Response to: Correspondence on "Association between occupational exposure to irritant agents and a distinct asthma endotype in adults" by Andrianjafimasy et al

We read with interest the letter by Burge *et al* related to our publication on occupational exposure to irritants and asthma endotypes.[1] Burge *et al* comment on the definition of irritants, an issue regularly discussed in the field of work-related asthma.[2]

A concern expressed by Burge *et al* is that the Occupational Asthma Job-Exposure Matrix (OAsJEM), used to evaluate exposure to irritant agents in our study, includes among the list of irritants some agents well-known as low molecular weight sensitisers, namely isocyanates, acrylates, epoxy resins and amines. We would like to take this opportunity to clarify some aspects of the OAsJEM. The OAsJEM, a revised version of the former asthma-specific JEM, evaluates exposure to 30 specific agents, classified in several large groups such as 'high molecular weight', 'low molecular weight' or 'irritant', based on a consensus from international experts, as described previously.[3] Because for many agents, the exact mechanism(s) involved in occupational asthma still needs to be elucidated, the experts choose a sensitive classification approach to assign agents to large groups, considering sensitising or irritant potential according to most recent literature, rather than an approach limited to definite classifications as sensitiser or irritant. As a consequence, agents for which mechanisms remain poorly understood, such as most low molecular weight agents and irritants, were sometimes classified in both categories. Specifically, of the 19 agents classified as 'irritants', 9 were also classified as 'low-molecular-weight agents'.[3] This includes isocyanates, acrylates, epoxy resins and amines. Indeed, in addition to their classification as sensitisers, these agents have been suggested as potential irritants, although with low to moderate level of evidence.[4 5]

Investigators using the OAsJEM should consider and interpret the impact of each agent with caution and to discuss potential mechanisms in the context of most recent literature, as well as their specific research question and study population. Our study was conducted in the Epidemiological study on the Genetics and Environments of Asthma (EGEA), based on a sample of individuals with asthma, their family members and population-based controls. In this population, very few participants were exposed to isocyanates, acrylates, epoxy resins or amines (<2% exposed to any of these agents,<1% exposed with high probability of exposure). More frequent exposures in participants exposed to irritants were high level disinfectants, cleaning products and solvents, followed by exhaust fumes and metals. Most of these exposures are in general not suspected to be sensitisers. In addition, when examining specifically low molecular weight agents, we did not observe an association with the endotype labelled 'CA1' (Current Asthma 1). We, thus, concluded that our results were not driven by exposure to a few specific sensitisers, and were likely mainly imputable to irritant exposures.

The entities 'occupational asthma' or 'work-related asthma' have the specificity to include the cause in the disease definition. However, in epidemiological association studies, exposures (potential causal agents) and outcomes (asthma) need to be considered separately. Thus, in the EGEA study, no attempt was made to identify causal agents at individual level through clinical testing (eg, specific challenges), and we cannot classify exposures as 'irritant' or 'sensitiser' based on clinical results in specific workers, hence the JEM approach. However, we do not see this as a limitation. Literature on work-related asthma includes both approaches, that is, description of cases of work-related asthma seen in occupational diseases clinics with evaluation of the causal agent at individual level, and population-based studies examining association between exposures and asthma outcomes defined independently of work causation. This is also true in recent literature on (work-related) asthma endotypes.[1 6] These approaches should be seen as complementary rather than as antagonist.

While the possibility to identify causal agents at individual level is favourable for workers with sensitiser induced occupational asthma, it may have led to an under-recognition of irritant-induced occupational asthma, for which causation is more difficult to prove in a specific worker.[7] This is well illustrated by a recent study using data from the Michigan occupational asthma surveillance system, in which a known sensitiser was identified as causal agent in less than half (48%) of occupational asthma cases, excluding reactive airways dysfunction syndrome.[8] The proportion of irritant-induced asthma among the remaining cases could not be determined with certainty, but might have been substantial.

For many other occupational diseases (eg, chronic obstructive pulmonary disease, cancers), workplace causation cannot be determined with confidence at individual level, and evidence for causality largely relies on epidemiological studies. This is also the case for irritant-induced asthma.[2 7] From the view of clinicians treating patients with occupational asthma, an 'irritant' label may still degrade the significance of exposure and associated health effects, and possibly hamper compensation. However, from an aetiological research perspective, ignoring the irritant potential of some substances would be counterproductive, as it would only contribute to mask associated health effects. We agree that stronger evidence is needed to definitely label some agents as respiratory irritants. Nonetheless, we believe that there is already sufficient epidemiological evidence to upgrade the significance of irritant exposure both in research and in clinical practice. Irritants, including in the context of common (non-high peak) exposures, should be more widely examined as true causal agents for occupational asthma.

