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1 Phenotyping occupational asthma caused by acrylates in a multicentre cohort study

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123

124 **ABSTRACT**

125 **Background** While acrylates are well-known skin sensitisers, they are not classified as respiratory
126 sensitisers although several cases of acrylate-induced occupational asthma (OA) have been reported.

127 **Objectives** The aim of this study was to evaluate the characteristics of acrylate-induced OA in a large
128 series of cases and compare those with OA induced by other low-molecular-weight (LMW) agents.

129 **Methods** Jobs and exposures, clinical and functional characteristics, and markers of airway
130 inflammation were analysed in an international, multicentre, retrospective cohort of subjects with OA
131 ascertained by a positive inhalation challenge to acrylates (n= 55) or other LMW agents (n=418)
132 including isocyanates (n=125).

133 **Results** Acrylate-containing glues were the most prevalent products and industrial manufacturing,
134 dental work and beauty care were typical occupations causing OA. Work related rhinitis was more
135 common in acrylate than isocyanate-induced asthma ($p<0.001$). The increase in post-challenge
136 fractional exhaled nitric oxide (FeNO) was significantly greater in acrylate-induced OA (26.0, 8.2-38.0
137 ppb) than in OA induced by other LMW agents (3.0, -1.0-10.0 ppb, $p<0.001$) or isocyanates (5.0, 2.0-
138 16.0 ppb, $p=0.010$). Multivariable models confirmed that OA induced by acrylates was significantly
139 and independently associated with a post-challenge increase in FeNO (≥ 17.5 ppb).

140 **Conclusions** Acrylate-induced OA shows specific characteristics, concomitant work-related rhinitis and
141 exposure-related increases in FeNO, suggesting that acrylates may induce asthma through different
142 immunological mechanisms than other LMW agents. Our findings reinforce the need for a re-
143 evaluation of the hazard classification of acrylates, and further investigation of the pathophysiological
144 mechanisms underlying their respiratory sensitizing potential.

145

146 **Highlights box**

147 **What is already known about this topic?**

148 Although several cases of acrylate-induced occupational asthma have been reported, the
149 characteristics of this disease are not known and acrylates are not classified as respiratory sensitisers.

150 **What does this article add to our knowledge?**

151 Work-related rhinitis was more frequent in acrylate-induced than isocyanate-induced occupational
152 asthma and the increase in post-challenge fractional exhaled nitric oxide was greater than in
153 occupational asthma induced by other low-molecular-weight agents or isocyanates.

154 **How does this study impact current management guidelines?**

155 Our study shows that acrylate-induced occupational asthma has phenotypic characteristics suggesting
156 that acrylates may induce occupational asthma through different immunological mechanisms than
157 other LMW agents.

158 **Key words:** Acrylate, cyanoacrylate, methacrylate, fractional exhaled nitric oxide, low-molecular-
159 weight agent, occupational asthma

160 **List of abbreviations:**

161	E-PHOCAS:	European network for the PHenotyping of OCCupational ASThma
162	FeNO:	Fractional exhaled nitric oxide
163	FEV ₁ :	Forced expiratory volume in one second
164	FVC:	Forced vital capacity
165	HEMA:	hydroxyethyl methacrylate
166	HMW:	High-molecular-weight
167	IQR:	Interquartile range
168	LMW:	Low-molecular-weight
169	MMA:	methyl methacrylate
170	NSBH:	Nonspecific bronchial hyperresponsiveness
171	OA:	Occupational asthma
172	ppb:	Parts per billion
173	QSAR:	Quantitative structure activity relationship
174	SIC:	Specific inhalation challenge
175		

176 Introduction

177 The terms “acrylic” or “acryl plastic” refer to synthetic polymers produced from acrylate resins. These
178 resins may be composed of a number of different primary cyanoacrylates, methacrylates and plain
179 acrylates although the generic term “acrylates” is often used for all of them. Table I presents some
180 common acrylate compounds and their uses. The harmful effects of acrylates are coupled to liquid-
181 phase resins containing reactive monomers and/or prepolymers while fully cured acrylic plastics are
182 generally not hazardous to health. Several acrylates are well known potent skin sensitizers and their
183 increasing use in nail and lash cosmetics has, in the last decade, resulted in an epidemic of allergic
184 contact dermatitis in beauticians and their customers (1).

185 No acrylates are yet classified as a respiratory sensitizer (2) and there remains some controversy about
186 their respiratory sensitizing potential (3). Notwithstanding, epidemiological studies have shown
187 increased risks of asthma in populations exposed to cyanoacrylates (4), methacrylates (5), and other
188 acrylates (6). Cases of occupational asthma (OA) confirmed by specific inhalation challenge (SIC) have
189 been reported from various acrylate compounds (7, 8), including cyanoacrylates (9-11), methacrylates
190 (12-17) and plain acrylates (7, 18-20). As with many other low-molecular-weight (LMW) agents that
191 cause OA, IgE-associated sensitization to acrylates has not been identified (7, 21).

