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Comment on “Application of the Key Characteristics Framework to Identify Potential Breast Carcinogens Using Publicly Available *in Vivo*, *in Vitro*, and *in Silico* Data”

Meriem Koual^{1,2,3}  and Xavier Coumoul^{2,3}

¹Department of Gynecologic and Breast Oncologic Surgery, Georges-Pompidou European Hospital, Paris, France

²Institut national de la santé et de la recherche médicale, Paris, France

³Université Paris Cité, Paris, France

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We read with interest the recent paper published by Kay et al.¹ We are particularly aware, through our work on breast cancer, of the need for strong and innovative research to characterize the contribution of the environment in the broad sense to the incidence of this disease, the leading cause of cancer deaths in women worldwide.² As Kay et al. point out, many chemical factors have been identified as contributing to the etiology of breast cancer—including ambient air pollution, certain personal care products, and persistent organic pollutants. We support this necessary approach of key characteristics assessment of chemicals for targeted exposure reduction and better evaluation of potential breast carcinogens.

We further believe future research perspectives in the evaluation of chemical substances should focus on key processes leading to the unfavorable evolution of cancer, the formation of metastases, and the response to antitumor treatments. Although chemicals are evaluated for their genotoxicity, endocrine-disrupting properties, and tumor formation in animals, their effects on cancer progression and metastasis formation are not yet investigated. Carcinogenesis is a multistage process involving tumor initiation, promotion, and malignant conversion, as well as metastatic progression. Recurrence due to metastasis is associated to poor prognosis, being responsible for the majority of deaths from solid tumors.³

In the last decade, an emerging literature shows a positive association between exposure to environmental chemicals, metastatic risk and prognosis.^{4,5} Experimental studies, including our own, show pro-metastatic effects of diverse chemicals with the activation of epithelial-to-mesenchymal transition and the acquisition of cancer stemness and potential role in chemoresistance.^{6–8} Interestingly, the causal link between the action of these pollutants and certain cellular characteristics specific to metastases can also be established, involving the aryl hydrocarbon receptor, for example.^{9,10}

It is especially important, as underlined by Jones and White in their invited perspective¹¹ accompanying the article by Kay et al., that further research be done to clarify the role of environmental

exposures in the etiology of estrogen receptor–negative tumors, a highly aggressive breast cancer that is mostly diagnosed in young women.¹² We agree with Jones and White that improving prevention efforts is fundamental, and such efforts could also focus on metastatic dissemination as secondary prevention for breast cancer patients and survivors.

Editor’s Note: In accordance with journal policy, both Kay et al. and Jones and White were invited to respond to this letter. They chose not to do so.

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Address correspondence to Meriem Koual, Gynecological and Breast Oncologic Surgery Department, European Georges-Pompidou Hospital, 20, rue Leblanc, 75908 Paris Cedex 15, France. Telephone: 331 56 09 25 63. Email: meriem.koual@aphp.fr

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