Miora Valérie Andrianjafimasy [1], **Mickaël Febrissy**[2], **Farid Zerimech**[3,4], **Brigitte Dananché**[5], **Hans Kromhout** [6], **Régis Matran**[3,4], **Mohamed Nadif**[2], **Dominique Oberson-Geneste**[7], **Catherine Quinot**[1], **Vivi Schlünssen**[8,9], **Valérie Siroux**[10], **Jan-Paul Zock**[11], **Nicole Le Moual** [1], **Rachel Nadif**[1], **Orianne Dumas** [1]

[1]Université Paris-Saclay, UVSQ, Université Paris-Sud, Inserm, Équipe d'Épidémiologie Respiratoire Intégrative, CESP, 94807, Villejuif, France
[2]LIPADE, Université de Paris Descartes, Paris, France
[3]Université de Lille, ULR 4483 – IMPECS, F-59000, Lille, France
[4]Institut Pasteur de Lille, CHU Lille, F-59000, Lille, France
[5]Industrial Hygiene Consulting, Courlaoux, France
[6]Utrecht University, Division of Environmental Epidemiology, Institute for Risk Assessment Sciences, Utrecht, The Netherlands
[7]Toxibio-Consultant, Lescar, France
[8]Aarhus University, Department of Public Health, Environment, Occupation and Health, Danish Ramazzini Centre, Aarhus, Denmark
[9]National Research Center for the Working Environment, Copenhagen, Denmark
[10]Université de Grenoble Alpes, Inserm, CNRS, Team of Environmental Epidemiology Applied to Reproduction and Respiratory Health, IAB, Grenoble, France
[11]Institute for Global Health (ISGlobal) and Universitat Pompeu Fabra (UPF), Barcelona, Spain

Correspondence to Dr Orianne Dumas, Inserm, CESP, Équipe d'Épidémiologie respiratoire intégrative, 94807 Villejuif, France; orianne.dumas@inserm.fr

Contributors OD wrote the response letter and all the other coauthors revised it and gave their consent for submission.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient consent for publication Not applicable.

Provenance and peer review Commissioned; internally peer reviewed.

To cite Andrianjafimasy MV, Febrissy M, Zerimech F, *et al*. *Occup Environ Med* 2022;**79**:359–360.

Received 30 November 2021
Accepted 18 December 2021
Published Online First 7 March 2022

► http://dx.doi.org/10.1136/oemed-2021-108116

Occup Environ Med 2022;**79**:359–360.
doi:10.1136/oemed-2021-108117

ORCID iDs
Miora Valérie Andrianjafimasy http://orcid.org/0000-0002-5791-0772
Hans Kromhout http://orcid.org/0000-0002-4233-1890
Nicole Le Moual http://orcid.org/0000-0002-2723-5569
Orianne Dumas http://orcid.org/0000-0001-8423-2826

REFERENCES

1 Andrianjafimasy MV, Febrissy M, Zerimech F, *et al*. Association between occupational exposure to irritant agents and a distinct asthma endotype in adults. *Occup Environ Med* 2022;79:155–61.
2 Vandenplas O, Wiszniewska M, Raulf M, *et al*. EAACI position paper: irritant-induced asthma. *Allergy* 2014;69:1141–53.
3 Le Moual N, Zock J-P, Dumas O, *et al*. Update of an occupational asthma-specific job exposure matrix to assess exposure to 30 specific agents. *Occup Environ Med* 2018;75:507–14.
4 Baur X. A compendium of causative agents of occupational asthma. *J Occup Med Toxicol* 2013;8:15.
5 Lillienberg L, Andersson E, Janson C, *et al*. Occupational exposure and new-onset asthma in a population-based study in northern Europe (Rhine). *Ann Occup Hyg* 2013;57:482–92.
6 Suojalehto H, Ndika J, Lindström I, *et al*. Endotyping asthma related to 3 different work exposures. *J Allergy Clin Immunol* 2021;148:1072–80.
7 Bernstein JA, Dumas O, de Blay F, *et al*. Irritant-induced asthma and reactive airways dysfunction syndrome. In: *Asthma in the workplace*. 5 edn, 2021.
8 Reilly MJ, Wang L, Rosenman KD. The burden of work-related asthma in Michigan, 1988-2018. *Ann Am Thorac Soc* 2020;17:284–92.