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

196

197 **Methods**

198 *Study design and population*

199 This retrospective, observational study included subjects with acrylate-induced OA who were
200 recruited from 20 tertiary centers participating in the European network for the PHenotyping of
201 Occupational Asthma (E-PHOCAS) (22, 23). The E-PHOCAS cohort recruited all subjects with a
202 diagnosis of OA ascertained by a positive SIC between January 2006 and December 2015. This resulted
203 in 446 patients with OA to LMW agents and complete data on important covariables. Eight of the
204 participating centres reported a total of 28 subjects with OA caused by acrylates (6.3% of all reported
205 cases of OA to LMW agents and 2.9% of all cases) and were asked to enter additional cases identified
206 outside of the 2006-2015 period if available, resulting in 31 additional subjects. Of the 59 reported
207 subjects, one was excluded because the acrylate was not precisely identified, and three due to missing
208 information on key clinical outcomes. The 55 subjects with documented acrylate-induced OA who
209 fulfilled the inclusion criteria were compared to subjects with OA due to 1) other LMW agents
210 including isocyanates (n=418) and 2) isocyanates (n=125) who fulfilled the same eligibility criteria in
211 the E-PHOCAS database.

212 *Ethics approval*

213 Each participating centre obtained approval from its local Institutional Review Board. The central
214 database at the Strasbourg University was approved by the “Comité Consultatif sur le Traitement de
215 l’Information en Matière de Recherche dans le Domaine de la Santé” and the “Commission Nationale
216 de l’Informatique et des Libertés”.

217 *SIC procedure*

218 The SIC aimed to recreate an exposure comparable to the patients’ work. Most SICs (49/55) were
219 performed by stirring or spreading liquid glues or related materials. Four were done by mixing a two-
220 pack methacrylate prosthetics kit, and two by grinding recently hardened acrylate products (1 case
221 artificial nails and 1 case dental prosthesis). The methodology of SIC conformed with international
222 recommendations in terms of safety precautions, “placebo” challenge, and duration of functional
223 monitoring (23, 24). The cumulative duration of SIC exposure, comprising one or more challenges, was
224 1-240 minutes (median 30 min). The placebo control challenges were performed on a separate day
225 using materials without acrylate ingredients, such as glues without acrylates, organic solvents or
226 saline.

227 *Acrylate categorization and prediction of respiratory sensitization potential from chemical structure*

228 After review of available safety data sheets of involved products, we categorised the causative acrylate
229 compounds into three subgroups based on their chemical structure: methacrylates, cyanoacrylates
230 and plain acrylates.

231 We obtained the chemical structures of specific acrylate compounds from the on-line chemical
232 database, PubChem (PubChem: (<https://pubchem.ncbi.nlm.nih.gov/>)) and converted structures to
233 molfiles using ChemDraw (Professional v.15.1) software. We then entered the molfile for each
234 compound into the most recent iteration of a quantitative structure activity relationship (QSAR) model
235 (25) to generate an 'asthma hazard index' (HI). The HI for a given compound is the QSAR model's
236 estimate of the probability that the compound has respiratory sensitisation potential based on its
237 chemical structure.

238 *Demographic and Clinical Characteristics*

239 We used a standardized Excel database to gather information on the following: 1) causative agent and
240 job; 2) demographic and clinical characteristics; 3) nature and timing of exposure to the causal agent
241 and work-related respiratory symptoms; 5) co-existing disorders; 6) detailed asthma medications; and
242 8) technique and materials for SIC (23). We graded the intensity of asthma treatment, *a posteriori*,
243 according to the steps proposed by the Global Initiative for Asthma (GINA) (26). Severe exacerbations
244 were defined as those requiring oral corticosteroids for at least three consecutive days or emergency
245 room visit or hospitalization (27, 28).

246 *Lung Function Assessments*

247 We collected the forced vital capacity (FVC) and forced expiratory volume in 1 sec (FEV₁) measured at
248 the time of the SIC, before challenge exposure to the causal agent. The levels of nonspecific bronchial
249 hyperresponsiveness (NSBH) at baseline and 24 hours after challenge were expressed as the
250 concentration or dose of the pharmacological agent inducing a 15% or 20% fall in FEV₁ according to
251 the bronchoprovocation method used in each center (23).

252 *Markers of airway inflammation*

253 Data pertaining to markers of airway inflammation were included, whenever available: 1) blood
254 eosinophils (within one month of the SIC procedure); 2) fractional exhaled nitric oxide concentration
255 (FeNO) at baseline and 24 hours after the SIC; and 3) sputum eosinophils and neutrophils expressed
256 as a percentage of total cell count at baseline and 24 hours post-challenge. Pre-post challenge
257 increases in sputum eosinophil count $\geq 3\%$ and in FeNO level ≥ 17.5 ppb were considered significant
258 (29).

