult-onset asthma and occupational exposures. Scand J Work Environ Health 1999;25:430-5.
6. Jaakkola MS, Leino T, Tammilehto L, Ylostalo P, Kuosma E, Alanko K. Respiratory effects of exposure to methacrylates among dental assistants. Allergy 2007;62:648-54.
7. Lillienberg L, Andersson E, Janson C, Dahlman-Hoglund A, Forsberg B, Holm M, et al. Occupational exposure and new-onset asthma in a population-based study in Northern Europe (RHINE). Ann Occup Hyg 2013;57:482-92.
8. Savonius B, Keskinen H, Tuppurainen M, Kanerva L. Occupational respiratory disease caused by acrylates. Clin Exp Allergy 1993;23:416-24.
9. Walters GI, Robertson AS, Moore VC, Burge PS. Occupational asthma caused by acrylic compounds from SHIELD surveillance (1989-2014). Occup Med (Lond) 2017;67:282-9.
10. Andujar R, Cruz MJ, Villar A, Morell F, Munoz X. High eosinophil levels and poor evolution in occupational asthma due to cyanoacrylate exposure. Am J Ind Med 2011;54:714-8.
11. Lindstrom I, Suojalehto H, Henriks-Eckerman ML, Suuronen K. Occupational asthma and rhinitis caused by cyanoacrylate-based eyelash extension glues. Occup Med (Lond) 2013;63:294-7.
12. Quirce S, Baeza ML, Tornero P, Blasco A, Barranco R, Sastre J. Occupational asthma caused by exposure to cyanoacrylate. Allergy 2001;56:446-9.
13. Pickering CA, Bainbridge D, Birtwistle IH, Griffiths DL. Occupational asthma due to methyl methacrylate in an orthopaedic theatre sister. Br Med J (Clin Res Ed) 1986;292:1362-3.
14. Piirila P, Hodgson U, Estlander T, Keskinen H, Saalo A, Voutilainen R, et al. Occupational respiratory hypersensitivity in dental personnel. Int Arch Occup Environ Health 2002;75:209-16.
15. Quirce S, Barranco P, Fernandez-Nieto M, Sastre B, del Pozo V, Sastre J. Occupational asthma caused by acrylates in optical laboratory technicians. J Investig Allergol Clin Immunol 2011;21:78-9.

