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**Phenoxyethanol, reproduction, and development: additional studies are needed**

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We read with attention the article of Dreno et al. [1] entitled "Safety review of phenoxyethanol when used as a preservative in cosmetics", published in the November 2019 supplemental issue funded by Cosmetique Active International. We would like to respond to their comments on the epidemiological studies we conducted investigating the possible role of phenoxyethanol exposure on reproduction and development.

Epidemiological studies, especially longitudinal cohort studies, provide a posteriori risk assessment in a real-life context to complement European chemical regulations, especially when data are insufficient. The PELAGIE mother-child cohort cited by Dreno et al. fulfils this purpose.

This cohort enrolled 3,421 pregnant women before 19 weeks of gestation between 2002 and 2006 in Brittany (France). Questionnaires and biological samples, collected at various times during pregnancy and childhood, allowed assessment of exposure to various contaminants and determination of other risk factors. First, phenoxyacetic acid (PhAA), a metabolite of phenoxyethanol measured in the prenatal urine samples, was detectable in 93% of the cohort population (LOD=0.05 mg/L), with a median value of 0.48 mg/L [2]. Then, higher maternal urinary levels of PhAA measured at inclusion were shown to be associated with (1) a longer time to pregnancy (TTP) [2], (2) variations in steroid levels at birth, including lower levels of hormones involved in the delta-5 pathway among boys [3], and (3) lower performance in Verbal Comprehension at age six using the Weschler Intelligence Scale for Children [4]. Conversely, we observed no association between prenatal PhAA urine levels and (1) major congenital malformations [5] or (2) male genital anomalies using a case-control study design nested in the cohort [6].

Dreno et al. reported most of these results but, inappropriately for a review, mentioned only limitations already extensively discussed by the PELAGIE investigators and only considered them for studies that showed statistically-significant associations. For example, assessment of

exposure with a single urinary spot for non-persistent compounds is well known to be insufficient to capture intra-individual variability; however, it partially reflects regular, chronic exposure, such as that from using cosmetics. Accordingly, a correlation between PhAA levels in a single urinary spot and a declaration of using cosmetics at work [5] or home [7] has already been reported. Dreno et al. also indiscriminately dismiss the methodology used in our analyses. Contrary to their claim, TTP measurement has been validated and is widely used to study couple fecundity in observational studies [8]. In addition, they argue that this study on TTP and phenoxyethanol “is the only study that showed such results”, failing to add that it is the only published study to have investigated this issue, which would relativize their statement. Finally, chance findings and uncontrolled confounding factors are systematic and common - but not always justified - elements that produce doubts in observational studies, but they are also common in toxicological studies, although this is not acknowledged by Dreno et al. Further support of the potential scope of our findings includes the specificity of the associations we found with PhAA relative to other glycol ether metabolites and their concordance with animal data, when available, which suggest, for example, an impact on ovarian function [9].

The conclusion of Dreno et al. that phenoxyethanol can be considered safe when used as a preservative, according to existing toxicological data, is inappropriate and neglects all observational studies. There are indications of potential toxicity and it is important, as acknowledged by the French National Agency for Medicines and Health Products [10], to pursue research on this substance, including toxicological studies (e.g. its endocrine-disrupting potential has only been studied for estrogenic activity [11]) and new epidemiological observations.

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