259 *Data analysis*

260 We summarized continuous measures by medians and interquartile ranges (IQR) and categorical
261 variables by their frequencies and proportions. We tested comparisons between subjects with
262 acrylate-induced OA and those with OA due to other LMW agents using Fisher's exact or chi-squared
263 tests for categorical variables and the Wilcoxon rank-sum test for numerical variables. In order to
264 verify whether post-SIC FeNO increase ≥ 17.5 ppb was independently related to acrylates, we used
265 multivariable logistic regression analyses with a binomial generalized linear model and a stepwise
266 procedure based on the Akaike information criterion to select the most parsimonious models. The
267 potential confounding variables included in this regression were selected based on univariable
268 analyses where $p < 0.10$ (table E1 in the Online Supplement).

269 The potential confounding variables included in this regression were selected based on univariable
270 analyses where $p < 0.10$. Statistical analysis was performed using R software version 3.4.4
271 (<https://cran.r-project.org>). A p value < 0.05 was considered statistically significant.

272

273 Results

274 *Hazard indexes of acrylates*

275 The HIs generated by the QSAR model (25) are shown in table I for specific examples of each of the
276 three acrylate subgroups. The HI was 1 for all the examples shown of cyanoacrylates and
277 methacrylates. The HIs for the plain acrylate examples were much lower but the *di*-(plain)acrylate has
278 a higher HI (0.26) than the *mono*-(plain)acrylates (0.11).

279 *Exposure and work tasks*

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

284 *Clinical characteristics*

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

291 *Lung function parameters*

292 Baseline spirometry (table IV) showed higher FEV₁/FVC ratios in acrylate induced OA than OA to other
293 LMW agents or isocyanates, but no significant differences in the number of cases with concomitant
294 FEV₁ <80% predicted value. There were no significant differences between the groups as regards the
295 pattern of asthmatic reactions, the level of baseline NSBH or change in NSBH after SIC.

296 *Markers of airway inflammation*

297 Peripheral blood eosinophilia or baseline FeNO did not significantly differ between OA to acrylates
298 and other LMW agents or isocyanates (table V). In contrast, subjects with acrylate-induced OA had a
299 significantly greater increase in post-SIC FeNO (26.0 ppb) compared to both other LMW agent (3.0
300 ppb) and isocyanate induced OA (5.0 ppb). Further, the proportion of subjects with a significant
301 increase in FeNO (≥ 17.5 ppb) was significantly higher in the acrylate induced asthma group (56%)

302 compared to other LMW agent (20%, $p=0.002$) and isocyanate induced asthma (24%, $p=0.03$) groups.
303 Multivariate analysis showed that OA induced by acrylates was significantly and independently
304 associated with a significant post-SIC increase in FeNO (OR: 5.59; 95% CI: 1.87-17.58; $p=0.002$) (table
305 E1 in the Online Supplement).

306 The number of acrylate-induced OA cases with available sputum samples before and after SIC was
307 small ($n=9$). The proportion of subjects who demonstrated a $\geq 3\%$ post-challenge increase in sputum
308 eosinophils was higher among those with acrylate-induced OA (88%) than among those with OA
309 caused by the other LMW agents (48%; $p=0.060$). All subjects with acrylate-induced OA showed a post-
310 challenge eosinophilic inflammatory pattern, while this pattern was present in only 61% of OA induced
311 by other LMW agents ($p=0.020$) and 67% of isocyanate-induced cases ($p=0.071$). Among 65 subjects
312 with OA caused by other LMW agents and available sputum samples before and after the SIC, 10 of
313 35 (29%) with a baseline noneosinophilic inflammatory pattern developed a post-challenge
314 eosinophilic pattern, whereas the 3 subjects with acrylate-induced OA who showed a noneosinophilic
315 inflammatory pattern at baseline became eosinophilic at the post-challenge assessment ($p=0.034$).
316 Further, both baseline and post-challenge sputum neutrophil percentages were lower in the acrylate-
317 induced asthma group than in those with OA caused by other LMW agents (table V).

318

319 Discussion

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

324

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

335 The same reactive vinyl group that allows polymerization has also been proposed as the reactive group
336 responsible for respiratory sensitization potential of methacrylates and plain acrylates (30). The
337 outward facing electrophilic carbon atom of this vinyl group is considered to have the ability to react
338 with an amine group of an amino acid side chain, such as lysine, present on a protein molecule in the
339 lining of the lung. The resulting hapten-protein conjugate can then potentially trigger an immune
340 response and ultimately cause bronchoconstriction. Cyanoacrylates have also been deemed by
341 mechanistic chemists to have potential for reactivity with similar protein side chains as a result of
342 having a sufficiently high 'electrophilic index' (31).

