

## Effects of Indoor Endocrine Disrupting Chemicals on Childhood Rhinitis

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Endocrine disrupting chemicals (EDCs) are ubiquitous in our environment and they pose a threat not just to indoor environment but to public health [1, 2]. Despite the widespread presence of these chemicals indoors, the understanding of the extent as well as the health effects of the exposure is limited by insufficient data on exposure patterns and the action of EDCs over the lifespan [3, 4]. Previous evidence suggested that both individual and co-exposure to low concentrations of EDCs in classrooms is associated with an increased risk of asthma, obesity and with an increased prevalence of nasal obstruction symptoms in the previous 3 months among children [5]. Furthermore, we found that the exposure to EDCs was also associated with changes in the autonomic nervous system, specifically parasympathetic dysautonomia, thus suggesting that EDCs may increase parasympathetic activity, resulting in a subsequent increase in the risk of asthma, respiratory symptoms, as well as obesity [5]. In addition to the observed effect of EDCs on nasal obstruction [5], one of the defining symptoms of rhinitis, asthma frequently coexists with allergic rhinitis (AR), being one of the risk factors for the development of asthma [6, 7]. However, no studies have yet addressed the effects of exposure to EDCs on rhinitis. Thus, we aimed to assess the effect of indoor individual or combined exposure to EDCs exposure on rhinitis in school children.

Data from a cross-sectional analysis of 845 participants from 20 schools in Porto, Portugal, were analyzed. The evaluation included a self-administered ISAAC-based questionnaire [8] and a physical and clinical assessment (supplementary file). Children were considered to have AR if there was a positive answer to the question “Has your child ever had a problem with sneezing, or a runny nose or blocked nose when he/she did not have a cold or the flu?” combined with a positive skin prick test to common allergens. Current allergic rhinitis (CAR) was defined if there was also a positive answer to the question “In the past 12 months, has your child had a problem with sneezing, or a runny nose or blocked nose when he/she did not have a cold or the flu?” [5]. The University Health Ethics Committee approved the study, and informed consent was obtained from children’s legal guardians. Among the 845 children included (49.2% girls), the prevalence of AR and CAR was 13.4%, 10.4%, respectively.

The indoor levels of 13 volatile organic compounds and 2 aldehydes identified as EDCs (toluene, o-xylene, m/p-xylene, hexane, ethylbenzene, styrene, cyclohexanone, butylated hydroxytoluene, benzene, benzaldehyde, tetrachloroethylene, 2-butoxyethanol, 2-ethyl-1-hexanol, formaldehyde and acetaldehyde) were measured in 71 classrooms over one week, during regular daily activities and under representative conditions of occupancy and use of the classrooms in winter. The complete sampling methodology has been described previously [5]. Principal component analysis (PCA) was used to identify major EDCs

patterns based on the 15 individual compounds. The PCA divided the EDCs into two principal components (PC1 and PC2). Generalized linear models and multinomial logistic regression models were used to measure the effect of individual or combined EDCs on AR and CAR. Analyses were performed without adjustments (model 0) and adjusted for age, sex, asthma, exhaled NO and body mass index (model 1). PCA and mixed effect models were analyzed using RStudio software, version 1.0.

Classrooms with higher median levels of formaldehyde (16.83 (13.3, 25.1)  $\mu\text{g}/\text{m}^3$  vs 14.93 (12.3, 20.1)  $\mu\text{g}/\text{m}^3$ ,  $p=0.018$ ) and higher PC2 scores (0.02 (-0.35, 0.77)  $\mu\text{g}/\text{m}^3$  vs -0.12 (-0.61, 0.35),  $p=0.014$ ) had a higher number of children with CAR. A positive association was found between PC2 and the risk of CAR (OR=1.44, 95% CI 1.11, 1.89). After adjustment, the effect size estimates were similar (OR=1.35, 95% CI 1.02, 1.80). No significant associations were observed between individual EDCs and AR and CAR, as well as between PC1 and rhinitis (Figure 1). In addition, levels of individual EDCs and scores of PC1 were negatively associated with velocity of constriction and baseline pupil diameter. Moreover, a positive association was found between constriction velocity and amplitude, and baseline pupil diameter.