16. Sauni R, Kauppi P, Alanko K, Henriks-Eckerman ML, Tuppurainen M, Hannu T. Occupational asthma caused by sculptured nails containing methacrylates. Am J Ind Med 2008;51:968-74.
17. Uriarte SA, Fernandez-Nieto M, Sastre J. Occupational asthma due to polyvinyl chloride and methyl methacrylate in a plumber. J Investig Allergol Clin Immunol 2013;23:437-8.
18. Vaccaro M, Guarneri F, Barbuzza O, Cannavo SP. Airborne contact dermatitis and asthma in a nail art operator. Int J Occup Med Environ Health 2014;27:137-40.
19. Lemiere C, Weytjens K, Cartier A, Malo JL. Late asthmatic reaction with airway inflammation but without airway hyperresponsiveness. Clin Exp Allergy 2000;30:415-7.
20. Reig Rincon de Arellano I, Cimarra Alvarez-Lovell M, Robledo Echarren T, Fernandez-Nieto M, Quirce Gancedo S, Seaone Plata C, et al. Occupational asthma due to acrylates in a graphic arts worker. Allergol Immunopathol (Madr) 2006;34:32-6.
21. Sanchez-Garcia S, Fernandez-Nieto M, Sastre J. Asthma induced by a thermal printer. N Engl J Med 2009;360:2375-6.
22. Helaskoski E, Suojalehto H, Kuuliala O, Aalto-Korte K. Prick testing with chemicals in the diagnosis of occupational contact urticaria and respiratory diseases. Contact Dermatitis 2015;72:20-32.
23. Vandenplas O, Godet J, Hurdubaea L, Rifflart C, Suojalehto H, Walusiak-Skorupa J, et al, European network for the PHenotyping of OCcupational AStHma (E-PHOCAS) investigators. Severe occupational asthma: insights from a multicenter European cohort. J Allergy Clin Immunol Pract 2019;7:2309-2318.e4.
24. Vandenplas O, Godet J, Hurdubaea L, Rifflart C, Suojalehto H, Wiszniewska M, et al. Are high- and low-molecular-weight sensitizing agents associated with different clinical phenotypes of occupational asthma? Allergy 2018;74:261-72.
25. Vandenplas O, Suojalehto H, Aasen TB, Baur X, Burge PS, de Blay F, et al. Specific inhalation challenge in the diagnosis of occupational asthma: consensus statement. Eur Respir J 2014;43:1573-87.
26. US National Library of Medicine. National Center for Biotechnology Information. PubChem. Available from: https://pubchem.ncbi.nlm.nih.gov/. Accessed September 2, 2019.
27. Global Initiative for Asthma. Global strategy for asthma management and prevention 2015. Available from: http://www.ginasthma.org/. Accessed September 2, 2019.
28. Bousquet J, Mantzouranis E, Cruz AA, Ait-Khaled N, Baena-Cagnani CE, Bleecker ER, et al. Uniform definition of asthma severity, control, and exacerbations: document presented for the World Health Organization Consultation on Severe Asthma. J Allergy Clin Immunol 2010;126:926-38.
29. Reddel HK, Taylor DR, Bateman ED, Boulet LP, Boushey HA, Busse WW, et al. An official American Thoracic Society/European Respiratory Society statement: asthma control and exacerbations: standardizing endpoints for clinical asthma trials and clinical practice. Am J Respir Crit Care Med 2009;180:59-99.
30. Vandenplas O, D'Alpaos V, Heymans J, Jamart J, Thimpont J, Huaux F, et al. Sputum eosinophilia: an early marker of bronchial response to occupational agents. Allergy 2009;64:754-61.
31. Enoch SJ, Seed MJ, Roberts DW, Cronin MT, Stocks SJ, Agius RM. Development of mechanism-based structural alerts for respiratory sensitization hazard identification. Chem Res Toxicol 2012;25:2490-8.
32. Enoch SJ, Roberts DW, Cronin MT. Mechanistic category formation for the prediction of respiratory sensitization. Chem Res Toxicol 2010;23:1547-55.
33. Lemiere C, NGuyen S, Sava F, D'Alpaos V, Huaux F, Vandenplas O. Occupational asthma phenotypes identified by increased fractional exhaled nitric oxide after exposure to causal agents. J Allergy Clin Immunol 2014;134:1063-7.
34. Ferrazzoni S, Scarpa MC, Guarnieri G, Corradi M, Mutti A, Maestrelli P. Exhaled nitric oxide and breath condensate pH in asthmatic reactions induced by isocyanates. Chest 2009;136:155-62.
35. Henriks-Eckerman ML, Korva M. Exposure to airborne methacrylates in nail salons. J Occup Environ Hyg 2012;9:D146-50.
36. Hiipakka D, Samimi B. Exposure of acrylic fingernail sculptors to organic vapors and methacrylate dusts. Am Ind Hyg Assoc J 1987;48:230-7.
37. Nayebzadeh A, Dufresne A. Evaluation of exposure to methyl methacrylate among dental laboratory technicians. Am Ind Hyg Assoc J 1999;60:625-8.
38. Zhong L, Batterman S, Milando CW. VOC sources and exposures in nail salons: a pilot study in Michigan, USA. Int Arch Occup Environ Health 2019;92:141-53.
39. European CHemical Agency. Substance evaluation conclusion as required by REACH Article 48 and evaluation report for methyl methacrylate. Maisons-Alfort, France: ANSES Unité UESC Département de l'Evaluation des Risques; 2018.
40. European CHemical Agency. Substance evaluation—CoRAP 2019. Available from: https://echa.europa.eu/information-on-chemicals/evaluation/community-rolling-action-plan/corap-table. Accessed September 2, 2019.
41. Moscato G, Pala G, Boillat MA, Folletti I, Gerth van Wijk R, Olgiati-Des Gouttes D, et al. EAACI position paper: prevention of work-related respiratory allergies among pre-apprentices or apprentices and young workers. Allergy 2011;66:1164-73.

J ALLERGY CLIN IMMUNOL PRACT
MARCH 2020

ONLINE REPOSITORY

TABLE E1. Multivariate analysis of the factors associated with a significant postchallenge increase in FENO

Factor	Odds ratio	95% CI	*P* value
Acrylates vs all other LMW agents	5.585	1.873-17.577	.002
Baseline FENO value	1.025	1.003-1.048	.026
Time elapsed since last work exposure	0.940	0.871-0.992	.061

Independent variables included in the multivariable logistic regression model were age, sex, atopy, smoking, inhaled corticosteroid dose, work-related rhinitis, sinusitis, time elapsed since last work exposure, duration of work-related asthma symptoms, FENO value before SIC, magnitude of asthmatic reaction, and isolated late reaction during SIC. A total of 122 subjects were included in this model.