343 The QSAR model (25) estimates the probability (HI) that a LMW organic compound can cause asthma
344 by sensitization based on analysis of its substructures. The HI value of 1 obtained for the
345 cyanoacrylates and methacrylates implies that the QSAR model interprets their chemical structures as
346 having the features required to cause asthma by sensitization, without making any a priori
347 assumptions about the chemical or pathophysiological mechanism. This high HI value needs to be
348 interpreted in the context of the model's external validation statistics (25) which suggested that
349 applying a cut-point HI of 0.39 enables respiratory sensitizers to be discriminated from controls with
350 sensitivity 90% and specificity 96%. The potency of a chemical to cause respiratory sensitization also

351 depends on its physico-chemical properties, even if theoretically it has the required chemically
352 reactive structural components. The HI values for the mono- and di-(plain)acrylate, are much lower
353 than for cyanoacrylates and methacrylates. One possible explanation is that the QSAR model assigns
354 these compounds falsely low HIs; another might be that they have lower potential to react with native
355 lung proteins than do cyanoacrylates or methacrylates.

356 While nothing substantial is known about the mechanisms behind the respiratory sensitizing hazard
357 of acrylates, our findings offer some interesting clues. Acrylate-induced OA cases were younger, better
358 educated, and the proportion of them who were women was higher than among those with OA to
359 other LMW agents, reflecting, presumably, differences in jobs that incur exposure to these agents.
360 Acrylate cases had shorter durations of symptomatic exposure, fewer asthma treatments and higher
361 FEV₁/FVC ratios. Taken together these factors suggest that OA from acrylates is identified at a
362 relatively early stage. In addition, the patients reported more work-related rhinitis, conjunctivitis and
363 urticaria than isocyanate-induced cases. Increases in FeNO after SIC exposure have been associated
364 with HMW agents (32), although are reported also after challenge with some LMW agents including
365 isocyanates (33). In our series, FeNO increase after SIC was more frequently recorded in acrylate-
366 induced OA than in OA induced by isocyanates or other chemical agents. FeNO has been previously
367 measured during SIC in only a few case reports of acrylate-induced OA, all included in our series. In
368 three cases an increase was reported (10, 16, 20). In another case FeNO did not increase during SIC
369 but was higher during a work period when compared to off work (9). We also found a trend towards
370 more eosinophilic inflammation in induced sputum after SIC in acrylate-induced asthma, although the
371 small number of cases (n=9) limited these analyses. Several cases of an increase in sputum eosinophils
372 during SIC in acrylate-induced asthma have been reported, some of them included in the present
373 series (9, 11, 14, 18-20). Comparisons of the eosinophil and FeNO responses to challenge with
374 acrylates with those in OA to other LMW agents may suggest greater involvement of TH2-type
375 mechanisms in the former. Skin prick tests with the inciting acrylate compounds were negative in all
376 tested patients. This finding is in line with former studies (7, 21) and indicates that this test is
377 insensitive to detect sensitization to acrylates, as it is for most LMW agents.

378 In the absence of at-risk denominators, our findings cannot shed light on the relative potency of
379 different acrylates. Moreover, the relevant exposures to acrylates will depend also on the physical
380 characteristics of the different acrylates and the environmental circumstances in which they are
381 encountered. Only small volumes of glue are typically used in industrial assembly and artificial eyelash
382 work, meaning that respiratory exposure to acrylates in these tasks is probably low. In painting and
383 molding, in nail care and in the preparation of prosthetics, the amount of acrylic product is higher
384 resulting in increased exposures, especially in confined workplaces. Grinding of newly hardened

385 acrylate plastics (e.g. prosthesis or nails) may produce high volumes of fine dust that contain residues
386 of reactive starting materials (14, 34, 35). Furthermore, respiratory exposure to reactive acrylates is
387 dependent on their volatility and mode of usage and consequently their concentration in the user's
388 breathing zone. Hydroxyethyl methacrylate (HEMA) and methyl methacrylate (MMA) are examples of
389 volatile acrylates that may produce relatively high airborne concentrations by evaporation, especially
390 in tasks such as coating of large areas or molding of prostheses or artificial nails. Air measurements of
391 acrylates are relatively scarce: small amounts of methacrylates have been detected in Finnish nail
392 salons (34). Higher levels of MMA were detected in dental laboratories (36) and recently in 15 out of
393 17 nail salons (37) in the USA.

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

400 A barrier to the prevention of OA from acrylates is that the Safety Data Sheets of acrylate products
401 often fail to identify that these compounds are potential respiratory sensitizers. Our series supports
402 the recent REACH substance evaluation process (38) which concluded that MMA should be classified
403 as a respiratory sensitizer, warranting the appropriate hazard statement. HEMA and ethyl
404 methacrylate are currently being evaluated (39) but there are no such plans for cyanoacrylates that
405 were a common causative agent in our series.