Our findings suggest that exposure to combined EDCs levels in classrooms is associated with an increased risk of CAR. Similar to our previous study [5], these findings suggest that exposure to combined EDCs may have an effect on the respiratory health of children, increasing the risk of one or more symptoms including sneezing, runny nose or blocked nose in past 12 months; these results also contribute to the understanding of the potential health risk of co-exposure. Additionally, EDCs represented by PC2 showed that the compounds may interact within or between classes, having different and even opposite effects, suggesting combinations of low doses of EDCs that are individually inactive may cause a biological effect [9]. EDCs represented by PC2 may act through different pathways or mechanisms compared to those PC1, suggesting that children may respond differently when exposed to different mixture of EDCs. As previously proposed for asthma [5] changes in autonomic nervous system, namely with a parasympathetic dysautonomia assessed through pupillometry, due to exposure to EDCs may also play an important role in the development of CAR. However, the cross-sectional design does not allow the establishment of causal relations between exposure to EDCs and rhinitis. Furthermore, no on-site monitoring data regarding indoor air pollution levels were considered in the analysis. Although several studies have identified the role of the environment in the development of allergic rhinitis [10-12], it is expected that the association between exposure to combined EDCs of PC2 and the increased risk of current allergic rhinitis is independent of other indoor exposures. Indicators of allergic rhinitis severity [13], including sleep disturbance, impairment of daily and school activities and severity of symptoms, and also of asthma severity were not considered. Thus, it will be important to assess the effect of long-term exposure to school indoor environment to understand the extent of health effects. In conclusion, the present study highlights the negative effect of co-exposure to EDCs in current allergic rhinitis,

contributing to implement recommendations to minimize exposures and to promote a healthy indoor environment.

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### **Conflict of interest**

The authors declare no conflict of interest.

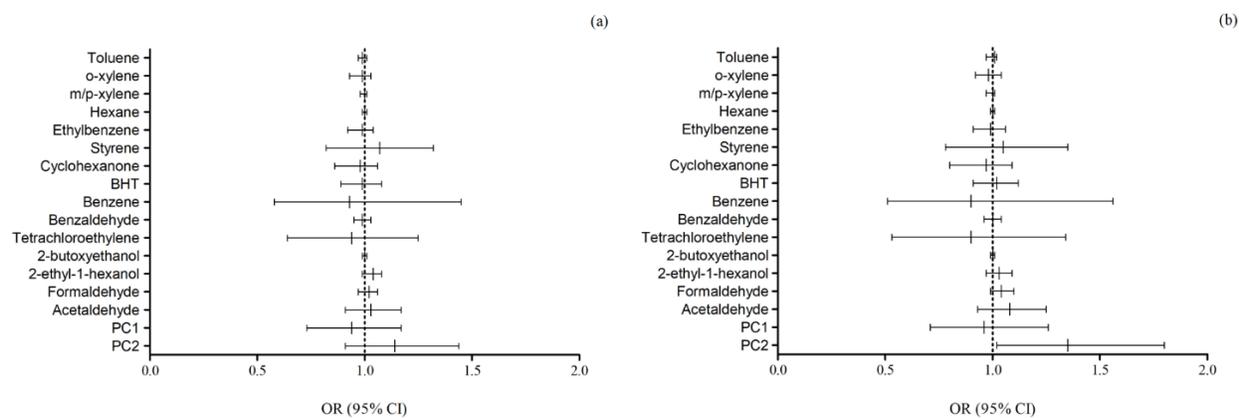
### **Data availability**

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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**Figure 1** Association between EDCs and (a) allergic rhinitis and (b) current allergic rhinitis



BHT: butylated hydroxytoluene; PC1: principal component 1 (toluene, o-xylene, m/p-xylene, ethylbenzene, styrene and benzene); PC2: principal component 2 (cyclohexanone, BHT, benzene, benzaldehyde, formaldehyde and acetaldehyde).

Results were adjusted for age, sex, asthma, exhaled NO and body mass index.