406 In conclusion, acrylate-induced OA shows some characteristics (concomitant work-related rhinitis and
407 a greater post-exposure increase in FeNO) that have been previously linked to OA caused by HMW
408 agents, suggesting that acrylates may induce OA through immunological mechanisms that are
409 different from other LMW agents. Moreover, the phenotypic differences between acrylates and other
410 LMW agents challenge the practice of pooling a wide variety of LMW agents into a single category,
411 presuming implicitly that they share similar pathophysiologic mechanisms (23). Physicians, workers
412 and employers should be informed about the respiratory hazards of acrylate products and how to
413 prevent them (40). The present and other reports of OA due to acrylates should be taken into account
414 when updating their hazard classifications.

415

416 **References**

- 417 1. Goncalo M, Pinho A, Agner T, Andersen KE, Bruze M, Diepgen T, et al. Allergic contact
418 dermatitis caused by nail acrylates in Europe. An EECDRG study. *Contact Dermatitis*.
419 2018;78(4):254-60.
- 420 2. ECHA (European CHEMical Agency). Harmonised classification and labelling of hazardous
421 substances. Annex VI to CLP Helsinki, Finland: European Chemicals Agency; 2018. Updated Sep
422 2018. Available from: <https://echa.europa.eu/fi/information-on-chemicals/annex-vi-to-clp>.
423 Last accessed: September 2019.
- 424 3. Borak J, Fields C, Andrews LS, Pemberton MA. Methyl methacrylate and respiratory
425 sensitization: a critical review. *Crit Rev Toxicol*. 2011;41(3):230-68.
- 426 4. Toren K, Jarvholm B, Brisman J, Hagberg S, Hermansson BA, Lillienberg L. Adult-onset asthma
427 and occupational exposures. *Scand J Work Environ Health*. 1999;25(5):430-5.
- 428 5. Jaakkola MS, Leino T, Tammilehto L, Ylostalo P, Kuosma E, Alanko K. Respiratory effects of
429 exposure to methacrylates among dental assistants. *Allergy*. 2007;62(6):648-54.
- 430 6. Lillienberg L, Andersson E, Janson C, Dahlman-Hoglund A, Forsberg B, Holm M, et al.
431 Occupational exposure and new-onset asthma in a population-based study in Northern
432 Europe (RHINE). *Ann Occup Hyg*. 2013;57(4):482-92.
- 433 7. Savonius B, Keskinen H, Tuppurainen M, Kanerva L. Occupational respiratory disease caused
434 by acrylates. *Clin Exp Allergy*. 1993;23(5):416-24.
- 435 8. Walters GI, Robertson AS, Moore VC, Burge PS. Occupational asthma caused by acrylic
436 compounds from SHIELD surveillance (1989-2014). *Occup Med (Lond)*. 2017;67(4):282-9.
- 437 9. Andujar R, Cruz MJ, Villar A, Morell F, Munoz X. High eosinophil levels and poor evolution in
438 occupational asthma due to cyanoacrylate exposure. *Am J Ind Med*. 2011;54(9):714-8.
- 439 10. Lindstrom I, Suojalehto H, Henriks-Eckerman ML, Suuronen K. Occupational asthma and
440 rhinitis caused by cyanoacrylate-based eyelash extension glues. *Occup Med (Lond)*.
441 2013;63(4):294-7.
- 442 11. Quirce S, Baeza ML, Tornero P, Blasco A, Barranco R, Sastre J. Occupational asthma caused by
443 exposure to cyanoacrylate. *Allergy*. 2001;56(5):446-9.
- 444 12. Pickering CA, Bainbridge D, Birtwistle IH, Griffiths DL. Occupational asthma due to methyl
445 methacrylate in an orthopaedic theatre sister. *Br Med J (Clin Res Ed)*. 1986;292(6532):1362-3.
- 446 13. Piirila P, Hodgson U, Estlander T, Keskinen H, Saalo A, Voutilainen R, et al. Occupational
447 respiratory hypersensitivity in dental personnel. *Int Arch Occup Environ Health*.
448 2002;75(4):209-16.
- 449 14. Quirce S, Barranco P, Fernandez-Nieto M, Sastre B, del Pozo V, Sastre J. Occupational asthma
450 caused by acrylates in optical laboratory technicians. *J Investig Allergol Clin Immunol*.
451 2011;21(1):78-9.
- 452 15. Sauni R, Kauppi P, Alanko K, Henriks-Eckerman ML, Tuppurainen M, Hannu T. Occupational
453 asthma caused by sculptured nails containing methacrylates. *Am J Ind Med*. 2008;51(12):968-
454 74.
- 455 16. Uriarte SA, Fernandez-Nieto M, Sastre J. Occupational asthma due to polyvinyl chloride and
456 methyl methacrylate in a plumber. *J Investig Allergol Clin Immunol*. 2013;23(6):437-8.
- 457 17. Vaccaro M, Guarneri F, Barbuza O, Cannavo SP. Airborne contact dermatitis and asthma in a
458 nail art operator. *Int J Occup Med Environ Health*. 2014;27(1):137-40.
- 459 18. Lemiere C, Weytjens K, Cartier A, Malo JL. Late asthmatic reaction with airway inflammation
460 but without airway hyperresponsiveness. *Clin Exp Allergy*. 2000;30(3):415-7.
- 461 19. Reig Rincon de Arellano I, Cimarra Alvarez-Lovell M, Robledo Echarren T, Fernandez-Nieto M,
462 Quirce Gancedo S, Seaone Plata C, et al. Occupational asthma due to acrylates in a graphic arts
463 worker. *Allergol Immunopathol (Madr)*. 2006;34(1):32-6.
- 464 20. Sanchez-Garcia S, Fernandez-Nieto M, Sastre J. Asthma induced by a thermal printer. *N Engl J*
465 *Med*. 2009;360(22):2375-6.

- 466 21. Helaskoski E, Suojalehto H, Kuuliala O, Aalto-Korte K. Prick testing with chemicals in the
467 diagnosis of occupational contact urticaria and respiratory diseases. *Contact Dermatitis*.
468 2015;72(1):20-32.
- 469 22. Vandenplas O, Godet J, Hurdubaea L, Riffart C, Suojalehto H, Walusiak-Skorupa J, et al. Severe
470 Occupational Asthma: Insights From a Multicenter European Cohort. *J Allergy Clin Immunol*
471 *Pract*. 2019.
- 472 23. Vandenplas O, Godet J, Hurdubaea L, Riffart C, Suojalehto H, Wiszniewska M, et al. Are high-
473 and low-molecular-weight sensitizing agents associated with different clinical phenotypes of
474 occupational asthma? *Allergy*. 2018;74(2):261-72.
- 475 24. Vandenplas O, Suojalehto H, Aasen TB, Baur X, Burge PS, de Blay F, et al. Specific inhalation
476 challenge in the diagnosis of occupational asthma: consensus statement. *Eur Respir J*.
477 2014;43(6):1573-87.
- 478 25. Jarvis J, Seed MJ, Stocks SJ, Agius RM. A refined QSAR model for prediction of chemical asthma
479 hazard. *Occup Med (Lond)*. 2015;65(8):659-66.
- 480 26. (GINA). Global strategy for asthma management and prevention 2015. Available from:
481 <http://www.ginasthma.org/>. Last accessed: September 2019.
- 482 27. Bousquet J, Mantzouranis E, Cruz AA, Ait-Khaled N, Baena-Cagnani CE, Bleecker ER, et al.
483 Uniform definition of asthma severity, control, and exacerbations: document presented for
484 the World Health Organization Consultation on Severe Asthma. *J Allergy Clin Immunol*.
485 2010;126(5):926-38.
- 486 28. Reddel HK, Taylor DR, Bateman ED, Boulet LP, Boushey HA, Busse WW, et al. An official
487 American Thoracic Society/European Respiratory Society statement: asthma control and
488 exacerbations: standardizing endpoints for clinical asthma trials and clinical practice. *Am J*
489 *Respir Crit Care Med*. 2009;180(1):59-99.
- 490 29. Vandenplas O, D'Alpaos V, Heymans J, Jamart J, Thimpont J, Huaux F, et al. Sputum
491 eosinophilia: an early marker of bronchial response to occupational agents. *Allergy*.
492 2009;64(5):754-61.
- 493 30. Enoch SJ, Seed MJ, Roberts DW, Cronin MT, Stocks SJ, Agius RM. Development of mechanism-
494 based structural alerts for respiratory sensitization hazard identification. *Chem Res Toxicol*.
495 2012;25(11):2490-8.
- 496 31. Enoch SJ, Roberts DW, Cronin MT. Mechanistic category formation for the prediction of
497 respiratory sensitization. *Chem Res Toxicol*. 2010;23(10):1547-55.
- 498 32. Lemiere C, S NG, Sava F, D'Alpaos V, Huaux F, Vandenplas O. Occupational asthma phenotypes
499 identified by increased fractional exhaled nitric oxide after exposure to causal agents. *J Allergy*
500 *Clin Immunol*. 2014;134(5):1063-7.
- 501 33. Ferrazzoni S, Scarpa MC, Guarnieri G, Corradi M, Mutti A, Maestrelli P. Exhaled nitric oxide and
502 breath condensate pH in asthmatic reactions induced by isocyanates. *Chest*. 2009;136(1):155-
503 62.
- 504 34. Henriks-Eckerman ML, Korva M. Exposure to airborne methacrylates in nail salons. *J Occup*
505 *Environ Hyg*. 2012;9(8):D146-50.
- 506 35. Hiiipakka D, Samimi B. Exposure of acrylic fingernail sculptors to organic vapors and
507 methacrylate dusts. *Am Ind Hyg Assoc J*. 1987;48(3):230-7.
- 508 36. Nayebzadeh A, Dufresne A. Evaluation of exposure to methyl methacrylate among dental
509 laboratory technicians. *Am Ind Hyg Assoc J* 1999 60(5):625-8.
- 510 37. Zhong L, Batterman S, Milando CW. VOC sources and exposures in nail salons: a pilot study in
511 Michigan, USA. *Int Arch Occup Environ Health*. 2019;92(1):141-53.
- 512 38. ECHA (European CHEMical Agency). Substance evaluation conclusion as required by REACH
513 Article 48 and evaluation report for methyl methacrylate. France: ANSES Unité UESC
514 Département de l'Évaluation des Risques; 2018 17 December 2018.

- 515 39. ECHA (European CHemical Agency). Substance evaluation - CoRAP 2019. Available from:
516 [https://echa.europa.eu/information-on-chemicals/evaluation/community-rolling-action-](https://echa.europa.eu/information-on-chemicals/evaluation/community-rolling-action-plan/corap-table)
517 [plan/corap-table](https://echa.europa.eu/information-on-chemicals/evaluation/community-rolling-action-plan/corap-table). Last accessed: September 2019.
- 518 40. Moscato G, Pala G, Boillat MA, Folletti I, Gerth van Wijk R, Olgiati-Des Gouttes D, et al. EAACI
519 position paper: prevention of work-related respiratory allergies among pre-apprentices or
520 apprentices and young workers. *Allergy*. 2011;66(9):1164-73.
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522

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

	Acrylates		
Acrylate subgroup/Characteristic	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, anaerobic sealants and screw lockers, printing colours and plates	wood lacquers, printing colours 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 hazard index (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

525 ECA=Ethyl cyanoacrylate, 2-HEMA=2-hydroxyethyl methacrylate, BA=Butylacrylate, MCA=methyl
526 cyanoacrylate, MMA=methyl methacrylate; EHA=ethyl hexylacrylate, TREGDMA=triethyleneglycol-
527 dimethacrylate; DEGDA=diethyleneglycol-diacrylate; HI=Hazard index, based on the model by Jarvis
528 *et al.* (25).

529

530

531 TABLE II. Exposures and jobs of patients with occupational asthma 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. tyres, infusion sets, jewelry, plastic elements) - laminating	-glues -paints -molding and laminating resins	cyanoacrylates (8) methacrylates (3)
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 ink - shoe making and repairing	-printing inks -glue	cyanoacrylates (1) plain acrylates (2)
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) -molding and grinding prostheses	-prosthesis powders and liquids	methacrylates (3)
Beauty care (12)			
Beauticians (7) hairdressers (5)	-attaching eyelash extensions -molding, structuring and grinding artificial nails	-eyelash glues -nail glues -nail gels, nail powders and liquids	cyanoacrylates (7) methacrylates (2) cyanoacrylates and methacrylates (3)

532 n=number of workers

533

534 **TABLE III. Demographic and clinical characteristics of subjects with occupational asthma caused by**
 535 **acrylates, other low-molecular-weight agents including isocyanates, and isocyanates.** Data are
 536 presented as n (% of available data) unless otherwise specified. Values in bold are statistically
 537 significant.

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, yr ^a	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 ^{2a}	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) ^b	6 (12.2)	103 (29.5)	0.010	39 (36.5)	0.002
Atopy ^c	23 (41.8)	193 (46.2)	0.570	54 (43.2)	1.000
Asthma pre-existing to the causal exposure	7 (12.7)	51 (12.2)	0.830	15 (12.0)	1.000
Duration of exposure before asthma onset, mo ^a	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 ^a	14 (9-36)	26 (12-60)	0.020	24 (12-60)	0.070
Interval since last work exposure, mo ^a	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/day	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

538 GINA, Global Initiative for Asthma (26); SABA, short acting β_2 agonist;

539 ^aMedian value with interquartile range (IQR) within parentheses;

540 ^b Number (%) of persons having only primary level education

541 ^cAtopy defined by the presence of ≥ 1 positive skin-prick test to at least one common allergen.

542

543 **TABLE IV. Functional characteristics of subjects with occupational asthma caused by acrylates,**
 544 **other low-molecular-weight agents including isocyanates, and isocyanates.** Data are presented as n
 545 (% of available data) unless otherwise specified. Values in bold are statistically significant.

	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 ^a	96 (88-105)	99 (89-108)	0.290	98 (88-107)	0.600
FEV ₁ , % pred ^a	93 (83-100)	91 (82-100)	0.570	89 (81-98)	0.250
FEV ₁ /FVC ^a	81 (76-85)	77 (71-82)	0.001	76 (70-82)	<0.001
Airflow obstruction ^b	3 (5.5)	48 (11.5)	0.250	13 (10.4)	0.400
Baseline level of NSBH:	(n=48)	(n=390)	0.760	(n=119)	0.080
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)	
Post-challenge change in NSBH ^c	(n=24)	(n=219)		(n=55)	
Pre/post-SIC NSBH ratio	2.0 (1.0-3.9)	2.0 (1.0-4.3)	0.730	2.3 (1.0-4.9)	0.430
Pattern of bronchial response to SIC	(n=54)	(n=385)		(n=113)	
Isolated early	12 (21.8)	112 (27.1)	0.270	23 (18.7)	0.680
Isolated late	24 (43.6)	141 (34.1)	0.270	44 (35.5)	0.320
Both early and late components	18 (32.7)	132 (31.9)	0.270	46 (36.8)	0.610

546 FEV₁: forced expiratory volume in one-second; FVC: forced vital capacity; NSBH: nonspecific bronchial
 547 hyperresponsiveness; SIC: specific inhalation challenge.

548 ^a Median value with interquartile range (IQR) within parentheses;

549 ^b Airflow obstruction defined by a FEV₁ <80% predicted value and a FEV₁/FVC ratio <70%;

550 ^c See ref (23) for the threshold values used for grading the level of NSBH.

551

552

553 **TABLE V. Airway inflammation markers in subjects with occupational asthma caused by acrylates,**
 554 **other low-molecular-weight agents including isocyanates, and isocyanates.** Data are presented as n
 555 (% of available data) unless otherwise specified. Values in bold are statistically significant.

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^{a}	200 (97-321)	212 (110-338)	0.310	242 (145-396)	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 ^a	15.0 (10.0-29.0)	19.0 (10.0-32.8)	0.300	20.0 (12.0-35.0)	0.140
Post-SIC change in FeNO, ppb ^{a,b}	(n=18)	(n=155)		(n=34)	
Pre/post-SIC change in FeNO ≥ 17.5 ppb ^b	26.0 (8.2-38.0)	3.0 (-1.0-10.0)	<0.001	5.0 (2.0-16.0)	0.010
	10 (55.6)	31 (20.0)	0.002	8 (24.2)	0.030
Baseline sputum eosinophils:	(n=9)	(n=79)		(n=19)	
% ^a	5 (2-10)	2 (1-6)	0.290	2.0 (1.0-8.5)	0.620
Post-challenge sputum eosinophils:	(n=8)	(n=65)		(n=17)	
% ^a	10.0 (5.0-14.4)	7.0 (2.0-15.5)	0.300	8.5 (2.2-13.2)	0.520
Post-SIC change, % ^a	6.1 (3.0-11.5)	2.0 (0.8-8.0)	0.110	4.0 (0.0-8.0)	0.220
Post-SIC increase in sputum eosinophils $\geq 3\%$	7 (87.5)	31 (47.7)	0.060	10 (58.8)	0.210
Baseline sputum neutrophils:	(n=9)	(n=84)		(n=21)	
% ^a	45.0 (37.0-50.0)	58.5 (44.4-72.2)	0.040	55.0 (42.0-78.5)	0.170
Post-challenge sputum neutrophils:	(n=8)	(n=70)		(n=19)	
% ^a	45.0 (41.0-47.0)	61.0 (45.0-73.0)	0.020	49.0 (28.0-64.0)	0.490
Post-SIC change, %	-1.5 (-11.8-5.0)	1.0 (-12.4-14.2)	0.620	-2.0 (-20.5-11.5)	0.710
Baseline sputum inflammatory pattern ^c :	(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	
Post-challenge sputum inflammatory pattern ^c :	(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)	

556 FeNO: fractional exhaled nitric oxide; SIC: specific inhalation challenge

557 ^amedian value with interquartile range (IQR) within parentheses; ^bcompared to baseline value

558 ^cThe sputum inflammatory pattern was characterized as "eosinophilic" (i.e. $\geq 3\%$ eosinophils and

559 $< 76\%$ neutrophils); "neutrophilic" (i.e. $\geq 76\%$ and $< 3\%$ eosinophils); "paucigranulocytic" (i.e. $< 3\%$

560 eosinophils and $< 76\%$ neutrophils); and "mixed granulocytic" (i.e. $\geq 76\%$ neutrophils and $\geq 3\%$

561 eosinophils.

562 Note: If you introduce the abbreviation SIC, you may use it throughout the table instead of “post-
563 challenge”
564